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Diet and nutrition for non-communicable diseases in low and middle-income countries

Edited by
Mainul Haque and Farhana Akter

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Diet and nutrition for non-communicable diseases in low and middle-income countries

Topic editors
Mainul Haque — National Defence University of Malaysia, Malaysia
Farhana Akter — Department of Endocrinology, Chittagong Medical College, Bangladesh

Topic coordinator
Rahnuma Ahmad — Medical College for Women and Hospital, Bangladesh

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Editorial: Diet and nutrition for non-communicable diseases in low and middle-income countries

Rahnuma Ahmad [1], Farhana Akter [2] and Mainul Haque [3]*

[1]Department of Physiology, Medical College for Women and Hospital, Dhaka, Bangladesh, [2]Department of Endocrinology, Chittagong Medical College Hospital, Chattogram, Bangladesh, [3]Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kuala Lumpur, Malaysia

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Mauro Serafini,
University of Teramo, Italy

*CORRESPONDENCE
Mainul Haque
runurono@gmail.com;
mainul@upnm.edu.my

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Editorial on the Research Topic
Diet and nutrition for non-communicable diseases in low and middle-income countries

The indicators of nutritional status, which include underweight, overweight, short stature, and obesity, are changing in low-to-middle-income countries (LMICs) (1). These indicators need to be researched with recent data and compared with past data to observe the changing scenario for nutritional status in these countries. Moreover, it is important to understand the government policies on food that are in place to overcome the burden of malnutrition and the extent of their application in the public health field. Unhealthy food consumption, including that of sugar, fast food, fat, and oil, in LMICs needs to be assessed.

Both undernutrition and overnutrition appear to be a growing burden on LMICs (2). Globally, about one-third of the population is affected by malnutrition, with approximately one billion individuals suffering from undernutrition due to inadequate protein, calorie, and micronutrient intake (3). The LMICs are facing the hurdles of the poor growth of children, deficiency of micronutrients, and adults with high BMI (4).

There has also been a rise in non-communicable disease (NCD) in LMICs owing to their populations suffering undernutrition at the early stages of life (in early childhood and mothers suffering undernutrition before and during pregnancy) and then becoming overweight during adulthood (5). An increased risk of growth stunting, NCD, and obesity in later life is suffered by children whose mothers were undernourished during pregnancy (6). Rapid weight gain in children may be related to the raised risk of cardiometabolic diseases and obesity later in life (7). Oumer et al. performed research on the dietary pattern among pregnant women in Eastern Ethiopia to understand the dietary pattern there and the possible factors influencing the dietary intake, since it is important to create a nutritional balance during pregnancy to prevent adverse pregnancy outcomes and the poor growth and development of children in the future.

Obesity among children is a growing concern, and children in LMICs are exposed to an unhealthy diet high in sugar and fat (8). Children suffering from obesity face the danger of developing chronic diseases in later life. Advertisements that encourage unhealthy food consumption are bombarding children, and thus there is a need for regulatory policies to keep the level of advertisements in check. Al-Jawaldeh and Jabbour analyzed the policies in place to regulate the marketing of food that targets children in the EMR

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(Eastern Mediterranean Region) to examine the extent of the implementation of the WHO-recommended food marketing policies framework that targets children. Obese and overweight children and adolescents become more susceptible to hypertension. Thus, the BMI of obese and overweight adolescents must be checked and kept within the normal range to combat the development of this non-communicable disease (9). However, measuring BMI is quite a tedious task, since there are multiple cut-off points in the case of children and adolescents. Recently, the tri-ponderal mass index has been reported to be more straightforward, with only four cut-off points, and more effective for the screening of body fat among those in the 7–18 age group (10, 11). Hu et al. performed a study comparing BMI and tri-ponderal mass index results for discrimination of hypertension among adolescents. They concluded that the tri-ponderal mass index has a better ability in hypertension prediction when compared to the use of BMI (Hu et al.).

The deficiency of common micronutrients is of public health significance in LMICs (12). Important micronutrients that may be deficient include iodine, iron, vitamin A, vitamin D, folate, and zinc. Such deficiencies may be the outcome of insufficient health care, poor quality of diet, lack of awareness, and poor sanitation (13). A deficiency of such micronutrients may lead to poor pregnancy outcomes, poor growth and development in children, and other health disorders, including goiter, poor vision, skin lesions, and even mental conditions such as depression (14). Zhang et al. delved into research to find a relationship between vitamin A and beta-carotene intake and depression to build awareness of affordable and accessible dietary means to combat the mental condition. They obtained a negative association between these micronutrients and depression and emphasized building collaboration between physicians and nutritionists while maintaining caution about the quantity and duration of intake (Zhang et al.).

Another essential micronutrient is zinc, which is required for the nucleic acid metabolism and stability for protein synthesis, gene expression, cell division, and enzyme activity. An imbalance in the diet may lead to mild-to-moderate zinc deficiency (15). Qorbani et al. reported an association between the serum zinc level and low HDL and fasting blood glucose levels but found no significant association between the serum zinc level and metabolic syndrome among children and adolescents in Iran, which may possibly be attributed to race and age, thus warranting future studies on the topic.

Several research works on possible determinants and preventive measures for undernutrition have been included in this “Research Topic.” Ntambara et al. observed that poor nutritional outcomes in children might be prevented with optimal birth spacing, an observation that governments can utilize in policymaking for maternal and child health programs. Zemene et al. noted a relationship of changes in thinness in adolescent girls with age, place of residence, marital status, and toilet facilities. Inadequate feeding may lead to malnutrition among infants under 6 months of age (16). Gessese et al. observed low breastfeeding performance among women experiencing higher socioeconomic conditions and with higher education levels in Ethiopia, meaning that intervention may be needed to improve this breastfeeding performance.

Overnutrition and obesity have also been showing a rising trend in LMICs in recent times (3), and studies need to be carried out to understand the gravity of the situation. Several articles on studies carried out on overweight and obese populations have been included here. Bhattarai et al. noted that in rural Nepal, the overweight and obese population are educated and belong to a high socioeconomic background. A Westernized dietary pattern was reported to be associated with obesity among Mexican men by Rodríguez-Ramírez et al., who have brought to attention the changing trends of diet that are becoming more energy dense and rich in sugar and fat and called for close nutritional monitoring policies. While analyzing a population survey in China from 2014 to 2020, Jiang et al. observed a gradual rise in BMI among elderly men and women, with a significant increase in the obese and overweight elderly population. Chronic diseases, poor dietary choices, lack of exercise, and day-to-day stress may have contributed to the trend (Jiang et al.). Inflammatory markers and metabolic markers such as C-reactive protein, macrophage inflammatory protein-1, and leptin levels were noted to be associated with red and processed meat consumption in obese and overweight Iranian women by Shiraseb et al. The environment of inflammation in the body may eventually lead to various inflammation-related diseases (17).

The resting metabolic rate (RMR) is the most significant component of total daily energy expenditure, which may be altered by ultra-processed food. Ultra-processed food (UPF) may cause a rise in inflammatory markers and alter the RMR. In their study, Bahrampour et al. noted an increase in inflammatory markers such as interleukin-1 beta (IL-1β) monocyte chemoattractant protein (MCP-1), plasminogen activator-1 (PAI-1), and C-reactive protein (hs-CRP) in individuals consuming UPF. Supplementary Table 1 depicts the studies included in the “Research Topic” regarding the determinants of malnutrition (both obesity and undernutrition) and obesity-determining tools. Inflammatory changes disrupt the body’s homeostasis and may pave the way for the development of non-communicable diseases (18).

Malnutrition may eventually lead to several non-communicable diseases (NCD), including hypertension, cardiometabolic disorders, diabetes mellitus, dementia, and even cancers (19–22). The nutritional imbalance may trigger insulin resistance, oxidative stress, and inflammation, eventually paving the way for NCD development (23). Nutritional status in early life may be related to cardiovascular disease (CVD) development (24). Keeping this in mind, Yan et al. researched the link between exposure at the early stages of life to the Great Famine in China and hypertrophy of the left ventricle. They observed that the possible mechanisms that may connect undernutrition in fetal life and childhood to this cardiac disorder are catch-up growth once famine is overcome, leading to obesity, endothelial dysfunction, insulin resistance, inflammation, and oxidative stress (Yan et al.).

Consumption of processed food has emerged as a cause of the development of cardiovascular disease (25). Ultra-processed food (UPF) contains components high in total fat, saturated fat, sugar, salt, and energy density and low in vitamins and fiber (26). Dietary, anthropometric, and biochemical assessments were performed by Hosseininasab et al. to observe the relationship between UPF intake and cardiometabolic disorders among obese and overweight women. However, as it was a cross-sectional study, recall bias of the subjects may have presented a limitation (Hosseininasab et al.).

The development of obesity and cardiovascular disease in LMICs may be attributed to insufficient dietary intake, lack of physical activity, urbanization, and socioeconomic factors (27, 28). Food globalization and rapid urbanization, with the dramatic change in dietary patterns to nutrition-poor, processed, energy-dense food, is causing a dramatic rise in dyslipidemia and CVD (29–31). With growing urbanization, the sale of unhealthy street food and poor dietary choices have risen among city dwellers looking for quick meals, which are unfortunately energy dense and high in sugar, sodium, and fats, leading to people's health spiraling down (32). The findings of the research performed by Sousa et al. on the pattern of street food sold by vendors in some bustling cities of Central Asia further re-enforce this understanding. They observed that the food in demand in the city centers is energy dense, while the food in demand in the peripheries is rich in trans and saturated fat. The researchers suggested such findings need to be used for public health interventions (Sousa et al.).

Xiang et al. extracted the sex–age-specific burdens as a result of risk related to the Chinese pattern of food consumption from the "Global Burden of Disease (GBD) Study 2019," which included "annual and age-standardized rates (ASRs) of death, disability-adjusted life years (DAILYs) and summary exposure values (SEVs) during 1990-2019".They noted a significant rise in the DALY number and dietary risk-based deaths over the years as the dietary pattern changed. The main reasons for death due to diet were ischemic heart disease, stroke, and colorectal cancers (Xiang et al.).

Vargas-Rosvik et al. assessed the association of dietary intake and sociodemographic factors with adiposity and cardiometabolic disorder among children between 6 and 8 years of age from the urban and rural regions of Ecuador. They highlighted the alarming rise in the risk of cardiometabolic disorder among children (Vargas-Rosvik et al.). Nawsherwan et al. reported the changing pattern and forecasted the burden of cardiovascular disease in the future in East Asia due to risk factors pertaining to diet. They highlighted that a diet high in sodium and low in whole grains and legumes were the major factors contributing to mortality due to ischemic heart disease (Nawsherwan et al.).

In LMICs, studies pertaining to modifiable risk factors, such as sarcopenia, contributing to the development of dementia and its relationship with obesity are few. It is important to bring such risk factors to attention, since improving physical activity and adopting a healthy diet may help prevent such conditions. O'Donovan et al. researched the existing relationship between sarcopenia, obesity, and dementia and observed an association between sarcopenia and dementia; they stressed on the need to develop of health policies that promote a healthy lifestyle. The occurrence of one of the most common malignancies, colorectal carcinoma, is increasingly likely due to the rising consumption of a diet rich in fat, sugar, and food from animal sources (33). Considering this, Seyyedsalehi et al. performed a study to observe the association between dietary fat consumption and colorectal carcinoma. Upon finding an association, they advised the promotion of a decrease in the high intake of fatty acids from industrial and animal sources (Seyyedsalehi et al.). Supplementary Table 2 shows the studies performed to find the link between dietary imbalance and the development of NCD.

Adopting a healthy dietary pattern may aid in lowering the development of non-communicable diseases (34). Several studies related to the influence of the pattern of food consumption on human physiology were included in this "Research Topic". Branched dietary branched-chain amino acids (BCAA) such as leucine, isoleucine, and valine are significant for protein synthesis, metabolism of glucose, and signaling pathways sensitive to nutrients (35). One study by Zheng et al. researched the association between dietary BCAA risk of cardiovascular diseases (CVD) in individuals with diabetes mellitus in China. They suggested that plant-based BCAA intake can reduce oxidative stress and degradation of protein and lower the risk of CVD (Zheng et al.). Another study was performed using cohort data from the China Health and Nutrition Survey 1997–2009 by Ren et al. to determine whether there is a link connecting intake of BCAA and hyperuricemia risk; they observed an inverse relationship between the two parameters. They noted that over the years, as the dietary pattern has changed, BCAA consumption has reduced, and the risk of hyperuricemia has increased (Ren et al.). Chalermsri et al. assessed the dietary diversity score (DDS) to find a relationship between dietary diversity and the risk of CVD and cardiometabolic disorders among the older population. Their research findings led them to advise the encouragement of a diverse diet for the aging population and the providing of lifelong education promoting a healthy diet to lower the risk of this most common non-communicable disease (Chalermsri et al.). Hypertension is a major risk factor for cardiovascular disease development; thus, it is necessary to take preventive measures to halt its development and progression (36). Diet may play a significant role in this aspect (37–39). Wang et al. thus performed a cross-sectional study, using "the subset of the Suzhou Food Consumption and Health State Survey in 2018–2019", on the effect of dietary patterns on hypertension. They emphasized that the dietary pattern has a preventive role in the development of hypertension (Wang et al.).

The relationship of dietary insulin load and dietary insulin index with the hypertriglyceridemic waist phenotype and brain-derived neurotrophic factors in Iranian adults was investigated by Hajhashemy et al., who mentioned that even though dietary insulin load and dietary insulin index cannot distinguish between healthy and unhealthy food, dietary insulin load may help lower the hypertriglyceridemic waist phenotype. The risk of diabetes is closely linked to diet; thus, studies need to be performed to learn more regarding the dietary components that may help maintain blood glucose levels. In this regard, Yang et al. conducted a prospective cohort study using the China Health and Nutrition Survey to find a relationship between the consumption of dairy products and the risk of diabetes mellitus. Their finding builds optimism toward a diet containing dairy products that may reduce the risk of diabetes mellitus. Further studies need to be performed, as per the researchers' recommendation, to know the optimal level of dairy consumption to prevent diabetes mellitus (Yang et al.).

It is also important to find certain nutritional supplements to improve the general population's health, emphasizing age groups more susceptible to nutritional imbalance and the development of non-communicable diseases. Two such articles have been included in this "Research Topic". Adolescence is when nutritional requirements are high, but in LMICs, the poverty-stricken population may find difficulty accessing adequate food with good nutritional value (40). Thus, finding cost-effective dietary supplements may aid in fulfilling their nutritional needs. Khanam et al. studied the effects of Moringa oleifera on hemoglobin, serum retinol levels, and underweight status among adolescent girls in Bangladesh. Moringa oleifera is cost-effective and high in nutritional value, and Khanam et al. suggested that Moringa oleifera should be promoted as part of a regular diet.

Another population susceptible to malnutrition is the elderly population. They often become frail and suffer from different NCDs. Gao et al. performed a 6-year longitudinal study on the effects of tea drinking on frailty among the older Chinese population. Tea drinking is an integral part of Chinese culture, and a negative correlation was found between tea drinking and the development of frailty. Their findings should be considered, and tea-drinking habits should be encouraged among the older population of LMICs (Gao et al.). Supplementary Table 3 shows the studies on dietary patterns that may positively impact human health.

The various research materials included in this "Research Topic" bring to light the recent changes in dietary patterns and their alarming consequences on the population of LMICs. The boost in urbanization has paved the way for demands for fast food high in energy, fat, and sugar. This is causing a significant portion of the population to become obese and develop life-altering NCDs, which is creating a personal, social, and government burden. On the other hand, some of the population suffers from undernutrition due to poverty and a lack of proper understanding. Several studies have repeatedly stressed the need for a healthy balanced diet and should be given importance. The LMICs need to develop policies to combat this emerging danger of malnutrition to secure a healthy and stable future for their population.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1179640/full#supplementary-material

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Associations of Dietary Vitamin A and Beta-Carotene Intake With Depression. A Meta-Analysis of Observational Studies

*Yi Zhang[1,2], Jun Ding[3] and Jieyu Liang[1,2]**

[1] Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, China, [2] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China, [3] Changsha Social Work College, Changsha, China

Edited by:
Mainul Haque, National Defence University of Malaysia, Malaysia

Reviewed by:
Sameer Dhingra, National Institute of Pharmaceutical Education and Research, India
Iffat Jahan, Eastern Medical College and Hospital, Bangladesh

***Correspondence:**
Jieyu Liang
jamesliang8@aliyun.com

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Zhang Y, Ding J and Liang J (2022) Associations of Dietary Vitamin A and Beta-Carotene Intake With Depression. A Meta-Analysis of Observational Studies. Front. Nutr. 9:881139. doi: 10.3389/fnut.2022.881139

Objective: To clarify the associations of dietary vitamin A and beta-carotene intake with depression based on a meta-analysis of observational studies.

Methods: An extensive literature search on February 2022 (PubMed, Web of Science and Embase) was employed to identify observational studies on the associations of dietary vitamin A and beta-carotene intake with depression. The pooled relative risk (RR) of depression for the highest vs. lowest dietary vitamin A and beta-carotene intake category, and the standard mean difference (SMD) of dietary vitamin A and beta-carotene intake for depression vs. control subjects, were calculated.

Results: A total of 25 observational studies (100,955 participants), which included 24 cross-sectional/case-control and 1 prospective cohort study, were included in this study. The overall multi-variable adjusted RR demonstrated that dietary vitamin A intake was inversely associated with depression (*RR* = 0.83, 95%CI: 0.70–1.00; *P* = 0.05). In addition, the combined SMD showed that the dietary vitamin A intake in depression was also lower than that in control subjects (SMD = −0.13, 95%CI: −0.18 to −0.07; *P* < 0.001). On the other hand, the overall multi-variable adjusted RR indicated that dietary beta-carotene intake was negatively associated with depression (*RR* = 0.63, 95%CI: 0.55–0.72; *P* < 0.001). The combined SMD showed that the dietary beta-carotene intake in depression was also lower than that in control subjects (SMD = −0.34, 95%CI: −0.48 to −0.20; *P* < 0.001).

Conclusion: Our results suggest that both dietary vitamin A and beta-carotene intake is inversely associated with depression. However, due to the limited evidence, further prospective cohort studies are still needed.

Keywords: dietary vitamin A intake, dietary beta-carotene intake, depression, meta-analysis, observational studies

INTRODUCTION

Depression, one of the most common global mental disorders, affects females twice as much as males (1). The usual symptoms of depression are exhaustion, sadness, lack of interest in daily activities and suicide (2). Depression has affected approximately 300 million people (3), and is estimated to be the leading cause of disability worldwide by 2030 (4). Most importantly, low- and middle-income countries (LMICs) may be disproportionally suffered from depression. More than 80% of global disability due to depression comes from LMICs, and the majority of subjects suffered from depression in LMICs do not receive appropriate treatment (5). Since emerging evidence has indicated the significant role of dietary factors in depression (6, 7), the identification of affordable and accessible dietary factors for depression is important in its clinical management, especially in LMICs.

Vitamin A, a generic term for compounds with retinol biological activity, is usually found in foods derived from animal products (8, 9). Generally speaking, vitamin A is related to several physiological processes, such as differentiation and function of immune system, embryo development, vision, and energy metabolism (10). On the other hand, synthesized by photosynthetic organisms, carotenoids are served as light-harvesting scavengers during photosynthesis. Beta-carotene, the most common carotene in nature (10), is served as an important vitamin A precursor. On the contrary to vitamin A, beta-carotene is mainly derived from plant products (8). As a natural antioxidant, carotenoids protect organisms from oxidative damage *via* removing reactive oxygen species (ROS) and other free radicals (11). Interestingly, fundamental evidence has indicated the antidepressant property of beta-carotene, which may be associated with the reduced levels of tumor necrosis factor-a (TNF-α) and interleukin-6 (IL-6), and increased levels of brain-derived neurotrophic factor (BDNF) (12). Therefore, it seems naturally that dietary vitamin A and beta-carotene intake is negatively associated with depression.

To our best knowledge, a number of observational studies have investigated the associations of dietary vitamin A and beta-carotene intake with depression (13–37). However, no final conclusion is obtained. The present meta-analysis is therefore employed to clarify the issue. It is hypothesized that both dietary vitamin A and beta-carotene intake is inversely associated with depression.

MATERIALS AND METHODS

Search Strategy

This meta-analysis study was employed according with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (38). The electronic database of PubMed, Web of Science and Embase were searched through during February 2022 (no restriction was set for the initiate time) using a combination of keywords and in-text words related to depression ("depression," "depressive"), vitamin A ("vitamin A," "retinol," "prepalin") and beta-carotene ("carotene," "carotin," "carotenoid"). No language restrictions were imposed in the search. To identify eligible studies, the titles and abstracts of all articles were first screened. Then, the full articles were read to include the eligible studies. Moreover, the references of the retrieved articles and reviews were also evaluated.

Study Selection

Two researchers reviewed the titles, abstracts and full texts of the retrieved studies independently for relevance evaluation, and disagreements (if any) were resolved by discussions. The included studies were required to meet the following criteria: (1) observational studies; (2) the associations of dietary vitamin A and beta-carotene intake with depression; (3) odds ratio (OR), relative risk (RR) or standard mean difference (SMD) reported. The exclusion criteria were listed as follows: (1) duplicated or irrelevant articles; (2) reviews, letters or case reports; (3) randomized controlled trials; and (4) non-human studies.

Data Extraction

The quality of each included study was evaluated in accordance with the Newcastle-Ottawa (NOS) criteria for non-randomized studies. It contains 8 items categorized into three dimensions: (1) the selection of study groups; (2) the comparability among different groups; (3) the identification of exposure or outcome of study cohorts, respectively. The included cross-sectional/case-control studies were assessed by using NOS for case-control studies, whereas cohort studies were assessed by using NOS for cohort studies. Disagreements (if any) were resolved through discussions until a consensus was reached.

The extracted data included the first author, year of publication, location, age, sex, sample size, study design, adjustments, exposure assessment, category of exposure, effect estimates, and diagnostic criteria of depression. The corresponding effect estimates with 95% CIs for the highest vs. lowest dietary vitamin A and carotene intake category were extracted (adjusted for the maximum number of confounding variables). Moreover, the dietary vitamin A and beta-carotene intake (mean ± SD) was also extracted for depression vs. control subjects to calculate the SMD.

Statistical Analyses

The RR for depression and SMD for dietary vitamin A and beta-carotene intake were the outcome measures in our study. The I^2 statistic was examined to measure the percentage of total variation across studies due to heterogeneity ($I^2 > 50\%$ was considered as heterogeneity). The random-effects model was accepted if significant heterogeneity was observed among the studies; otherwise, the fixed effects model was utilized. The publication bias was assessed by Begg's test (39). A p-value < 0.05 was considered as statistically significant. Moreover, subgroup analysis was employed for geographical region, exposure assessment, sex, population, sample size, study design, and adjustment of BMI and energy intake.

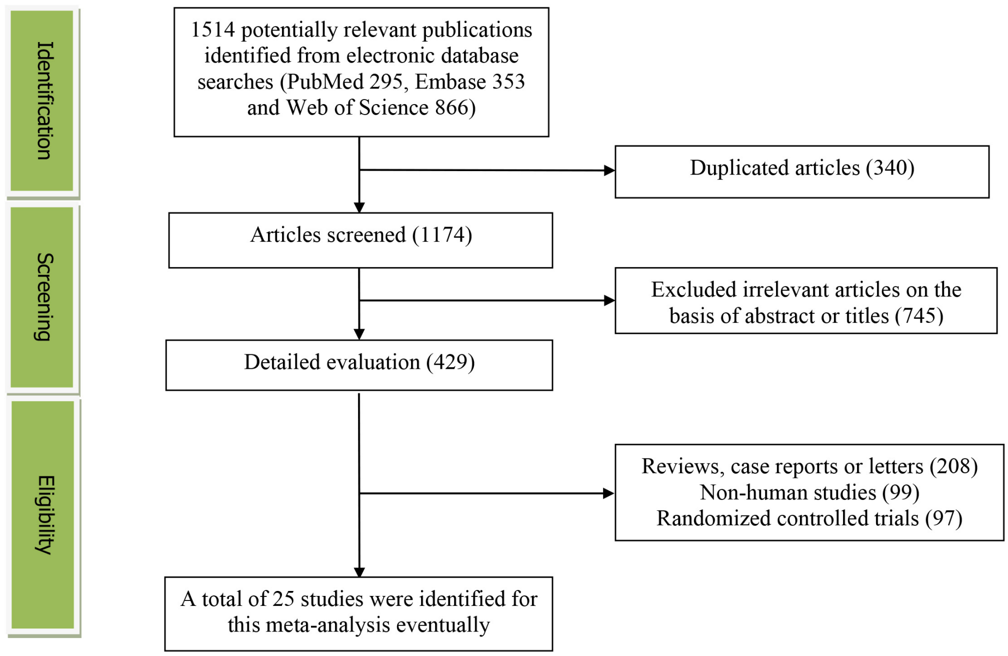

FIGURE 1 | The detailed flow diagram of the study identification and selection in this meta-analysis.

RESULTS

Study Identification and Selection

Figure 1 presents the study screening process. During the initial literature search, a total of 1,514 potentially relevant articles (295 for PubMed, 353 for Embase and 866 for Web of Science) were retrieved. After eliminating 340 duplicated articles, 1,174 articles were screened according to the titles and abstracts. 745 irrelevant studies were removed. Then, 208 reviews, case reports or letters, 99 non-human studies and 97 randomized control trials studies were excluded. Eventually, 25 studies (24 cross-sectional/case-control and 1 prospective cohort study) were selected for this meta-analysis (13–37).

Study Characteristics

The characteristics and NOS score of all the included studies are shown in **Table 1**. These studies were published between 2009 and 2022. 14 of the included studies were performed in Asian countries [Korea (14, 20, 21, 25, 29, 30, 35, 36), Iran (18, 31, 33), Japan (13, 23) and China (28)], and the other ones were conducted in United States (15, 17, 27, 32, 34), Brazil (26, 37), Australia (16), Spain (22, 24), and Turkey (19). Male, female and both male and female participants were recruited in 1 (18), 8 (14, 20, 26, 28, 30, 31, 33, 36), and 16 (13, 15–17, 19, 21–25, 27, 29, 32, 34, 35, 37) studies, respectively. The sample size ranged from 41 to 17,401 for a total number of 100,955. The exposure was assessed by food-frequency questionnaire (FFQ) in 16 studies (13–16, 18, 20, 21, 23–25, 28, 29, 31, 33, 36, 37), and recall method in 9 studies (17, 19, 22, 26, 27, 30, 32, 34, 35). The diagnostic criteria of depression were Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (15, 17, 19, 24), Patient Health Questionnaire-9 (PHQ-9) (27, 29, 32, 34), Center for Epidemiological Studies Depression Scale (CES-D) (13, 14, 16, 22, 28, 30), Beck Depression Inventory (BDI) (18, 20, 21, 26, 33, 36), Geriatric Depression Scale (GDS) (23), Clinical Interview Schedule Revised (CIS-R) (37), and Depression, Anxiety, Stress Scale (DASS) (31), respectively.

Relative Risk of Depression for the Highest vs. Lowest Category of Dietary Vitamin A Intake

The overall multi-variable adjusted RR demonstrated that dietary vitamin A intake was negatively associated with depression ($RR = 0.83$, 95%CI: 0.70–1.00; $P = 0.05$) (**Figure 2**). No substantial level of heterogeneity was observed among various studies ($P = 0.49$, $I^2 = 0\%$). No evidence of publication bias existed according to the Begg's rank-correlation test ($P = 1.00$). **Table 2** presents the results of subgroup analysis. Such results only existed in females ($RR = 0.75$, 95%CI: 0.58–0.98; $P = 0.03$), cohort ($RR = 0.72$, 95%CI: 0.53–0.98) and adjustment of BMI ($RR = 0.75$, 95%CI: 0.56–0.99; $P = 0.04$) and energy intake ($RR = 0.70$, 95%CI: 0.53–0.92; $P = 0.01$) studies.

Standard Mean Difference of Dietary Vitamin A Intake for Depression vs. Control Subjects

The overall combined SMD showed that dietary vitamin A intake in depression was lower than that in control subjects (SMD = −0.13, 95%CI: −0.18 to −0.07; $P < 0.001$) (**Figure 3**). A substantial level of heterogeneity was observed among the various studies ($P = 0.005$, $I^2 = 53.4\%$). No evidence

TABLE 1 | Characteristics of the individual studies included in this meta-analysis.

References	Location	Age years	Sex	Sample size	Study design	Adjustments	Exposure	Category of exposure	Effect estimates	Diagnostic criteria of depression	NOS
Oishi et al. (13)	Japan	65–75	Both	401	Cross-sectional	Age, chronic diseases, BMI and social support	FFQ	Male		CES-D	8
								Vitamin A			
								Tertile 1	1.00		
								Tertile 2	0.67 (0.23, 1.70)		
								Tertile 3	0.78 (0.28, 2.17)		
								Beta-carotene			
								Tertile 1	1.00		
								Tertile 2	0.52 (0.19, 1.45)		
								Tertile 3	0.36 (0.13, 0.98)		
								Female			
								Vitamin A			
								Tertile 1	1.00		
								Tertile 2	0.52 (0.20, 1.37)		
								Tertile 3	1.00 (0.39, 2.58)		
								Beta-carotene			
								Tertile 1	1.00		
								Tertile 2	0.55 (0.21, 1.40)		
								Tertile 3	0.52 (0.20, 1.35)		
Park et al. (14)	Korea	20	Female	130	Case-control	NA	FFQ		Vitamin A	CES-D	7
								Control	641.3 (587.4, 695.2)		
								Depression	539.5 (484.4, 594.6)		
									Beta-carotene		
								Control	2656.0 (2394.1, 2917.9)		
								Depression	2076.6 (1773.9, 2379.3)		
Payne et al. (15)	United States	>60	Both	278	Case-control	NA	FFQ		Beta-carotene	DSM-IV	7
								Control	4136.7 (3663.0, 4610.4)		
								Depression	3759.0 (3275.1, 4242.9)		
Purnomo et al. (16)	Australia	>18	Both	58	Case-control	NA	FFQ		Vitamin A	CES-D	5
								Control	1524.8 (925.6, 2124.0)		
								Depression	801.5 (593.1, 1009.9)		
Beydoun et al. (17)	United States	20–85	Both	1,798	Cross-sectional	NA	Recall method	Male	Beta-carotene	DSM-IV	8
								Control	2190.2 (1875.6, 2504.8)		
								Depression	1535.7 (1223.1, 1848.3)		
								Female	Beta-carotene		
								Control	2364.5 (2127.6, 2601.4)		
								Depression	1368.4 (857.3, 1879.5)		
Prohan et al. (18)	Iran	18–25	Male	60	Case-control	NA	FFQ		Beta-carotene	BDI	6
								Control	2890.6 (2713.0, 3068.2)		
								Depression	2425.1 (2223.8, 2626.4)		

(Continued)

TABLE 1 | (Continued)

References	Location	Age years	Sex	Sample size	Study design	Adjustments	Exposure	Category of exposure	Effect estimates	Diagnostic criteria of depression	NOS
Kaner et al. (19)	Turkey	18–60	Both	59	Case-control	NA	Recall method	 Control Depression	Vitamin A 670.5 (449.6, 1249.6) 516.6 (467.7, 683.5)	DSM-IV	6
Kim et al. (20)	Korea	12–18	Female	849	Case-control	Energy intake and menstrual regularity	FFQ	Vitamin A Tertile 1 Tertile 2 Tertile 3 Beta-carotene Tertile 1 Tertile 2 Tertile 3	 1.00 0.73 (0.43, 1.22) 0.60 (0.32, 1.13) 1.00 0.79 (0.48, 1.31) 0.54 (0.29, 0.99)	BDI	7
Jeong et al. (21)	Korea	20–65	Both	734	Cross-sectional	NA	FFQ	Male Control Depression Female Control Depression	Vitamin A 1177.0 (476.2, 1877.8) 792.8 (536.4, 1049.2) Vitamin A 820.4 (752.8, 888.0) 829.9 (619.7, 1040.1)	BDI	7
Rubio-López et al. (22)	Spain	6–9	Both	710	Cross-sectional	NA	Recall method	 Control Depression	Vitamin A 481.9 (472.8, 491.0) 461.7 (442.7, 480.7)	CES-D	7
Nguyen et al. (23)	Japan	>65	Both	1,634	Cross-sectional	NA	FFQ	 Control Depression Control Depression	Vitamin A 401.3 (384.6, 418.0) 361.6 (342.5, 380.7) Beta-carotene 2176.6 (2096.5, 2256.7) 1158.1 (1029.5, 1286.7)	GDS	7
Sánchez-Villegas et al. (24)	Spain	38	Both	13,983	Cohort	Sex, age, physical activity, BMI, energy intake, special diets, smoking, alcohol intake and prevalence of CVD, HTA or T2DM	FFQ	Vitamin A Inadequacy Adequacy	 1.00 0.72 (0.53, 0.98)	DSM-IV	9

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TABLE 1 | (Continued)

References	Location	Age years	Sex	Sample size	Study design	Adjustments	Exposure	Category of exposure	Effect estimates	Diagnostic criteria of depression	NOS
Seo and Je (25)	Korea	19–64	Both	10,591	Cross-sectional	Age, survey year, total energy intake, BMI, marital status and physical activity	FFQ	Male Control Depression Male Control Depression Female Control Depression Female Control Depression	Vitamin A 583.2 (581.2, 585.2) 563.2 (561.1, 565.3) Beta-carotene 2852.6 (2850.6, 2854.6) 2724.7 (2722.6, 2726.8) Vitamin A 563.6 (561.6, 565.6) 560.4 (558.3, 562.5) Beta-carotene 2777.2 (2096.5, 2256.7) 2761.7 (2759.6, 2793.8)	Physician diagnosis	7
de Oliveira et al. (26)	Brazil	50–69	Female	41	Case-control	NA	Recall method	 Control Depression	Vitamin A 878.5 (498.2, 1258.8) 515.9 (285.7, 746.1)	BDI	5
Iranpour and Sabour (27)	United States	> 18	Both	4,737	Cross-sectional	NA	Recall method	 Control Depression Control Depression	Vitamin A 628.8 (606.5, 651.1) 470.0 (393.3, 546.7) Beta-carotene 1905.5 (1804.1, 2006.9) 1233.6 (969.1, 1498.1)	PHQ-9	8
Li and Li (28)	China	42–52	Female	2,762	Cross-sectional	Age, race/ethnicity, total family income, sex hormone binding globulin, DBP, BMI, TG, LDLC, HDLC, SHBG, Dietary caloric intake and Dietary Fat intake	FFQ	 Control Depression Beta-carotene Quartile 1 Quartile 2 Quartile 3 Quartile 4	Beta-carotene 2.07 (1.33, 3.38) 1.83 (1.18, 3.03) 1.00 0.88 (0.69, 1.12) 0.76 (0.59, 0.97) 0.74 (0.57, 0.94)	CES-D	7
Park et al. (29)	Korea	20–60	Both	5,897	Cross-sectional	NA	FFQ	Male Control Depression Male Control Depression	Vitamin A 839.7 (791.4, 888.0) 820.8 (720.3, 921.3) Beta-carotene 4117.3 (3894.8, 4399.8) 4185.9 (3635.4, 4736.4)	PHQ-9	7

(Continued)

TABLE 1 | (Continued)

References	Location	Age years	Sex	Sample size	Study design	Adjustments	Exposure	Category of exposure	Effect estimates	Diagnostic criteria of depression	NOS
								Female	Vitamin A		
								Control	740.5 (698.0, 783.0)		
								Depression	616.7 (559.6, 673.8)		
								Female	Beta-carotene		
								Control	3771.7 (3526.4, 4017.0)		
								Depression	3184.2 (2869.1, 3499.3)		
Park et al. (30)	Korea	22	Female	178	Cross-sectional	NA	Recall method		Vitamin A	CES-D	7
								Control	552.5 (493.7, 611.3)		
								Depression	447.9 (383.0, 512.8)		
Farhadnejad et al. (31)	Iran	15–18	Female	263	Cross-sectional	Age, BMI, physical activity, mother/father's education level, dietary fiber, and total energy intake	FFQ		Beta-carotene	DASS	7
								Control	4460.0 (4013.6, 4906.4)		
								Depression	4305.0 (3589.7, 5020.3)		
								Beta-carotene			
								Tertile 1	1.00		
								Tertile 2	0.48 (0.25, 0.90)		
								Tertile 3	0.46 (0.23, 0.95)		
Ge et al. (32)	United States	18–80	Both	17,401	Cross-sectional	Age and gender, ethnicity, educational level, BMI, annual family income, work activity, recreational activity, hypertension, diabetes, smoking status, drinking status, and total energy intake	Recall method		Beta-carotene	PHQ-9	8
								Control	1112.5 (1076.3, 1148.7)		
								Depression	669.0 (592.6, 745.4)		
								Beta-carotene			
								Quartile 1	1.00		
								Quartile 2	0.65 (0.51, 0.83)		
								Quartile 3	0.54 (0.42, 0.70)		
								Quartile 4	0.59 (0.47, 0.75)		
Khayyatzadeh et al. (33)	Iran	12–18	Female	988	Cross-sectional	Age, energy intake, menstruation, family members, parental death, parental divorce, physical activity and BMI	FFQ		Vitamin A	BDI	7
								Control	600.7 (574.3, 627.1)		
								Depression	584.6 (487.1, 682.1)		
									Beta-carotene		
								Control	3558.0 (3349.5, 3766.5)		
								Depression	3024.0 (2737.8, 3310.2)		
								Beta-carotene			
								Quartile 1	1.00		
								Quartile 2	0.91 (0.58, 1.42)		
								Quartile 3	0.77 (0.50, 1.20)		
								Quartile 4	0.42 (0.26, 0.69)		

(Continued)

TABLE 1 | (Continued)

References	Location	Age years	Sex	Sample size	Study design	Adjustments	Exposure	Category of exposure	Effect estimates	Diagnostic criteria of depression	NOS
Lin and Shen (34)	United States	> 18	Both	4,105	Cross-sectional	Age, gender, marital status, race, educational level, body mass index, smoke, alcohol drinking, family income, work activity, recreational activity, hypertension, hypercholesterolemia, diabetes, total daily energy intake, zinc intake, selenium intake, magnesium intake, total polyunsaturated fat intake, vitamin B6 intake, vitamin B12 intake and folate intake	Recall method	 Control Depression Beta-carotene Tertile 1 Tertile 2 Tertile 3	Beta-carotene 1060.5 (991.0, 1130.0) 625.0 (451.6, 798.4) 1.00 0.77 (0.47, 1.26) 0.81 (0.48, 1.38)	PHQ-9	8
Nguyen et al. (35)	Korea	> 10	Both	16,371	Cross-sectional	NA	Recall method	 Control Depression	Vitamin A 481.4 (473.7, 489.3) 392.8 (358.8, 430.0)	Physician diagnosis	8
Park et al. (36)	Korea	45–69	Female	2,190	Cross-sectional	Age, BMI, education level, household income, marital status, job, current alcohol drinking, current smoking, physical activity, chronic disease status, sleep duration, family history of depression, stress, menopause status, and total energy intake	FFQ	 Control Depression Beta-carotene Quartile 1 Quartile 2 Quartile 3 Quartile 4	Beta-carotene 6.5 (6.3, 6.6) 6.0 (5.7, 6.2) 1.00 0.82 (0.59, 1.12) 0.90 (0.64, 1.27) 0.82 (0.55, 1.22)	BDI	8
Ferriani et al. (37)	Brazil	35–74	Both	14,737	Cross-sectional	Total calorie, age, race, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive drug, diabetes, and smoking, cardiovascular disease and physical activity	FFQ	 Control Depression Vitamin A Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	Vitamin A 910.7 (695.9, 1125.5) 877.9 (684.4, 1071.4) 1.00 1.03 (0.81, 1.32) 0.86 (0.67, 1.12) 0.86 (0.66, 1.12) 0.97 (0.75, 1.26)	CIS-R	9

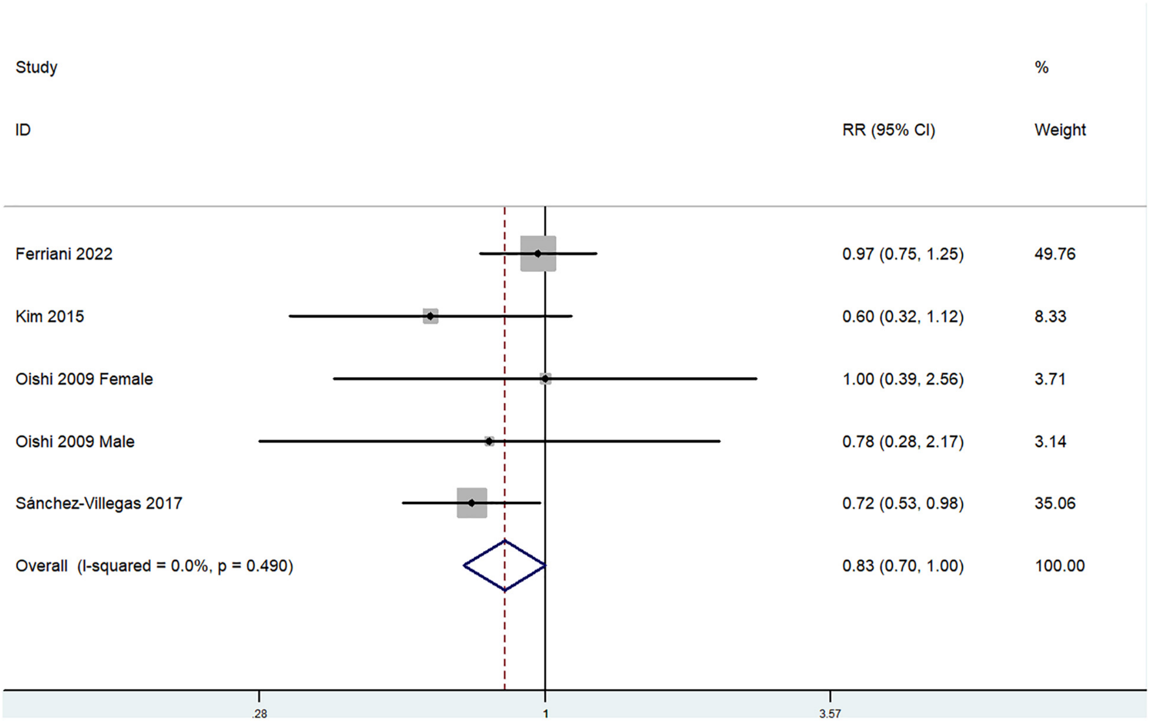

FIGURE 2 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of depression for the highest vs. lowest category of dietary vitamin A intake.

TABLE 2 | Subgroup analysis of depression for the highest vs. lowest category of dietary vitamin A intake.

Stratification	Number of studies	Pooled RR	95% CI	*P*-value	Heterogeneity
All studies	4	0.83	0.70, 1.00	$P = 0.05$	$P = 0.49$; $I^2 = 0\%$
Sex					
Male	2	0.77	0.48, 1.24	$P = 0.29$	$P = 0.98$; $I^2 = 0\%$
Female	3	0.75	0.58, 0.98	$P = 0.03$	$P = 0.65$; $I^2 = 0\%$
Study design					
Cross-sectional	3	0.90	0.72, 1.13	$P = 0.38$	$P = 0.56$; $I^2 = 0\%$
Cohort	1	0.72	0.53, 0.98	/	/
Adjustment of BMI					
Adjusted	2	0.75	0.56, 0.99	$P = 0.04$	$P = 0.81$; $I^2 = 0\%$
Unadjusted	2	0.91	0.71, 1.15	$P = 0.41$	$P = 0.17$; $I^2 = 48\%$
Adjustment of energy intake					
Adjusted	2	0.70	0.53, 0.92	$P = 0.01$	$P = 0.61$; $I^2 = 0\%$
Unadjusted	2	0.96	0.75, 1.22	$P = 0.74$	$P = 0.92$; $I^2 = 0\%$

of publication bias existed according to the Begg's rank-correlation test ($P = 0.149$). **Table 3** presents the results of subgroup analysis.

Relative Risk of Depression for the Highest vs. Lowest Category of Dietary Beta-Carotene Intake

The overall multi-variable adjusted RR demonstrated that dietary beta-carotene intake was negatively associated with depression ($RR = 0.63$, 95%CI: 0.55–0.72; $P < 0.001$) (**Figure 4**). No substantial level of heterogeneity was observed among various studies ($P = 0.308$, $I^2 = 15.1\%$). No evidence of publication bias existed according to the Begg's rank-correlation test ($P = 0.251$). **Table 4** presents the results of subgroup analysis. Such results only existed in adjustment of BMI ($RR = 0.62$, 95%CI: 0.54–0.72; $P < 0.001$) studies.

Standard Mean Difference of Dietary Beta-Carotene Intake for Depression vs. Control Subjects

The overall combined SMD showed that dietary beta-carotene intake in depression was lower than that in

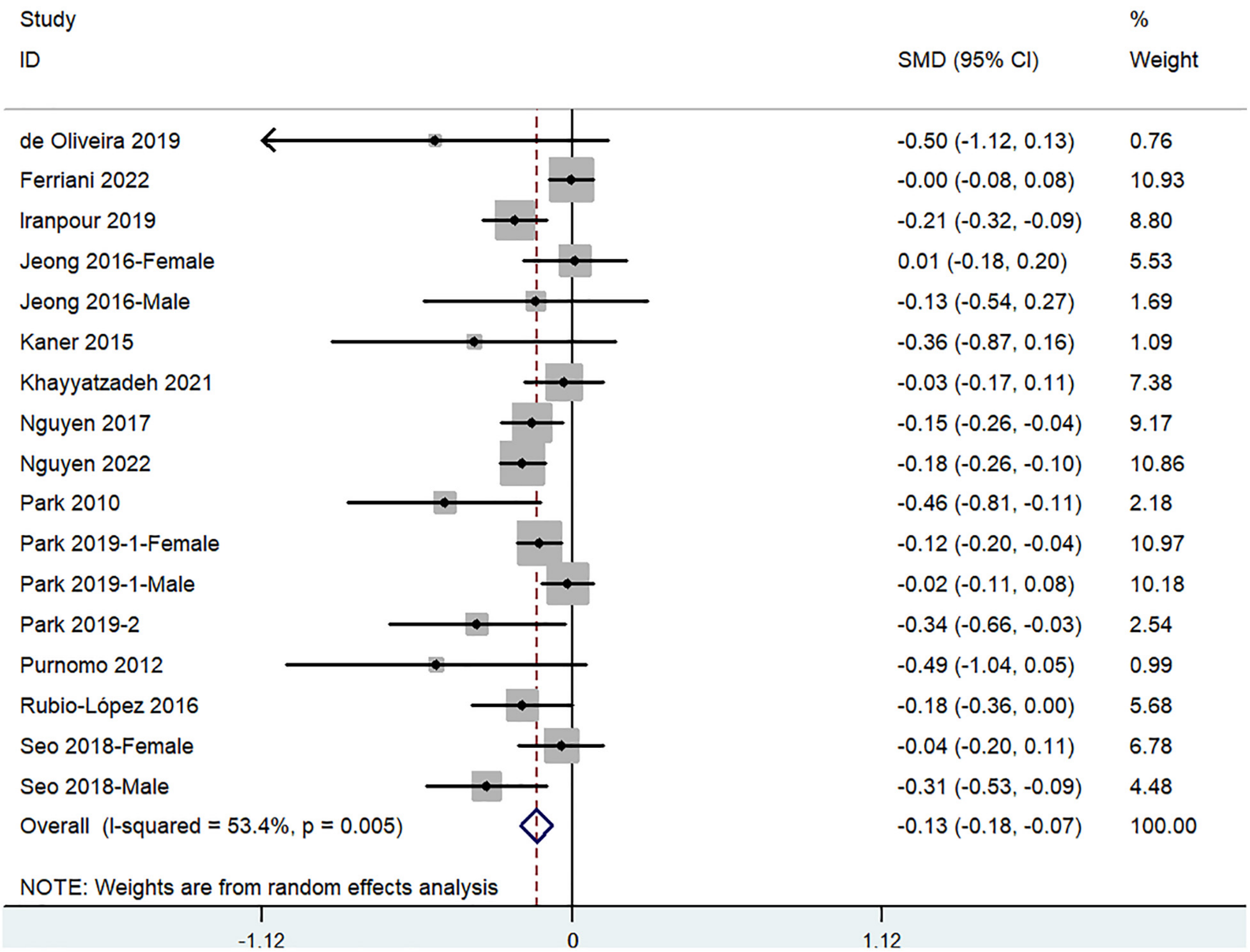

FIGURE 3 | Forest plot of meta-analysis: SMD of dietary vitamin A intake for depression vs. control subjects.

TABLE 3 | Subgroup analysis for SMD of dietary vitamin A intake in depression vs. control subjects.

Stratification	Number of studies	Pooled SMD	95% CI	*P*-value	Heterogeneity
All studies	14	−0.13	−0.18, −0.07	$P < 0.001$	$P = 0.005$; $I^2 = 53\%$
Geographical region					
Asia	7	−0.13	−0.20, −0.06	$P < 0.001$	$P = 0.03$; $I^2 = 51\%$
Non−Asia	7	−0.14	−0.25, −0.02	$P = 0.02$	$P = 0.02$; $I^2 = 59\%$
Exposure assessment					
FFQ	8	−0.07	−0.11, −0.03	$P < 0.001$	$P = 0.03$; $I^2 = 50\%$
Recall method	6	−0.20	−0.26, −0.14	$P < 0.001$	$P = 0.82$; $I^2 = 0\%$
Sex					
Male	5	−0.06	−0.12, 0.01	$P = 0.10$	$P = 0.16$; $I^2 = 38\%$
Female	9	−0.11	−0.20, −0.03	$P = 0.007$	$P = 0.02$; $I^2 = 56\%$
Population					
Adolescent	4	−0.20	−0.38, −0.03	$P = 0.02$	$P = 0.07$; $I^2 = 58\%$
Middle aged and elderly	12	−0.12	−0.18, −0.06	$P < 0.001$	$P = 0.01$; $I^2 = 54\%$
Sample size					
<1,000	8	−0.13	−0.22, −0.05	$P = 0.002$	$P = 0.11$; $I^2 = 39\%$
>1,000	6	−0.11	−0.18, −0.05	$P < 0.001$	$P = 0.004$; $I^2 = 66\%$

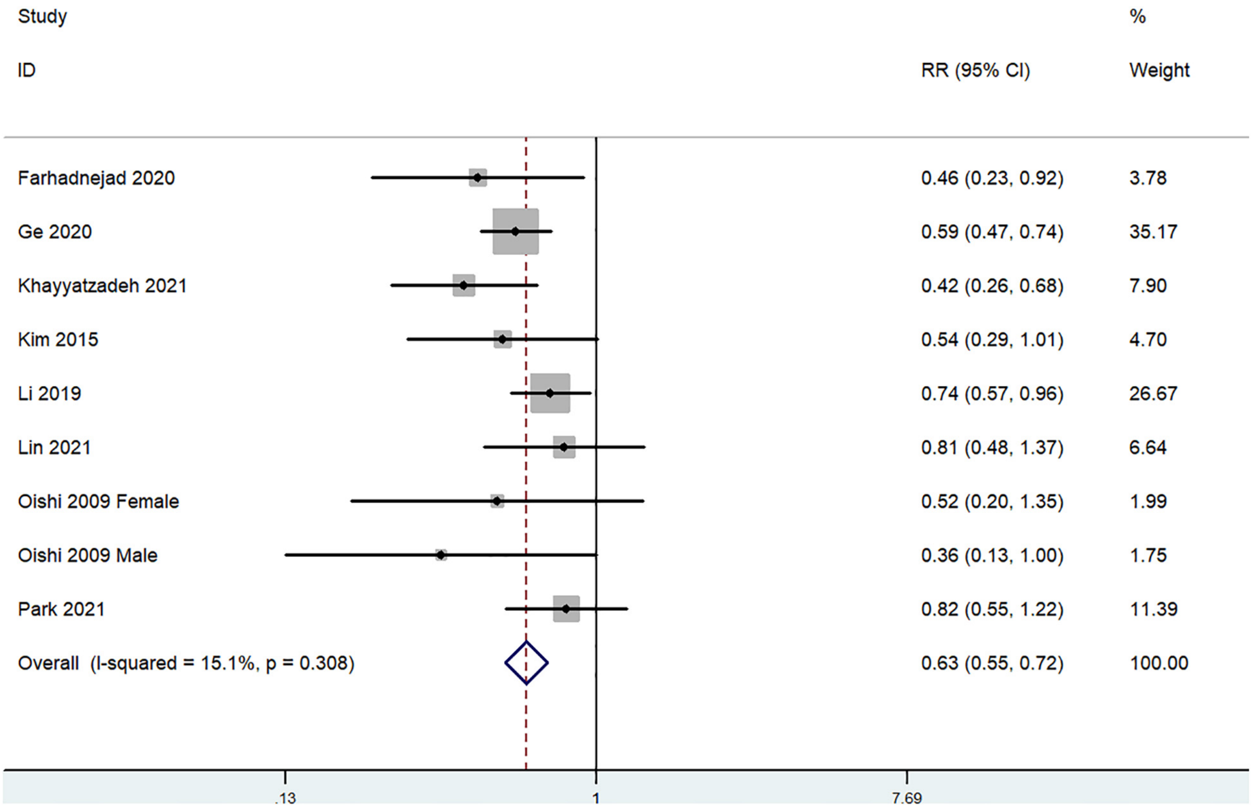

FIGURE 4 | Forest plot of meta-analysis: Overall multi-variable adjusted RR of depression for the highest vs. lowest category of dietary beta-carotene intake.

TABLE 4 | Subgroup analysis of depression for the highest vs. lowest category of dietary beta-carotene intake.

Stratification	Number of studies	Pooled RR	95% CI	*P*-value	Heterogeneity
All studies	8	0.63	0.55, 0.72	$P < 0.001$	$P = 0.31$; $I^2 = 15\%$
Geographical region					
Asia	6	0.64	0.54, 0.76	$P < 0.001$	$P = 0.22$; $I^2 = 27\%$
Non-Asia	2	0.62	0.50, 0.76	$P < 0.001$	$P = 0.28$; $I^2 = 16\%$
Exposure assessment					
FFQ	6	0.64	0.54, 0.76	$P < 0.001$	$P = 0.22$; $I^2 = 27\%$
Recall method	2	0.62	0.50, 0.76	$P < 0.001$	$P = 0.28$; $I^2 = 16\%$
Sex					
Male	1	0.36	0.13, 1.00	/	/
Female	6	0.65	0.54, 0.78	$P < 0.001$	$P = 0.23$; $I^2 = 28\%$
Population					
Adolescent	3	0.46	0.33, 0.64	$P < 0.001$	$P = 0.82$; $I^2 = 0\%$
Middle aged and elderly	4	0.67	0.58, 0.78	$P < 0.001$	$P = 0.42$; $I^2 = 0\%$
Sample size					
$< 1{,}000$	4	0.46	0.34, 0.62	$P < 0.001$	$P = 0.95$; $I^2 = 0\%$
$> 1{,}000$	4	0.68	0.59, 0.80	$P < 0.001$	$P = 0.37$; $I^2 = 5\%$
Adjustment of BMI					
Adjusted	6	0.62	0.54, 0.72	$P < 0.001$	$P = 0.22$; $I^2 = 28\%$
Unadjusted	2	0.68	0.46, 1.02	$P = 0.06$	$P = 0.33$; $I^2 = 0\%$
Adjustment of energy intake					
Adjusted	5	0.61	0.52, 0.71	$P < 0.001$	$P = 0.27$; $I^2 = 22\%$
Unadjusted	3	0.69	0.54, 0.89	$P = 0.003$	$P = 0.34$; $I^2 = 8\%$

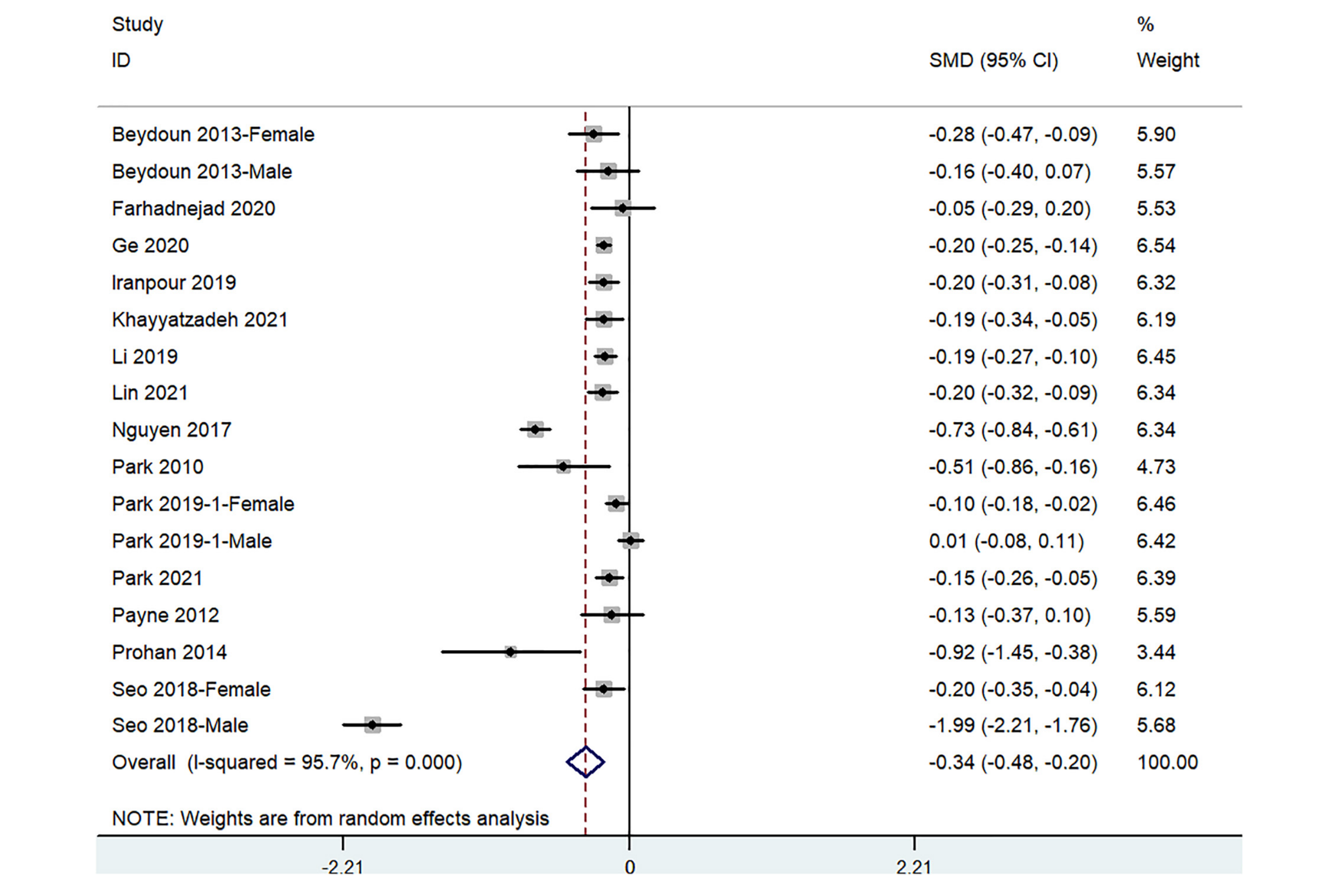

FIGURE 5 | Forest plot of meta-analysis: SMD of dietary beta-carotene intake for depression vs. control subjects.

TABLE 5 | Subgroup analysis for SMD of dietary beta-carotene in depression vs. control subjects.

Stratification	Number of studies	Pooled SMD	95% CI	*P*-value	Heterogeneity
All studies	14	−0.34	−0.48, −0.20	$P < 0.001$	$P < 0.001$; $I^2 = 96\%$
Geographical region					
Asia	9	−0.43	−0.67, −0.20	$P < 0.001$	$P < 0.001$; $I^2 = 97\%$
Non−Asia	6	−0.20	−0.24, −0.16	$P < 0.001$	$P = 0.96$; $I^2 = 0\%$
Exposure assessment					
FFQ	10	−0.41	−0.63, −0.18	$P < 0.001$	$P < 0.001$; $I^2 = 97\%$
Recall method	4	−0.20	−0.24, −0.16	$P < 0.001$	$P = 0.95$; $I^2 = 0\%$
Sex					
Male	5	−0.63	−1.32, 0.07	$P = 0.08$	$P < 0.001$; $I^2 = 99\%$
Female	9	−0.16	−0.20, −0.12	$P < 0.001$	$P = 0.33$; $I^2 = 13\%$
Population					
Adolescent	4	−0.33	−0.59, −0.06	$P = 0.02$	$P = 0.01$; $I^2 = 73\%$
Middle aged and elderly	10	−0.34	−0.50, −0.17	$P < 0.001$	$P < 0.001$; $I^2 = 97\%$
Sample size					
<1,000	5	−0.27	−0.47, −0.07	$P = 0.008$	$P = 0.02$; $I^2 = 65\%$
>1,000	9	−0.35	−0.52, −0.18	$P < 0.001$	$P < 0.001$; $I^2 = 97\%$

control subjects (SMD = −0.34, 95%CI: −0.48 to −0.20; $P < 0.001$) (**Figure 5**). A substantial level of heterogeneity was observed among the various studies ($P < 0.001$, $I^2 = 95.7\%$). A publication bias existed according to the Begg's rank-correlation test ($P = 0.044$). **Table 5** presents the results of subgroup analysis. Such results only existed in females (SMD = −0.16, 95%CI: −0.12 to −0.20; $P < 0.001$) study.

DISCUSSION

A total of 25 observational studies were included in the present meta-analysis. The pooled analysis showed that both dietary vitamin A and beta-carotene intake was inversely associated with depression.

The negative associations of dietary vitamin A and beta-carotene intake with depression can be explained as follow. First, oxidative stress plays a significant role in the pathophysiology of depression (40, 41). Equipped with extended π-electron system, carotenoids stabilize unpaired electrons after radical quenching. As potent scavengers for singlet oxygen and peroxyl radicals, carotenoids act through hydrogen acceptance/abstraction, donation, electron acceptance, or physical quenching (42, 43). Second, the levels of IL-6 and TNF-α are significantly increased in depression, which impairs the expression of BDNFs and then contributes to depression (44). Beta-carotene may lead to a reduction in levels of IL-6 and TNF-α mRNA *in vivo* (12). Third, carotenoids may act through indirect pathways and cellular signaling cascades, such as nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK) and nuclear factor erythroid 2-related factor 2 (Nrf2) (45, 46), which are closely associated with the pathology of depression (47–50). On the other hand, randomized controlled trials have indicated the potential therapeutic effect of vitamin A supplementation on depression (51), and the dietary pattern rich in vitamin A may also exert beneficial effect on depression (52–54). Taken together, current fundamental and clinical evidence is consistence with our results.

Interestingly, some of our findings are only obtained in females [the females may be more precise and reliable in the exposure assessment (55)], it may be attributed to the potential genetic sexual differences in diet-related pathology of depression (56, 57). Importantly, the inverse relationship between dietary vitamin A intake and depression only exists in prospective cohort study, but not cross-sectional study. Although the number of prospective cohort studies is rather limited (only 1), the factors that matter the dietary vitamin A and beta-carotene intake may change after depression. For instance, depressive subjects may consume less dietary vitamin A and beta-carotene due to the reduced appetite (reversed causality). Moreover, the result of subgroup analysis suggests that BMI and energy intake may also influence the overall result. Taken together, more well-designed prospective cohort studies with sexual specification are still needed.

Since vitamin A and beta-carotene are affordable and accessible nutritional factors, our findings may build an awareness with the potential collaboration between physicians and nutritionists (especially in LMICs). Nevertheless, the safety issue should also be emphasized. For instance, excessive carotenoid intake may lead to orange/yellowish skin coloration (carotenoderma or carotenemia) (58). Moreover, long-term intake of vitamin A for several months can lead to a chronic toxicity (10 mg/day for adults and 7.5–15 mg/day in children) (59). In addition, acute vitamin A toxicity cannot be ignored neither (more than 500 mg/day in adults, and 100 mg/day in children or 30 mg/day in infants) (58). The main symptoms include irritability, nausea, blurry vision, vomiting, reduced appetite, hair loss, headaches, papilledema, hemorrhage, muscle pain, weakness, altered mental status, and drowsiness (60, 61). Therefore, a careful validation for its clinical application is still needed.

Several strengthens in our study should be emphasized. First, this is the first meta-analysis study on the associations of dietary vitamin A and beta-carotene intake with depression based on observational studies. Moreover, our findings may encourage to build the potential collaboration between physicians and nutritionists for depression management (especially in LMICs). Our study is also restricted to the following issues. First, due to the limited evidence, only 1 prospective cohort studies were identified (precludes causal relationships). Second, our results may be influenced by the substantial level of heterogeneity. Third, the classification of exposure and diagnostic criteria of depression varies greatly among individuals. Forth, the adjusted factors were not uniform. Fifth, the circulating level of vitamin A and beta-carotene is not considered due to the limited evidence. The significance of our study may be weakened by these limitations.

CONCLUSION

Our results suggest that both dietary vitamin A and beta-carotene intake is inversely associated with depression. However, due to the limited evidence, further well-designed prospective cohort studies with sexual specification are still needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ and JL conceived the idea and drafted this manuscript and guarantor of the overall content. JD and JL selected and retrieved relevant manuscript, and assessed each study. All authors revised and approved the final manuscript.

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Predictors of Major Dietary Patterns Among Pregnant Women Attending Public Health Facilities in Eastern Ethiopia: A New Epidemiological Approach

Abdu Oumer, Mihret Abraham and Aliya Nuri*

Department of Public Health, College of Medicine and Health Sciences, Dire Dawa University, Dire Dawa, Ethiopia

Background: Dietary pattern analysis is a robust statistical procedure that efficiently characterize the dietary intakes of individuals. However, there is a lack of robust dietary intake evidence beyond nutrient intake in Ethiopia. This study was to answer, what are the major dietary consumption patterns and its predictors among pregnant women in Ethiopia.

Methods: A facility-based survey among 380 randomly selected pregnant women using a contextualized food frequency questionnaire (FFQ) over 1 month recall was used. The frequency of food consumption was standardized to daily frequency equivalents, and a sequential exploratory factor analysis was used to derive major dietary patterns. A multivariable ordinary logistic regression model was fitted with all its assumptions.

Results: Three major dietary patterns ("fruits and animal-source foods," "cereals, tubers, and sweet foods," "legumes and vegetables"), explaining 65% of the total variation were identified. Women snacks (AOR = 1.93; 1.23–2.75), without food aversion (AOR = 1.59; 1.08–2.35), non-fasting (AOR = 0.75; 1.12–2.12), and receiving nutritional counseling (AOR = 1.96; 1.25–3.07) were significantly positively associated with a higher tercile of fruits and animal-source food consumption. Non-working mothers (AOR = 1.8;1.23–2.76), chronic disease (AOR = 1.88; 1.14–3.09), or received nutritional counseling (AOR = 1.33; 0.88–2.01), were fasting (AOR = 1.33;0.88–2.01), and no food cravings (AOR = 4.27;2.67–6.84), and aversion (AOR = 1.60;1.04–2.44) had significantly higher odds of consuming cereals, tubers, and sweet foods. Literacy (AOR = 1.87; 1.14–3.09), urban residence (AOR = 2.10; 1.10–3.93), low socioeconomic class (AOR = 2.68; 1.30–5.23), and skipping meals (AOR = 1.73; 1.15–2.62) were associated with higher odds of legume and vegetable consumption.

Conclusion: Socioeconomic class, literacy, occupation, getting nutritional counseling, habits of food craving, food aversion, and fasting can predict a woman's dietary pattern.

Keywords: dietary pattern, food frequency, pregnant, factor analysis, ordinal logistic regression

Edited by:
Farhana Akter, Chittagong Medical College, Bangladesh

Reviewed by:
Sameer Dhingra, National Institute of Pharmaceutical Education and Research, India
Kona Chowdhury, Gonoshathaya Samaj Vittik Medical College, Bangladesh

****Correspondence:***
Abdu Oumer
omab2320@gmail.com

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Abbreviations: ANC, Antenatal Care; A/COR, Crude odds ratio; CI, Confidence Interval; DASH, Dietary Approach to Stop Hypertension; EFA, Exploratory Factor Analysis; FFQ, Food Frequency Questionnaire; GDM, Gestational Diabetes Mellitus; KMO, Kaiser-Meyer-Olkin; OLS, Ordinal logistic regression; PCA, Principal Component Analysis.

INTRODUCTION

Pregnancy is one of the most critical nutritionally sensitive periods in human development for optimal maternal and newborn health outcomes (1). The need for macro and micronutrients in increased during pregnancy, specifically the need for protein, iron, folic acid, energy, vitamins, and other micronutrients is greatly increased. These could be addressed through increased meal frequency (at least one extra meal), diversified dietary consumption and avoiding harmful substances (2, 3). Preventing pregnancy-related over and undernutrition requires optimal nutrition from a variety of nutritious foods (4). Maternal malnutrition is strongly associated with an increased morbidity and mortality burden due to low birth weight, preterm birth, cognitive dysfunction, anemia, neural tube defects, and other negative consequences for the mother and newborns. Poor nutrition has long-term consequences, including an increased risk of chronic diseases in adulthood (4–8).

Macro and micronutrient malnutrition is a major public health concern among pregnant women in developing countries. Globally, a significantly higher number of pregnant women are victims of vitamin A deficiency (19 million) and anemia (40%) (9). Above all poor access to nutritious diet, prevailing non-communicable diseases and repeated pregnancies among women in low socioeconomic class makes malnutrition and adverse consequences more common (3). In Africa, about 23.5% of pregnant women are malnourished (10). An estimated 23.3 and 60% of women had chronic energy deficiency and zinc deficiency and its adverse consequences (11). In Ethiopia, undernutrition (38%) (12), anemia (32%), iodine deficiency (38%) (13), and vitamin A deficiency (14) were a major public health problems affecting a large number of pregnant women nationally.

Furthermore, the maternal mortality rate of 412/100,000 live births, stunting among young children (37%), and under-five mortality (43 deaths/1,000) (15) are consequences of poor maternal nutrition during embryonic life. Malnutrition is one of the key modifiable contributors to many adverse pregnancy outcomes, especially in developing countries (16, 17). On the other hand, having excessive weight gain due to extra energy consumption, increases the risk of operative delivery, obstructed labor, hypertensive disorders of pregnancy, and gestational diabetes mellitus (18, 19). Hence, the dietary practices of pregnant women are of paramount importance in maintaining optimal health (9). An unhealthy dietary pattern is also associated with gestational diabetes (20), poor fetal growth, preterm births (21), malnutrition, and other adverse consequences (22).

Due to the complexity of human dietary intakes, reporting the usual nutrient intake and/or individual food consumption is not reliable and valid approach (23) (24). A comprehensive and robust dietary intake assessment is a feasible way of characterizing the dietary habits, quality, and implications of usual intakes (25, 26). Dietary pattern analysis allow us to identify the cumulative and interactive effects of each dietary component and allows us to better characterize dietary consumption (27, 28). Individual nutrient intake assessments usually fall short of accounting for the higher multicollinearity and correlation among food groups and individual nutrients in foods, which means one cannot definitely attribute a particular nutrient or food exposure (25, 28).

Despite the fact that concrete evidence on dietary quality and consumption patterns is crucial to designing and implementing appropriate nutrition interventions for pregnant women, such evidence is lacking in Ethiopia. Previous studies conducted (29–31) used a simple dietary practice tool which did not consider the complexity of the diet and interactions among dietary components. One study also indicated that more than half, 75% (30), and (61%) (31) of women had poor dietary practices, despite having better knowledge of optimal feeding (61%) (31). This urges further evidence on the overall dietary consumption of pregnant women and identifies the potential factors associated with poor/unhealthy dietary consumption of pregnant women. Such concrete evidence will inform a refined policy recommendation for better and healthier nutrition during pregnancy. Thus, having a reliable food frequency questionnaire (FFQ), one can capture the food consumption frequency over a period of time. This can be better treated statistically under exploratory factor analysis to identify major dietary patterns instead of individual food item consumption (26, 28). The current paper is pioneering research to characterize the dietary consumption of pregnant women in a more robust statistical approach, where such evidence is lacking, but guides further maternal nutrition interventions in the country. This study was to answer two research questions; what are the major dietary consumption patterns and predictors of these major dietary patterns among pregnant women in Ethiopia, as summarized in **Figure 1**.

MATERIALS AND METHODS

Study Design and Settings

This is a health facility-based survey conducted among pregnant women visiting public health facilities in Dire Dawa, which is located 526 km (eastern parts of Ethiopia). Dire Dawa is a place for a multi-ethnic society with a diverse culture and eating habits. The total population is about 506,936, of which more than half reside in urban areas. There are diverse ethnic groups, with diverse lifestyles and dietary habits, which makes the data more representative. Agriculture in rural Dire Dawa and surrounding areas focuses on sorghum, maize, potatoes, and other cash crops. In addition, fruit and vegetable production are also present in the rural parts of the area.

Population and Eligibility Criteria

A random sample of 380 pregnant women attending ANC in selected public health facilities were included in this study selected from all pregnant women attending public health facilities during the study period.

Sample Size and Sampling Procedure

The sample size required to assess the dietary patterns of pregnant women was estimated using a sample size estimation formula for single proportion. We assumed a 95% confidence level, a 5% significance level, and the prevalence of poor dietary practice

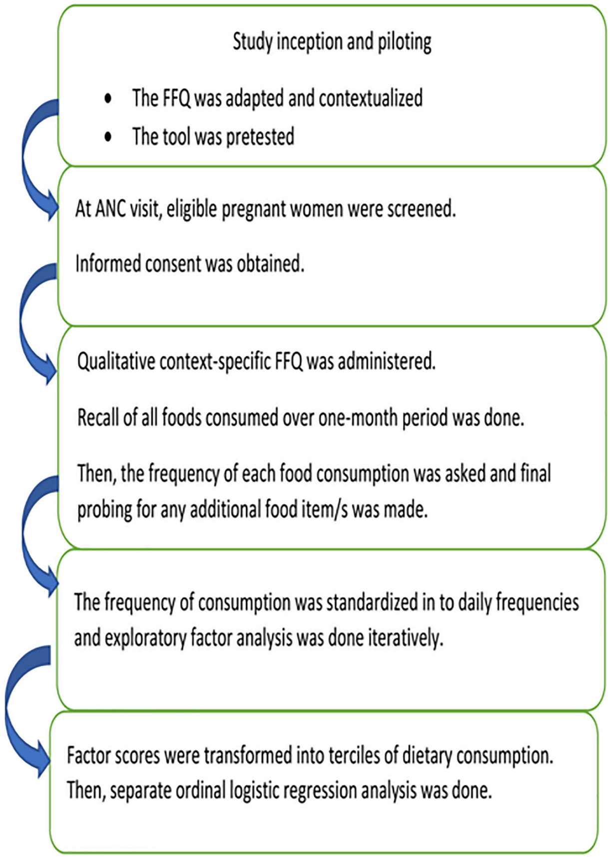

FIGURE 1 | Flowchart showing overview of the study procedures, from inception and final report.

(66%) (32), and a 10% non-response rate. The sample size became 380. A sample size was also estimated for a cross-sectional study comparing the risks of poor dietary practice by different exposure variables, but the estimated sample was below 380. Thus, a total of 380 pregnant women having ANC visits from the selected public facilities were included.

A stratified sampling with proportional allocations (based on 3-month case load) was conducted where proportional samples were taken from urban and rural areas. Then, pregnant women visiting public health facilities at every two sampling intervals were included in this study using a systematic random sampling procedure. The first women to be interviewed were selected using simple random sampling and women visiting the health facility every two intervals were included.

Data Collection Procedures

The data was obtained through a face-to-face interviewer administered interview technique using a pretested semi-structured questionnaire prepared in English and local languages. The tool includes sociodemographic characteristics, household asset ownership, dietary consumption, and a 40-item FFQ. The modified form of the FFQ was used to collect data on food consumption over the past 1-month recall period. The consumption frequency was captured on a nine-scale ranging from never to three times a day. The current FFQ is a relatively simple, valid, and reliable dietary assessment method that can be used to derive dietary patterns (33, 34). Evidence shows that the FFQ is a valid tool to predict micronutrient intakes (33, 35, 36). In Ethiopia, the FFQ was shown to have a high correlation with a range of micronutrient intakes and was suitable for ranking individual intakes (37), which we tried to rank based on food consumption frequencies. We utilized a 1-month recall for the FFQ, as a relatively shorter recall period allows us to capture individuals' usual food consumption, increase response rate, and reduce recall bias and respondent burden (38, 39). A team of five trained health extension workers, supervised by two bachelor's degree holders, collected data from Monday to Friday, when regular ANC services are provided. Data was collected on representative days, including fasting and feasting days of the week. Respondents were elicited about any foods consumed, and again, specific foods were asked about in the questionnaire one-by-one.

Data Analysis

The cleaned data was analyzed with SPSS version 20. Categorization and recoding of variables for further analysis were done. The data was summarized into mean, standard deviation, and percentages, and presented with statistical tables and graphs. The wealth index was derived from individual household assets using principal component analysis, and factor scores were ranked to generate wealth quintiles. Items which fulfill the assumptions of PCA were considered for the analysis and determination of factor scores (40).

An exploratory factor analysis (EFA) was done with the assumption checks to identify the major dietary patterns based on frequency of consumption. First, the consumption frequency of individual foods was standardized and converted to a daily frequency based on literature. Then, to minimize the complexity of the factor analysis and to be able to identify major factors that explain the highest variation, the individual food group consumptions under pre-specified food groups were summed up in accordance with literature (41). The assumptions of EFA were checked, and those variables that did not fulfill the criteria were iteratively excluded from the analysis. The Kaiser–Meyer–Olkin (KMO) $p > 0.05$) and Bartlett's test of sphericity ($p < 0.05$) were used to check for adequacy of the sample and the presence of significant correlation between items, to be considered for factor analysis (42). The EFA was conducted under orthogonal rotation with the varimax method, which allows one to identify interpretable, independent dietary patterns. Food groups with a factor loading above 0.5 were retained in the final EFA model. Considering the eigen value above 1, the scree plot, and/or the percentage of variation explained by the principal components, were used to decide on the final dietary patterns (43).

Furthermore, the factor score was generated using the Bartlett procedure, which is a robust and unbiased estimate of the true factor score based on the factor loading and daily consumption of food groups. The factor scores were further categorized (ranked) into three terciles (low, medium, and high) and are considered as response variables (44). The higher the factors tend to indicate more frequent or higher amounts of food consumption. Bivariable and multivariable ordinal logistic regression (OLS) models were considered to assess the factors associated with each dietary pattern tercile. The proportional odds assumption, and constant slope parameter over the three categories were checked using a test of parallel lines. Variables with a p-value below 0.2 in bivariable OLS were considered for multivariable OLS, where the model fitness was checked accordingly.

Ethical Considerations

Ethical approval was obtained from Dire Dawa University's Institutional Research Ethical Review Committee. The study was conducted in accordance with the standards and regulations of the ethical committee. A written informed consent was obtained from each pregnant woman.

RESULTS

Baseline Characteristics of Pregnant Women

A total of 380 pregnant women with a median age of 28 years ($IQR_{25,75}$: 24–32 years) were included in the current study. About 50.8 and 28.9% of pregnant women were Muslims and orthodox Christian in religion, respectively. Almost all (94%) were married, with only 74.4% of pregnant women being literate. The majority, 69 and 62%, of respondents were not primigravidae and from urban areas. More than half (56%) and 66% of women were not currently working and belonged to middle and lower socioeconomic groups. Regarding the dietary habits of women, 47% did not fast, 65% did no snacking, and 48% had some type of food aversion. Of the total participants, only 147 (38.7%) received nutritional counseling during their recent antenatal care visit.

Major Dietary Patterns of Women

Before PCA, the food frequency collected under nine scales was standardized to a daily equivalent based on literature (45). Then, the foods were aggregated into major food groups and the daily frequency of consumption score was summed up (**Table 1**). Before performing the analysis, the PCA assumptions were double-checked. The nine-scale frequency was reclassified and scored as 0, 0.1, 0.25, 0.571, 1, and 2, depending on the consumption frequency. The sampling adequacy was checked by KMO (0.69), and there was a significant correlation among items (X^2 = 546.7, df = 28; $P < 0.0001$). Three major dietary patterns were identified and explained 65% of the total variation in the dietary consumption of women. The identified dietary patterns had a factor loading above 0.6 in each food group (**Table 1**).

Food group items with a complex structure (a higher loading for more than one factor) were excluded and we derived three major dietary patterns with dominant food item loadings for each component. These are fruits and animal-source foods, which load higher for fruits, poultry, fish, milk and meat products, cereals, tubers, and sweet foods, and pulses and vegetables. A factor score was generated using the Bartlett procedure, which is a robust and unbiased estimate of the true factor score. Then, the factor score was categorized into three terciles (low, medium, and high) (44). Three dietary patterns, including "animal-source foods and fruits," "cereals, tubers, and sweety foods," and "pulses (legumes) and vegetables" were identified (**Table 1**).

Factors Associated With Major Dietary Patterns

The proportional odds assumption was checked for all predictor variables using the test of parallel lines, and the assumption was fulfilled for the majority of variables, except for a few variables ($p > 0.05$). After checking the assumptions, bivariable and multivariable ordinal logistic regression (OLS) were run for potential predictors of each of the identified dietary patterns. Those women who were single (COR = 1.74; 95% CI: 1.26–3.72) and living in urban areas (COR = 2.13; 95% CI: 1.44–3.14) were 1.74 and 2 times more likely to consume more fruit and animal-source foods, than those who were married and from rural areas, respectively, than those who are married and lived-in rural areas. Women's literacy (COR = 1.86; 95% CI: 1.2–2.87) and husband's literacy (COR = 2.1; 95% CI: 1.30–3.40) were significantly related to higher consumption of fruits and animal-source food (**Supplementary Material 1**).

Having nutritional counseling, fasting, snack consumption, and food aversion were significantly associated with a higher

TABLE 1 | Summary table for factor loading, factor scores, and variance explained by the major dietary patterns for each food groups among pregnant women in Eastern Ethiopia.

	Food groups	Factor 1[a]	Factor 2[a]	Factor 3[a]	Loading
1	Milk and meat products	0.819			0.593
2	Fruits	0.751			0.578
3	Poultry and Fish	0.768			0.584
4	Sweet foods		0.757		0.681
5	Tubers		0.737		0.644
6	Cereals		0.841		0.712
7	Pulses			0.881	0.786
8	Vegetables			0.614	0.594
Median factor score ($IQR_{25,75}$)		–0.40 (–0.59, 0.24)	–0.29 (-0.88, 0.62)	–0.29 (–0.53, 0.17)	
Variation explained		26%	23%	16%	

[a]*Dietary pattern 1 refers to "animal-source foods and fruits," dietary pattern 2 refers to "cereals, tubers, and sweety foods," and dietary pattern 3 refers to "pulses (legumes) and vegetables".*

consumption of fruits and animal-source foods. Women who received nutritional counseling (AOR = 1.96; 95% CI: 1.25–3.07) and those with snacking habits (AOR = 1.93; 95% CI: 1.23–2.75) had twice the odds of consuming a higher tercile of fruits and animal-source foods as compared to their counterparts. Women who did not fast (AOR = 1.75; 95% CI: 1.12–2.12) and with no food aversion (AOR = 1.59; 95% CI: 1.08–2.35) were nearly twice as likely to consume fruits and animal-source foods (**Table 2**).

Women who were not currently working (AOR = 1.84; 95% CI: 1.23–2.76), who received nutritional counseling (AOR = 1.54; 95% CI: 1.01, 2.34), with no food aversion (AOR = 1.60; 95% CI: 1.04–2.44) and craving (AOR = 4.27; 95% CI: 2.67–6.84), and who had chronic disease (AOR = 1.88 (1.14–3.09) had 1.8–1.54, 1.6, 4.3, and 1.9-fold higher odds of consuming cereals, tubers, and sweet foods, respectively. In addition, maternal educational status, wealth status, residence, and meal skipping were significant predictors of higher consumption of food from legumes and vegetables (**Table 2**).

TABLE 2 | Multivariable OLS for factors associated with major dietary patterns among women in Dire Dawa Ethiopia.

Factors	Categories	AOR (95% CI)	*P*-value
Dietary pattern 1			
Husband's education	Literate	1.45 (0.86, 2.45)	0.169
	Illiterate	1	
Nutrition counseling	Yes	1.96 (1.25, 3.07)	0.003*
	No	1	
Fasting	Yes	1	0.008*
	No	1.75 (1.12, 2.12)	
Snack consumption	Yes	1.93 (1.23, 2.75)	0.004*
	No	1	
Food aversion	Yes	1	0.019*
	No	1.59 (1.08, 2.35)	
Dietary pattern 2			
Maternal occupation	Not working	1.84 (1.23, 2.76)	0.003*
	Working	1	
Chronic diseases	Yes	1.88 (1.14, 3.09)	0.013*
	No	1	
	No		
Nutrition counseling	Yes	1.54 (1.01, 2.34)	0.047*
	No	1	
Fasting	Yes	1.33 (0.88, 2.01)	0.178*
	No	1	
Food aversion	Yes	1	
	No	1.60 (1.04, 2.44)	0.032*
Food craving	Yes	1	
	No	4.27 (2.67, 6.84)	0.0001*
Dietary pattern 3			
Educational status	Literate	1.87 (1.14, 3.09)	0.014*
	Illiterate	1	
Maternal occupation	Not working	1	0.143
	Working	1.38 (0.9, 2.12)	
Residence	Urban	2.10 (1.10, 3.93)	0.027*
	Rural	1	
Wealth status	Poor	2.68 (1.30, 5.23)	0.008*
	Middle	2.68 (1.32, 5.46)	0.007
	Wealthy	1	
Skip meals	Yes	1.73 (1.15, 2.62)	0.009
	No	1	

**Statistical significance declared at p-value below 0.05. 1 refers to the reference category, where the estimated odds ratio is compared to. AOR, Adjusted odds Ratio. Dietary pattern 1 refers to "animal-source foods and fruits," dietary pattern 2 refers to "cereals, tubers, and sweety foods," and dietary pattern 3 refers to "pulses (legumes) and vegetables".*

DISCUSSION

In this current paper, we identified three major dietary patterns and predictors of each dietary pattern among pregnant women in east Ethiopia. These are "animal-source foods and fruits," "cereals, tubers, and sweety foods," and "pulses (legumes) and vegetables." Studies have shown that women's dietary patterns are linked to the risk of adverse pregnancy outcomes like low birth weight, preterm birth, and maternal obesity and diabetes risks (23, 46, 47). Also, increased intake of Mediterranean and dietary approach to stop hypertension (DASH) diets, rich in fruits, cereals, and vegetables showed to lower the risk of hypertension and gestational diabetes mellitus (GDM) (46). In this study, we found that cereal consumption was significant, while fruit and vegetable consumption was quite low. This can potentially predispose to prevailing micronutrient deficiencies (vitamin A, iron, folic acid, and Zinc deficiency). This is evidenced by the higher prevalence of malnutrition (24%) (10) and iron deficiency anemia (32%) (48) among pregnant women in Ethiopia.

Another study from northern Ethiopia showed that 38.4 and 61% of pregnant women had poor knowledge and poor dietary practices (49). Only less than one-fifth of pregnant women (19.6%) had good dietary practices (50). This widespread poor knowledge of proper nutrition, coupled with a higher illiteracy rate and poor socioeconomic status, predispose pregnant women to poor dietary habits and prevailing malnutrition. On the other hand, a dietary pattern with non-nutritious and sweet food consumption predisposes women to obesity, impaired blood glucose, GDM, and other non-communicable diseases, especially in high socioeconomic class women (23, 46, 51).

Some baseline characteristics, such as poor socioeconomic status (AOR = 2.68) and being from urban areas (AOR = 2.10) were positively associated with a higher consumption of legumes and vegetables. For people living in low-income households, staple cereals contribute significantly to daily energy and nutrient intake and are relatively inexpensive food items (52). However, access to animal-source foods which showed over 62% price inflation, and fruits is non-affordable for the majority of the poor in Ethiopia, which significantly hinder access for consumption (53, 54). Thus, pregnant women tend to have less diverse and monotonous diets, which don't allow them to fulfill increased physiological requirements of pregnancy for better pregnancy outcomes (54, 55).

Dietary behaviors of pregnant women in relation to food aversion and snacking habits are associated with the major dietary patterns. This study found that women with a snacking habit (AOR = 1.93; 95% CI: 1.23–2.75), but no food aversion (AOR = 1.59; 95% CI: 1.08–2.35) had higher consumption of fruits and animal-source foods. It is known that pregnant women's energy and nutrient requirements are high, where they need an extra meal per day. Thus, women with snacks tend to opt for fruits and animal-source foods, which are rich sources of bioavailable minerals and vitamins for optimal neonatal growth (51). On the other hand, extra energy consumption from animal source foods might be related to increased obesity and its complications, as it is related to higher trans-fat consumption from fried foods and excessive weight gain during pregnancy (56). Another study showed that food aversion was common (69%), where cereals were the most commonly averted food groups (57). In this study, 52% of women had a habit of food aversion, suggesting that such harmful cultural practices usually predispose women to malnutrition, low birth weights, and other adverse maternal and newborn health outcomes (58).

Furthermore, women who do not have a habit of food craving (AOR = 4.27; 95% CI: 2.67–6.84) or aversion (AOR = 1.60) had a higher likelihood of eating cereal, tubers, and sweet foods. It is clear that habits of pica, food aversions, and cravings predispose women to low food intakes and ultimately malnutrition in developing countries. Thus, pregnant women to avoid nutritious foods such as animal-source foods, cereals, and legumes, aggravating the risk of micronutrient deficiencies (8, 57). Hormonal changes during pregnancy and culturally specific food taboos are the main drivers of consumption of non-nutritious foods and non-food items (59). Furthermore, such dietary restrictions have been linked to anemia, preeclampsia (60), low birth weight, and delayed child development (61). It is also associated with increased risk of chronic non-communicable diseases (hypertension, diabetes, cancer, and strokes) as well (62). It is mainly due to the fact that mothers usually crave high energy, fatty, and sweet foods, which are unhealthy foods (63). This will also adversely decrease zinc, iron, and other mineral bioavailability and increase occurrence of anemia and zinc deficiency (60%) (11).

In this study, women who received nutritional counseling were more likely to have a higher fruits and animal source food consumption. Also, more than half (61%) of women did not receive dietary counseling during the recent ANC visit. This indicates the need for integrated dietary counseling, which can help to pregnancy related physiological food craving, aversion, and promoting a healthy dietary consumption for better life (64). Studies also indicated that it is linked to a reduced risk of obesity and undernutrition among women (65–67). In addition, evidence from Ethiopia showed that women who received dietary counseling had 7–8 times better dietary practices (AOR = 7.2; 95% CI: 4.49, 11.49). These urges for enhanced comprehensive and targeted dietary counseling for pregnant women should be strengthened for a better maternal and fetal nutrition in Ethiopia (8).

Finally, it would be good to consider FFQ with the inclusion of comprehensive food items would be helpful to characterize and study the link with different health outcomes at a population level. Furthermore, using a quantitative FFQ would help to quantify the amount of nutrients consumed per day and it may allow to triangulated with other dietary assessment approaches. The current study involves an ethnically diverse population with diverse cultures and food consumption behaviors, which can potentially supplement targeted nutrition interventions in the area. Beyond this, such types of robust dietary assessments approaches targeting women would have a great policy implications than individual food and nutrient intake assessments, which are victims of multicollinearity and systematic errors (24, 26, 27).

Limitations of the Study

The finding of this study should be thought in the light some inherent limitations of the paper. despite strong measures during data collection to control for social desirability, the tendency of the respondents to overreport their dietary consumptions could not be ruled out. In addition, the result of this study strongly stands on the fulfillments of the assumption of PCA, which may not hold true for all assumptions. Due to the multicultural and diverse nature of the community, minor food items n consumed by the majority might not be captured in the FFQ used for this study.

CONCLUSION

Generally, three major dietary patterns, composed of cereals and tubers, legumes and vegetables, and fruits, explain the major variation in dietary consumption of pregnant women were identified. Consumption of fruits, animal-source foods, and vegetables is by far too low. Socioeconomic classes, fasting, having dietary counseling, habits of food craving aversion, and meal skipping were important predictors of the dietary patterns of pregnant women. Dietary pattern analysis can be easily used to characterize the diet of such diverse population in Ethiopia and allows to associate with many functional outcomes.

RECOMMENDATIONS

We strongly recommend enhanced targeted and guided dietary counseling for pregnant women during the regular ANC visits. Also, health professionals' capacity to effectively counsel women should be strengthened through regular capacity-building schemes. On the other hand, measures to enhance the economic capacity of individuals and mechanisms to increase the affordability of nutritionally-rich foods through wide-scale macro and microeconomic interventions. Dietary counseling messages should be designed in a way to address culture-specific unhealthy dietary behaviors that hinder nutrition-dense food consumption. Finally, we recommend further dietary assessments to consider dietary pattern analysis in the characterization of dietary consumption in addition to the usual food and nutrient intake analysis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the DDU IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA participated in conceptualization, fund acquisition, design, data curation, resource, project administration, data analysis, writing a report, and reviewing and approving the manuscript. AO participated in conceptualization, design, validation, supervision, methodology, data acquisition, data preparation, data visualization, and formal data analysis and contributed to writing the draft manuscript, manuscript preparation, reviewing, and submitting the manuscript. AN participated in drafting the manuscript, critically reviewing, and editing the drafted manuscript. All authors reviewed and approved the final manuscript and decided on the journal to submit to.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.855149/full#supplementary-material

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REVIEW
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Marketing of Food and Beverages to Children in the Eastern Mediterranean Region: A Situational Analysis of the Regulatory Framework

Ayoub Al-Jawaldeh[1†] *and Jana Jabbour*[1,2*†]

[1] *Regional Office for the Eastern Mediterranean, World Health Organization, Cairo, Egypt,* [2] *Department of Nutrition, School of Health Sciences, Modern University for Business and Sciences, Beirut, Lebanon*

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Ayukafangha Etando,
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Eswatini*

***Correspondence:**
*Jana Jabbour
jjabbour@mubs.edu.lb*

† These authors have contributed equally to this work

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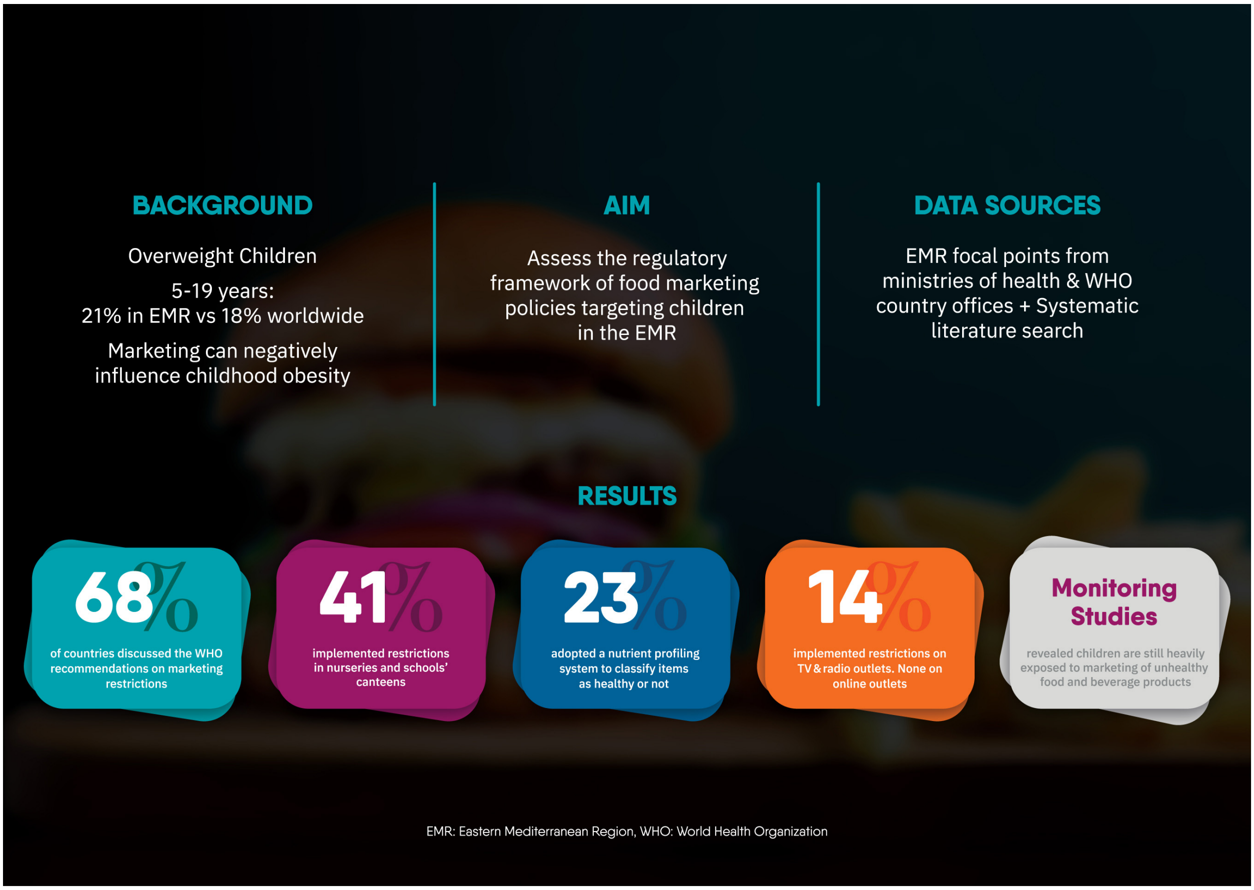
Marketing of food items high in added saturated and/or trans-fat, sugar, or sodium (HFSS) negatively affect consumption patterns of young children. The World Health Organization (WHO) advised countries to regulate the marketing of foods and non-alcoholic beverages to young populations. The aim of this manuscript is to provide a situational analysis of the regulatory framework of food marketing policies targeting children in the Eastern Mediterranean Region (EMR). A semi structured questionnaire was shared with the focal points of EMR member states inquiring about the reforms and monitoring initiatives in place. Electronic databases were searched for relevant publications between 2005 and 2021. Results revealed that even though 68% of countries discussed the recommendations, progress toward the WHO set goals has been slow with only 14% of countries implementing any kind of restrictions and none executing a comprehensive approach. Reforms have focused on local television and radio marketing and left out several loopholes related to marketing on the internet, mobile applications, and cross border marketing. Recent monitoring initiatives revealed a slight improvement in the content of advertised material. Yet, unhealthy products are the most promoted in the region. This review identified the need to intensify the efforts to legislate comprehensive food marketing policies within and across EMR countries.

Keywords: Eastern Mediterranean Region, marketing, childhood obesity, media, unhealthy food

INTRODUCTION

The Eastern Mediterranean Region (EMR) has been facing many health challenges due to unhealthy lifestyle patterns, political instability, and fragile health systems (1, 2). As a result, chronic diseases have increased from 6% in 1980 to 14% in 2014 and the burden of obesity on Disability-Adjusted Life-Years (DALYs) grew from 4% in 1990 to 8% in 2013 (3, 4). Obesity has been weighing heavily on children in the region. Compared to 5.7% of children under five around the world, 7.7% of EMR children were overweight or obese in 2020 (5, 6) (**Figure 1**). Similarly, the prevalence rate of overweight and obesity for children and adolescents aged 5-19 years in 2016 was 20.5% in the EMR compared to 18.4% worldwide (5) (**Figure 1**). The EMR has five [Kuwait, Kingdom of Saudi Arabia (KSA), Qatar, Oman, Libya] and two (Oman and Iran) out of the ten countries in the world with the highest prevalence and relative change in overweight children aged 2–4, respectively (7).



GRAPHICAL ABSTRACT |

Malnutrition manifestations differ based on the countries' Human Development Index, progress in nutrition transition, political stability, environmental status, mean population age, etc. (3, 8). Low- and middle-income countries have been struggling with the "double burden" of malnutrition with co-existence of wasting and obesity within the same population (9, 10).

Children, starting from a young age, are exposed to food marketing at home, nurseries, schools, and in public spaces, most of which are for products high in added saturated and/or trans fatty acids, sugar and sodium (HFSS) (11, 12). Marketing of food and beverages influences children' knowledge of products, preferences, acquisitions, and dietary patterns (13–16). In 2004, the World Health Organization (WHO) called on the private sector to adopt a responsible marketing approach toward children (17). Beyond corporate social responsibility, the need for legal reforms to enhance dietary patterns has been highlighted recurrently (18, 19). In 2010, the World Health Assembly (WHA) adopted the WHO Set of Recommendations on Marketing of Foods and Non-alcoholic Beverages to Children (WHO Recommendations) and called on all countries to integrate policies to regulate the marketing of unhealthy foods to young populations (20). Best practice policies to protect children up to 18 years from the harmful impact of food marketing include legislation of all relevant foods, cover all forms of marketing and are robustly monitored and enforced with meaningful sanctions (21). A WHO report assessed the implementation of marketing restriction in the EMR up to 2018 and found a limited integration of reforms in the legal framework of the EMR region (22). This project is timely in view of the scarcity of scholarly articles assessing the progress of the EMR countries in implementing the WHO Recommendations. The aim of this paper is to provide an updated situational analysis of the progress of EMR countries in integrating a regulatory framework of food marketing policies targeting children.

MATERIALS AND METHODS

Data Sources: Questionnaire and Search Strategy

A semi-structured questionnaire evaluating countries' progress toward the WHA recommendations was administered on all EMR country representatives (selected from the countries ministries of health and/or the WHO country offices). The questionnaire was shared by email via the WHO EMR office in December 2021 in Arabic and English languages (English

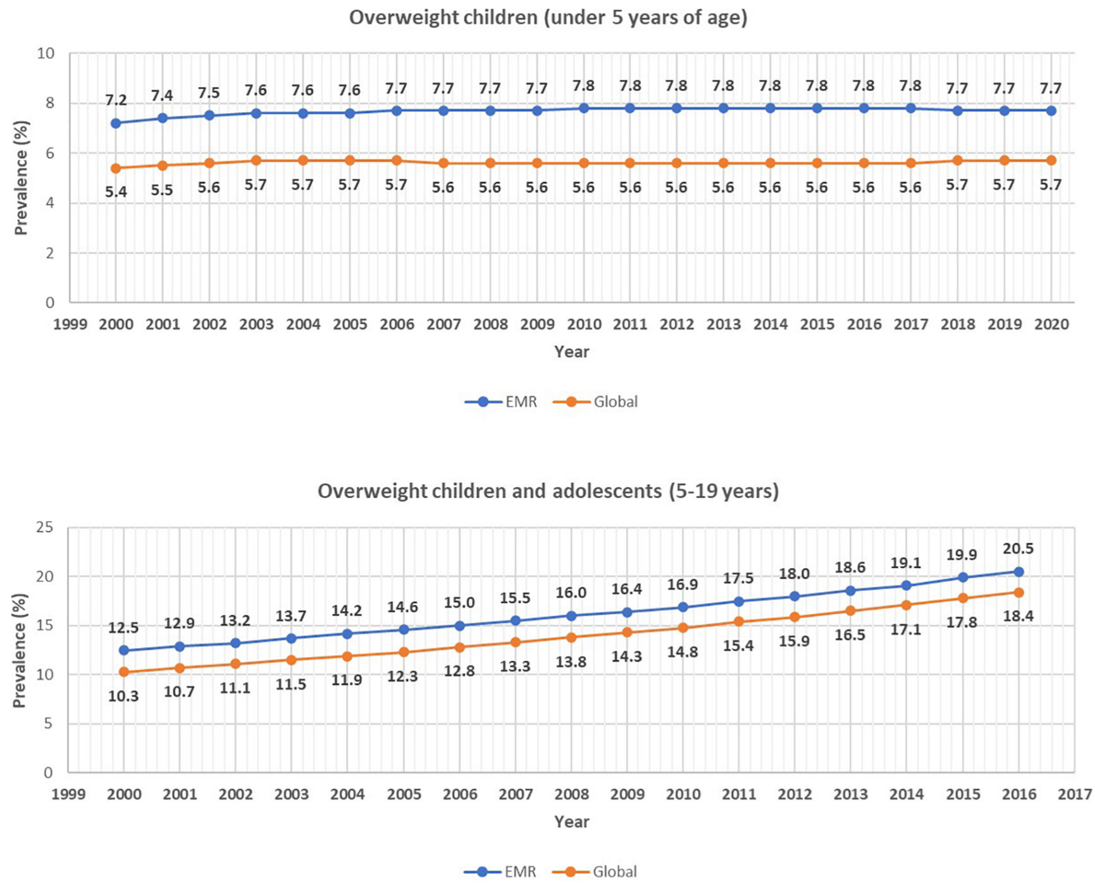


FIGURE 1 | Prevalence of overweight children under five years (top panel) and aged 5–19 years (bottom panel) in the Eastern Mediterranean Region (EMR) and globally. Overweight was defined as % weight for height 2 standard deviations above median for children under 5 years of age and as 1 standard deviation above median body mass index for age for children and adolescents aged 5–19 years. Source: Numbers have been extracted from the Global Health Observatory [5, 6].

version available in **Supplementary Material**). It inquired from country representatives if restrictions on marketing of unhealthy food and beverage items to children (up to 18 years old) have been discussed and/or implemented, on the presence of voluntary pledges by the food industry, on the stakeholders involved in the relevant discussions and legislations, and on the monitoring initiatives undertaken by governmental and/or non-governmental bodies. The extent of the implementation of a recommendation/discussion/legislation across the region was calculated by dividing the number of countries which implemented a recommendation by the total number of member states in the EMR region (n = 22). Results were rounded to the nearest integer. Moreover, a systematic literature search was implemented on the following databases: Medline, PubMed, Scopus, Embase, Google Scholar, Al Manhal, Arab World Research Source, E-Marefa, and Iraqi Academic Scientific Journals. The last four databases were chosen as they provide data sources that are specific to the region, since Arabic is the language most spoken in EMR countries. Manual search was conducted on the websites of the WHO and Food and Agriculture Organization. Inclusion criteria included manuscripts, governmental documents, reforms, and policy briefs in countries of the EMR. The following terms were used: "Eastern Mediterranean Region" countries OR "Middle East" OR each state alone AND "Children" OR "Child" OR "Toddler" AND "Diet" OR "Diet Therapy" OR "Nutrient" OR "Consumption" OR "Saturated Fat" OR "Trans Fat" OR "Sodium" OR "Salt" OR "Sugar" OR "Juice" OR "Sugar Sweetened Beverages" OR "Soft Drinks" OR "Obesity" OR "Overweight" AND "Marketing" OR "Promotion" OR "Advertisements" OR "Policy" OR "Reform" OR "Pledge." The literature search was restricted to the Arabic, English and French languages and to publications between January 1, 2005, until November 7, 2021. Individual EMR countries included in the search were selected based on the WHO country categorization: Afghanistan, Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, KSA, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Occupied lands of Palestine, Pakistan, Qatar, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates (UAE), and Yemen (23).

Food Marketing Regulatory Framework: Defining Concepts

In order to understand this situational analysis, we define in this section a few concepts relevant to the food marketing regulatory framework. The effectiveness of marketing is a function of two elements: the exposure of children to the marketing message and the power of the communication. The WHO defines power in marketing as the "content, design and creative strategies used to target and persuade" (20). Marketing is not limited to advertisements. It incorporates promotion on several media such as television, radio, billboard, magazine, packaging design, point of sale, and digital media, including mobile applications, "advergames" and blogs.

The industry and the government are the main regulatory actors that design and implement food marketing restrictions. Regulation can be done in a voluntary approach when the industry initiates and monitors the restrictions or in a mandatory manner when governmental entities design the policies and implement judiciary actions (24). Comprehensive and stepwise approaches are two commonly employed methods for integrating legal reforms. While the former method is more inclusive, the latter may be more practical to stakeholders as it progresses in phases by gradually incorporating additional outlets, food and beverage items, marketing mediums and/or settings (25). The WHO favors the comprehensive approach as the stepwise method may leave loopholes in the regulatory framework that the food industry can benefit from (26). Yet, if the comprehensive approach is not deemed feasible, the initiation of a stepwise approach is favored over the absence of any implementation (26).

Nutrient profiling is the practice of classifying a product as "healthy" or "unhealthy" based on its salt, fat and sugar content (27). Profiling facilitates the identification of products that need prohibition by legal reforms by laying a common framework for policy makers (28). The WHO office in the EMR adopted the European nutrient profiling model that assesses 18 food categories and identifies products with elevated HFSS (27).

HEALTH REFORMS IN THE EASTERN MEDITERRANEAN REGION

Legal Reforms

Table 1 provides an overview of the actions taken by EMR member states to prepare for the endorsement of the WHO Recommendations on marketing restrictions of unhealthy foods to children based on the questionnaire collected from country representatives. No information could be collected from the following countries: Djibouti, Libyan Arab Jamahiriya, and Somalia. Most countries (68%) discussed the WHO Recommendations on regulating marketing of unhealthy foods and beverages (**Table 1**). Afghanistan, Iraq, Syria, and Yemen reported not having discussed the Recommendations. Most countries that discussed the marketing restrictions did so after 2016. Ministries of health were the common stakeholder in the discussions and legal reforms. Other stakeholders included ministries of education, of trade and commerce, and municipalities and radio and television commissions. Voluntary pledges by the food industries were implemented in the KSA and UAE and less than a quarter of EMR countries (23%) adopted a nutrient profiling system (**Table 1**) (22).

Table 2 presents an overview of the legislation and implementation of restrictions relevant to the WHO Recommendations. While 14% had legislation for media outlets, 41% of countries had restrictions in nurseries and schools' canteens (**Table 2**). The mapping exercise revealed that no country implemented a comprehensive regulatory approach to limit marketing of unhealthy food and beverages to children on media outlets. Iran, KSA, Oman, Pakistan, Qatar, Tunisia, and the UAE started planning and/or implementing some levels of reforms. Iran adopted the widest level of reforms compared to other counties. The decision to ban all advertisements from kindergartens, schools, and public places where children are present was ruled in 1978 and reinforced in 2010. In 2009, it was prohibited to include children in advertisements. In 2016, a decision to ban promotion of food products during children's TV and radio programs and to avoid featuring obese children in advertisements was taken. In 2020, a legislation targeting the general public identified 19 HFSS food products as unhealthy items that should not be marketed (22, 29, 30). Reforms included nutrient profiling and involved several governmental bodies such as the Ministry of Health, Ministry of Industry, National Standards Organization, and The Islamic Republic of Iran Broadcasting (22, 29). Yet, disrespect of these reforms has not been linked to any judiciary action. In Pakistan, provincial food authorities banned sale of soft drinks in and around teaching institutions. Following this decision, local media outlets took the initiative to stop advertising for unhealthy food and beverage items during children television programs. No relevant legislation has been passed in the country. In Oman, in compliance with the "Child Law," the Ministry of Information passed legislation banning the promotion of food products during children's programs on television and radio stations and prohibiting advertisement of printed material related to medical and pharmaceutical products without the approval of the Ministry of Health. Reforms in Pakistan and Oman have major loopholes, neither do they incorporate a step for nutrient profiling, nor do they include components of marketing on social media networks, roads, supermarkets, and restaurants. Moreover, the definitions of unhealthy food items in Pakistan differed based on the provinces with some limiting unhealthy items to "sugary foods and drinks" while others employed wider definitions that incorporated sodium rich snacks as well. Some countries like Morocco and UAE adopted nutrient profiling and legislated regulatory actions for marketing of unhealthy items to children but have not implemented relevant reforms yet. The UAE legislation provides general guidelines on the need to prohibit marketing of unhealthy foods to children but does not incorporate any implementation mechanism. Legislation was hence not considered present at this point (**Table 2**). Egypt, the KSA, Qatar and Tunisia have policy briefs currently under revision by their respective governments (**Table 2**). Whereas KSA and Qatar adopted nutrient profiling systems, Tunisia prepared one but has not adopted it yet and Egypt neither adopted nor implemented any system (**Table 1**) (31). Qatar's proposed legislation involves a ban of children's toy incentives in fast food restaurants, prohibition of advertising of unhealthy foods to children, regulation of the promotions of unhealthy foods

TABLE 1 | Summary of the actions taken by EMR countries to prepare and complement the implementation of legal reforms of marketing restrictions of unhealthy foods and beverages to children.

Countries	Discussed WHO recommendations	Stakeholders involved in discussions and legislation	Voluntary pledge by the private sector	Nutrient profiling system
Afghanistan	x	-	x	x
Bahrain	✓	Ministries: Health and Commerce and Trade	¥	x
Egypt	✓	Ministry of Health	x	x
Iran	✓	Undersecretary of Public Health; Ministries of Health and Culture and Islamic Guidance, Iran's Standard Organization Iran's Food and Drug Organization, Iran's Medical Council, High council of Health and Nutrition Security, and the food industry	x	✓
Iraq	x	-	x	x
Jordan	✓	Ministries: Education, Health, Media and Industry, Trade and Supply. Jordan Food and Drug Administration.	x	x
KSA	✓	Ministries: Education, Health, Municipalities, Trade and Investment. Radio and Television Commission and audio-visual commission and the food industry	✓	✓
Kuwait	✓	Ministries: Health and Trade. Public Authority for Food and Nutrition	x	x
Lebanon	✓	Ministries of Health and Education	x	x
Morocco	✓	Stakeholders in the field of health, regulation, communication, education, research, agriculture, food industry, and civil society	x	✓
Oman	✓	Ministries: Health, Trade, and Municipalities	¥	x
Palestine	✓	Ministries: Health, Education, National Economy, Agriculture, Finance. Palestine Standards Institution, Higher Council for Youth, and Sport, Palestinian Food Industries Union. NGOs, bakeries	x	x
Pakistan	✓	Ministries: Health, Science and Technology. Provincial Food Authorities	x	x
Qatar	✓	Ministries: Commerce and Industry, Education and Higher Education, Finance, Municipality, Public Health. Health care centers, Qatar Olympic Committee, Qatar Diabetes Association, Universities, Ministry of Sports and Youth, Qatar Media Corporation, Customs General Authority, and the Food Industry	¥	✓
Sudan	✓	The Sudanese Standards and Metrology Organization, Federal Ministry of Health, Ministry of industry, Food security Technical Secretariat and private sector.	x	x
Syria	x	-	x	x
Tunisia	✓	Ministries: Health, Trade, Industry, Communication, Agriculture, Education, Social, Women, and Family. Representatives from the Civil Society.	x	Planned
UAE	✓	Ministries: Health and Prevention, Economy, Justice, Dubai Health Authority, Telecommunications and Digital Government Regulatory Authority, Department of Health—Abu Dhabi, National Media Council.	✓	✓
Yemen	x	Ministries: Health, Trade and Industry, Agriculture, Irrigation, Fish Wealth and Water and Environment and Local Administration	x	x

x, absent; ✓, present; ¥, pledge signed but not implemented according to local focal points. KSA, Kingdom of Saudi Arabia; NGOs: Non-Governmental Organizations, UAE, United Arab Emirates.

in or around schools. Tunisia's National Institute of Nutrition and Food Technology drafted a policy brief for restriction of marketing of food and beverages on television, on the internet and during sports and cultural festivities (22). Yet, the proposed policy does not impose restrictions on product packaging and on displaying cartoon characters on products, which may reduce its effectiveness.

Weak multisectoral collaboration is a challenge identified in the implementation of policies across the region. A recent scoping review revealed that regulation of marketing of food is weakly implemented in Iran due to weak scientific criteria in the legal reforms, lack of judiciary actions linked to violations, poor collaboration across sectors, and inadequate monitoring (30). Qualitative studies among stakeholders of childhood obesity in Iran criticized the weak coordination between stakeholders and the top-down approach in policy making. On the field stakeholders are poorly consulted, leading to weak implementation of these reforms (32, 33). In Pakistan, a content analysis of infant and children feeding policies identified the lack of clarity of the responsibilities of collaborators and

TABLE 2 | Summary of the legislation and restrictions implemented in canteens of educational facilities and on media outlets.

Countries	Legislation relevant to the WHO recommendations		Implementations of restrictions during children's programs on media outlets		
	Media outlets	Nursery and schools' canteens	Television	Radio	Social media networks
Afghanistan	x	x	x	x	x
Bahrain	x	✓	x	x	x
Egypt	Draft under review	x	x	x	x
Iran	✓	✓	✓	✓	x
Iraq	x	x	x	x	x
Jordan	x	✓	x	x	x
KSA	Draft under review	x	x	x	x
Kuwait	x	✓	x	x	x
Lebanon	x	x	x	x	x
Morocco	✓	x	x	x	x
Oman	¥	x	✓	✓	x
Palestine	x	✓	x	x	x
Pakistan	x	✓	✓	x	x
Qatar	Draft under review	✓	x	x	x
Sudan	x	x	x	x	x
Syria	x	x	x	x	x
Tunisia	Draft under review	x	x	x	x
UAE	x	✓	x	x	x
Yemen	x	✓	x	x	x

x, absent; ✓, present; ¥, limited. KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates.

poor stakeholders' collaboration as the areas that need to be strengthened (34).

Monitoring Initiatives

Governmental and academic bodies assessed the nature and quality of food marketing on media outlets in the EMR countries. A content analysis of the advertisements mostly viewed by a sample of 7–12-year-old children on local television channels in Egypt in 2015–2016 revealed that 74% of commercials were for unhealthy products such as sweets, chips and soft drinks (35). In Oman, a review of Pan-Arab TV stations popular among children and local radio and print media in 2015–2016 showed that print media advertisements rarely promoted unhealthy snacks but 71% of television and 44% of radio advertisements promoted HFSS items (36), with the majority of promotions being between children's programs. Sweetened beverages were the most commonly sold products to students in stores around schools. These stores included promotions on HFSS products and featured cartoon characters for products at the point of sale (36). In Lebanon, an assessment of marketing on local television channels conducted in 2016–2017 revealed that 100 and 85% of commercials advertised during children's programs and general audience programs were for unhealthy products, respectively. Moreover, around 80% of the commercials that included a health claim were for unhealthy food and beverages (37). An analysis of Iranian television commercials in 2016 revealed that the length of food and beverage advertisements was significantly shorter compared to previous years. Yet, 60% of television commercials remained food related, promoted items elevated in sugar and sodium, and favored sweetened fruit products over natural fruits (38). In KSA the Saudi Food and Drug Authority identified the YouTube channels that are most viewed by children in the country between years 2016 and 2021. A review of videos on these channels revealed that HFSS food items are commonly promoted through commercials, promotion codes, video characters consuming them prior to a competition, etc. (39). Moreover, a content analysis of printed and social media coverage of childhood obesity in the UAE revealed that excess weight among children was commonly presented as the result of bad parents' choices. The influence of structural elements related to policies and the role of the food and beverage industry was found to be minimized in the media (40).

Self-Regulation of the Food Industry

Prior to the governments' policy changes, the food industry had responded to a call by the WHO in 2004 to regulate food marketing. Eight global food and beverage companies in countries of the Gulf Country Cooperation signed the Responsible Food and Beverage Marketing to Children Pledge in 2010 (41). Through this pledge, companies committed to market products deemed healthy to children under 12 years of age and to stop sales of unhealthy products in primary schools. This pledge was further strengthened in 2016 with companies harmonizing the evaluation criteria employed (42). In 2020, the International Food and Beverage Alliance's (IFBA) compliance monitoring report to the pledge in the KSA and UAE revealed a 100% adherence rate with food marketing on television, printed material and the internet (43). Yet, these pledges and monitoring initiatives have been criticized for leaving major loopholes (22). While the IFBA pledges cover radio, television, company owned websites, cinemas, and mobile marketing, they exclude points of sale marketing, sponsorship of pediatric activities and are limited to children's programs (22). Since children tend to watch programs that are not specifically for their age group, to access websites other than those owned by companies' websites, and to attend to public spaces that do not have marketing restrictions, the latter monitoring studies can underestimate the rate of children exposure to the marketing of unhealthy products (22, 44). Moreover, the IFBA pledge limits its scope to children under 12 years of age and leaves out the age group of 12–18 years who is also much affected by marketing of HFSS (45).

DISCUSSION

Marketing of Unhealthy Food and Beverages in the Eastern Mediterranean Region: Where Do We Stand Today?

This review showed legislative action to regulate food marketing to children is very limited in the EMR. In the absence of comprehensive marketing legislation approaches, a few countries started implementing legislative actions through a stepwise approach and a few others have started planning for the change.

This report highlighted how the few legal reforms implemented have been mainly limited to local television and radio outlets. This finding identifies several challenges. First, despite the rise in the adoption of digital media and the displacement of legacy media, mobile applications and online outlets and products' packaging have been frequently omitted from legal reforms (46). Yet, online platforms have been found to incorporate food and beverage advertisements of non-core food more than other marketing outlets (47). Digital media can be even more dangerous than television and radio outlets as it employs personal data collected on children's behavioral patterns, interest, geolocation, etc. (48). It can hence exploit children using identified vulnerabilities. The limited focus on online outlets devices, print and packaging in legal reforms is not limited to the EMR; it's a common gap identified worldwide (49). Second, limiting legislative measures and monitoring to local or national media channels creates a loophole that the food industry can take advantage of. As many EMR countries speak the same languages, advertisements on regional channels can influence the behavior of children across states' borders, a phenomenon defined as cross-border marketing. Moreover, in the EMR, regional televisions have greater funding and influence than most national channels (22). At a WHO regional virtual meeting on childhood obesity in the EMR, stakeholders identified digital marketing as a challenging medium to target and cross-country collaboration as an important component to drive progress in reaching the WHO goals on marketing of unhealthy foods and beverages to children (50). Participants saw that the difficulty of integrating legal reforms on digital media should not stop them from initiating legal reforms on traditional forms of marketing—such as television, radio and print advertising and marketing in or around schools. Country representatives identified mapping of digital marketing in the region and receiving training on monitoring methodology on food marketing as pre-requisites to reaching regional goals (50).

The WHO EMR office assessed the adoption of nutrient profiling in years 2013, 2015, and 2017 (27). This study revealed a marked improvement in the adoption of nutrient profiling with 23% of states implementing them as a pre-requisite for marketing regulations. Moreover, adoption of reforms is likely to be associated with the countries' political stability, Gross Domestic Product, and the level of government commitment. Indeed, countries in political instability like Djibouti, Iraq, Lebanon, Libya, Somalia, Somalia, Syria, and Yemen have not adopted any kind of restrictions. Food authorities are likely addressing the urgent crises in their territories. Countries that have taken actions toward regulating marketing of non-nutritious products are mainly middle- or high-income countries. This reflects the abundance of resources that these countries can allocate to combat childhood obesity compared to low-income states.

We learn from other countries around the globe that reliance on the industry's self-regulation has yielded limited success. Even though the food industry funded reports suggest an impressive level of compliance with voluntary pledges, there exists a great deal of discrepancy with the results of scholarly articles and evaluations (51). Companies take advantage of loopholes to attract children to their products, implement lenient restrictions and assess compliance "mercifully" (52). An evaluation of products marketed to children in Canada revealed that 73% of unhealthy products were for companies which have committed to pledges on responsible marketing (53). Even though reliance on the industry's self-regulation is not recommended, experts agree on the importance of collaboration with the private sector for the success of any change. Involvement of the industry and governmental entities in the regulatory design has been promoted by the theory of Responsive Regulation and has proven successful in nutritional legal reforms (54–57). As the risk of conflict of interest from engagement with the food industry is elevated, the WHO recommends implementation of safeguards to prevent and manage conflicts of interest in the area of nutrition, and this is important to protect against any involvement that may undermine governments' efforts to protect children from marketing (58).

Recommendations

The lack of overall progress to date, and the finding that no country in the EMR has implemented a comprehensive approach, suggest that the recommendations of the WHO 2018 report on implementation of marketing restrictions in the region remain largely relevant (22). EMR countries are urged to develop as comprehensive approach as possible on unhealthy food marketing to children, tackling both exposure and power. Countries are called on to form multisectoral working groups to develop regulation and to build legal capacity so that those responsible for drawing up the draft legislation can withstand potential legal challenges. Countries should include monitoring and evaluation processes to regularly assess if the implemented reforms are efficient in reaching desired goals. The WHO has encouraged countries to adopt an evidence-based nutrient profiling system to identify items covered by the marketing ban. If a comprehensive approach is not feasible, countries were advised not to delay their intervention and to implement a stepwise policy, focusing on the most popular media where children are exposed to marketing, until a comprehensive approach becomes feasible. Finally, regional collaboration and cooperation are vital to safeguard youngsters from cross-border marketing (22).

Limitations and Strengths

This study provides an overview from governmental and academic bodies on the status of EMR countries in reaching goals for marketing legal reforms. Its strength is in filling an important literature gap and in employing a solid methodology. A systematic search on major databases and governmental websites was applied to yield a comprehensive overview on the subject. For completeness and since such legal reforms may not be found in scientific databases, the search was coupled with a survey of country representatives. The study has several limitations as well. Even though we employed a systematic search strategy, articles were not screened in duplicates. Moreover, data was missing from some countries due to lack of policy digitization and the lack of monitoring studies in these nations. Lastly, many countries lacked data on the extent of implementation of the legal reforms.

CONCLUSION

To our knowledge, this is the first scholarly article that analyzes the regulatory framework of food marketing restrictions toward children in the EMR. Reinforcing the results of the 2018 WHO report (21), this study revealed that the road toward achieving the WHO recommendations for marketing of unhealthy foods and non-alcoholic beverages to children has been rarely traveled in the EMR. The majority of countries only discussed the WHO Recommendations and have not taken any legal action. Countries adopting legal reforms are doing so in a stepwise approach. Implemented reforms have been limited to the traditional media, leaving out the more influential media outlets. An analysis of the marketing media children in EMR countries are exposed to showed that most commercials are for unhealthy products even in countries where legislation is present. EMR states should coordinate among stakeholders within their countries and across the region to legislate food marketing policies in view of the heavy burden of childhood obesity and the impact of marketing on children's dietary patterns.

AUTHOR CONTRIBUTIONS

AA-J and JJ: conceptualization, methodology, and writing—review and editing. JJ: investigation and writing—original draft preparation. Both authors have read and agreed to the published version of the manuscript.

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The Relationship Between Famine Exposure During Early Life and Left Ventricular Hypertrophy in Adulthood

Yu-qin Yan[1], Lin Liu[2], Shuo Sun[2], Ying-qing Feng[2], Jie Li[2] and Yu-qing Huang[2]**

[1] Department of Cardiology, People's Hospital of Shenzhen Baoan District, Shenzhen, China, [2] Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Background: Although the evidence was still limited, some studies suggested that childhood malnutrition might affect cardiac function and structure in adulthood. To address the knowledge gap, this study investigated if the Great Chinese Famine exposure during early life had affected left ventricular hypertrophy (LVH).

Methods: This research was a cross-sectional study. It included participants who had cardiac ultrasound assessments and were born in Guangdong, China, from 1 October 1952 to 30 September 1964. They were classified according to their exposure period to famine, namely, no exposure, fetal-, early-, mid-, and late childhood. Multivariate logistic regression and subgroup analysis have been conducted to determine the odds ratio (*OR*) and confidence intervals (*CI*s) between famine exposure and LVH.

Results: This research included 2,543 participants, 1,612 women, their mean age was 59.07 ± 3.65 years, and 704 participants had LVH. LVH prevalence was 122 (23.6%), 87 (25.1%), 133 (27.3%), 184 (29.2%), and 178 (31.7%), in non-, fetal-, early-, mid-, and late-childhood exposed groups, respectively ($p = 0.031$), while in the non-exposed group, the *OR*s for developing carotid plaque as a result of fetal, early-, mid- to late-childhood exposure were 1.08 (95% *CI*: 0.76, 1.59, $p = 0.619$), 1.24 (95% *CI*: 1.03, 1.79, $p = 0.031$), 1.49 (95% *CI*: 1.10, 2.01, $p = 0.009$), and 1.64 (95% *CI*: 1.25, 2.18, $p = 0.001$), respectively (*p* for trend = 0.003). There was no interactive effect between gender, obesity, or hypertension history with how the famine influenced LVH, as the subgroups analyses demonstrated (all *p* for interaction > 0.05).

Conclusion: This research has demonstrated the potential relationship between Great Chinese Famine exposure during childhood and LVH in adults.

Keywords: left ventricular hypertrophy (LVH), famine exposure, early life, adulthood, famine

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Yongjie Chen, Tianjin Medical University, China

****Correspondence:***
Jie Li
leomoku1981@163.com
Yu-qing Huang
hyq513@126.com

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INTRODUCTION

Left ventricular growth, also known as left ventricular hypertrophy (LVH), occurs as a result of growth in the size of cardiomyocytes due to the coexistence of hemodynamic and non-hemodynamic components (1, 2). It was generally accepted that LVH was a common problem and could occur due to many disorders, such as hypertension, hypertrophic cardiomyopathy, aortic stenosis, infiltrative heart muscle disease, metabolic disorders, athletic training, and storage (3). Early detection and prevention of LVH were necessary because progressive LVH could lead to maladaptation and develop into progressive left ventricular dysfunction or heart failure, and seriously threaten the patient's life (3). LVH is currently believed to be the result of genetics and the environment, and its pathogenesis has not been fully elucidated. Recently, the relationship between nutritional status and cardiovascular diseases (CVDs) has gained increasing interest, especially nutritional status during early life. More importantly, previous disease hypotheses suggested that the risk of developing the disease in adulthood was closely related to nutritional and environmental factors during the fetal or early life childhood stage (4, 5). This theory may explain why most chronic CVDs, such as coronary heart disease and hypertension, were associated with the Great Chinese Famine exposure in childhood in the Netherlands, Ukraine, and Great Chinese Famine (6–9). Nevertheless, until today, this association was still pending for verification in multiple populations.

MATERIALS AND METHODS

Study Population

The data for this study were retrieved from The Early Screening and Comprehensive Intervention Program for High CVD Risk Population, which included participants born in Guangdong, China. The program was within the China-PEACE Million Persons Project, funded by the government to identify the at-risk population who may develop CVD in China (10, 11). The cardiac ultrasound assessment was conducted on 10,984 persons in Guangdong from 01/01/2017 to 31/12/2018. This research included participants who had this assessment and were born from 01/10/1952 to 30/9/1964, while participants born from 01/10/1958 to 30/09/1959 and 01/10/1961 to 30/09/1962 were eliminated due to the uncertain start and end dates for the Chinese famine's start and end dates. In addition, participants who lacked data on covariates were excluded. Consequently, 2,543 participants were enlisted for the analysis (**Figure 1**). The Institute of Guangdong Provincial People's Hospital's ethics committee has approved this research protocol [No.GDREC2016438H (R2)].

Famine Exposure

From 1959 to 1961, the Great Chinese Famine occurred. The participants were classified into five groups (12, 13) as follows, (1) non-, (2) fetal-, (3) early-, (4) mid-, and (5) late-childhood exposed groups, which represents participants born between 01/10/1962 and 30/09/1964 ($n = 517$), 01/10/1959 and 30/09/1961 ($n = 346$), 01/10/1956 and 30/09/1958 ($n = 488$), 01/10/1954 and 30/09/1956 ($n = 630$), and 01/10/1952 and 30/09/1954 ($n = 562$), respectively.

Left Ventricular Hypertrophy Measurement

All examinations were conducted using a standardized approach by the same sonographer. The cardiac ultrasound assessment results were collected by the Vivid-S6 and 2.5–3.5 MHz-phased array probe usage, such as two-dimensional, M-mode, and Doppler ultrasound (12, 13). The left ventricular dimension, posterior wall thickness, inter-ventricular septum, left ventricular septum, and left ventricular end-diastolic diameter were measured using the parasternal long-axis view's procedures following the Echocardiography American Society guidelines (14). The left ventricular mass index (LVMI) and left ventricular mass (LVM) counting were performed using the Devereux formula (15). The LVH was graded as LVMI >115 g/m^2 and >95 g/m^2 in men and women, respectively (16).

Covariate Data Collection

Face-to-face interviews were conducted to collect socio-demographic data, such as gender, age, education, income and residential area, lifestyle behaviors, such as smoking and drinking, as well as chronic diseases (hypertension, coronary heart disease, diabetes, and stroke), and current medications (hypoglycemic, antihypertensive, and lipid-lowering drugs). Besides, height, weight, blood pressure, blood glucose, triglyceride, low- and high-density lipoprotein, and total cholesterol were also measured. The body mass index (BMI) was calculated, and BMI $\geq$25 kg/m^2 was considered overweight (17). Participants who reported having diabetes, using glucose-lowering drugs, or having a fasting blood glucose level $\geq$126 mg/dl were classified as diabetic (18), while those who reported having hypertension, using antihypertensive drugs, or having a blood pressure $\geq$140/90 mmHg were classified as hypertensive (16).

Statistical Analysis

The continuous and categorical variables were reported as mean $\pm$ standard deviation (SD), and a frequency or percentage, respectively. A normality test was first performed on all

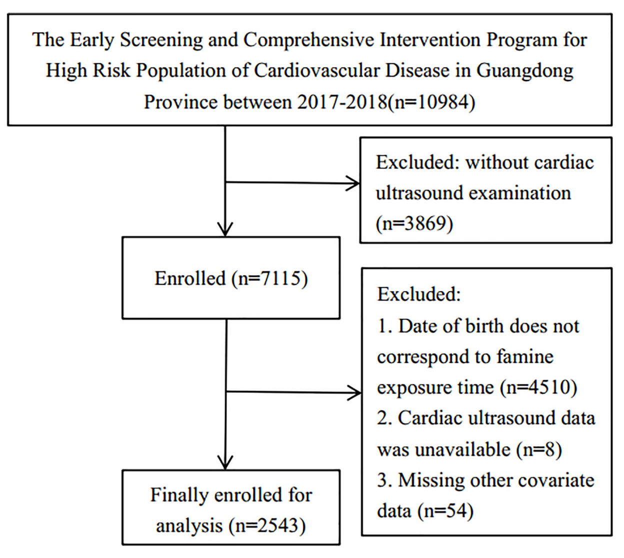

FIGURE 1 | Research flowchart.

TABLE 1 | Baseline characteristics between subjects with and without LVH group.

	Overall	No-LVH	LVH	*P*
Number	2,543	1,839	704	
Age, years	59.07 ± 3.65	58.92 ± 3.68	59.44 ± 3.52	0.001
SBP, mmHg	143.44 ± 22.99	141.02 ± 22.64	149.77 ± 22.72	< 0.001
DBP, mmHg	83.17 ± 12.38	82.34 ± 12.14	85.36 ± 12.76	< 0.001
BMI, kg/m^2	24.79 ± 3.35	24.51 ± 3.30	25.52 ± 3.36	< 0.001
TC, mmol/L	5.84 ± 1.52	5.85 ± 1.54	5.81 ± 1.48	0.459
TG, mmol/L	1.93 ± 1.08	1.91 ± 1.04	2.00 ± 1.16	0.065
HDL-C, mmol/L	1.64 ± 0.47	1.63 ± 0.47	1.66 ± 0.46	0.103
LDL-C, mmol/L	3.40 ± 1.26	3.43 ± 1.27	3.29 ± 1.21	0.017
FBG, mmol/L	6.14 ± 1.90	6.14 ± 1.94	6.16 ± 1.78	0.786
LVM, g	150.07 ± 39.48	135.67 ± 28.08	187.68 ± 40.21	< 0.001
LVMI, g/m^2	91.85 ± 21.09	82.75 ± 13.03	115.63 ± 19.54	< 0.001
PW, mm	9.50 ± 1.52	9.13 ± 1.21	10.47 ± 1.80	< 0.001
IVS, mm	9.77 ± 1.41	9.37 ± 1.14	10.82 ± 1.48	< 0.001
LVEDD, mm	45.32 ± 4.34	44.26 ± 3.87	48.09 ± 4.27	< 0.001
Gender—female (%)	1,612 (63.4)	1,058 (57.5)	554 (78.7)	< 0.001
Urban (%)	766 (30.1)	591 (32.1)	175 (24.9)	< 0.001
Hypertension (%)	1,565 (61.5)	1,047 (56.9)	518 (73.6)	< 0.001
Diabetes (%)	502 (19.7)	348 (18.9)	154 (21.9)	0.094
Stroke (%)	36 (1.4)	31 (1.7)	5 (0.7)	0.062
CHD (%)	93 (3.7)	72 (3.9)	21 (3.0)	0.262
Education-High school or above (%)	576 (22.7)	457 (24.9)	119 (16.9)	< 0.001
Income-more than 50 k per years (%)	1,282 (50.4)	953 (51.8)	329 (46.7)	0.022
Current smoke (%)	475 (18.7)	405 (22.0)	70 (9.9)	< 0.001
Current drinking (%)	134 (5.3)	114 (6.2)	20 (2.8)	0.001
Lipid-lowering drug (%)	155 (6.1)	99 (5.4)	56 (8.0)	0.015
Antihypertensive drug (%)	764 (30.0)	480 (26.1)	284 (40.3)	< 0.001
Hypoglycemic drug (%)	206 (8.1)	145 (7.9)	61 (8.7)	0.519

Continuous variables were expressed as the mean ± standard deviation (SD), and categorical variables were described as frequencies and percentages.
A normality test was first performed on all continuous variable data; comparisons that passed the normality test were analyzed by a Students t-test, and those that did not were analyzed with the Mann–Whitney U-test.
For comparing the baseline categorical characteristics, the chi-square test was used for categorical variables.
LVH left ventricular hypertrophy, LVM left ventricular mass, LVMI left ventricular mass index, IVS inter-ventricular septum, PW posterior wall, LVEDD left ventricular end diastolic diameter, CHD coronary heart disease, SBP systolic blood pressure, DBP diastolic blood pressure, FBG fasting blood glucose, TC total cholesterol, TG triglyceride, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, BMI body mass index.

continuous variable data; comparisons that passed the normality test were analyzed by a Student *t*-test, and those that did not were analyzed with the Mann–Whitney *U*-test. The chi-square test was used for categorical variables to compare the baseline categorical characteristics. Multiple group comparisons passing the normality test were analyzed using analysis of variance (ANOVA) with *post hoc* tests, whereas non-parametric multiple group comparisons were analyzed using the Kruskal–Wallis test with Dunnett's *post hoc* testing when ANOVA assumptions were not met. Categorical characteristics were compared using the chi-square test, and the Bonferroni method was applied to correct the value of *p* when comparing the multiple groups in pairs. For evaluating famine exposure and LVH association, the crude and adjusted odds ratio (*OR*) values were calculated. For determining the *OR* and confidence interval (*CI*), the multivariate logistic regression and interaction test had been used. No covariate was adjusted in model I, while age and gender were adjusted in model II. Meanwhile, age, gender, region, education, income, smoking, drinking, BMI, low-density lipoprotein cholesterol (LDL-C), hypertension, diabetes, stroke, coronary heart disease, and lipid-lowering drugs were adjusted in model III. Subgroups and interaction analyses were performed based on gender, BMI ($\geq$25.0 or $<$25 kg/m^2), and hypertension history. A two-sided $p < 0.05$ was considered statistically significant. R version 3.3.2 had been used to conduct all the statistical analyses.

RESULTS

Participants' Characteristics

This research has included 2,543 participants, of which 1,612 were women, whose mean age was 59.07 ± 3.65 years. As demonstrated in **Table 1**, compared with subjects without LVH, subjects with LVH had older age, higher blood pressure, higher BMI, higher levels of LVM, LVMI, posterior wall (PW), inter-ventricular septum (IVS), and left ventricular end diastolic diameter (LVEDD), a higher proportion of women, lower proportion of participants living in urban areas, lower education

TABLE 2 | Baseline characteristics among different famine exposure groups.

	No exposure	Fetal exposure	Early childhood	Mid childhood	Late childhood	*P*
Number	517	346	488	630	562	
Age, years	53.32 ± 0.67	56.34 ± 0.66*	59.34 ± 0.64*†	61.33 ± 0.67*†‡	63.25 ± 0.62*†‡§	< 0.001
SBP, mmHg	140.19 ± 23.45	140.77 ± 22.30	143.77 ± 22.64*†	144.10 ± 22.22*†	147.05 ± 23.60*†‡§	< 0.001
DBP, mmHg	84.25 ± 13.00	83.34 ± 13.20	83.13 ± 12.46	82.30 ± 11.75	83.08 ± 11.87	0.128
BMI, kg/m^2	25.10 ± 3.40	25.05 ± 3.39	24.71 ± 3.47*†	24.41 ± 3.19*†	24.86 ± 3.32*†	0.004
TC, mmol/L	5.95 ± 1.47	5.96 ± 1.55	5.82 ± 1.53	5.81 ± 1.52	5.72 ± 1.53*†	0.062
TG, mmol/L	1.97 ± 1.10	1.92 ± 1.14	1.91 ± 1.04	1.88 ± 1.04	1.99 ± 1.09	0.397
HDL-C, mmol/L	1.63 ± 0.48	1.67 ± 0.48	1.66 ± 0.47	1.64 ± 0.45	1.61 ± 0.46	0.358
LDL-C, mmol/L	3.53 ± 1.29	3.48 ± 1.25	3.35 ± 1.23*	3.40 ± 1.25*	3.26 ± 1.26*†‡§	0.008
FBG, mmol/L	6.09 ± 1.94	6.01 ± 1.61	6.15 ± 1.89†	6.06 ± 1.64‡	6.36 ± 2.25*†‡§	0.024
LVM, g	148.66 ± 39.72	145.82 ± 35.18*	148.59 ± 40.79†	150.74 ± 38.22*†	154.51 ± 41.65*†‡§	0.013
LVMI, g/m^2	89.49 ± 20.55	89.30 ± 18.93	91.44 ± 21.24*†	93.00 ± 20.37*†‡	94.68 ± 23.04*†‡§	< 0.001
PW, mm	9.43 ± 1.19	9.34 ± 1.12	9.39 ± 1.28	9.66 ± 2.20*†‡	9.59 ± 1.22*†‡	0.002
IVS, mm	9.70 ± 1.47	9.70 ± 1.37	9.76 ± 1.48	9.78 ± 1.35	9.89 ± 1.37	0.177
LVEDD, mm	45.30 ± 4.45	45.06 ± 3.80	45.22 ± 4.32	45.22 ± 4.45	45.71 ± 4.40	0.174
Gender—female (%)	184 (35.6)	108 (31.2)*	168 (34.4)	246 (39.0)*†‡	225 (40.0)*†‡§	0.040
Urban (%)	136 (26.3)	119 (34.4)*	142 (29.1)*†	202 (32.1)*‡	167 (29.7)*†	0.092
Hypertension (%)	278 (53.8)	191 (55.2)*	306 (62.7)*†	397 (63.0)*†	393 (69.9)*†‡§	< 0.001
Diabetes (%)	100 (19.3)	61 (17.6)	106 (21.7)†	111 (17.6)‡	124 (22.1)†	0.204
Stroke (%)	6 (1.2)	3 (0.9)	5 (1.0)	15 (2.4)*‡	7 (1.2) §	0.211
CHD (%)	14 (2.7)	12 (3.5)	21 (4.3)	28 (4.4)	18 (3.2)	0.497
Education-High school or above (%)	119 (23.0)	100 (28.9)*	133 (27.3)*†	118 (18.7)*†‡	106 (18.9)*†‡	< 0.001
Income-more than 50 k per years (%)	266 (51.5)	180 (52.0)	242 (49.6)	330 (52.4)	264 (47.0)*†§	0.361
Current smoke (%)	99 (19.1)	57 (16.5)*	79 (16.2)*	137 (21.7)†‡	103 (18.3)	0.130
Current drinking (%)	29 (5.6)	19 (5.5)	29 (5.9)	32 (5.1)	25 (4.4)	0.844
Lipid-lowering drug (%)	16 (3.1)	18 (5.2)*	27 (5.5)*	45 (7.1)*†‡	49 (8.7)*†‡§	0.002
Antihypertensive drug (%)	108 (20.9)	85 (24.6)*	154 (31.6)*†	205 (32.5)*†	212 (37.7)*†‡§	< 0.001
Hypoglycemic drug (%)	31 (6.0)	24 (6.9)	41 (8.4)*†	48 (7.6)*	62 (11.0)*†‡§	0.034
LVH (%)	122 (23.6)	87 (25.1)	133 (27.3)*†	184 (29.2)*†‡	178 (31.7)*†‡§	0.031

Continuous variables were expressed as the mean ± SD, and categorical variables were described as frequencies and percentages.

Multiple group comparisons passing normality test were analyzed using analysis of variance (ANOVA) with post hoc tests, whereas non-parametric multiple group comparisons were analyzed using the Kruskal–Wallis test with Dunnett's post hoc testing, when ANOVA assumptions were not met.

Categorical characteristics were compared using the chi-square test, and the Bonferroni method was applied to correct the value of p when comparing the multiple groups in pairs.

* $p < 0.05$ compared with the no exposure group.

† $p < 0.05$ compared with the fetal exposure group.

‡ $p < 0.05$ compared with the early childhood group.

§ $p < 0.05$ compared with the mid childhood group.

LVH left ventricular hypertrophy, LVM left ventricular mass, LVMI left ventricular mass index, IVS inter-ventricular septum, PW posterior wall, LVEDD left ventricular end diastolic diameter, CHD coronary heart disease, SBP systolic blood pressure, DBP diastolic blood pressure, FBG fasting blood glucose, TC total cholesterol, TG triglyceride, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, BMI body mass index.

level, lower smoking and drinking rate, accompanied with a higher prevalence of hypertension and the use of antihypertensive drugs (all $p < 0.05$). **Table 2** shows that the LVH prevalence in non-, fetal-, early-, mid-, and late-childhood exposed groups was 122 (23.6%), 87 (25.1%), 133 (27.3%), 184 (29.2%), and 178 (31.7%), respectively ($p = 0.031$). Significant subgroup differences were noticed in age, systolic blood pressure, LVMI, education level, history of hypertension, and taking antihypertensive drugs (all $p < 0.05$).

Famine Exposure and LVH Associations

Table 3 shows the famine exposure and LVH association as explored by multivariate logistic regression analysis. In model I, with no variables adjusted, the *OR*s for LVH from fetal-, early-, mid-, and late-childhood exposure were 1.09 (95% *CI*: 0.79, 1.49, $p = 0.603$), 1.21 (95% *CI*: 0.91, 1.61, $p = 0.183$), 1.34 (95% *CI*: 1.02, 1.75, $p = 0.033$), and 1.50 (95% *CI*: 1.15, 1.97, $p = 0.003$) (p for trend was 0.001), respectively. In model II, age and gender were adjusted, the *OR*s for LVH from fetal-, early-, mid-, and late-childhood exposure were 1.05 (95% *CI*: 0.76, 1.45, $p = 0.779$), 1.23 (95% *CI*: 0.93, 1.68, $p = 0.134$), 1.49 (95% *CI*: 1.14, 1.97, $p = 0.004$), and 1.63 (95% *CI*: 1.24, 2.09, $p = 0.002$) (p for trend was < 0.001), respectively. In model III, age, gender, region, education, income, smoking, drinking, BMI, LDL-C, hypertension, diabetes, stroke, coronary heart disease, and lipid-lowering drugs were all adjusted, in comparison with the non-exposed group, the *OR*s for developing LVH as a result of fetal, early-, mid-, and late-childhood exposure were 1.08 (95%

TABLE 3 | Relationship between famine exposure and LVH among different groups.

	Model I			Model II			Model III		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
No exposure	Ref			Ref			Ref		
Fetal exposure	1.09	0.79, 1.49	0.603	1.05	0.76, 1.45	0.779	1.08	0.67, 1.59	0.619
Early childhood exposure	1.21	0.91, 1.61	0.183	1.23	0.93, 1.68	0.134	1.24	1.03, 1.79	0.031
Mid childhood exposure	1.34	1.02, 1.75	0.033	1.49	1.14, 1.97	0.004	1.49	1.10, 2.01	0.009
Late childhood exposure	1.50	1.15, 1.97	0.003	1.63	1.24,2.09	0.002	1.64	1.25, 2.18	0.001
P for trend			0.001			< 0.001		0.003	0.003

Data are presented as OR and 95% CI. Values of p are for the comparison of the difference in famine exposure groups.
OR odds ratio, CI confidence interval, LVH left ventricular hypertrophy.
Model I adjust for none;
Model II adjust for age and gender;
Model III adjust for age, gender, region, education, income, smoking, drinking, body mass index, LDL-C, hypertension, diabetes, stroke, coronary heart disease, and lipid-lowering drugs.

TABLE 4 | Subgroup analysis among different famine exposure groups.

Group	No exposure	Fetal exposure			Early childhood			Mid childhood			Late Childhood			P for interaction
		OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	
Gender														0.140
Male (n = 931)	Ref	0.99	0.69, 1.49	0.571	1.04	0.72, 1.51	0.532	1.06	0.75, 1.97	0.415	1.18	0.63, 2.23	0.210	
Female (n = 1612)	Ref	1.14	0.60, 2.98	0.334	1.35	1.01, 2.41	0.040	1.68	1.19, 2.38	0.024	1.72	1.26, 2.10	0.003	
Hypertension														0.203
No (n = 978)	Ref	1.10	0.81, 2.06	0.316	1.31	1.05, 2.32	0.036	1.73	1.16, 2.98	0.028	1.84	1.28, 3.29	0.017	
Yes (n = 1565)	Ref	0.98	0.59, 1.29	0.675	0.99	0.66, 1.47	0.350	1.38	0.96, 1.81	0.087	1.30	0.97, 2.10	0.160	
BMI, kg/m^2														0.941
≥ 0.9 (n = 1152)	Ref	1.02	0.63, 1.34	0.553	1.17	0.75, 1.82	0.476	1.33	0.88, 2.04	0.183	1.36	0.89, 2.09	0.164	
< 25 (n = 1391)	Ref	1.18	0.90, 2.00	0.328	1.34	1.05, 2.19	0.040	1.55	1.14, 2.43	0.008	1.76	1.33, 2.52	0.001	

Data are presented as OR and 95% CI.
Values of p are for the comparison of the difference in subgroup condition.
OR odds ratio, CI confidence interval, BMI body mass index.

CI: 0.76, 1.59, p = 0.619), 1.24 (95% *CI*: 1.03, 1.79, p = 0.031), 1.49 (95% *CI*: 1.10, 2.01, p = 0.009), and 1.64 (95% *CI*: 1.25, 2.18, p = 0.001), respectively (p for trend = 0.003).

Subgroup Analysis

Table 3 demonstrates that subgroup analyses and interaction tests were performed according to gender, BMI, and history of hypertension. As shown in **Table 4**, we found that famine exposure in early-, mid-, and late childhood was linked to high risks for LVH in women, subjects without hypertension, and subjects with BMI < 25 kg/m^2. In addition, no famine exposure in the fetal period and LVH in adults' correlation were found. Nevertheless, there were no famine exposure and LVH interaction in any subgroup variable (all p for interaction > 0.05).

DISCUSSION

In the present study, the Great Chinese Famine exposure during the early, middle, and late stages of childhood, was associated with LVH development in adulthood. Although the interaction tests were not significant, preliminary evidence might suggest that the influence of famine exposure on the LVH development in adulthood being more pronounced in women, subjects with normal weight, and people without hypertension.

Fetal development and infancy were early life stages defined by organ structure and systems' rapid growth, development, and maturation (19). The food quality and quantity taken by pregnant women or infants may have long-lasting and profound impacts on growing tissues and it may alter the body's response pattern (19–22). After multivariate adjustment, we demonstrated the association between famine exposure in childhood and LVH in adulthood. However, research about the Dutch famine demonstrated that the prenatal famine and adult LVH (estimated by electrocardiographic) had no significant association (23). This discrepancy in findings might be attributed to the variation in LVH assessment methods, ethnicity, the extent and timing of exposure to famine, and covariates being adjusted.

In the current research, we noticed that exposure to the fetal and early childhood had less effect on the development of LVH in adulthood than exposure to middle and late childhood. We speculated that individuals who were extremely malnourished in the fetus or early childhood may have been miscarried or died, and the surviving individuals received additional attention from their families. However, the precise mechanism of this phenomenon is yet to be explored.

In addition, subgroup analysis demonstrated a greater famine exposure effect during childhood on LVH in women than men. On the one hand, the traditional Chinese ideology of "prioritizing boys over girls" has played a major role. In traditional Chinese society, the family paid more attention to boys, so they may have received better nutrition as they grew up. On the other hand, most participating women in this study were already in perimenopause or menopause, and the estrogen's protective effect on the cardiovascular system was no longer obvious. Additionally, we found that famine exposure in childhood had a greater effect on LVH in adults among people without comorbid hypertension, as well as in normal weight subjects. It is possible that famine exposure during childhood was strongly linked to hypertension development and obesity in adulthood (24, 25), and the possible nutritional status of non-hypertensive and obese individuals was deficient. However, it is notable that the interaction tests were not significant, so the proposed mechanisms as mentioned above should be verified in further studies.

Although famine exposure in childhood and LVH in adulthood had a strong association, the mechanism was not entirely clear. First, subjects who passed the famine alive may have catch-up growth and may result in over-nutrition, which has a significant association with cardiac structure and function (26, 27). Second, a previous study found that exposure to famine during gestation was linked to insulin resistance and increased oxidative stress responsiveness (8). In addition, poor nutrient status, the inflammation, and oxidative stress were closely related, which may have a vital impact on the immune system (28). Finally, nutritional status was closely related to endothelial dysfunction (29, 30) and sympathetic activity (31, 32). Numerous previous studies from basic science have confirmed that oxidative stress, inflammatory processes, endothelial dysfunction, and insulin resistance play important roles in developing LVH (33–36).

There were several strengths in the present study. On the one hand, this research was one of the first studies in indicating that famine exposure during early life could develop an LVH risk in adults. On the other hand, the present study provided new ideas for the early prevention of LVH. In addition, since the Great Chinese Famine had a huge impact on all of China, theoretically, our research findings can be extrapolated to other regions of China. Meanwhile, we should be aware of several limitations of this study. First, the cardiac ultrasound data acquisition was performed manually, so there may be measurement errors. Second, it cannot draw a causal relationship between famine exposure in childhood and LVH in adulthood given that it was a cross-sectional survey. Well-designed prospective studies were needed to clarify this association in the future. Third, some variables as measured at baseline, such as current use of medication and chronic diseases history, came from self-reported data and may have recall bias. Fourth, although the famine exposure was classified by the birthdate of the participants, the influence of age on LVH could not be fully eliminated, which was a common limitation for studies examining famine-disease relationship. Fifth, some populations may have died due to famine, which could have led to survivor bias on the influence of famine exposure and LVH development. Finally, the current study has no data on birth weight, time of pregnancy, and hematological or biological markers to assess nutritional status.

CONCLUSION

In conclusion, the Great Chinese Famine exposure in childhood was linked to an increased LVH incidence in adults. No obvious association was observed for famine exposure in the fetal period and LVH, but exposure in early, middle, and late childhood were independently associated with LVH in adulthood. Our finding identifies the at-risk population that should receive more attention in preventing LVH.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee at the Institute of Guangdong Provincial People's Hospital [No. GDREC2016438H (R2)]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YY, YH, JL, and YF: conceptualization and study design. SS and LL: investigation. YY, JL, and YH: manuscript preparation. LL and YH: statistical analysis and data interpretation. All authors reviewed and approved this manuscript.

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Secular Difference in Body Mass Index From 2014 to 2020 in Chinese Older Adults: A Time-Series Cross-Sectional Study

*Ying Jiang[1], Xiaomin Zhang[1], Tianwei Xu[2], Weiqi Hong[3], Zhiqi Chen[1], Xiang Gao[4] and Renying Xu[1]**

[1] Department of Clinical Nutrition, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [2] Department of Psychology, Stockholm University, Stockholm, Sweden, [3] Caolu Community Health Service Center, Shanghai, China, [4] Department of Nutrition and Food Hygiene, School of Public Health, Fudan University, Shanghai, China

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Eastern Medical College and Hospital, Bangladesh

***Correspondence:**
Renying Xu
721001735@shsmu.edu.cn
orcid.org/0000-0003-2608-5586

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Background: Body mass index (BMI) is the most widely used parameter to assess the body weight status. Both the increase of BMI (overweight and obesity) and decrease of BMI (underweight) has been associated with high risk of adverse outcome, such as stroke, disability, and even death. However, recent data on secular differences in BMI in the Chinese aged population are limited. The present study provides robust new evidence about the evolving epidemic of obesity among aged adults in China.

Objective: Evaluating secular difference in BMI in a group of Chinese older adults.

Materials and Methods: We analyzed 7 continuous survey years (2014–2020), including 50,192 Chinese aged participants (25,505 men and 24,687 women, aged 71.9 ± 6.1 years, age range: 65–99 years). Information on sex, age, height, and body weight, was collected based on medical history. Participants were classified into four groups: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 kg/m$^2 \leq$ BMI < 25 kg/m^2), overweight (25 kg/m$^2 \leq$ BMI < 30 kg/m^2), and obesity (BMI ≥ 30 kg/m^2). Linear regressions were used to assess the secular difference in BMI. Sex and age differences were also evaluated by stratified analyses.

Results: From 2014 to 2020, age-adjusted mean BMI increased by 0.3 kg/m^2 (95% *CI*: 0.1, 0.5 kg/m^2) in men, and 0.5 kg/m^2 (95% *CI*: 0.2, 0.7 kg/m^2) in women. Age-standardized prevalence of underweight decreased from 3.0 to 2.3% in men, and from 3.0 to 2.1% in women. Age-standardized prevalence of overweight increased in both men (from 40.1 to 41.7%) and women (from 37.8 to 39.8%), and so as obesity (men: from 4.1 to 6.1%; women: from 5.8 to 8.7%).

Conclusion: Our results confirmed that BMI gradually increased from 2014 to 2020. The age-adjusted mean BMI increased by 0.3 kg/m^2 in older men, and 0.5 kg/m^2 in older women. The age- and sex-standardized prevalence of overweight and obesity significantly increased, especially in 70–79-year age group, while the prevalence of underweight decreased. The combination of a balanced-diet and physical exercise is needed to maintain optimal BMI range for the aged population.

Keywords: body mass index (BMI), the elderly, underweight, overweight, obesity

INTRODUCTION

The number of aged population has dramatically increased in both the developed and the developing countries. Statistics showed that the proportion of older adults (≥ 65 years) in the global population has exceeded 7%, and it is expected to reach 22.59% by the end of this century (1). China, the most populous country in the world, has been experiencing a very fast pace of the population aging process and has the largest older population (2).

The aged population is threatened by both underweight (often referred as malnutrition) and overweight (referred as overweight and obesity). Underweight is much higher among older adults in India, as a recent nationwide community-dwelling survey in India showed that the prevalence of underweight among people aged 65 years and over was 28.4% (3). Underweight in older adults is associated with an increased risk of mortality and morbidity (4, 5), poor self-reported health (6, 7) and physical decline, which have wide ranging acute implications for activities of daily living and quality of life in general (8). Overweight in older adults is associated with a range of chronic diseases, such as cardiovascular diseases, diabetes, some types of cancers, and musculoskeletal disorders (9–15). The constant temptation of making poor health choices like lack of balance in diet, too little exercise and day to day stress are adding to this rising problem worldwide and needs to be addressed.

A Chinese national survey reported that the prevalence of underweight, overweight, and obesity was 5.7, 34.8, and 12.4%, respectively, in population aged 60 years and over, however, they did not report secular change in BMI. Furthermore, data were collected between 2010 and 2013, so it may not reflect BMI changes in the last decade. (16). Moreover, a recent study on 8,244 Korean older persons emphasized the gender differences with men showing higher prevalence of underweight and lower prevalence of overweight/obesity (17), which was not depicted in the recent Chinese studies. Further, not all studies reported the prevalence of underweight. For example, prevalence of underweight has been reported in South Korea (17) and Spain (18), but not in an earlier study in the United States (19), where the prevalence of overweight and obesity was shown to be higher than South Korea and Spain (19).

Body mass index (BMI) is the most widely used parameter to assess body weight status (20). Both the increase of BMI (overweight and obesity) and decrease of BMI (underweight) has associated high risk of adverse outcome, such as stroke, disability, and even death. However, recent data (i.e., after year 2015) on secular differences in BMI or prevalence of obesity in Chinese aged population is limited. To the best of our knowledge, only two studies were identified. One study reported a steady rise in mean BMI and obesity among adults aged 18–69 years from 2004 to 2018, however, with seniors over 70 years old excluded (21). Another study found increasing prevalence of obesity and overweight in Chinese older adults during the period between 2013 and 2018 but did not examine the trend in mean BMI (22).

Therefore, we aimed to evaluate the secular difference in BMI among older people collected from a community-based population annually from 2014 to 2020 comprising a total of 50,192 men and women.

MATERIALS AND METHODS

Study Population

The initial recruitment included 58,947 Chinese aged participants who were from two different community parts: 28,633 participants (17,527 men and 11,106 women, 72.3 ± 6.7 years) were from the Health Management Center, the Renji Hospital, and 30,314 participants (11,880 men and 18,434 women, 72.8 ± 6.8 years) were from the Caolu Community Health Service Center, Shanghai. After excluding participants without information on height and body weight (BW) (n = 8,755), a total number of 50,192 participants, whose mean age was 71.9 ± 6.1 years, were finally included in the study (**Supplementary Figure 1**). Mean BMI was slightly lower for the participants from the Renji Hospital than those from the Caolu Community Health Service Center (24.5 ± 3.2 kg/m^2 *vs.* 25.2 ± 3.6 kg/m^2, $p < 0.01$), while the participants from the Renji Hospital is older than those from the Caolu Community Health Service Center (72.1 ± 6.5 years *vs.* 71.8 ± 5.8 years, $p < 0.01$).

Assessment of Body Mass Index

Body weight and height were measured in light clothes with bare foot. BMI was calculated as weight in kilograms divided by squared height in meters. To facilitate cross-country comparisons, we defined overweight and obesity by the World Health Organization (WHO) criteria (23). Participants were classified into: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2), and obesity (BMI ≥ 30 kg/m^2).

Statistical Analysis

In the descriptive statistics, continuous variables were presented as means and standard deviations (SD) while categorical variables were shown as proportion or percentage. We computed age-standardized prevalence of underweight, overweight, and obesity based on the 2020 census of the Shanghai aged population by the direct method (24).

To assess the secular difference in mean BMI where "year" served as the exposure and "BMI" served as the outcome after adjustment of age and sex. As a supplementary, we also analyzed the secular difference of height and body weight, by treating them as separate outcomes. For assessing the prevalence of BMI categories over the time; we further treated prevalence of each BMI category as separate outcomes.

We used linear regressions for all analyses. The p-values for trends were determined by linear regression analyses after setting year as a continuous variable.

Men and women were separated in all analyses.

We also showed age-related trends in height, weight, and BMI.

We examined the age-based tendency of BMI, height, and body weight within each individual year in the sensitivity analyses. All statistical analyses were performed with SAS version

9.4 (SAS Institute Inc., Cary, NC, United States). Statistical significance was determined at p-value < 0.05.

Ethics Statement

N/A. As a re-identified analysis, the consent was waived by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University.

RESULTS

Descriptive Analysis

A total number of 50,192 Chinese aged participants (25,505 men and 24,687 women, mean age: 71.9 ± 6.1 years, age range: 65–99 years) were included in the study, with a mean annual sample of 7,170 individuals. Mean height, body weight, and BMI was 160.5 ± 8.7 cm, 64.2 ± 10.9 kg, and 24.9 ± 3.4 kg/m^2, respectively (**Tables 1A,B**). Mean BMI was associated with natural year in women in all age groups, while it was associated with natural year only in 70–79-year-old men (**Tables 1A,B**).

Age-Specific Trends in Height, Body Weight, and Body Mass Index

Height, body weight, and BMI decreased with age in both men and women (**Table 2**). For example, compared with men aged 65–69 years (served as reference), men aged 70–79 years lost an average of 1.5 cm (95% *CI*: 1.3, 1.7 cm) in height, 2.0 kg (95% CI: 1.7, 2.3 kg) in body weight and 0.3 kg/m^2 (95% *CI*: 0.2, 0.4 kg/m^2) in BMI, and men aged 80 years or more lost an average of 2.8 cm (95% *CI*: 2.6, 3.1 cm) in height, 5.4 kg (95% *CI*: 5.0, 5.8 kg) in body weight and 1.1 kg/m^2 (95% *CI*: 1.0, 1.2 kg/m^2) in BMI (**Table 2**). For subgroup analysis, similar secular differences in height and body weight were confirmed in each individual year (**Supplementary Table 1**).

Secular Difference in Mean Body Mass Index

Mean BMI increased with natural year in both men and women after adjustment of age (**Table 3**). From 2014 to 2020, age-adjusted mean BMI increased by 0.3 kg/m^2 (95% *CI*: 0.1, 0.5 kg/m^2) in men, and 0.5 kg/m^2 (95% *CI*: 0.2, 0.7 kg/m^2) in women. For subgroup analysis, similar trends were confirmed in women of all age groups, but only in men aged 70–79 years (**Supplementary Tables 2A,B**).

Secular Difference in the Prevalence of Body Mass Index Categories

The prevalence of underweight decreased only in men aged 70–79 years (p for trend = 0.02) while it was similar in other groups. The prevalence of overweight increased in both men and women aged 70–79 years (both p for trend < 0.05). The prevalence of obesity increased with natural year in men aged 70–79 years and all women except 65–69 years (all p for trend < 0.05) (**Table 4**).

TABLE 1A | General characteristics of 25,505 Chinese aged men from 2014 to 2020.

Age group	Variables	Men (*n* = 25,505)							*p*-value
		2014 (*n* = 2,706)	2015 (*n* = 2,719)	2016 (*n* = 3,226)	2017 (*n* = 5,248)	2018 (*n* = 5,615)	2019 (*n* = 3,244)	2020 (*n* = 2,747)	
65–69 y	Height (cm)	167.1 (6.1)	167.7 (6.0)	168.1 (6.0)	167.8 (6.0)	166.9 (6.7)	167.1 (6.2)	167.6 (6.0)	< 0.01
	BW (kg)	69.8 (9.8)	70.2 (9.5)	70.7 (9.4)	70.4 (10.0)	70.2 (10.1)	70.2 (10.0)	70.5 (9.9)	0.43
	BMI (kg/m^2)	25.0 (3.0)	24.9 (3.0)	25.0 (3.0)	25.0 (3.1)	25.2 (3.1)	25.1 (3.1)	25.1 (3.1)	0.24
70–79 y	Height (cm)	165.8 (6.1)	166.5 (5.8)	166.6 (6.2)	166.2 (6.1)	165.6 (6.6)	165.5 (6.4)	165.6 (6.3)	< 0.01
	BW (kg)	67.3 (10.0)	67.9 (9.7)	68.3 (9.7)	68.4 (9.8)	68.4 (10.0)	68.7 (10.7)	68.5 (10.5)	0.02
	BMI (kg/m^2)	24.5 (3.2)	24.5 (3.1)	24.6 (3.2)	24.7 (3.1)	24.9 (3.2)	25.0 (3.3)	25.0 (3.4)	< 0.01
≥ 80 y	Height (cm)	164.7 (5.9)	165.1 (5.7)	164.7 (6.0)	164.9 (6.0)	164.4 (6.7)	163.6 (6.0)	163.5 (5.5)	< 0.01
	BW (kg)	64.9 (10.0)	65.4 (9.8)	64.7 (9.9)	64.6 (9.7)	64.8 (9.9)	65.5 (10.6)	65.6 (10.4)	0.69
	BMI (kg/m^2)	23.9 (3.4)	24.0 (3.3)	23.8 (3.4)	23.7 (3.3)	24.0 (3.3)	24.4 (3.4)	24.5 (3.5)	0.05

TABLE 1B | General characteristics of 24,687 Chinese aged women from 2014 to 2020.

Age group	Variables	Women (*n* = 24,687)							*p*-value
		2014 (*n* = 1,582)	2015 (*n* = 1,577)	2016 (*n* = 1,964)	2017 (*n* = 5,500)	2018 (*n* = 5,457)	2019 (*n* = 4,527)	2020 (*n* = 4,080)	
65–69 y	Height (cm)	155.1 (5.5)	155.7 (5.8)	156.0 (5.7)	155.7 (5.8)	156.6 (6.4)	155.9 (5.7)	155.9 (5.4)	< 0.01
	BW (kg)	59.8 (9.1)	60.1 (9.3)	59.2 (8.7)	60.5 (9.3)	61.4 (9.7)	60.9 (9.3)	61.1 (9.2)	< 0.01
	BMI (kg/m^2)	24.8 (3.5)	24.8 (3.4)	24.3 (3.3)	24.9 (3.5)	25.0 (3.5)	25.0 (3.5)	25.1 (3.5)	< 0.01
70–79 y	Height (cm)	153.4 (5.5)	154.0 (5.7)	154.2 (5.6)	153.3 (5.7)	154.0 (6.4)	153.5 (5.9)	153.7 (5.6)	< 0.01
	BW (kg)	58.3 (8.9)	57.4 (8.5)	57.7 (8.7)	58.6 (9.4)	59.8 (9.6)	59.8 (9.8)	59.9 (9.3)	< 0.01
	BMI (kg/m^2)	24.7 (3.4)	24.2 (3.3)	24.3 (3.3)	24.9 (3.7)	25.2 (3.6)	25.4 (3.8)	25.3 (3.6)	< 0.01
≥ 80 y	Height (cm)	150.5 (5.8)	151.4 (6.3)	151.8 (5.2)	150.6 (6.2)	149.9 (7.1)	150.5 (6.7)	150.7 (6.2)	< 0.01
	BW (kg)	54.2 (8.5)	54.6 (9.2)	55.4 (9.0)	55.5 (9.4)	55.8 (9.4)	56.1 (9.7)	56.1 (9.3)	0.15
	BMI (kg/m^2)	23.9 (3.4)	23.8 (3.6)	24.0 (3.5)	24.5 (4.0)	24.8 (3.9)	24.7 (3.8)	24.7 (3.7)	< 0.01

BMI, body mass index; BW, body weight.
Data are expressed as means (standard deviations).
The difference among the year groups was tested by F test.

The age-standardized prevalence of underweight, overweight, and obesity from 2014 to 2020 were shown in **Figure 1**. From 2014 to 2020, age-standardized prevalence of underweight decreased from 3.0 to 2.3% in men and from 3.0 to 2.1% in women. Overweight was more prevalent in men than in women. Age-standardized prevalence of overweight increased in both men (from 40.1 to 41.7%) and women (from 37.8 to 39.8%) and so as obesity (men: from 4.1 to 6.1%; women: from 5.8 to 8.7%).

DISCUSSION

In the present study including 50,192 Chinese aged participants, we determined that the height, body weight, and BMI decreased with age. From 2014 to 2020, the age-standardized prevalence of underweight decreased while overweight and obesity slightly increased in both men and women.

We found that the height and body weight decreased with age in the current aged population. The English Longitudinal Study of Aging found that reduction in height is an important phenomenon among respondents aged 50 years and over. On average, physical stature decline occurs at an annual rate of between 0.08 and 0.10% for men, and 0.12 and 0.14% for women, which approximately translates into a 2–4 cm reduction in height over the life course (25). In addition to osteoporosis and certain kinds of arthritis, height shrinkage during aging is also associated with socioeconomic status (26). The similar age-related decline in weight was also observed several prospective studies (27–29). A longitudinal study also reported that BMI declined significantly among older adults. The difference in BMI was 0.435 kg/m^2 in the younger-old (60–77 years) and was 3.48 kg/m^2 in the older-old ($\geq$ 78 years) during 15 years of follow up (30). Unintentional weight loss and associated adverse outcomes in older people may be attributable to protein-energy malnutrition, cachexia, the physiological anorexia of aging, or some combination of chronic diseases (31).

The similar downward trend in underweight in aged population was confirmed in both Chinese (22) (2013–2018) and Korean (17) (1998–2014) nationwide previous studies, but somewhat different from the Japanese aged population (2003–2016), in whom the prevalence of underweight decreased in men, but increased in women (32). In Brazil (33), Nepal (34), the Philippines, and Taiwan (35), the prevalence of underweight was higher in women. These studies were in line with our study.

Similar to our findings, some studies also reported increasing trend in overweight and obesity in both older men and women, such as a Iranian (36) study (2002–2014) and a Chinese (22) previous study (2013–2018). A Japanese study (2002–2016) was somewhat different, which reported that overweight and obesity increased in older men but decreased in older women (32). Conversely, the mean body weight of older Norwegians (65–79 years) decreased in both men and women from 2007 to 2016 (37). A previous study which such as Chinese elderly (60–69 years) reported annual changes in mean BMI (calculated as the absolute difference mean BMI between the start and end years divided by total number of years covered) from 2010 to 2018 was 0.08 kg/m^2 in men, while 0.04 kg/m^2 in women (21). Sex differences in growth rate were opposite to our findings that in Chinese adults ($\geq$ 65 years), annual changes in the mean BMI from 2014 to 2020 was 0.05 kg/m^2 in men, while 0.08 kg/m^2 in women. The reason might lie on study period, age distribution, and cities where the participants were recruited. The increasing trend in overweight and obesity may be caused by increased consumption of animal food, soft beverage, and decreased physical activities (38, 39). Obesity is the result of disrupted energy balance, which is partially the consequence of alterations in the hypothalamic melanocortin circuitry. Although our understanding of energy management and the interactions between intake, metabolism, and expenditure are not yet fully understood (40), evidences suggested that unhealthy diet and lifestyles could impair the sophisticated hypothalamic circuits that regulate energy homeostasis, thus contributing to obesity (41). Unhealthy diet and lifestyle, such as less home cooking, more reliance on convenience food, frequent snacking, sweets, soft drinks, and fast food, sedentary behavior, and less physical activity, are important risk factors for obesity (42–44).

TABLE 2 | Age-specific trends in anthropometric data in 50,192 Chinese aged participants.

Variable	Sex	Age group		
		65–69 y	70–79 y	≥ 80 y
BMI, kg/m^2	Men	25.0 (25.0, 25.1)	24.8 (24.7, 24.8)	23.9 (23.8, 24.1)
Difference in BMI, kg/m^2		Ref.	−0.3 (−0.4, −0.2)	−1.1 (−1.2, −1.0)
BMI, kg/m^2	Women	24.9 (24.9, 25.0)	25.0 (25.0, 25.1)	24.5 (24.4, 24.7)
Difference in BMI, kg/m^2		Ref.	0.1 (−0.01, 0.2)	−0.4 (−0.5, −0.2)
Height, cm	Men	167.4 (167.3, 167.6)	165.9 (165.8, 166.1)	164.6 (164.4, 164.8)
Difference in height, cm		Ref.	−1.5 (−1.7, −1.3)	−2.8 (−3.1, −2.6)
Height, cm	Women	156.0 (155.9, 156.1)	153.7 (153.6, 153.8)	150.6 (150.4, 150.8)
Difference in height, cm		Ref.	−2.3 (−2.4, −2.1)	−5.4 (−5.6, −5.1)
BW, kg	Men	70.3 (70.1, 70.5)	68.3 (68.1, 68.5)	64.9 (64.6, 65.3)
Difference in BW, kg		Ref.	−2.0 (−2.3, −1.7)	−5.4 (−5.8, −5.0)
BW, kg	Women	60.7 (60.5, 60.9)	59.2 (59.0, 59.4)	55.7 (55.4, 56.0)
Difference in BW, kg		Ref.	−1.5 (−1.8, −1.2)	−5.0 (−5.4, −4.6)

BMI, body mass index; BW, body weight.
The difference between the age groups was tested by linear regression analysis.
Data are expressed as means (95% confidence interval).

TABLE 3 | Trends in anthropometric parameters in 50,192 Chinese aged participants from 2014 to 2020.

Variable	Sex	2014	2015	2016	2017	2018	2019	2020
BMI, kg/m^2	Men	24.6 (24.5, 24.8)	24.6 (24.5, 24.8)	24.7 (24.6, 24.8)	24.7 (24.6, 24.8)	24.9 (24.8, 25.0)	25.0 (24.9, 25.1)	24.9 (24.8, 25.0)
Difference in BMI, kg/m^2		Ref	–0.001 (–0.2, 0.2)	0.1 (–0.2, 0.3)	0.1 (–0.1, 0.3)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)
BMI, kg/m^2	Women	24.7 (24.5, 24.9)	24.4 (24.2, 24.6)	24.3 (24.1, 24.4)	24.8 (24.8, 25.0)	25.1 (25.0, 25.2)	25.1 (25.0, 25.2)	25.2 (25.0, 25.3)
Difference in BMI, kg/m^2		Ref	–0.3 (–0.6, 0.04)	–0.4 (–0.7, –0.1)	0.2 (–0.1, 0.4)	0.4 (0.1, 0.6)	0.4 (0.2, 0.7)	0.5 (0.2, 0.7)
Height, cm	Men	166.3 (166.1, 166.5)	166.9 (166.6, 167.1)	167.1 (166.9, 167.3)	166.8 (166.7, 167.0)	166.1 (165.9, 166.2)	166.0 (165.8, 166.2)	166.2 (166.0, 166.5)
Difference in Height, cm		Ref	0.6 (0.1, 1.0)	0.8 (0.4, 1.2)	0.5 (0.2, 0.9)	–0.2 (–0.6, 0.1)	–0.3 (–0.8, 0.1)	–0.1 (–0.5, 0.4)
Height, cm	Women	153.7 (153.4, 154.0)	154.3 (154.0, 154.6)	154.6 (154.3, 154.8)	154.1 (153.9, 154.2)	154.7 (154.5, 154.9)	154.2 (154.0, 154.3)	154.2 (154.1, 154.4)
Difference in Height, cm		Ref	0.6 (0.1, 1.2)	0.9 (0.4, 1.4)	0.4 (–0.05, 0.8)	1.0 (0.6, 1.4)	0.4 (0.02, 0.9)	0.5 (0.1, 1.0)
BW, kg	Men	68.2 (67.8, 68.6)	68.7 (68.3, 69.0)	69.0 (68.6, 69.3)	68.9 (68.6, 69.1)	68.8 (68.5, 69.1)	68.9 (68.5, 69.2)	68.9 (68.6, 69.3)
Difference in BW, kg		Ref	0.4 (–0.2, 1.1)	0.7 (0.1, 1.4)	0.6 (0.05, 1.2)	0.6 (–0.01, 1.2)	0.7 (0.004, 1.3)	0.7 (0.03, 1.4)
BW, kg	Women	58.4 (57.9, 58.9)	58.2 (57.8, 58.7)	58.0 (57.6, 58.4)	59.1 (58.9, 59.4)	60.0 (59.8, 60.3)	59.8 (59.5, 60.1)	59.9 (59.6, 60.2)
Difference in BW, kg		Ref	–0.2 (–1.0, 0.6)	–0.4 (–1.2, 0.4)	0.7 (0.03, 1.4)	1.6 (1.0, 2.3)	1.4 (0.7, 2.1)	1.5 (0.8, 2.2)

BMI, body mass index; BW, body weight.
P value for trend was tested by linear regression analyses after adjustment of age.
Data are expressed as means (95% confidence interval).

TABLE 4 | The prevalence of underweight, overweight and obesity in 50,192 Chinese aged participants from 2014 to 2020.

Sex	BMI category	Age	Year							P-trend
			2014	2015	2016	2017	2018	2019	2020	
Men (*n* = 25,505)	Underweight	65–69 y	1.5	1.2	1.3	1.0	1.0	1.3	0.7	0.12
		70–79 y	3.5	3.2	3.0	2.7	2.1	2.0	2.6	0.02
		≥ 80 y	4.9	4.5	5.4	5.6	4.9	5.5	5.1	0.39
	Overweight	65–69 y	45.1	42.2	43.0	43.4	45.1	45.3	41.8	0.87
		70–79 y	38.6	37.1	38.9	42.5	40.8	42.5	42.2	0.02
		≥ 80 y	32.4	31.8	29.7	29.0	35.6	35.8	40.3	0.06
	Obesity	65–69 y	4.7	4.8	5.1	5.6	6.4	5.1	6.3	0.06
		70–79 y	3.8	3.8	4.5	4.5	5.9	6.7	6.0	< 0.01
		≥ 80	3.7	4.7	4.2	4.7	3.2	6.4	5.8	0.16
Women (*n* = 24,687)	Underweight	65–69 y	2.8	1.8	1.9	1.8	2.3	1.7	1.6	0.12
		70–79 y	1.8	2.7	3.1	3.0	2.2	1.9	1.5	0.39
		≥ 80 y	5.3	6.1	3.7	5.3	3.4	4.6	4.0	0.18
	Overweight	65–69 y	38.3	36.4	34.3	38.5	39.3	38.4	38.3	0.37
		70–79 y	38.5	33.7	37.0	37.8	40.9	40.3	42.0	< 0.05
		≥ 80 y	36.0	27.9	33.6	34.4	35.1	36.9	38.7	0.14
	Obesity	65–69 y	6.7	7.2	5.0	8.3	7.5	7.6	9.0	0.13
		70–79 y	6.5	4.6	3.7	8.9	9.6	10.8	9.8	0.04
		≥ 80 y	3.3	4.1	4.1	7.5	9.6	8.8	6.6	< 0.05

World Health Organization (WHO) criteria was used to classify participants into four groups: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2), and obesity (BMI ≥ 30 kg/m^2).
P-values for trends were determined by linear regression after setting year as the continuous variable.

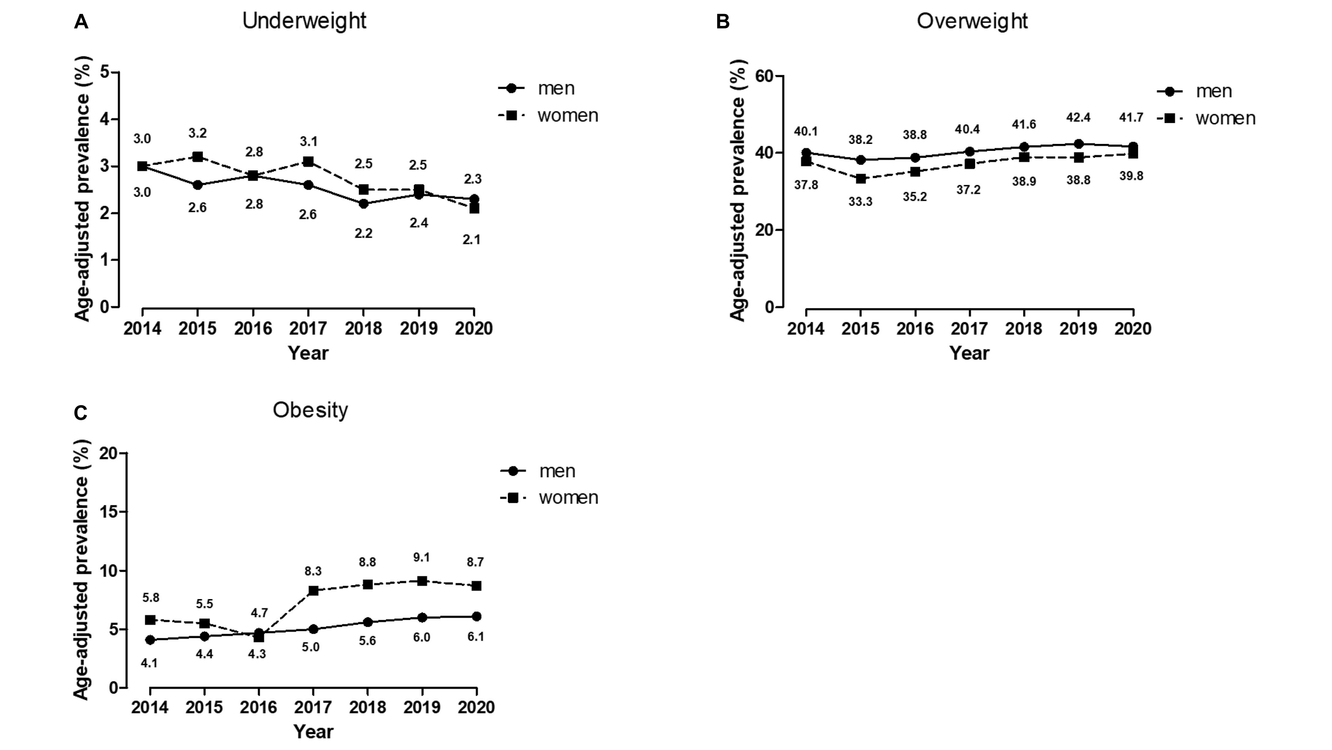

FIGURE 1 | Age-standardized prevalence of underweight, overweight and obesity in 50,192 Chinese aged participants from 2014 to 2020. The estimated prevalence was age-standardized to the 2020 census of the Shanghai Aged population by the direct method. **(A)** Age-adjusted prevalence of underweight; **(B)** Age-adjusted prevalence of overweight; **(C)** Age-adjusted prevalence of obesity.

In 2017, China have released the 13th Five-Year Plan for Healthy Aging, the first national policy, to promote healthy living among the older population (45). This was an important landmark, signaling healthy aging as a key priority in the national political agenda for health (46). Furthermore, the China National Nutrition Plan 2017–2030, has included "senior nutrition improvement action" as one of the major initiatives of the country (47), which included regularly monitoring and evaluating nutritional status of the elderly, providing dietary guidance and consultation for the elderly, and carrying out special nutritional interventions for the elderly with low body weight. Our findings are helpful in dealing with nutrition problems for the older population and designing evidence-based policies to reduce both underweight and overweight/obesity in the Chinese aged population.

Recommendations

Although further screening is needed to assess the longer-term trends and changing patterns, the present study findings highlight the pressing need for more targeted health policies to reduce further increases in obesity in Chinese aged population, with a gradual shift toward placing more emphasis on older women.

Strengthens and Limitations

Our study has several strengths, such as a large sample size, and reliable measurements by trained staff in each survey. However, some limitations should also be considered. First, this was a cross-sectional study, which could not identify cause-and-effect relationships. Second, measurements of body fatness were not available. Thus, we cannot distinguish whether these differences resulted from body fat or muscle mass changes or both, which might underestimated the prevalence of muscle loss (48). Finally, other factors that may lead to an increased or decreased risk of underweight and overweight, such as socioeconomic status (7, 21), tobacco use (49), dietary habits, and physical activity were missing.

CONCLUSION

Our results confirmed that BMI gradually increased from 2014 to 2020. The age-adjusted mean BMI increased by 0.3 kg/m^2 in older men, and 0.5 kg/m^2 in older women. The age- and sex-standardized prevalence of overweight and obesity significantly increased, especially in 70–79-year age group, while the prevalence of underweight decreased. The combination of a balanced-diet and physical exercise is needed to maintain optimal BMI range for aged population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YJ performed the analysis, interpreted the data, and drafted the manuscript. YJ, RX, XZ, ZC, and XG contributed to the conception and design of the study. WH contributed to the access of data. TX provided suggestions on the revision of statistical codes and supports on epidemiological insights. RX was the guarantor analyses of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the critical revision and approval to submit the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.923539/full#supplementary-material

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Patterns of Street Food Purchase in Cities From Central Asia

**Sofia Sousa[1,2,3], Inês Lança de Morais[4], Gabriela Albuquerque[1,2], Marcello Gelormini[4], Susana Casal[1,2,5], Olívia Pinho[3,5], Carla Motta[6], Albertino Damasceno[1,2,7,8], Pedro Moreira[1,2,3,9], João Breda[10], Nuno Lunet[1,2,7] and Patrícia Padrão[1,2,3]*

[1] EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal, [2] Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal, [3] Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto, Porto, Portugal, [4] Nutrition, Physical Activity and Obesity Programme, Division of Noncommunicable Diseases and Life-Course, World Health Organization (WHO) Regional Office for Europe, Copenhagen, Denmark, [5] LAQV/REQUIMTE, Laboratório de Bromatologia e Hidrologia, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal, [6] Departamento de Alimentação e Nutrição, Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA), Lisboa, Portugal, [7] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal, [8] Faculdade de Medicina, Universidade Eduardo Mondlane, Maputo, Mozambique, [9] Centro de Investigação em Atividade Física, Saúde e Lazer, Universidade do Porto, Porto, Portugal, [10] WHO Regional Office for Europe, Athens, Greece*

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***Correspondence:**
Patrícia Padrão
patriciapadrao@fcna.up.pt

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Street food makes a significant contribution to the diet of many dwellers in low- and middle-income countries and its trade is a well-developed activity in the central Asian region. However, data on its purchase and nutritional value is still scarce. This study aimed to describe street food purchasing patterns in central Asia, according to time and place of purchase. A multicentre cross-sectional study was conducted in 2016/2017 in the main urban areas of four central Asian countries: *Dushanbe* (Tajikistan), *Bishkek* (Kyrgyzstan), *Ashgabat* (Turkmenistan) and *Almaty* (Kazakhstan). Street food markets ($n = 34$) and vending sites ($n = 390$) were selected by random and systematic sampling procedures. Data on the purchased foods and beverages were collected by direct observation. Time and geographic location of the purchases was registered, and their nutritional composition was estimated. A total of 714 customers, who bought 852 foods, were observed. Customers' influx, buying rate and purchase of industrial food were higher in city centers compared to the outskirts (median: 4.0 vs. 2.0 customers/10 min, $p < 0.001$; 5.0 vs. 2.0 food items/10 min, $p < 0.001$; 36.2 vs. 28.7%, $p = 0.004$). Tea, coffee, bread and savory pastries were most frequently purchased in the early morning, bread, main dishes and savory pastries during lunchtime, and industrial products in the mid-morning and mid-afternoon periods. Energy and macronutrient density was highest at 11:00–12:00 and lowest at 09:00–10:00. Purchases were smaller but more energy-dense in city centers, and higher in saturated and *trans*-fat in the peripheries. This work provides an overview of the street food buying habits in these cities, which in turn reflect local food culture. These findings from the main urban areas of four low- and middle-income countries which are currently under nutrition transition can be useful when designing public health interventions customized to the specificities of these food environments and their customers.

Keywords: street food, ready-to-eat food, purchasing patterns, food choice, nutritional value, Central Asia, low- and middle-income countries, nutrition transition

INTRODUCTION

In the last few decades, most low- and middle-income countries (LMIC) have been experiencing rapid socioeconomic development, accompanied by a wide and abrupt increase in urban agglomerations and industrialization (1, 2). In central Asia, countries have undergone remarkable gross domestic product growth during the last decade, averaging around 5% per year (3), and urban population has grown from ∼25 million to more than 35.5 million people between 2000 and 2019, the latter representing almost half of the total central Asian population (4).

These major demographic and economic changes have led to marked lifestyle shifts, such as the growing participation of women in the workforce to the detriment of housework, and the increase in time spent working or commuting. This has hindered household food preparation and consumption, making away-from-home food sources, such as street-vended foods, to be seen by the urban dwellers as excellent alternatives for their everyday meals (5–8). Other factors such as the low cost, convenience and taste have strengthened street food's popularity, which is currently consumed everyday by millions of people worldwide (6). In cities from central Asia, street food trade is a well-developed activity, being often organized in typical markets called *bazaars*. Street food vending sites are common, reflecting the high cultural and dietary importance of street food in the region (9–12).

Frequent consumption of foods outside the home has been reported as a risk factor for overweight and obesity (13, 14), as well as higher energy and fat intake and lower micronutrient intake (15). In line with other LMIC (16), in urban areas from central Asia, street food has been reported as source of foods frequently rich in total fat, saturated and *trans* fatty acids, as well as sodium. Availability data showed that although local foods remain common, globalized ultra-processed food products such as industrial snacks and soft drinks are frequently available (9–12, 17–19). However, to the best of our knowledge, no systematic characterization of the purchasing patterns of street food in these settings is available. A recent scoping review also showed that, even though research on street food has been growing, its purchase and consumption are amongst the least studied topics (20). As such, the objective of this study was to describe the patterns of street food purchase in the main urban areas of four central Asian countries, Tajikistan, Kyrgyzstan, Turkmenistan and Kazakhstan, considering the food items bought and their nutritional composition, overall and according to time of the day and place of purchase. In this study, we go beyond the simple characterization of street food purchases and their nutritional value, by identifying where and when specific patterns of purchase emerge. With this approach, we hope to contribute to a more in-depth understanding of the street food buying practices in these cities (both in terms of meal context and city location), thus allowing the design of public health strategies customized not only to the reality of these food environments, but also to their customers' food habits.

MATERIALS AND METHODS

Overview

This study was implemented in the context of the FEEDCities project, which is based on a stepwise standardized characterization of the street food environment in cities from Central Asia and Eastern Europe. The general methodology of this research project is published elsewhere (21). For the purpose of this study, four cross-sectional evaluations of street food customers were conducted in the largest and most urbanized cities of Tajikistan, Kyrgyzstan, Turkmenistan and Kazakhstan (22), respectively *Dushanbe* (between April and May 2016), *Bishkek* (June and July 2016), *Ashgabat* (October 2016) and *Almaty* (August 2017).

Eligibility Criteria

Street food was defined by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), as "ready-to-eat foods and beverages prepared and/or sold by vendors or hawkers especially in the streets and other similar places" (23, 24). Eligible street food vending sites were those which sold street food in accordance to this definition, including both fixed and mobile units selling directly to the streets. As such, food establishments within four permanent walls or permanent storefront business not selling directly to the street, vending sites selling exclusively non-prepared fresh fruits, vegetables or other raw foods not ready-to-eat, such as fish or meat, or food stalls and carts that are part of permanent stores or licensed establishments, were excluded from the study.

Any customer approaching one selected street food vending site to buy ready-to-eat foods and/or beverages during a pre-specified time period was eligible for the study.

Sampling Procedure

In the four cities assessed, all public markets were identified ($n = 89$), in accordance to information provided by local authorities and collected during preliminary field visits, as described elsewhere (9–12, 17, 18). Ten markets were randomly selected in each city, except for *Ashgabat*, where four markets were selected by local authorities. To identify the study area in each city, buffers with a diameter of 500 m were drawn around the centroid of each selected market, that way covering the whole market and surrounding areas. Within each study area, all publicly accessible streets were canvassed by pairs of field researchers, who identified all street food vending sites eligible for the study.

Taking into account the density of vending sites encountered in each study area and the expected overall number of customers, a systematic selection of the vending sites was performed, in which one out of every ten (*Dushanbe*), one out of every four (*Bishkek* and *Almaty*) and all vending sites (*Ashgabat*) were selected for customer observation.

Each selected vending site was observed for a maximum period of 15 min to collect data on the street food items purchased. Each observation ended when four consecutive customers were observed, or whenever the maximum period was reached. When no customers were observed within the pre-specified period, field researchers moved on to the next selected vending site. Observations were performed on consecutive days of the week, and covering all businesses' working hours, from 08:00 to 17:00.

Data Collection

Data was collected by direct observation of each selected street food vending site. Observations were performed by local field researchers, located at enough distance not to disturb the vendors' regular activity or the customers' usual behavior.

Data was collected by two observers who, for each customer observed, independently registered the foods and/or beverages purchased and respective quantities. Prior to data collection, all field researchers were trained (including both theoretical, practical and field training) aiming at the improvement and standardization of observations.

Inter-observer concordance was evaluated using Cohen's kappa (K) with 95% confidence interval (95% CI), being high to very high, regarding the foods and/or beverages purchased (97.6% agreement, $K = 0.98$, 95% CI 0.97–0.99) and their quantities (95.3% agreement, $K = 0.94$, 95% CI 0.92–0.97), as detailed elsewhere (25). Disagreements on the foods and/or beverages purchased or their quantities were eliminated using a set of standardized criteria: (1) if the two observers registered two different foods and/or beverages, the conflicting items were checked for their availability on the corresponding vending site (if only one of the conflicting items was available, this observation was assumed; if the conflicting items were both available or not available, both observations were disregarded); (2) if the two observers registered the same food and/or beverage, but with different degrees of specificity, the broadest observation was assumed; (3) if the two observers registered a different number of foods and/or beverages for the same customer, the observation with the higher number of food items was assumed, unless the conflicting item(s) was(were) not available in the corresponding vending site; and (4) if the two observers registered the same food and/or beverage, but different quantities, the average quantity between the two observations was assumed.

Based on the WHO nutrient profile model (26) and considering similarities of nature and/or composition, the purchased foods and beverages were grouped into six sub-categories each: (1) savory pastries and snacks; (2) main dishes; (3) sweet pastries and confectionery; (4) bread; (5) sandwiches; (6) fruit; (7) tea and coffee; (8) soft drinks and juices; (9) traditional beverages (non-alcoholic); (10) alcoholic beverages; (11) milk; and (12) water. Foods and beverages were also classified as *homemade* (foods and beverages that were prepared and/or cooked at home or in the street, even if using industrial ingredients) or *industrial* (foods and beverages that were produced by the food industry and sold as such, with no further preparation).

For each vending site observed, Global Positioning System (GPS) coordinates were recorded, as well as time of beginning and end of observation. The selected markets were classified as central or peripheral, according to their distance (below or above 3 km, respectively) to a city center reference point, assigned in each setting taking into account information provided by the respective WHO Country Offices and local collaborating institutions. The duration of the observation was calculated for each vending site, as well as the customers' influx (which was computed as the number of customers observed per 10 min of observation) and the food items buying rate (number of foods and/or beverages purchased per 10 min of observation). Purchases were then categorized taking into account time of the day, on an hourly basis (i.e. [09:00–10:00], [10:00–11:00], etc.) and city location (city center vs. periphery).

Nutritional Composition Estimation

The nutritional composition of all purchased street foods and beverages was estimated, either using data from chemical analysis or using information provided by food labels, standardized recipes and food composition tables.

During the first step of the research project, which assessed street food availability, the most frequently available street foods and beverages in each city were documented (9–12, 17, 18). Taking this information into account, chemical analyses of the most common street foods were performed, as previously described in detail (9–12, 17, 18), and included macronutrients (protein, total fat and carbohydrates by difference), fatty acids (saturated, monounsaturated, polyunsaturated and *trans*), sodium and potassium, as well as energy calculated using the Atwater general factors, following validated and standardized methodology (27). In *Ashgabat*, exceptionally, the samples collected were not analyzed for protein and carbohydrates contents, those being estimated using food composition tables, standardized recipes or food labels, as described below.

For the foods and beverages which were not sampled and subjected to chemical analysis, nutritional composition was estimated using: (1) food labels of the brands most commonly available in each setting, in the case of industrial foods or beverages (e.g. chocolate, soft drinks); (2) standardized recipes from each city, in the case of prepared and/or cooked homemade foods or beverages; (3) food composition tables, namely the Food Composition Table for Pakistan (28) and the Turkish National Food Composition Database (29), in the case of *in natura* foods or beverages (e.g. fruits, nuts) or recipe ingredients. Energy, protein, carbohydrates and total fat were estimated for all these foods and beverages, as well as sodium for industrial and *in natura* foods. Sodium contents of homemade foods and beverages were not estimated, due to the great variation in the quantities of salt added during their preparation or cooking.

Among all the foods and beverages purchased ($n = 852$), the nutritional composition of 582 (68.3%) was estimated using data from chemical analysis, and the remaining ($n = 270$, 31.7%) using food labels, standardized recipes and food composition tables. The nutritional value of the street food purchases of each customer was then computed by summing up the estimated energy, macro- and micronutrients of all foods and beverages purchased by the same customer on a single occasion.

Statistical Analysis

Absolute and relative frequencies were used to describe the foods and beverages purchased. Customers' influx, food items buying rate and number of food items purchased per customer, as well as the nutritional composition of the purchases were described through median and percentiles 25 and 75. Pearson's Chi-squared test was used to compare the street food purchases throughout the day and by city location. Mann-Whitney's and Kruskal–Wallis tests were used to compare the customers' influx, food items buying rate and number of food items purchased per customer, as well as the nutritional composition of the purchases, either throughout the day or by city location, respectively. Differences were considered statistically significant when the critical level of significance (p) was less than 0.05. Statistical analysis was performed using *Stata*® version 15.0 (StataCorp., College Station, TX, USA).

RESULTS

A total of 390 street food vending sites were observed (71 in Tajikistan, 137 in Kyrgyzstan, 93 in Turkmenistan and 89 in Kazakhstan), corresponding to the completion of 4,769 min of observation. A total of 714 customers were observed, who bought 852 foods and beverages. In each vending site, a median of 2 customers were observed over a median period of 15 min.

The median customers' influx and food items buying rate varied across countries, being the lowest in Tajikistan (1.3 customers and 1.3 food items per 10 min of observation, respectively) and the highest in Turkmenistan (5.9 customers and 6.4 food items per 10 min of observation, respectively). The number of food items purchased by customer was similar in all countries, with a median of 1.0 (**Figure 1**). No customers were observed from 08:00 to 09:00 and from 16:00 to 17:00. Throughout the day, customers' influx and food items buying rate varied, being highest between 12:00 and 13:00 (median: 3.0 customers/10 min; 4.1 food items/10 min). The number of food items purchased by customer was constant (median of 1 in all hours of the day), although between 15:00 and 16:00, a higher proportion of customers (47.1%) purchased two or more foods and/or beverages (**Figure 2**). City centers showed higher customers' influx (4.0 vs. 2.0 customers/10 min, $p < 0.001$) and food items buying rate (5.0 vs 2.0 food items/10 min, $p < 0.001$) than the peripheries (**Figure 3**).

Purchase of foods was the highest between 12:00 and 13:00 (90.8%), whereas beverages were more frequently purchased in both the beginning (59.0%) and end of the day (52.9%). Between 15:00 and 16:00, it was observed a greater frequency of joint purchase of foods and beverages (35.3%). The purchase of foods was higher in the city center (86.8 vs. 74.2%, $p = 0.004$) while beverages were more frequently bought in the periphery (38.6 vs. 18.7%, $p < 0.001$; **Figure 4**). Purchase of homemade food items surpassed 80% from 9:00 to 10:00 and 15:00 to 16:00, while industrial products buying frequency was the highest between 10:00 and 11:00 (40.2%), and between 14:00 and 15:00 (38.8%). Customers purchasing industrial food items were significantly more frequent in the city center (36.2 vs. 28.7%, $p = 0.004$) (**Figure 5**). From all customers buying foods and beverages together ($n = 71$), more than half (59.2%) purchased both foods and beverages homemade (mostly savory pastries with coffee or tea) and one out of every three (35.2%) bought one or more homemade foods with one industrial beverage (mostly main dishes, sandwiches or savory pastries, plus soft drinks).

The distribution of groups of foods and beverages throughout the day and by city location is presented in **Table 1**. Among customers who bought foods, savory pastries and snacks were most frequently purchased from 09:00 to 11:00 and 15:00 to 16:00, main dishes between 11:00 and 13:00, sweets pastries and confectionery from 13:00 to 15:00, bread from 09:00 to 10:00 and 12:00 to 13:00, and sandwiches between 15:00 and 16:00. Among the purchases which included beverages, tea and coffee were most frequently purchased in the first time period, soft drinks and juices between 15:00 and 16:00, and water from 12:00 to 14:00. Bread and sweet pastries and confectionery were more commonly bought in the city center, while the purchases of savory pastries and snacks, as well as main dishes, were higher in the periphery.

The observed customers purchased a median amount of 120 g of foods and 200 g of beverages. **Table 2** presents the estimated nutritional composition of the purchases observed, including foods and beverages, throughout the day and by city location. Between 11:00 and 12:00, purchases were more energy-dense and richer in protein, carbohydrates and fat, the opposite being observed from 09:00 to 10:00. Saturated and *trans* fatty acids contents were both highest between 13:00 and 14:00. Purchases made in the city center were significantly more energy-dense and richer in all macronutrients, while in the periphery purchases showed higher saturated and *trans* fatty acids contents. The temporal and spatial distribution of the estimated nutritional composition of the street food purchases observed, without beverages, is presented in **Supplementary Table 1**.

DISCUSSION

Street food purchase in these four central Asian urban centers was frequent and reached its maximum around lunchtime. Purchases consisted of a diverse set of both local and westernized foods and beverages, and varied throughout the day and by city location. Tea, coffee, bread and savory pastries were frequently purchased in the early morning; bread, main dishes and savory pastries at lunch; and industrial snacks (both savory and sweet) and beverages (mainly soft drinks and juices) were mostly bought in the mid-morning and mid-afternoon periods. Purchase of industrial foods and beverages, sweet pastries and confectionery and bread was more frequent in the city center, while main dishes, savory pastries and snacks were mostly bought in the periphery. Energy and macronutrient density was highest around lunchtime and lowest in the early morning. Purchases were smaller but more energy-dense in city centers, and higher in SFA and TFA in the peripheries.

Customers' influx and food items buying rate was the highest between 12:00 and 13:00, which was also when the frequency of purchase of foods reached its peak. Nine out of 10 customers purchased foods during this time period, mostly bread, main dishes and savory pastries, suggesting that these food groups may

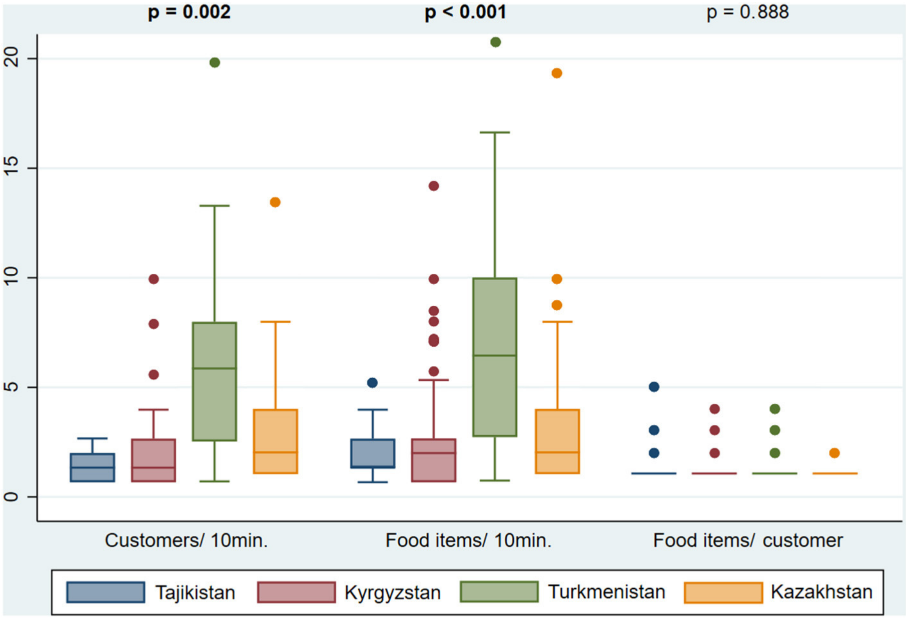

FIGURE 1 | Customers' influx (customers/10 min), food items buying rate (food items/10 min) and number of food items purchased per customer (food items/ customer), in street food vending sites observed in *Dushanbe* (Tajikistan), *Bishkek* (Kyrgyzstan), *Ashgabat* (Turkmenistan) and *Almaty* (Kazakhstan). Values in bold represent statistically significant differences according to Kruskal–Wallis test with a significance level of 0.05.

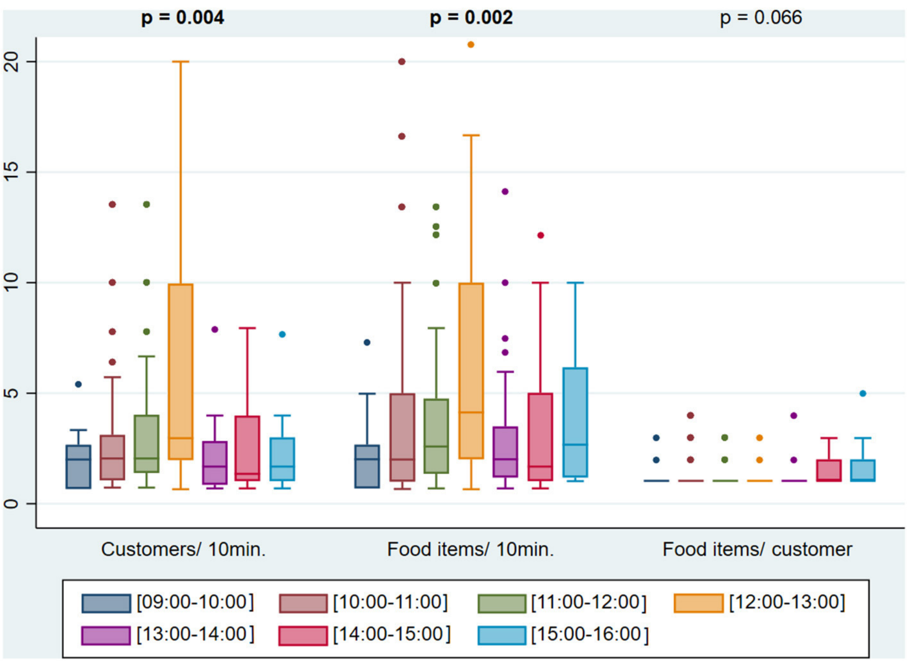

FIGURE 2 | Customers' influx (customers/10 min), food items buying rate (food items/10 min) and number of food items purchased per customer (food items/ customer) throughout the day. Values in bold represent statistically significant differences according to Kruskal–Wallis test with a significance level of 0.05.

be frequently consumed by street food customers at lunch. This is in line with evidence showing that street food is often consumed as a substitute for home-cooked main meals (6, 30), and may be closely associated with changes in time allocation patterns occurring in Asian LMIC, toward an increasingly accelerated and much more work-oriented daily life (31, 32). One important aspect of the urban lifestyle is the increase in the number of time-limited consumers, which in turn increases the demand for

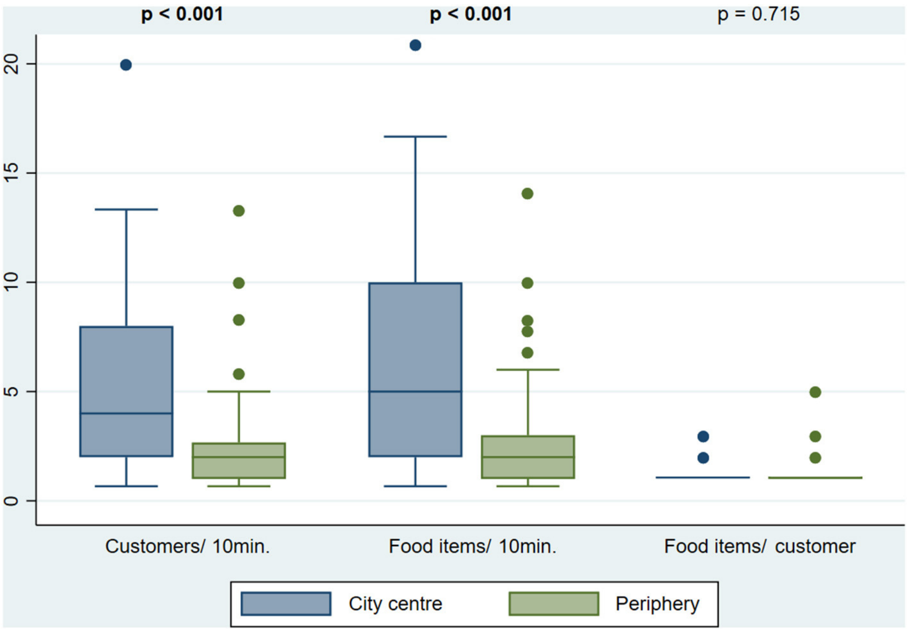

FIGURE 3 | Customers' influx (customers/10 min), food items buying rate (food items/10 min) and number of food items purchased per customer (food items/customer) by city location. Values in bold represent statistically significant differences according to Mann-Whitney's test with a significance level of 0.05.

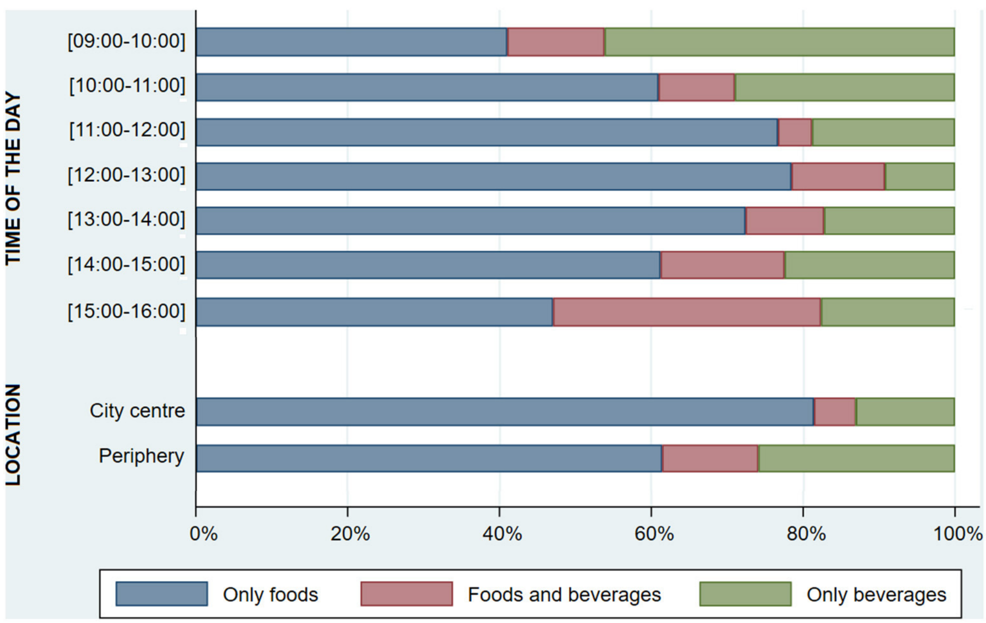

FIGURE 4 | Proportion of customers purchasing foods and/or beverages, throughout the day and by city location ($n = 714$).

convenience foods (31). Besides convenience, street food also offers affordable and fulfilling food options, gaining momentum in LMIC over more formal alternatives such as restaurants (6, 8, 16, 30). Customers' influx and food items buying rate was also higher in the city centers when compared to their outskirts, which was expected. These urban centers, similarly to other LMIC, have undergone abrupt growth and development, with an accelerated construction of infrastructures and increased concentration of companies, services and people. As a consequence, a large increase in the size of the labor force has occurred, especially in these city centers (2, 33). As reported in other LMIC, street food customers are usually urban workers but rural or peri-urban

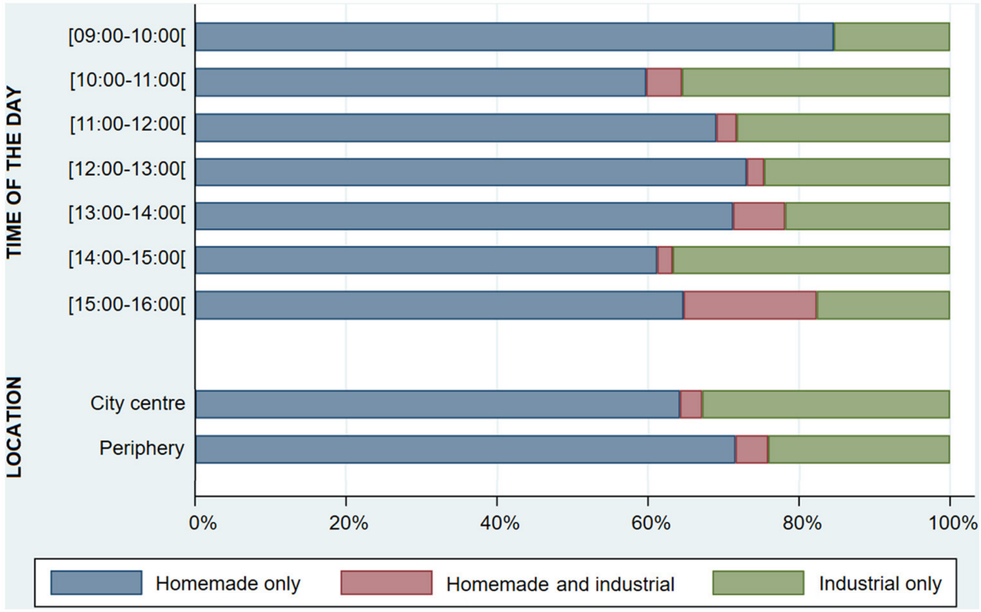

FIGURE 5 | Proportion of customers purchasing homemade and/or industrial food items, throughout the day and by city location ($n = 714$).

dwellers, who often need to make long commutes between house and the workplace on a daily basis (34, 35), and therefore have little availability to travel back home for their meals during the day. Accordingly, street food sites are often located near people gathering spaces, such as working places or main public transportation stations (6, 36), where it is expected that there will be a greater influx of people and higher demand for these ready-to-eat food options.

Frequency of purchase of industrial food products was highest in the periods between 10:00 and 11:00, and between 14:00 and 15:00. These acquisitions were mostly constituted of savory snacks, sweet pastries and confectionery, as well as soft drinks and juices. This suggests that these industrial foods and beverages may be commonly preferred by the street food customers as mid-morning or mid-afternoon snacks. Sweet pastries and confectionery were most frequently purchased between 13:00 and 15:00 which may as well correspond to an after lunch time period, suggesting that some of these foods may have also been consumed in the context of a dessert. However, we cannot exclude the possibility of sweet pastries being consumed as the main meal, since these foods are fulfilling and have a low cost per calorie (37), and in contexts of economic restriction, they may be seen by consumers as a good option to supply energy needs. Furthermore, food-based dietary guidelines and nutrition education programmes are still lacking in these countries, so there may be a lack of knowledge about which foods are suitable to consume at different meals throughout the day. Soft drinks and juices were less purchased between 12:00 and 14:00, and during this time period mainly tea and water were bought. This is consistent with the types of beverages that are traditionally consumed during lunchtime (38), and may indicate a lower preference of street food consumers for soft drinks during this meal.

Frequency of purchase of industrial foods was also higher in the city centers, and was mostly comprised of sweet pastries and confectionery (mainly candies, ice-cream and chocolates). This can either be explained by spatial variations on street food buying habits, or be a reflection of these foods' availability on central vs. peripheral vending sites. According to information from the first step of the FEEDcities project, there was a similar proportion of vending sites selling sweet pastries and confectionery in central and peripheral markets (unpublished data), which indicates that in city centers there seems to be a greater preference of street food consumers for these westernized foods. Industrial beverages, such as soft drinks and juices, were equally and frequently bought in both city subareas, suggesting that their consumption might be an already widely implemented habit. The acquisition of those ultra-processed sweetened beverages occurred at all hours of the day, almost always surpassing that of other common drinks, such as water, milk and non-alcoholic traditional beverages, the latter mostly comprised of fermented milk-based drinks (e.g. *kefir*, *ayran*, *chalap*). These results make us hypothesize that soft drinks and industrialized juices may be consumed as a substitute for others with a potentially healthier profile. Our results are in line with the increasing availability and consumption of ultra-processed foods and beverages that is happening in the region, arising from quick economic and technological development, as well as globalization, which have been transforming food systems in Asian LMIC (39, 40). The consumption of ultra-processed foods and beverages have been increasingly recognized as a risk factor for a set of adverse health effects, including overweight, obesity, cancer, type II diabetes, cardiovascular diseases and all-cause mortality (41, 42), being also associated to lower dietary quality by providing excessive amounts of fat, sugar, and/or sodium in an energy-dense and nutrient-poor food matrix (43). This is particularly concerning since excess weight, as well as

TABLE 1 | Distribution of the street food purchases throughout the day and by city location, by food and beverage groups.

	N^a	Savory pastries and snacks	Main dishes	Sweet pastries and confectionery	Bread	Sandwiches	Fruit	N^b	Tea and coffee	Soft drinks and juices	Non-alcoholic traditional beverages[c]	Water	Alcoholic beverages[d]	Milk
		n (%)							*n* (%)					
Time of the day														
[09:00–10:00]	21	11 (52.4)	2 (9.5)	1 (4.8)	6 (28.6)	2 (9.5)	0 (0.0)	23	16 (69.6)	4 (17.4)	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)
[10:00–11:00]	120	54 (45.0)	23 (19.2)	25 (20.8)	13 (10.8)	10 (8.3)	2 (1.7)	66	25 (37.9)	24 (36.4)	5 (7.6)	11 (16.7)	2 (3.0)	1 (1.5)
[11:00–12:00]	181	48 (26.5)	52 (28.7)	47 (26.0)	20 (11.0)	18 (9.9)	3 (1.7)	52	9 (17.3)	20 (38.5)	14 (26.9)	3 (5.8)	6 (11.5)	0 (0.0)
[12:00–13:00]	118	23 (19.5)	35 (29.7)	20 (16.9)	39 (33.1)	4 (3.4)	0 (0.0)	28	14 (50.0)	4 (14.3)	4 (14.3)	6 (21.4)	0 (0.0)	0 (0.0)
[13:00–14:00]	72	15 (20.8)	12 (16.7)	22 (30.6)	15 (20.8)	18 (25.0)	2 (2.8)	24	8 (33.3)	3 (12.5)	5 (20.8)	5 (20.8)	3 (12.5)	0 (0.0)
[14:00–15:00]	38	8 (21.1)	9 (23.7)	13 (34.2)	9 (23.7)	1 (2.6)	1 (2.6)	19	9 (47.4)	7 (36.8)	2 (10.5)	0 (0.0)	0 (0.0)	2 (10.5)
[15:00–16:00]	14	7 (50.0)	3 (21.4)	0 (0.0)	0 (0.0)	4 (28.6)	0 (0.0)	9	0 (0.0)	8 (88.9)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
p-**Value**		**<0.001**	**0.007**	**0.010**	**<0.001**	**0.027**	0.720		**<0.001**	**<0.001**	0.080	**0.020**	0.076	**0.032**
City location														
City center	237	47 (19.8)	42 (17.7)	76 (32.1)	58 (24.5)	21 (8.9)	5 (2.1)	51	17 (33.3)	18 (35.3)	7 (13.7)	8 (15.7)	1 (2.0)	2 (3.9)
Periphery	327	119 (36.4)	94 (28.8)	52 (15.9)	44 (13.5)	26 (8.0)	3 (0.9)	170	64 (37.6)	52 (30.6)	26 (15.3)	17 (10.0)	11 (6.5)	1 (0.6)
p-**Value**		**<0.001**	**0.025**	**0.001**	**0.025**	0.854	0.809		0.614	0.611	0.865	0.538	0.625	0.718

Values in bold represent statistically significant differences according to Pearson's Chi-squared test with a significance level of 0.05.

The proportions presented are relative to the number of customers purchasing foods (in the case of food groups) or beverages (in the case of beverage groups) in each time period or city location.

[a]*Number of customers purchasing foods (n = 564).*

[b]*Number of customers purchasing beverages (n = 221).*

[c]*Non-alcoholic traditional beverages included ayran (dairy-based fermented beverage made from sheep's milk), chalap (beverage made from fermented milk, salt and carbonated water;), dugob (fermented beverage made with sour milk or buttermilk), kefir (fermented milk drink prepared by inoculating cow, goat or sheep milk with kefir grains), maksym (fermented beverage made from grain, usually malt), tamshan (mix of maksym and chalap), kozhe (cold drink made by boiling rice, millet or pearl barley with a mixture of dairy products such as ayran or kefir) and yogurt.*

[d]*Alcoholic beverages included beer, vodka and some traditional beverages with a low alcohol content, such as kvass (a fermented beverage made from rye bread), bozo (a fermented beverage made from millet) and kymyz (a fermented product made from mare's milk).*

TABLE 2 | Estimated nutritional composition of the street food purchases observed (foods and beverages combined), throughout the day and by city location (n = 714).

	Amount purchased	Energy density	Protein	Carbohydrates	Total fat	SFA	MUFA	PUFA	TFA	Sodium	Potassium
	g	kcal/100 g	g/100 g	g/100 g	g/100 g	g/100 g of fat	g/100 g of fat	g/100 g of fat	g/100 g of fat	mg/ 100 g	mg/ 100 g
Time of the day											
[09:00–10:00]	200 (135–200)	88 (16–314)	2.5 (0.0–11.7)	15.6 (4.0–33.1)	1.0 (0.0–9.5)	34.1 (20.7–42.9)	27.1 (25.5–32.2)	35.2 (19.4–49.7)	1.98 (1.65–5.46)	500 (329–599)	109 (51–144)
[10:00–11:00]	200 (100–350)	228 (48–557)	6.3 (0.8–17.5)	26.0 (10.0–79.0)	6.2 (0.3–18.7)	36.0 (19.4–45.3)	28.8 (26.2–33.6)	29.4 (18.5–49.6)	1.94 (1.19–2.59)	597 (356–1,136)	309 (151–529)
[11:00–12:00]	200 (96–265)	310 (126–585)	9.1 (4.3–17.0)	45.1 (13.5–70.5)	10.0 (2.2–20.1)	35.5 (20.7–46.5)	29.3 (26.2–33.6)	34.5 (18.5–49.3)	1.67 (0.95–3.65)	490 (348–1,136)	279 (145–454)
[12:00–13:00]	120 (100–286)	286 (128–404)	8.5 (3.9–11.0)	40.6 (16.7–56.8)	4.5 (1.7–15.3)	22.3 (15.8–41.0)	26.6 (18.0–32.1)	49.4 (19.4–66.3)	1.08 (0.67–2.68)	467 (394–917)	170 (150–443)
[13:00–14:00]	150 (120–278)	233 (130–329)	9.0 (3.9–12.5)	33.3 (12.9–57.6)	2.5 (1.5–13.2)	38.6 (19.4–60.3)	27.3 (23.9–29.0)	24.9 (7.8–51.9)	3.33 (0.67–5.36)	472 (141–620)	166 (136–303)
[14:00–15:00]	156 (96–300)	274 (89–522)	5.6 (2.5–10.6)	42.1 (12.0–65.1)	7.7 (0.3–20.9)	31.1 (21.8–39.6)	28.3 (24.1-–33.0)	32.0 (18.0–52.3)	2.50 (1.08–7.57)	497 (402–1,041)	244 (121–446)
[15:00–16:00]	265 (172-–494)	233 (117–286)	4.3 (2.7–8.5)	27.9 (17.3–40.9)	10.1 (4.0–13.4)	32.1 (23.1–37.5)	27.7 (24.7–31.8)	37.5 (28.6–51.1)	1.39 (1.08–2.14)	484 (197–1,264)	227 (122–461)
p-Value	0.458	**0.001**	**0.011**	**0.008**	**<0.001**	**0.008**	**<0.001**	**0.002**	**<0.001**	0.256	**<0.001**
City location											
City center	120 (96–265)	308 (206–552)	9.1 (4.0–17.1)	56.8 (20.6–80.2)	10.0 (1.7–20.1)	27.6 (19.4–41.6)	27.8 (24.0–32.0)	37.7 (18.5–52.9)	1.20 (0.81–2.15)	484 (435–1,042)	305 (150–507)
Periphery	200 (117–306)	216 (77–419)	6.6 (2.4–12.3)	26.0 (10.0–57.6)	4.6 (0.6–14.1)	33.9 (20.4–42.9)	27.9 (25.5–32.9)	34.5 (18.5-–51.1)	2.25 (1.29–5.46)	490 (294–980)	205 (125–402)
p-Value	**<0.001**	**<0.001**	**0.003**	**<0.001**	**<0.001**	**0.005**	0.055	0.094	**<0.001**	0.254	**<0.001**

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TFA, trans fatty acids.
All values are presented as median (P25–75). Values in bold represent statistically significant differences according to Kruskal–Wallis (throughout the day) and Mann-Whitney's tests (by city location) with a significance level of 0.05.

mortality and morbidity from non-communicable diseases, have been increasing during the last decades in central Asia. According to data from the Global Nutrition Report 2016, in this region overweight affected almost half of the adult population (49.8% of women and 49.2% of men) (44). In 2019, non-communicable diseases were responsible for approximately 84.7% of total deaths and 72.9% of total disability-adjusted life years in the region (45).

The highest purchase of homemade foods and beverages was observed between 09:00 and 10:00, indicating a preference by street food customers for home-like food options in the context of a breakfast. Nearly half of customers purchasing foods bought savory pastries during this time period, although they are usually consumed at any time of the day (38), which is consistent with our results. Bread, tea and coffee are also purchased at almost all hours of the day, but mainly between 09:00 and 10:00, and 12:00 and 13:00. These food items are traditionally consumed in the context of breakfast, or as part of lunch (38), our results indicate that this habit seems to remain amongst the street food consumers of these cities. Purchase of sandwiches was less common, occurring mostly in the afternoon (in the periods from 13:00 to 14:00 and from 15:00 to 16:00). Although their consumption in the region is not unusual (38), sandwiches can be potentially easier to prepare at home, and transported without losing quality, which may explain in part the lower purchase. On the other hand, the time periods in which there was a higher purchase of sandwiches suggest that this type of foods may be consumed by street food customers mainly at lunch as a main course [as reported elsewhere (17)] or as an afternoon snack. The sandwiches bought were most frequently filled with cheese, sausage or meat [e.g. *shawarma* (kebab), hamburger, hot-dog]. Similarly, savory pastries and main dishes were very often meat-based: the most frequently purchased savory pastries were *sambusa*, *piroshky* and *chebureki*, which are all traditional pastries, usually fried or baked and filled with meat; whereas the most commonly bought main dishes were *plov* (rice cooked in a seasoned broth with a mixture of spices, usually with meat and vegetables) and *shashlik* (skewered grilled cubes of meat, alone or with alternating pieces of meat, fat and vegetables). This reflects the importance of meat in this region's gastronomy, as it can be present in any meal and it is the primary source of protein in central Asian diets (38).

Fruit was the least frequently bought street food in all cities studied. This may be a direct reflection of the low ready-to-eat fruit availability that was found in the selected street food vending sites, which ranged from 1.0% in *Almaty* to 4.5% in *Dushanbe* (9–12, 17, 18). The Global Burden of Disease Study (46) and the EAT-Lancet Commission (47) provided targets for fruit consumption, at 200 and 250 g of fruit per day, respectively. In Central Asia, data from the FAOSTAT food balances show that fruit supply has been consistently rising throughout the years, and in 2018 it reached 72.61 kg/capita/year (48), which corresponds to approximately 199 g/capita/day. Since fruit supply do not correspond directly to actual consumption, due to factors such as edible portions and food waste losses, these values indicate that overall consumption of fruit may still be inadequate. However, the growth in fruit availability in the region also suggests that it may be possible to reach these consumption targets in the near future. A study conducted in former Soviet Union countries (including Kyrgyzstan and Kazakhstan) found a positive correlation between the number of shops selling fruits and vegetables and their consumption (49). Improving access to fruits and vegetables by increasing their availability in the streets have also showed to have positive results in the consumption of these foods (49, 50). As such, there seems to be a window of opportunity to raise fruit consumption in these street food contexts through availability policies.

Regarding the nutritional composition of the purchases, the highest energy and macronutrient density was observed between 11:00 and 12:00, mostly due to a high level of purchase of main dishes and energy-dense sweets and savory pastries and snacks. On the contrary, purchases were poorer in energy and macronutrients from 09:00 to 10:00, which was also when the highest proportion of customers bought beverages, most of them with a very low nutritional value. Saturated fatty acids were the highest contributors to total fat in almost all hours of the day, reaching its highest content in purchases made between 13:00 and 14:00. *Trans*-fat was also high, and above the limit of 2 g/100 g of total fat (51, 52) between 13:00 and 15:00. These results can be explained by a high acquisition of sweets pastries and confectionery during these time periods. Some of these foods, particularly wafers, chocolate and ice-cream, were identified as rich sources of both saturated and *trans*-fat in these street food environments (9–12, 17, 18), which was particularly concerning due to their proximity to schools, as observed *in loco*. In the city centers, purchases were smaller but more energy-dense; however, in the periphery purchases had higher proportions of saturated and *trans*-fat, mostly due to the high percentage of customers buying savory pastries and snacks, as well as main dishes, some of them also providing high contents of those fatty acids (9–12, 17, 18).

Limitations of the present study should be discussed. We were unable to perceive purchasing variations throughout the week, or between week days and weekends. Although observation efforts comprised all days of the week (from Monday to Sunday), most street food markets were assessed during one or two consecutive days, due to logistical reasons. Future work could eliminate this limitation by assessing each market during a whole week. The fact that the observations were made during all days of the week was, nevertheless, an asset for this work, because it allowed us to ensure that variability over the 7 days of the week was covered when analyzing the patterns of purchase either throughout the day or by city location. Another limitation was that time of purchase may not directly mean time of consumption. However, all foods and beverages were ready-to-eat, purchased in small quantities and mostly unpackaged, suggesting that these purchases were made mostly for immediate consumption. Purchases including foods or beverages not ready-to-eat were not included in this study, thus eliminating purchases intended for household consumption.

To our knowledge, this is the first study describing street food purchasing patterns in cities from this region. The present results provide an overview of the street food buying habits in these cities, which may indirectly reflect consumption habits. Among the strengths of this study, the data collection through direct observation of customers by trained researchers instead of face to face interviews should be underlined, since it allowed us to minimize behavior alterations and social approval bias (53). We also highlight the high level of concordance between observers regarding the street food purchases. This reflects an underlying work of rigorous training, standardization of procedures and constant supervision, and resulted in a high reliability of these observational data. Finally, although generalizability of our results is very limited due to local gastronomic specificities, the FEEDCities standardized methodology (21) allows for data comparability among different cities, countries or regions.

CONCLUSIONS

In conclusion, street food purchases in *Dushanbe* (Tajikistan), *Bishkek* (Kyrgyzstan), *Ashgabat* (Turkmenistan) and *Almaty* (Kazakhstan) varied widely across time and space, showing higher rates in city centers and during lunch. Different types of foods and beverages were bought at different frequencies throughout the day and by city location, reflecting specific patterns of purchase. The present study is the first to report on spatial and temporal distributions of street food purchases, that way contributing to a better understanding of the street food buying habits in these settings, which should be considered when designing public health strategies and defining targets of action more specific to the reality of these food environments, their customers and their gastronomic identity. Further research on the prevalence, frequency and determinants of street food consumption by these populations, would also be an important step in future work.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Institute of Public Health of the University of Porto. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MG, PM, JB, NL, and PP designed the study. GA, IL, and MG supervised the study implementation and data collection. OP and SC were responsible for the laboratorial analyses of the food samples collected in Tajikistan, Kyrgyzstan and Kazakhstan. CM coordinated the laboratorial analyses in Turkmenistan. SS, NL, and PP performed the analysis and interpretation of the results. SS drafted the first version of the manuscript. All authors critically revised the manuscript and gave their final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.925771/full#supplementary-material

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Westernized and Diverse Dietary Patterns Are Associated With Overweight-Obesity and Abdominal Obesity in Mexican Adult Men

Sonia Rodríguez-Ramírez[1], Brenda Martinez-Tapia[2], Dinorah González-Castell[1], Lucía Cuevas-Nasu[2] and Teresa Shamah-Levy[2]*

[1] Center for Research on Nutrition and Health, National Institute of Public Health, Cuernavaca, Mexico, [2] Center for Research on Evaluation and Surveys, National Institute of Public Health, Cuernavaca, Mexico

Introduction: The prevalence of overweight and obesity in Mexican adults is very high. To identify the dietary characteristics related with this disorder is necessary to design intervention. The objective was to analyze the association between dietary patterns and obesity in Mexican adults.

Materials and Methods: This is a cross-sectional study carried out in Mexican adults (20–59 years old) participating in the Halfway National Health and Nutrition Survey 2016. Participants ($n = 5,735$) were classified as having normal weight, overweight-obesity and by their abdominal circumference as having abdominal obesity or not. With information from a 7-day food frequency questionnaire, we used a K-means cluster analysis to derive dietary patterns and calculated a healthy diet indicator to evaluate quality. The association between dietary patterns and overweight-obesity and abdominal obesity was assessed with Poisson regression models adjusted by some characteristics.

Results: We identified a Rural pattern characterized by tortilla, legumes and egg consumption; a Diverse pattern, characterized by fruits, meat and poultry, vegetables, and dairy beverages, and desserts; and a Westernized pattern, characterized by sweetened non-dairy beverages, fast food, bakery and cookies, candies and salty snacks. In men, Westernized pattern was associated with overweight-obesity (PR = 1.11, 95% CI 0.97–1.27), and abdominal obesity (PR = 1.15, 95% CI 1.00–1.33), the Diverse pattern was associated with overweight-obesity (PR = 1.18, 95% CI 1.00–1.38), and abdominal obesity (PR = 1.27, 95% CI 1.07–1.50), compared with the Rural pattern. In women, these dietary patterns were not associated with obesity.

Discussion: Westernized and Diverse patterns are associated with overweight and obesity and abdominal obesity in men. Gender-specific recommendations and surveillance are necessary in the Mexican adult population.

Keywords: adult population, dietary patterns, cluster analysis, obesity, abdominal obesity, Mexico, gender difference

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Sameer Dhingra, National Institute of Pharmaceutical Education and Research, India

***Correspondence:**
Brenda Martinez-Tapia
ciee18@insp.mx

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INTRODUCTION

According to national estimates, the prevalence of overweight and obesity has increased in Mexico over the past decades. The increase was more pronounced between 2000 and 2006, compared to the 2006–2012 period (1). In 2016, the prevalence in adult population rose to 72.5% (2) and reached 75.2% (3) in 2018.

This increase has been accompanied by non-communicable chronic diseases as diabetes and hypertension. For instance, in 2016, the prevalence of type 2 diabetes was 9.4% (previously diagnosed) (4) and 25.5% for hypertension. Of those with hypertension, 40% did not know they had the condition (5). Furthermore, there is evidence that increase of body mass index is associated with increased rates of type 2 diabetes, pre-diabetes, and hypertension in Mexican population (6).

The relationship between diet and obesity has been well-established in the literature. Studies on the dietary factors associated with excess weight and obesity conducted in the past decades focused on specific dietary components such as macronutrients and fiber (7). However, foods are consumed in complex combinations that can have synergistic or antagonistic effects and it is difficult to isolate the impact of individual foods and nutrients (8).

Overweight and obesity are caused by the interaction between genetics, environment, and human behavior. When energy intake exceeds energy expenditure, adipose tissue accumulates, and can eventually lead to obesity. Furthermore, the evidence show that dietary patterns characterized by high carbohydrate from refined grains are associated with obesity due to high glycemic index carbohydrates causes rapid changes in blood glucose and insulin levels, and sugar causes addictive cravings, glucose, and insulin signal the midbrain limbic system to change dopamine levels triggering inducement of food addiction (9).

To address these issues, several authors have proposed to study overall dietary patterns by considering how foods and nutrients are consumed together. The association between dietary patterns and obesity has been investigated in various studies (9–12), showing an association between dietary patterns characterized mainly by foods high in fat, meat, dairy, and processed foods and obesity. Likewise, certain food groups have been shown to have a protective effect against obesity such as fruits, vegetables, and fish (11).

Many studies have analyzed gender differences on the association between dietary patterns and disease risk, founding inconsistent results (13–15). In Mexico, there are few studies that have explored the relationship between dietary patterns and obesity by gender (16–19). For example, a study carried out in adult (20–59 years old) participants of the National Health and Nutrition Survey 2006, described three dietary patterns and found that individuals who consumed what they called a traditional dietary pattern based on maize and maize foods, beans and legumes, had lower Body Mass Index (BMI), and higher physical activity than the other two patterns (19).

Due to the sustained increase in the prevalence of obesity in Mexico, it becomes relevant to identify the characteristics of the dietary pattern that increase the possibility to present obesity in the different genders. Therefore, the objective of this study was to analyze the association of dietary patterns and overweight and obesity and abdominal obesity in Mexican adult (20–59 years old) participants from the Halfway National Health and Nutrition Survey 2016 (ENSANUT MC-2016 by its acronym in Spanish).

MATERIALS AND METHODS

Study Population

This is a cross-sectional study from the ENSANUT MC-2016, which is a probabilistic, multistage, stratified survey that has national, regional and urban/rural area representativeness. Data collection was performed from May to October 2016. A detailed description of the design and sampling procedures has been published by Romero-Martínez et al. (20).

Dietary Information

The dietary data was obtained from a random subsample of the adult population aged 20–59 years old ($n = 6{,}196$).

Trained personnel administered a 7-day food frequency semi quantitative questionnaire (FFQ), which included information from 140 foods and beverages. This questionnaire was previously validated for energy and nutrient intake in adult population (21). Through days, times per day, portion size, and number of portions consumed, consumption was estimated in grams. Data of consumption $>$ 4 standard deviations (SD) above the mean by gender, area and region for each food or beverage were considered implausible and the mean consumption was imputed (22). Participants with $\geq$7 foods and beverages with imputed consumption were excluded from the analysis ($n = 45$). Afterwards, energy intake was estimated through a nutrient database compiled by the INSP [National Public Health Institute 2013, Database on food nutritional value, compiled by Instituto Nacional de Salud Publica (Unpublished)[1]].

Energy requirement predicted (pER) was estimated through the Institute of Medicine equations (23) and the Mifflin-St Jeor equation was used to estimate resting metabolic rate (24). Participants who had a ratio of intake/energy requirement (EI/pER) $>$3 SD above the mean by sex were excluded ($n = 54$), as well as those with energy intake under half of their resting metabolic rate ($n = 165$).

We classified food and beverages in 25 groups according to their nutritional characteristics and cooking procedures, excluding plain water: (1) Dairy sweetened beverages, (2) Dairy non-sweetened beverages, (3) Sweetened non-dairy beverages, (4) Non-sweetened, non-dairy beverages, (5) Fruits, (6) Vegetables, (7) Non-beverage dairy products, (8) Legumes, (9) Cereal based salty dishes, (10) Corn based salty dishes, (11) Fast food, (12) Egg, (13) Meat and poultry, (14) Processed meat, (15) Bakery and cookies, (16) Candies, (17) Dessert, (18) Salty snacks, (19) Seeds, (20) Added fats, (21) Tortilla, (22) Soups, (23) Ready to eat cereals, (24) Bread, and (25) Potatoes (Example of the food included in each group are in **Supplementary Table 1**).

[1]Instituto Nacional de Salud Publica. Compilación de bases de datos de valor nutritivo de los alimentos. [National Institute of Public Health. Food Composition Table]. Cuernavaca: National. Institute of Public Health (Unpublished).

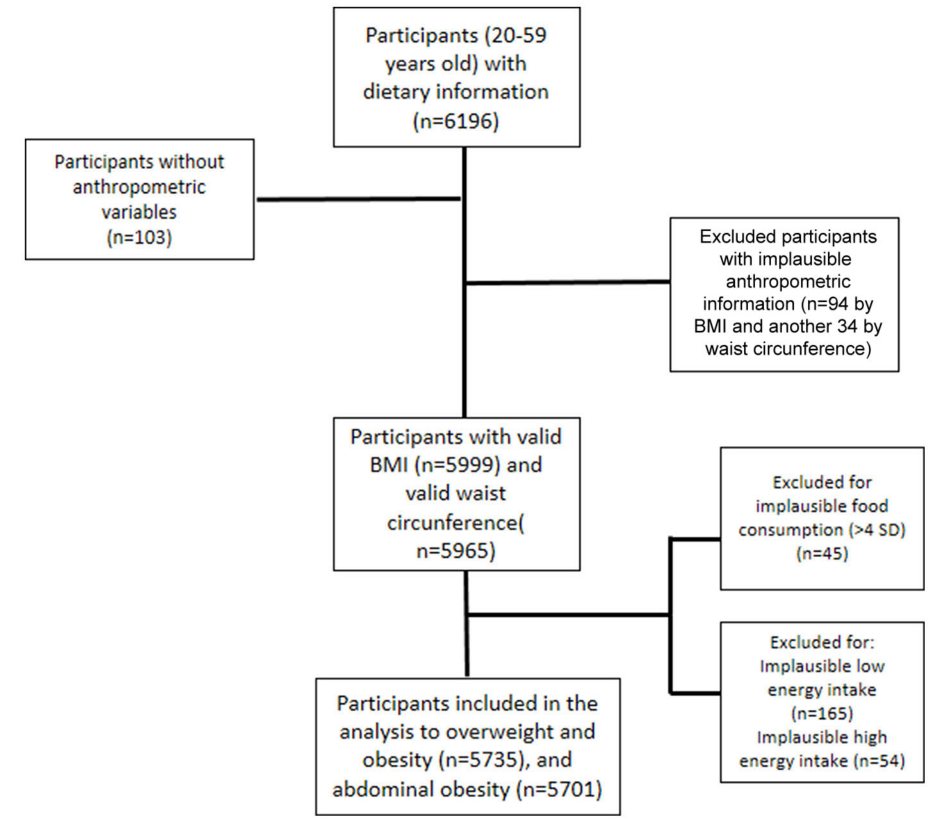

FIGURE 1 | Flow chart of sample size of Mexican adults, National Health and Nutrition Survey 2016.

Dietary Patterns

The energy contribution (%) by each food group was estimated and a standardized transformation from the contribution variables was made by subtracting the mean and dividing by the SD. This variable was used in a cluster analysis, by k-means to classify adults in non-overlapping groups, based on their eating patterns. We tested 2–6 solutions to select the number of clusters for analysis by comparing the Calinski-Harabasz index (CH index). The solution with the highest CH index is considered the most optimal solution based on the average between- and within-cluster sum of squares (25). In addition, nutritional interpretability and sample size were also considered.

Healthy Diet Indicator (HDI)

This index is based on the World Health Organization chronic disease prevention diet and nutrition guides (26, 27). It contains nine components, with dichotomous answers according to the compliance of each one (0 = not compliant; 1 = compliant); the maximum score was 9 points (28). These components and adherence values (score = 1) were: saturated fat (≤10% of energy), polyunsaturated fat (6–10% of energy), protein (10–15% of energy) and carbohydrates (≥50–≤70% of energy), fiber (>25 g), fruits and vegetables (>400 g), consumption of legumes and seeds (>30 g), and cholesterol intake (≤300 mg), and sugar (≤10% of energy). The free sugars were not available in this database and were replaced by mono- and disaccharides, as suggested in another study (28). We estimated the percentage of participants who met each component of the HDI, the score as a continuous variable for each participant and estimated the mean of the HDI score into each dietary pattern.

Anthropometric Information

Personnel were trained according to international procedures to measure height, weight and waist circumference (29, 30). Bodyweight was measured using an electronic scale Seca model-874 (200 kg and a precision of 100 g, Hamburg, Germany) and the height using a stadiometer Seca model-206 (220 cm and a precision of 1 mm Hamburg, Germany).

We excluded 103 participants without anthropometric information. Valid height values were considered between 1.3 and 2.0 m and the BMI values between 10 and 58 kg/m^2. Data beyond these intervals were excluded from the analysis (n = 94).

Regarding waist circumference, valid values were considered between 50 and 200 cm. Data outside of this interval were excluded ($n = 34$).

The final sample of study with valid anthropometric information and valid dietary intake was 5,735 adults (**Figure 1**).

BMI was categorized according to WHO cut-off points (normal weight if BMI < 25 and overweight and obesity if BMI ≥ 25 kg/m^2) (31) and abdominal obesity was classified according to

TABLE 1 | General characteristics of Mexican adults population National Health and Nutrition Survey 2016†.

Characteristics	National‡ Mean (SE)	With normal weight§ Mean (SE)	With Overweight or obesity‖ Mean (SE)	Without abdominal obesity¶ Mean (SE)	With abdominal obesity†† Mean (SE)
Age (y)	37.1 ± 0.27	34.0 ± 0.50	38.3 ± 0.32*	32.9 ± 0.50	38.4 ± 0.31*
BMI (Kg/m²)	28.3 ± 0.13	22.4 ± 0.08	30.5 ± 0.13*	23.0 ± 0.12	30.0 ± 0.13*
Waist circumference (cm)§§	94.1 ± 0.32	81.3 ± 0.31	98.9 ± 0.33*	80.2 ± 0.29	98.6 ± 0.31*
	% (CI 95%)	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**	**% (CI 95%)**
Male sex	46.8 (44.4–49.0)	51.5 (47.3–55.8)	44.9 (42.2–47.7)	70.8 (66.7–74.7)	39.0 (36.4–41.7)*
Urban area	74.6 (71.6–77.4)	74.7 (70.9–78.1)	74.6 (71.4–77.6)	71.3 (66.9–75.3)	75.7 (72.5–78.7)
Region					
North	20.1 (17.4–23.2)	19.9 (16.2–24.2)	20.2 (17.4–23.4)	17.6 (13.4–22.8)	21.1 (18.1–24.4)
Center	33.8 (30.8–36.9)	37.9 (33.1–42.9)	32.2 (29.1–35.5)	34.0 (29.5–38.9)	33.5 (30.2–37.0)
Mexico City	15.4 (13.2–18.0)	14.0 (10.5–18.3)	16.0 (13.7–18.6)	15.6 (11.7–20.5)	15.4 (13.0–18.0)
South	30.6 (27.1–34.5)	28.2 (23.9–32.9)	31.6 (27.6–35.8)	32.8 (28.2–37.7)	30.0 (26.1–34.3)
SES, %					
Low	22.3 (19.9–25.0)	25.4 (21.5–29.7)	21.1 (18.5–24.0)	27.6 (23.5–32.1)	20.6 (18.1–23.3)*
Middle	30.6 (28.3–33.0)	28.2 (24.6–32.0)	31.5 (28.8–34.3)	30.9 (26.7–35.4)	30.4 (28.0–33.1)
High	47.1 (44.0–50.3)	46.4 (41.6–51.2)	45.6 (41.3–49.9)	41.5 (36.6–46.5)	48.9 (45.6–52.3)
Physical activity‖‖					
Inactive	13.2 (11.6–14.9)	12.3 (9.7–15.4)	13.5 (11.7–15.5)	10.4 (7.9–13.6)	14.1 (12.1–16.2)
Moderate	9.5 (8.4–10.8)	9.7 (7.5–12.4)	9.5 (8.1–11.0)	9.6 (6.9–13.1)	9.5 (8.3–11.0)
Active	77.3 (75.1–79.3)	78.0 (74.3–81.3)	77.0 (74.6–79.2)	80.0 (75.9–83.6)	76.4 (73.9–78.7)

BMI, Body mass index; WC, Waist circumference; SES, Socio-Economic status.
† *Adjusted by sampling design.*
‡ *Expanded sample = 49,575,450 adults.*
§ *Expanded sample = 13,589,962 adults.*
‖ *Expanded sample = 35,985,488 adults.*
¶ *Expanded sample = 12,076,628 adults.*
†† *Expanded sample = 37,316,040 adults.*
§§ *Waist circumference measurement not available in 34 participants.*
‖‖ *Physical activity measurement not available in 142 participants.*
**Significant difference compared with population without overweight or obesity, or abdominal obesity ($P < 0.05$).*

the International Diabetes Federation (≥80 and ≥90 centimeters in women and men, respectively) (32).

Sociodemographic Variables

Age was calculated in years at the date of the interview.

Geographical Region

The 32 states of the country were divided in four regions: North, Center, Mexico City, and South, using the previous classification used by the ENSANUT (20).

Area

Localities with <2,500 inhabitants were considered rural areas and those with ≥2,500 inhabitants were urban.

Socioeconomic Status (SES)

It was estimated through principal component analysis with dwelling characteristics (roof, wall and floor materials, drainage, and water availability) and possessions like a television, computer, radio, phone, cable, refrigerator, microwave oven, stove, boiler, and washing machine. We obtained a continuous variable, which was divided into tertiles: low, medium, and high socioeconomic level (33). This methodology has been used in other ENSANUTs and is useful for considering inequality between participant households (34).

Physical Activity

The international Physical Activity Questionnaire (IPAQ) short form was used to measure physical activity. This questionnaire included a period of 7 days, and has been previously validated in Mexican adults (35). Self-reported minutes per day were included for: (1) vigorous physical activity (VPA), (2) moderate physical activity (MPA), and (3) walking. Three categories of physical activity were included in the analysis: Inactive (participants with <150 min/w of MPA–VPA); moderate active (participants with 150–299 min/w of MPA–VPA; and very active (participants with ≥300 min/w of MPA–VPA.

Ethics

The survey protocol was approved by the ethics board from the INSP and prior informed consent was obtained from all participants.

Statistical Analysis

To analyze difference in characteristic of the population groups, we used T-test for continuous variables with normal distribution and chi square for categorical variables. To analyze differences

TABLE 2 | Contribution of energy (%) by food group and dietary pattern.

	Dietary pattern					
	Rural (% = 26.9)*		Westernized (% = 42.5)†		Diverse (% = 30.6)‡	
Food groups	Mean	SE	Mean	SE	Mean	SE
Dairy sweetened beverages	1.39	0.07	1.84	0.08	3.27	0.14
Dairy non sweetened beverages	1.66	0.07	1.97	0.07	4.66	0.15
Sweetened non-dairy beverages	10.35	0.18	19.36	0.28	7.76	0.16
Non-sweetened, non-dairy beverages	0.87	0.04	0.84	0.04	1.6	0.06
Fruits	4.03	0.09	3.61	0.08	9.53	0.17
Vegetables	2.38	0.05	2.38	0.05	5.92	0.13
Dairy products no beverages	1.89	0.06	2.51	0.07	4.96	0.13
Legumes	4.55	0.09	1.97	0.05	2.69	0.06
Cereal based salty dishes	2.78	0.06	2.13	0.05	3.31	0.08
Corn based salty dishes	6.56	0.09	7.67	0.21	4.81	0.15
Fast food	1.02	0.05	5.66	0.14	3.18	0.11
Egg	4.05	0.1	3.76	0.09	3.54	0.09
Meat and poultry	3.76	3.76	6.42	0.12	8.89	0.15
Processed meat	1.05	0.04	1.70	0.05	1.47	0.05
Bakery and cookies	4.17	0.11	7.97	0.19	4.88	0.13
Candies	0.34	0.02	1.48	0.07	0.67	0.03
Desserts	0.62	0.03	1.4	0.06	1.97	0.08
Salty snacks	0.53	0.03	1.8	0.07	0.68	0.04
Seeds	0.27	0.02	0.63	0.04	0.53	0.04
Added fats	0.63	0.04	1.12	0.06	0.96	0.05
Tortilla	42.86	0.3	16.32	0.21	16.94	0.24
Soup	0.59	0.2	0.65	0.02	1.48	0.04
Ready to eat cereals	0.14	0.01	0.38	0.02	1.23	0.06
Bread	2.45	0.09	5.50	0.19	3.77	0.13
Potatoes	1.06	0.02	0.92	0.04	1.25	0.05

Expanded population = 15,182,063 adults. †Expanded population = 21,064,950 adults. ‡Expanded population = 13,328,437 adults.

of energy and nutrient intake between dietary patterns (which did not have a normal distribution), quantile regression models were used.

To analyze the association between dietary pattern (independent variables) and overweight-obesity and abdominal obesity (dependent variables), we used Poisson regression models adjusted by age, area, and region. Also, we included an interaction term of dietary pattern and gender. As a sensitivity analysis, we did the association analysis in the sample with physical activity information ($n = 5{,}593$).

For statistical difference by nutrition status and gender, the p-value considered was <0.05. For multiple comparison among dietary patterns in dietary characteristics, the $p < 0.016$ was considered as significant (Bonferroni method) (36). In the models, $p < 0.10$ for the interaction term, was considered. All statistical analyses were done in STATA 14.0 (StataCorp, 2011. College Station, TX: Stata Press), considering the sample design of the survey.

RESULTS

We analyzed data from 5,735 participants, who represented 49,575,450 adults between 20 and 59 years old in Mexico. The 47% of the population was men (the 39% was men in the population with abdominal obesity). Three quarters of the population lived in urban area and 47% had high SES (**Table 1**).

We found three dietary patterns: Rural, Diverse, and Westernized. Compared with the other dietary patterns, the Rural pattern was characterized by higher energy intake percentage from tortillas (42.9%), legumes (4.5%), and eggs (4.0%); the Westernized pattern by sweetened non-dairy beverages (19.3%), fast food (5.7%), bakery and cookies (7.9%), bread (5.5%), and to a lesser extent, candies and salty snack groups (2.8%); and the Diverse pattern was characterized by a higher percentage of energy intake from fruits (9.5%), meat and poultry (8.9%), vegetables (5.9%), and dairy beverages (sweetened or not) (7.9%) (**Table 2**).

With respect to the contribution of energy and nutrients, men had a higher energy intake than women (2,206–2,644 kcal/d in men vs. 1,515–1,937 kcal/d in women among the three patterns, $P < 0.05$). The population with a Westernized pattern presented higher energy, carbohydrates, fat (total and saturated), sugar, and cholesterol intake compared with Rural and Diverse patterns ($p < 0.05$). Also, the population with a Westernized pattern showed lower fiber intake compared with the other dietary patterns (fiber

TABLE 3 | Daily energy and nutriments intake by dietary pattern and gender in Mexican adults (n = 5,735)[1].

Men	Dietary patterns					
	Rural		Westernized		Diverse	
	Median	p25, p75	Median	p25, p75	Median	p25, p75
Energy (kcal)	2,206[a]	1,632, 2,709	2,644[b]	2,050, 3,487	2,242[a]	1,664, 3,024
Carbohydrates (g)	354.1[a]	275.1, 447.4	367.8[a]	286.3, 495.4	301.1[b]	231.4, 391.3
Fat (g)	51.8[a]	35.9, 70.9	79.9[b]	59.2, 110.3	74.7[b]	50.8,100.2
Fat (energy %)	21.8[a]	17.6, 25.4	29.6[b]	24.3, 33.4	30.0[b]	26.0, 34.8
Protein (g)	67.0[a]	48.8, 82.6	79.2[b]	60.6, 107.3	81.0[b]	(61.3, 109.3
Fiber (g)	35.2[a]	27.2, 47.5	26.9[b]	20.0, 36.3	31.6[a]	23.8, 41.3
Sugar (g)	86.9[a]	54.9, 113.5	155.5[b]	107.2, 217.9	115.2[c]	84.2, 173.7
Saturated fat (g)	16.2[a]	10.7, 23.4	29.4[b]	20.9, 38.7	27.7[b]	17.9, 37.4
Saturated fat (energy %)	6.7[a]	5.2, 9.0	10.3[b]	8.4, 12.0	10.7[b]	8.9, 13.3
Polyinsatured fat (g)	15.0[a]	10.2, 19.9	18.5[b]	13.4, 27.2	14.7[a]	10.1, 24.1
Polyinsatured fat (energy %)	6.0[a]	5.0, 7.6	6.7[b]	5.2, 8.9	6.1[a]	5.0, 7.5
Cholesterol (mg)	191.9[a]	99.5, 300.0	335.2[b]	207.6, 489.2	295.2[b]	177.1, 412.3
Women						
Energy (kcal)	1,515[a]	1,151, 1973	1,937[b]	1,448, 2,447	1,590[a]	1,174, 2,010
Carbohydrates (g)	246.3[a]	186.3, 314.9	263.8[a]	207.2, 350.7	224.5[b]	168.8, 285.9
Fat (g)	38.1[a]	27.4, 56.3	64.6[b]	46.5, 84.3	51.2[b]	36.1, 70.5
Fat (energy %)	22.9[a]	18.3, 27.7	29.9[b]	25.8, 34.5	29.1[b]	24.3, 34.0
Protein (g)	47.7[a]	36.1, 62.4	59.3[b]	45.3, 76.6	58.8[b]	42.8, 74.9
Fiber (g)	26.2[a]	18.7, 34.1	19.1[b]	14.4, 25.7	23.3[c]	17.0, 31.3
Sugar (g)	56.8[a]	38.1, 82.9	108.4[b]	78.2, 164.5	89.4[c]	64.3, 122.0
Saturated fat (g)	12.5[a]	8.4, 18.8	23.4[b]	16.9, 31.9	19.1[c]	13.2, 26.7
Saturated fat (energy %)	7.3[a]	5.3, 9.4	11.1[b]	9.0, 13.2	10.7[b]	8.4, 12.8
Polyinsatured fat (g)	11.0[a]	7.5, 15.1	14.2[b]	10.5, 20.4	10.8[a]	7.2, 15.8
Polyinsatured fat (energy %)	6.2[a]	5.0, 8.1	6.9[b]	5.3, 8.8	5.9[a]	4.7, 7.4
Cholesterol (mg)	146.5[a]	76.0, 246.3	227.4[b]	148.6, 341.7	206.1[b]	126.4, 291.7

Values within a column with unlike superscript letter were significantly different (P < 0.016, using quantile regression model).
[1]*Expanded sample = 49, 575,450 adults.*

intake in men was 26.9 g/d in Westernized Pattern, vs. 35.2 in Rural and 31.6 g/d in Diverse pattern; in women, it was 19.1 g/d in Westernized vs. 26.2 in Rural and 23.3 g/d in Diverse pattern, $p < 0.016$; **Table 3**).

According to the healthy diet indicator components, adherence for fruits and vegetables was higher in the Diverse pattern, also in both sexes. The total HDI score was higher ($P < 0.001$) in the Rural pattern in men (6.1, 95% CI 5.9–6.2) and women (5.7, 95% CI 5.5–5.9) and the Diverse pattern (5.2, 95% CI 5.0–5.5 in men and 4.9, 95% CI 4.7–5.1 in women) P<0.05, compared to the Westernized pattern (4.7, 95% CI 4.6–4.9 in men and 4.3, 95% CI 4.2–4.5 in women) ($P < 0.05$; **Table 4**).

Table 5 shows the association analysis between dietary pattern and overweight and obesity and abdominal obesity, including interaction term of dietary pattern and gender. Using the Rural pattern as a reference, in men, we found a significant association between a Westernized pattern in (PR = 1.11, 95% CI 0.97–1.27), and Diverse Pattern (PR = 1.18, 95% CI 1.00–1.38), with overweight and obesity ($p < 0.10$). Including physical activity variable in the model, the association of Westernized and Diverse patterns was slightly higher ($p < 0.05$).

Compared with the Rural pattern, Westernized, and Diverse patterns were associated with abdominal obesity in men (Westernized pattern PR = 1.15, 95% CI 1.00–1.33; Diverse pattern PR = 1.27, 95% CI 1.07–1.50, $p < 0.05$). In the sensitivity analysis, including physical activity variable the association was higher ($p < 0.05$).

DISCUSSION

This study shows that in Mexican adults, dietary patterns characterized by high energy, saturated fat, protein, and sugar intake and low fiber intake were associated with overweight and obesity (measured by BMI) and abdominal obesity in men, and these patterns have a lower diet quality indicator score. However, this association was not present in women.

We identified three dietary patterns: Rural, Diverse, and Westernized. These patterns are consistent with several studies carried out in adult populations. The Westernized pattern, in some studies called "modern" or "unhealthy," is consistently energy dense, high in sugar and fats (total and saturated), and

TABLE 4 | Adherence to the healthy diet indicator components and score by dietary pattern and gender, in Mexican adults.

	Dietary patterns in men					
	Rural		Westernized		Diverse	
Men	%	95% CI	%	95% CI	%	95% CI
Saturated fat, <10% of TE	88.0[a]	84.0–91.0	47.7[b]	42.2–53.3	37.9[b]	31.0–45.3
Polyinsaturated fat, 6–10% of TE	44.0	38.5–49.8	44.1	39.1–49.3	43.9	36.0–52.1
Protein, 10–15% of TE	85.2[a]	81.5–88.3	69.8[b]	65.1–74.2	52.4[c]	44.6–60.0
Carbohydrates, 50–70% of TE	66.3[a]	60.6–71.6	76.5[b]	72.2–80.3	72.3[ab]	64.5–79.0
Fiber, >25 g/d	79.2[a]	74.1–83.5	56.1[b]	50.3–61.6	71.8[a]	64.5–78.2
Fruits and vegetables, >400 g/d	20.0[a]	15.6–25.5	26.4[a]	21.8–31.6	64.8[b]	57.6–71.4
Legums and seeds, >30 g/d	52.2[a]	45.2–59.1	36.8[b]	31.9–42.0	42.0[ab]	34.3–50.1
Sugar, <10% of TE	94.0[a]	91.1–96.1	71.9[b]	66.5–76.7	87.7[a]	81.7–91.9
Cholesterol, <300 mg/d	76.9[a]	71.2–81.8	44.0[b]	39.0–49.2	49.2[b]	41.6–56.8
Total score HDI[†]	6.1[a]	5.9–6.2	4.7[b]	4.6–4.9	5.2[c]	5.0–5.5
Women						
Saturated fat, <10% of TE	78.4[a]	73.2–82.8	35.1[b]	30.1–39.7	37.4[b]	32.8–42.1
Polyinsaturated fat, 6–10% of TE	41.6	37.2–46.2	46.8	42.1–51.6	40.2	35.1–45.4
Protein, 10–15% of TE	80.6[a]	76.5–84.1	71.5[b]	67.1–75.5	58.1[c]	53.0–63.1
Carbohydrates, 50–70% of TE	70.4	65.2–75.1	74.1	69.6–78.1	69.4	63.4–74.8
Fiber, >25 g/d	55.3[a]	49.8–60.7	27.6[b]	23.3–32.3	43.8[a]	38.7–49.0
Fruits and vegetables, >400 g/d	13.3[a]	10.6–16.5	19.1[a]	15.5–23.2	55.7[b]	50.7–60.6
Legums and seeds, >30 g/d	50.6[a]	45.8–55.4	23.1[b]	19.3–27.5	28.1[b]	24.3–32.2
Sugar, <10% of TE	95.6[a]	94.0–96.7	72.3[b]	67.3–76.7	82.8[c]	78.8–86.2
Cholesterol, <300 mg/d	84.2[a]	78.9–88.4	66.2[b]	61.0–71.1	74.9[ab]	70.0–79.3
Total score HDI[†]	5.7[a]	5.5–5.9	4.3[b]	4.2–4.5	4.9[c]	4.7–5.1

TE, Total Energy; HDI, Healthy Diet Indicator. [†]Values are means.
Percentages within a column with unlike superscript letters were significantly different (P < 0.016, using chi square test for categorical variables and T-test for HDI).

has been associated with overweight and obesity and abdominal obesity in adult populations (11, 17, 37, 38); these characteristics may explain the mechanism underlying this association.

The Rural pattern, as defined in our study, has been described in other studies as a "traditional pattern," (11, 16, 19). The Rural pattern in men was protective against overweight and obesity, which is consistent with the results from a Brazilian study, in which a traditional Brazilian pattern (consisting of traditional foods like rice and beans) was protective against excess weight among men (11). In addition, a Mexican study found that adults that consumed the traditional pattern (with maize, maize foods, beans, and legumes) had a lower risk of presenting excess weight (19).

There are some hypotheses as to why the Rural pattern has a protective effect: (1) the high variety of healthy foods included in this pattern, (2) the high content of tortilla and legumes, and (3) the lower consumption of fat and sugar (39).

On the other hand, the results of the association between Westernized and Diverse patterns with obesity, have an unclear mechanism, but some hypotheses have been made regarding the role of the carbohydrates intake and energy density in appetite control. First, unlike the Rural pattern, in our study, Westernized y Diverse pattern were high in sugar. Westernized pattern was characterized for higher consumption of bread, salty snacks and potato. As we all know, refined grains are major source of dietary carbohydrate, and previous evidence indicates that high carbohydrate from refined grains are associated with obesity (40). Second, Diverse pattern was characterize by higher consumption of meat, ready to cereals, and dairy sweetened and non-sweetened beverages. Meat could increases the energy density, which may be a key component in body-weight regulation because it may alter appetite control signals (i.e., hunger and satiety). Although protein intake has been shown to increase satiety in intervention studies, the long-term effect of the consumption of a large amount of meat, remains unknown (41).

We did not find an association between dietary pattern and obesity in women. The available evidence of the relationship between dietary patterns and obesity stratified by sex has not been conclusive. A study carried out in the United States among Hispanic and non-Hispanic women found that a Westernized pattern was associated with a higher prevalence of overweight and obesity in both Hispanic and non-Hispanic white women (42). Another study carried out in Australian adults estimated the association between diet quality and change in obesity, finding an inverse association between diet quality and obesity in men, but not in women (43). However, there is a study than evidence that the main difference is that men habits were characterized by travel and eating out much more, consume more alcohol and tobacco, which represent more energy compared to women (44). The lack of association in women may be due to three reasons:

TABLE 5 | Association between dietary patterns with overweight and obesity and abdominal obesity in Mexican adults, in the complete sample and sample with physical activity ENSANUT-2016†.

	Complete sample		Sample with physical activity information††	
Overweight and obesity‡	**PR**	**CI, 95%**	**PR**	**CI, 95%**
Dietary pattern				
Rural	Reference		Reference	
Westernized	1.04	0.96–1.12	1.02	0.95–1.10
Diverse	0.96	0.89–1.04	0.95	0.88–1.03
Gender	0.84	0.75–94.3	0.83	0.74–0.92
Interaction (Westernized pattern—male gender)	1.11	0.97–1.27	1.14*	0.99–1.3
Interaction (Diverse pattern—male gender)	1.18*	1.00–1.38	1.20	1.02–1.41
Abdominal obesity§				
Dietary pattern				
Rural	Reference		Reference	
Westernized	1.02	0.96–1.08	1.00	0.95–1.06
Diverse	0.97	0.93–1.02	0.96	0.92–1.01
Gender	0.64	0.56–0.73	0.63	0.55–0.72
Interaction (Westernized pattern—male gender)	1.15*	1.00–1.33	1.17*	1.00–1.36
Interaction (Diverse pattern—male gender)	1.27*	1.07–1.50	1.28*	1.07–1.52

† Poisson regression models adjusted by age, area, and region.
**P-value for interaction term <0.10.*
‡ n = 5,735 adultos (expanded population = 49,575,450 adults).
§ n = 5,701 adultos (expanded population = 49,392,668 adults).
†† Physical activity was not available in 142 participants.

(1) possible underreporting of energy in those with a higher BMI (women presented more overweight and obesity prevalence) (45), (2) the possibility that overweight women adopt a healthier diet to manage their weight (Dieting is an issue mostly observed in female participants) (46), and (3) the possibility of differences in food groups distribution even in the same dietary pattern.

Regarding the characteristics of the dietary patterns and obesity in adults, the findings obtained here are consistent with those found in a longitudinal study of adults in the United States. It demonstrated that individuals who followed a healthy dietary pattern had lower BMI, waist circumference, and blood pressure compared to more eastern dietary patterns. Individuals who followed a dietary pattern characterized by red meat, potatoes, and sweet foods had higher levels of glycosylated hemoglobin (47).

Furthermore, our results showed higher adherence to the HDI components in the Rural pattern than in the Westernized pattern, in both genders. The analysis with this indicator confirms the results with cluster analysis, showing better diet quality in the rural pattern compared to the Westernized pattern.

Limitations of the Study

This study has some limitations. First, as the diet information is self-reported, the recall bias cannot be eliminated. However, the interviewers were trained in the FFQ methodology, which could have minimized it. Second, the *a posteriori* approach to derive dietary pattern includes certain subjectivity, such as the selection of food groups and number of patterns (48). However, once the dietary patterns were identified, we evaluated their adherence to diet quality recommendations with an *a priori* index, and we found that the results with both methodologies were consistent. The third possible limitation is the relatively short period for which dietary information was collected (7-day FFQ), which may not have been enough time to capture the intake variability in women. This could explain why we did not find an association between diet and overweight and obesity in women. Another limitation is that we did not count with a precise measurement of physical activity such as accelerometry, however, we got information from self-report of physical activities in a part of the sample, which was useful to adjust the final model, founding higher associations between Westernized and Diverse patterns and obesity in male population.

Strengths of the Study

This study has some strengths as well. Data come from a nationally representative nutrition survey. The FFQ that was used has been validated to identify dietary patterns in the Mexican adult population (49). In addition, trained personnel obtained standardized anthropometrical measures to avoid a systematic error. This despite the fact that in recent years, strategies to improve nutrition have been implemented in Mexico, such as the tax on sugar-sweetened beverages and non-essential energy-dense foods (50). Also, both cluster and diet quality methodologies used to identify dietary patterns support the evidence that a healthier diet is important for preventing obesity in the adult population. However, it is necessary to analyze other factors to understand how dietary patterns are related to obesity in women.

The findings of the present study confirm the impact of dietary patterns on the weight of Mexican adults and expand the overview to investigate behavioral aspects in men that could relate biological aspects. The food groups and moreover dietary patterns highlight the importance of epigenetic studies focused on obesity development.

In conclusion, Westernized and Diverse patterns characterized by sweetened non-dairy beverages, fast food, bakery and cookies, corn based salty dishes, bread, candies, and salty snacks are associated with overweight and obesity and abdominal obesity in Mexican men. Our findings are politically relevant, and align with evidence that highly energy dense and ultra-processed foods are associated with obesity. They also emphasize the urgent need for future studies which should examine dietary patterns with a gender perspective, as social roles could be important in the result of strategies and recommendations to promote healthy diets. Dietary pattern research has great potential for use in nutrition policy, particularly as it demonstrates the importance of total dietary intake in health promotion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Institute of Public Health in Mexico (INSP). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SR-R is responsible for conceiving the study, developing the overall research plan, and overseeing the study. SR-R and BM-T analyzed the data and primarily responsible for the final content. SR-R wrote the first draft and BM-T and DG-C added important intellectual content. LC-N and TS-L did the final revision and provided contributions. All authors read and approved the final submitted manuscript.

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SUPPLEMENTARY MATERIAL

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Dietary Patterns in Association With Hypertension: A Community-Based Study in Eastern China

Cuicui Wang[1,2†], *Yanmin Zheng*[3†], *Ya Zhang*[1,2], *Dong Liu*[1,2], *Li Guo*[4], *Bo Wang*[3*] and *Hui Zuo*[1,2*]

[1] School of Public Health, Medical College of Soochow University, Suzhou, China, [2] Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Medical College of Soochow University, Suzhou, China, [3] Department of Nutrition and Food Hygiene, Suzhou Center for Disease Control and Prevention, Suzhou, China, [4] Department of Disease Prevention and Health Care, Soochow University Hospital, Soochow University, Suzhou, China

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Edited by:
Farhana Akter,
Chittagong Medical College, Bangladesh

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Rita Akutsu,
Rita de Cássia Coelho de Almeida Akutsu, Brazil
Shelly R. McFarlane,
University of the West Indies, Jamaica

***Correspondence:**
Bo Wang
153652012@qq.com
Hui Zuo
zuohui@suda.edu.cn

† These authors have contributed equally to this work and share first authorship

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Objective: This study aimed to explore the association between dietary patterns and hypertension based on a community–based survey in Suzhou, Eastern China.

Methods: This cross–sectional analysis was undertaken from the subset of the Suzhou Food Consumption and Health State Survey in 2018–2019. Adults aged ≥ 18 years were invited to participate in this survey. Dietary intake was collected by a 24–h dietary recall and a weighing method over three consecutive days (including two weekdays and one weekend day). Dietary patterns were defined using factor analysis. Association between the dietary patterns and hypertension was examined by multivariable logistic regression models with adjustment for covariates. Moreover, sensitivity analysis was used to reinforce our findings.

Results: A total of 2,718 participants were included in the final analysis. Rice-vegetable pattern, fast food pattern, fruit-dairy pattern, and wheat-meat pattern were identified. We observed that the fruit-dairy pattern was inversely associated with hypertension after adjustment for all the covariates (OR = 0.55; 95% CI: 0.40, 0.75; $P = 0.002$). The association between the wheat-meat pattern and hypertension was attenuated and became statistically nonsignificant in sensitivity analyses. The other two patterns were not significantly associated with hypertension ($P > 0.05$).

Conclusion: The fruit-dairy pattern was inversely associated with the risk of hypertension among Chinese adults. Our findings further emphasize the important role of optimal diet combination in the prevention of hypertension.

Keywords: dietary pattern, factor analysis, hypertension, dietary recall, cross-sectional study

INTRODUCTION

Hypertension is one of the major risk factors affecting the global burden of disease and is one of the most important risk factors for cardiovascular disease (1). It was reported that a 10 mmHg reduction in systolic blood pressure (BP) could lower the risk of major stroke by 27%, heart failure by 28%, and cardiovascular disease events by 20% (2). Therefore, the primary prevention of hypertension has now become a top priority for global public health. Furthermore, hypertension is the leading modifiable risk factor for cardiovascular disease, the top cause of death in China (3). In

China, five waves of nationwide hypertension surveys have been conducted since the 1950s (1959, 1979, 1991, 2002, and 2012, respectively). Based on the survey data, the prevalence of hypertension continuously increased from 5.11% in 1959 to 23.2% in 2012 among adults (4).

Accumulating evidence has suggested that diet plays a significant role in the development and progression of hypertension (5–7). Dietary pattern was more comprehensive to reflect the synthesized effect of foods or nutrients compared with individual food or nutrient (8). It has been widely used as an alternative method to assess the relationship between whole diet and hypertension (9). Over the past few decades, dietary patterns, such as Dietary Approaches to Stop Hypertension (DASH) (10) and Mediterranean Dietary Pattern (MDP) (11), have been suggested to have a protective effect on hypertension.

With the rapid development of China's economy in recent years, China has undergone a rapid nutritional transition. Meanwhile, due to China's vast territory and rich food variety, dietary patterns may vary between different regions and cultural environments. For example, in North China, the diet in Inner Mongolia was characterized by "high protein," "traditional northern," "modern," and "condiments" patterns (12). In Southwest China, Diqing of Yunnan Province, three dietary patterns were identified, namely, "Grassland healthy," "Tuber and meat," and "Fruit and vegetable" (13). In Yangtze River Delta region, people tended to adhere to a healthy diet pattern named as "Southern River-style dietary pattern," including high consumption of vegetables and fruits in season, freshwater fish and shrimp, and legumes, and moderate consumption of whole-grain rice, plant oils (mainly rapeseed oil), and red meat (14). However, there were limited studies on the association between dietary patterns and hypertension in Eastern China (15). Moreover, high economic development in Eastern China may be accompanied by high levels of environmental pollution and corresponding food contaminants (16, 17). Hence, the aim of this study was, therefore, to provide the latest evidence on the association between dietary patterns and hypertension among community residents in Eastern China.

METHODS

Participants and Setting

The subset of the Suzhou Food Consumption and Health State Survey was a cross-sectional study conducted in Suzhou, Eastern China, in 2018–2019. A multistage stratified cluster random sampling method was used to recruit potential participants. A total of 3,595 participants were invited. Among them, 112 participants did not complete the dietary survey. We excluded 599 participants under the age of 18 years and those with implausible dietary data (energy intake < 800 or > 6,000 kcal in males, energy intake <600 or >4,000 kcal in females) (n = 13). In addition, we excluded those participants with BMI < 14 kg/m^2 or BMI > 45 kg/m^2 (n = 153). A total of 2,718 participants (males =1,288, females = 1,430) were included in the final analysis (**Figure 1**).

Dietary Assessment

Dietary data were collected using a 24-h dietary recall and a weighing method over 3 consecutive days (including 2 weekdays and 1 weekend day) by trained investigators. Participants were asked to recall the types and quantities of food consumed during a 24-h dietary recall *via* a face-to-face interview. A weighing method was used to collect the information on daily consumption of major seasonings, including cooking oil, salt, sugar, monosodium glutamate, soy sauce, and vinegar. This method has been used in the China National Nutrition Surveys and is widely accepted by international researchers (18). This was done by interviewers at the participants' homes after dinner at night. Consumption of condiments was obtained by weighing condiments purchased and wasted. The survey was conducted following a standardized protocol.

Definition of Hypertension

Data on hypertension was based on a measurement of BP and self-report *via* a questionnaire. BP was measured using an electronic sphygmomanometer (Omron Hp-1300, OMRON Corporation, Japan) on the right arm positioned at heart level after a 5-min rest period in a sitting position following standard procedures. BP was measured two times at 2-min intervals, and the mean value of two measurements was used for data analysis. Meanwhile, participants were asked the following questions: "Have you been diagnosed with hypertension by a qualified doctor in a township or higher level hospital?" and "Have you taken any antihypertensive medicine within the last 2 weeks?" Participants were considered as hypertensive if they had a systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, diagnosis of hypertension, or antihypertensive medication.

Covariates

The participants' information, including age, gender, education, smoking status, alcohol drinking, sleeping disorders, and family history of hypertension, were collected by a reviewer-administrated questionnaire at enrollment. Education was classified into three categories, namely, low: illiterate/primary school; medium: junior middle school; and high: senior middle school/university. Smoking status was categorized into three groups, namely, non-smokers, ex-smokers, and current smokers. Participants were defined as drinking alcohol if the average drinking frequency was $\geq$ once a month in the last 12 months (19). Participants were considered as having sleep disorders if they had self-reported sleep-disordered breathing or insomnia (20). Participants were asked the following question: "How much time do you usually spend sitting every day? (including all sedentary time, such as working, studying, reading, watching TV, using computer, and taking rest whenever sitting). Sedentary time was divided into tertiles. The weighing method over 3 consecutive days (including 2 weekdays and 1 weekend day) in the population was performed to estimate the salt intake as described in a recent study (21). Daily salt intake was divided into three categories, namely, < 4 g/day, 4–6 g/day, and >6 g/day.

Self-reported history of diabetes, dyslipidemia, coronary heart disease, stroke (ischemic and hemorrhagic stroke), and other chronic diseases [including chronic obstructive pulmonary

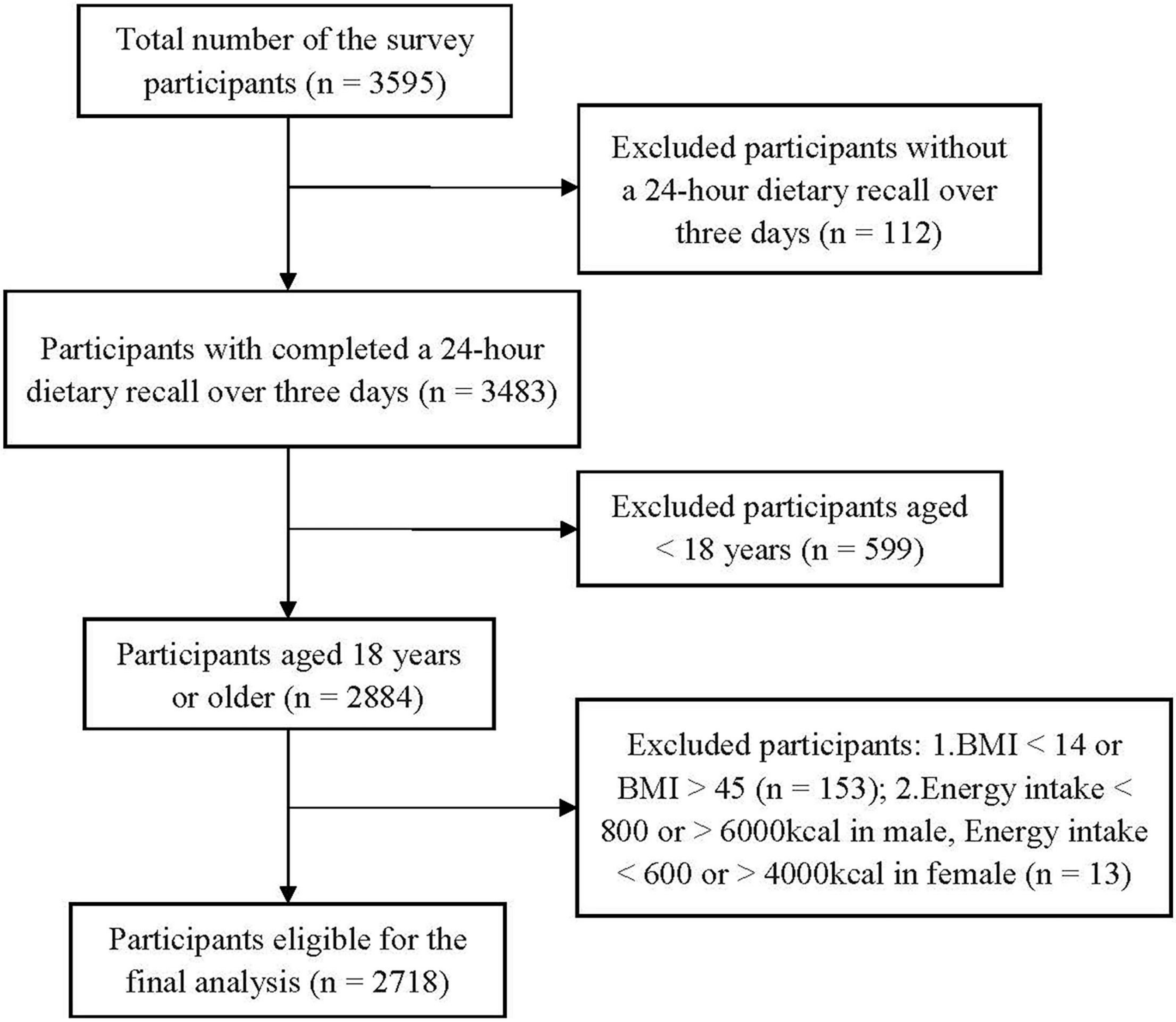

FIGURE 1 | Flowchart of study selection.

disease, asthma, bone and joint disease, and neck or waist diseases (such as cervical spondylopathy, lumbar strain, and spinal disc herniation), chronic digestive system disease, chronic urinary system disease, and malignant tumor] ever diagnosed in a township or higher-level hospital by a qualified doctor were recorded.

Waist circumference (WC) was measured midway between the lowest rib and the iliac crest or 1 cm above the umbilicus, against bare skin, but subtracting 1 cm if on top of undergarments (22). WC was continuously measured two times to the nearest 0.1 cm using a soft non-stretchable tape, and the average of two measurements was used for data analysis. The waist circumference threshold for abdominal obesity was $\geq$ 85 cm in women and $\geq$ 90 cm in men, respectively (23).

Statistical Analysis

The sociodemographic and lifestyle characteristics were described as medians (interquartile ranges) for continuous variables and frequencies with percentages for categorical variables. The chi-square test was used to compare the characteristics of participants with and without hypertension for categorical variables, and Kruskal-Wallis tests were used for continuous variables.

We grouped food items according to similar nutrient contents. Accordingly, all of the foods were classified into 21 groups, including rice and products, vegetables (fresh leafy and non-leafy vegetables), aquatic products, red meat, other crops and potatoes, eggs, soybeans and products, phycomycetes (mushroom, *Auricularia auricula*, *Porphyra*, and kelp), nuts, poultry, fast food, snacks, beverages, dairy, fruit, yogurt, sweets,

TABLE 1 | Sociodemographic and lifestyle characteristics between participants with and without hypertension: The Suzhou Food Consumption and Health Survey.

	Hypertension (n = 727)	No hypertension (n = 1991)	*P-trend*
Age, yrs	63 (54, 69)	40 (33,35)	<0.001
Male (%)	385 (53.0)	903 (45.4)	<0.001
Education (%)			<0.001
Low	178 (24.6)	237 (12.0)	
Medium	229 (31.6)	379 (19.1)	
High	317 (43.8)	1,367 (68.9)	
Smoking (%)			<0.001
Never smoker	462 (63.5)	1,543 (77.9)	
Ex-smoker	85 (11.7)	77 (3.9)	
Current smoker	180 (24.8)	361 (18.2)	
Alcohol drinking (%)			<0.001
Yes	271 (37.4)	577 (29.2)	
No	453 (62.6)	1,397 (70.8)	
Sleeping disorders (%)			<0.001
Yes	446 (61.5)	700 (35.8)	
No	279 (38.5)	1,258 (64.2)	
WC (%)			<0.001
Normal	302 (41.5)	1,311 (65.8)	
Abdominal obesity	425 (58.5)	680 (34.2)	
Family history of hypertension (%)			<0.001
Yes	162 (22.3)	842 (42.3)	
No	458 (63.0)	842 (42.3)	
Unknown	107 (14.7)	307 (15.4)	
Daily salt intake (g/d)			0.244
<4	270 (37.1)	675 (33.9)	
4–6	196 (27.0)	543 (27.3)	
> 6	261 (35.9)	773 (38.8)	
Sedentary time (h/d)			0.001
< 3	300 (41.3)	701 (35.2)	
3–6	271 (37.3)	727 (36.5)	
> 6	156 (21.4)	563 (28.3)	
Energy intake (kcal/d)	1,546.9 (1,194.7, 2,006.8)	1,605.6 (1,251.1, 2,076.4)	0.037

WC, waist circumference. Abdominal obesity was defined as waist circumference ≥ 85 cm and ≤ 90 cm for women and men, respectively. Data are presented as median (p25, p75) for continuous measures and n (%) for categorical measures. P-values were determined by chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

TABLE 2 | Factor loading of dietary patterns.

	Rice-vegetable	Fast food	Fruit-dairy	Wheat-meat
Rice and products	0.59	–	–	–
Vegetables	0.69	–	–	–
Aquatic products	0.57	–	–	–
Red meat	0.40	–	–	0.56
Other crops and potatoes	0.28	–	0.31	–
Eggs	0.36	–	0.20	0.23
Soybean and products	0.27	0.41	–	–
Phycomycete	0.30	0.39	–	–
Nuts	0.28	0.36	–	–
Poultry	0.41	0.32	–	–
Fast food	−0.23	0.59	–	–
Snacks	–	0.38	–	–
Beverages	–	0.45	–	–
dairy	–	0.22	0.44	–
Fruit	–	–	0.63	–
Yogurt	–	–	0.45	–
Sweets	–	–	0.23	–
Desserts	–	–	0.20	−0.34
Pickles	–	–	−0.35	−0.31
Wheat and products	–	–	–	0.62
Alcohol	–	–	–	−0.31
Variance explained (%)	10.3	6.53	6.01	5.63

Absolute values <0.20 are indicated by a dash for simplicity.

desserts, pickles, wheat and wheat products, and alcohol. Dietary patterns were identified by factor analysis. The number of factors retained was determined using the scree plot (eigenvalues > 1) and the interpretability of every factor. Orthogonal (varimax) rotation was applied to improve interpretability and minimize the correlation between the factors. As a result, four dietary patterns were extracted, and dietary pattern scores were categorized into quartiles.

Association between each dietary pattern and hypertension was tested by binary logistic regression with adjustment for potential confounding factors. Three sensitivity analyses were performed to determine the robustness of findings in the primary analysis. First, we restricted the risk-association analyses to those participants without self-reported diabetes, dyslipidemia, coronary heart disease, stroke, and other chronic diseases. Second, we analyzed the risk associations among participants without self-reported hypertension to minimize the possibility of reverse causation. Third, we further examined the risk associations by taking the participants with prehypertension [defined as systolic BP ≥ 120 mmHg and < 140 mmHg or diastolic BP ≥ 80 mmHg and < 90 mmHg (24)] as a separate group using ordinal logistic regression models. All statistical tests were two-tailed, and a *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc.).

RESULTS

Participant Characteristics

Of the 2,718 eligible participants, 727 participants reported with hypertension. Compared to those without hypertension, individuals with hypertension were generally older and had abdominal obesity ($P < 0.001$). The participants with hypertension were more likely to be men, current smoker, alcohol drinker, and have high education level ($P < 0.001$). In addition, there were significant differences in energy intake, sleeping disorders, family history of hypertension, daily salt intake, and sedentary time ($P < 0.05$) between the participants with and without hypertension (**Table 1**).

Dietary Patterns

Four dietary patterns were identified, namely, the rice-vegetable pattern, the fast food pattern, the fruit-dairy pattern, and the wheat-meat pattern, respectively, based on their main food components. The rice-vegetable pattern was characterized by a high intake of vegetables, rice and products, and aquatic products. The fast food dietary pattern was highly correlated with intakes of fast food, beverages, soybean, and products. The fruit-dairy dietary pattern was related to high intakes of fruits, yogurt, and milk. The wheat-meat pattern was distinguished by high intakes of wheat, red meat, and desserts. The four dietary patterns accounted for 28.5% of the variance in the total food intake, as shown in **Table 2**.

Characteristics According to Dietary Patterns

The characteristics of the participants across the quartile of the four dietary patterns are presented in **Table 3**. Participants in the highest quartile of the rice-vegetable pattern were more likely to be older, male, current smoker, and alcohol drinker; have lower level of education; and exhibit a higher proportion of sleeping disorders, higher energy intake, abdominal obesity, and higher intake of salt than those in the lowest quartile ($P < 0.05$). Participants with higher adherence to the fast food pattern tended to be younger, had higher levels of education; and had more sedentary time ($P < 0.001$). In addition, there were also significant differences in the family history of hypertension and sleeping disorders across the fast food pattern ($P < 0.05$). Participants in the highest quartile of the fruit-dairy pattern were more likely to be younger, female, have higher level of education, never smoker, no drinking, and exhibit significantly lower WC and prevalence of hypertension than those in the lowest quartile ($P < 0.05$). Participants in the highest quartile of the wheat-meat pattern were more likely to be younger, male, and without hypertension than their counterparts in the lowest quartiles ($P < 0.001$). Moreover, there were significant differences in sleeping disorders, level of education, and family history of hypertension across the quartile of the wheat-meat pattern ($P < 0.05$).

Associations Between Dietary Patterns and Hypertension

As shown in **Table 4**, the fruit-dairy pattern was inversely associated with hypertension both in the crude model (P for trend = 0.029) and in the model adjusted for age, sex, energy, education, smoking, alcohol drinking, sleeping disorders, daily salt intake, sedentary time, WC, and family history of hypertension (P for trend = 0.002). Compared with the lowest quartile of the pattern, participants at the highest quartile had lower odds of hypertension (OR = 0.55; 95% CI: 0.40, 0.75; $P = 0.002$). Meanwhile, the wheat-meat pattern was also inversely associated with hypertension prevalence in crude model and model adjusted confounders (OR = 0.70; 95% CI: 0.51, 0.97; $P = 0.049$). In contrast, we did not observe significant associations between the other two patterns with hypertension (P trend > 0.05). In the first two sensitivity analyses, the association between the fruit-dairy pattern and hypertension remained consistently significant. However, this risk association was rendered statistically non-significant between the wheat-meat pattern and hypertension (data not shown). As shown in **Supplementary Table S1** , the association between the fruit-dairy pattern and hypertension remained significant if the participants with prehypertension were regarded as a separate group (OR = 0.67; 95% CI: 0.53, 0.84; $P = 0.001$).

DISCUSSION

In this study, we observed that the fruit-dairy pattern was independently and inversely correlated with hypertension. No significant associations were found for the other three dietary patterns identified after multivariable adjustments and by sensitivity analyses. The crude prevalence of hypertension in our study was 26.7%, which was at an intermediate level compared with the rates in other areas in China (estimated range: 18.0–44.7%) (25, 26).

Factor analysis deriving dietary patterns in our study yielded simple structure and great interpretability (27). It has been widely used to explore the association between multiple dietary components and chronic diseases, which allows for comparisons in different regions (28).

The Four Dietary Patterns and Hypertension

The fruit-dairy pattern was associated with a lower risk of hypertension, which was consistent with the previous studies (29, 30). A cohort study conducted in Shanghai suggested that more adherence to a fruit and milk pattern characterized by fruit and milk was associated with a decreased prevalence of both pre-hypertension and hypertension (31). The fruit and milk pattern was similar to the fruit-dairy pattern identified in our study in that fruit and yogurt were the primary components of the pattern. A number of mechanisms may explain this finding.

First, nutrients included in fruits and dairy have been reported to be effective in lowering BP (32, 33). Marques et al. (34) found that a high intake of dietary fiber from fruit has a protective effect on hypertension and other cardiovascular diseases *via* changing gut microbiota. Second, when we examined each individual fruit in the fruit-dairy pattern, a strong positive association was observed for apples and citrus fruits. It has been reported that the consumption of apples and citrus fruits may help to regulate BP (35). Nutrients, including vitamin C, potassium, and magnesium, rich in apples and citrus fruits, may play important roles in BP regulation pathways (36). Indeed, we observed that the participants in the highest quartile of the fruit-dairy pattern were more likely to have higher intakes of vitamin C, potassium, and magnesium than those in the lowest quartile ($P < 0.01$).

TABLE 3 | Sociodemographic, lifestyle, and anthropometric characteristics of the study participants across quartiles of the dietary patterns scores (n = 2,718).

	Rice–vegetable		Fast food		Fruit–dairy		Wheat–meat	
	Q1	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**
Age	41 (33, 58)	51 (37, 62)**	54 (38, 64)	39 (32, 56)**	52 (36, 63)	43 (33, 59)**	54 (38, 64)	41 (34, 57)**
Male (%)	269 (39.6)	414 (61.0)**	337 (49.6)	345 (50.8)	402 (59.2)	244 (35.9)**	299 (44.0)	392 (57.7)**
Education (%)								
Low	93 (13.7)	112 (16.6)**	134 (19.8)	75 (11.1)**	142 (20.9)	72 (10.7)**	137 (20.3)	89 (13.2)**
Medium	115 (16.9)	184 (27.3)	183 (27.0)	118 (17.5)	185 (27.3)	122 (18.1)	186 (27.6)	128 (19.0)
High	471 (69.4)	379 (56.2)	360 (53.2)	482 (71.4)	351 (51.8)	481 (71.3)	352 (52.2)	458 (67.9)
Smoking (%)								
Never smoker	538 (79.2)	452 (67.1)**	472 (70.0)	512 (75.5)	417 (61.5)	573 (84.9)**	497 (73.4)	468 (69.3)
Ex–smoker	31 (4.6)	52 (7.7)	50 (7.4)	31 (4.6)	47 (6.9)	33 (4.9)	44 (6.5)	41 (6.1)
Current smoker	110 (16.2)	170 (25.2)	152 (22.6)	135 (19.9)	214 (31.6)	69 (10.2)	136 (20.1)	166 (24.6)
Alcohol drinking (%)								
Yes	182 (27.0)	249 (37.1)**	216 (32.0)	212 (31.5)	254 (37.6)	167 (24.8)**	221 (32.8)	232 (34.5)
No	492 (73.0)	423 (62.9)	460 (68.0)	461 (68.5)	422 (62.4)	507 (75.2)	453 (62.2)	441 (65.5)
Sleeping disorders (%)								
Yes	251 (37.5)	309 (46.3)*	306 (45.5)	266 (39.9) *	292 (43.8)	294 (44.0)	328 (44.9)	280 (42.0)*
No	419 (62.5)	358 (53.7)	367 (54.5)	401 (60.1)	375 (56.2)	374 (56.0)	343 (51.1)	387 (58.0)
WC (%)								
Normal	414 (61.0)	360 (53.0)**	376 (55.4)	410 (60.4)	380 (56.0)	433 (63.8) *	365 (53.8)	420 (61.9)*
Abdominal obesity	265 (39.0)	319 (47.0)	303 (44.6)	269 (39.6)	299 (44.0)	246 (36.2)	314 (46.2)	259 (38.1)
Family history of hypertension (%)								
Yes	311 (45.8)	351 (51.7)	318 (46.8)	321 (47.3)*	299 (44.0)	347 (51.1)	344 (50.7)	286 (42.1)**
No	262 (38.6)	224 (33.0)	268 (39.5)	239 (35.2)	251 (37.0)	238 (35.1)	216 (31.8)	287 (42.3)
Unknown	106 (15.6)	104 (15.3)	93 (13.7)	119 (17.5)	129 (19.0)	94 (13.8)	119 (17.5)	106 (15.6)
Daily salt intake (g/d)								
< 4	246 (36.2)	225 (33.1)*	245 (36.1)	225 (33.1)	235 (34.6)	249 (36.7)	245 (36.1)	242 (35.6)
4–6	212 (31.2)	173 (25.5)	203 (29.9)	184 (27.1)	170 (25.0)	192 (28.3)	174 (25.6)	179 (26.4)
> 6	221 (32.6)	281 (41.4)	231 (34.0)	270 (39.8)	274 (40.4)	238 (35.1)	260 (38.3)	258 (38.0)
Sedentary time (h/d)								
< 3	215 (31.7)	271 (39.9)*	273 (40.2)	199 (29.3)**	277 (40.8)	239 (35.2)	247 (36.4)	236 (34.8)
3–6	258 (38.0)	244 (35.9)	253 (37.3)	257 (37.9)	232 (34.2)	241 (35.5)	252 (37.1)	271 (39.9)
> 6	206 (30.3)	164 (24.2)	153 (22.5)	223 (32.8)	170 (25.0)	199 (29.3)	180 (26.5)	172 (25.3)
Hypertension (%)	141 (20.8)	210 (30.9)**	210 (30.9)	137 (20.2)**	223 (32.8)	142 (20.9)**	246 (36.2)	140 (20.6)**
Energy intake (kcal/d)	1,280.7 (1,026.6, 1,596.1)	2,134.0 (1,647.0, 2,820.4)**	1,483.6 (1,153.9, 2,002.6)	1,864.6 (1,495.2, 2,378.4)**	1,574.2 (1,223.5, 2,063.7)	1,764.1 (1,418.6, 2,274.3)**	1,450.1 (1,130.8, 1,909.0)	1,989.6 (1,619.2, 2,464.2)**

*Q, quartile; WC, waist circumference. *P for trend < 0.05, **P for trend < 0.001.*

Data are presented as median (p25, p7 + 5) for continuous measures and n (%) for categorical measures. P–values were determined by chi–square tests for categorical variables and Kruskal–Wallis tests for continuous variables.

TABLE 4 | Adjusted odds ratio (95% CI) for the association between dietary patterns and hypertension (n = 2,718).

	Quartile (Q) of the dietary pattern scores				***P–trend***
	Q1	**Q2**	**Q3**	**Q4**	
Rice–vegetable					
Model 1	1 (Reference)	1.19 (0.88, 1.59)	1.22 (0.91, 1.63)	1.23 (0.91, 1.65)	0.509
Model 2	1 (Reference)	1.19 (0.88, 1.62)	1.25 (0.91, 1.72)	1.23 (0.86, 1.75)	0.539
Model 3	1 (Reference)	1.91 (0.87, 1.63)	1.22 (0.88, 1.69)	1.13 (0.79, 1.62)	0.629
Fast food					
Model 1	1 (Reference)	1.14 (0.87, 1.48)	1.19 (0.90, 1.57)	1.02 (0.76, 1.37)	0.584
Model 2	1 (Reference)	1.12 (0.85, 1.49)	1.15 (0.86, 1.54)	1.05 (0.77, 1.44)	0.777
Model 3	1 (Reference)	1.14 (0.86, 1.52)	1.13 (0.83, 1.52)	1.08 (0.78, 1.43)	0.810
Fruit–dairy					
Model 1	1 (Reference)	0.94 (0.71, 1.23)	0.95 (0.72, 1.25)	0.67 (0.50, 0.89)	0.029
Model 2	1 (Reference)	0.88 (0.66, 1.17)	0.91 (0.68, 1.22)	0.59 (0.43, 0.80)	0.006
Model 3	1 (Reference)	0.83 (0.62, 1.12)	0.85 (0.63, 1.15)	0.55 (0.40, 0.75)	0.002
Wheat–meat					
Model 1	1 (Reference)	0.74 (0.56, 0.97)	0.65 (0.49, 0.86)	0.62 (0.47, 0.82)	0.003
Model 2	1 (Reference)	0.78 (0.59, 1.04)	0.70 (0.52, 0.94)	0.66 (0.48, 0.91)	0.041
Model 3	1 (Reference)	0.76 (0.57, 1.02)	0.70 (0.52, 0.95)	0.70 (0.51, 0.97)	0.049

WC, waist circumference.
Model 1, adjusted for sex and age. Model 2, further adjusted for energy intake, education, smoking, alcohol drinking, sleeping disorders, daily salt intake, sedentary time, and WC. Model 3, additionally adjusted for family history of hypertension.

Third, milk and yogurt are rich sources of both calcium and vitamin D, which have been shown to work together in vascular smooth muscle cells to regulate BP through the regulation of intracellular calcium concentrations (37). Fourth, the fruit-dairy pattern can indirectly lower BP *via* body weight regulation, whereas overweight/obese is one of the major risk factors for hypertension (38). A study comprising two cohorts showed that increased intake of fruit was beneficial to mitigate body weight (39). Panahi et al. (40) demonstrated that frequent yogurt consumption meant a healthier diet quality, as consumption of yogurt can effectively control body weight, energy homeostasis, and glycemic level, thus contributing to better metabolic health. Fifth, our study indicates that subjects who belonged to the highest quartile of the fruit-dairy pattern were more likely to be alcohol abstainers and have a normal WC, compared with those in the lowest quartile. Emerging evidence has shown that alcohol drinking and abdominal obesity were closely related to the elevation of BP (41–43).

In our study, the fruit-dairy pattern was a new pattern compared with a previous study conducted in Eastern China in 2016 (15), which implies that the eating habits have been in transition in this area (44). Meanwhile, the fruit-dairy pattern was inversely associated with hypertension, which provides a new direction to prevent and control hypertension among community residents in Eastern China.

The other three patterns were not significantly associated with hypertension in our study. The null association of the rice-vegetable observed in our study was inconsistent with a previous report (15). The potential antihypertensive effect of vegetable consumption may be offset by the detrimental effect of polished rice, oil, and salt use (when stir-frying vegetables in Chinese cuisine) (45). Another explanation is that rice and vegetable in the region may have relatively high levels of lead and cadmium (16, 17), which were related to BP. For the fast food pattern, our finding was supported by a cross-sectional study, including 2,560 Chinese participants, which showed that Western fast food patterns were not associated with hypertension (46). The fast food pattern was similar to the high fast food pattern, which was reported as a risk factor for cardiovascular disease (47), but participants with better adherence to the fast food pattern tended to be younger and had fewer sleeping disorders in our study. Younger and better sleeping quality has been considered as protective factors for BP (48, 49). Moreover, participants in the highest quartile of the fast food pattern were more likely to have higher nuts intake than those in the lowest quartile ($P < 0.001$). Nuts are potentially protective against hypertension because of their complex compositional characteristics, such as high amounts of beneficial minerals (calcium, magnesium, and potassium) and low level of sodium (50). The wheat-meat pattern was somewhat comparable with the modern pattern reported by the China Health and Nutrition Survey (51). Although red meat intake was recognized as a risk factor for hypertension, this pattern was inversely associated with the consumption of desserts, another risk factor for BP (52). The participants in the highest quartile of the wheat-meat pattern were more likely to avoid dessert intake than those in the lowest quartile ($P < 0.05$).

Strengths and Limitations

The main strengths of this study include its representative sample of the residents in Suzhou, Eastern China, and the latest evidence on dietary patterns and hypertension, which could provide new insight into the prevention of hypertension in this area. However, limitations also need to be considered in the interpretation of our findings. First, bias may exist for dietary data collected by a 24-h dietary recall. A 24-h dietary recall may not be able to well reflect long-term eating habits among the participants (53). Second, we were unable to assess the salt intake using 24-h urine sodium excretion considered as the least biased method, since urine samples were not collected (54). Third, although a wide range of sociodemographic and health-related variables were included as potential covariates in this study, residual confounding may still exist. Fourth, the cross-sectional design of this study limited causal inference, and reverse causation cannot be completely precluded.

CONCLUSION

This study provided the latest evidence on the association between dietary patterns and hypertension among community residents in Eastern China. Four dietary patterns were derived in this study by using factor analysis. We observed that the fruit-dairy pattern was inversely associated with the risk of hypertension among the study participants. We suggest that it is necessary to consider the whole diet when making hypertension prevention recommendations for policy-makers. Also, more prospective studies are warranted to determine the relationship between dietary quality and hypertension in different areas in China.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Suzhou Center for Disease Control and Prevention (SZJK2018-YY001). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CW formulated the research questions. YZhe and CW analyzed the data, interpreted the findings, and wrote the manuscript. YZha, DL, and LG compiled the drawings, proofread, and corrected the original manuscript. BW and HZ designed the study, supervised the work, critically revised the manuscript, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.926390/full#supplementary-material

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EDITED BY
Mainul Haque,
National Defence University, Malaysia

REVIEWED BY
Iffat Jahan,
Eastern Medical College and Hospital, Bangladesh
Susmita Sinha,
Khulna City Medical College and Hospital, Bangladesh

*CORRESPONDENCE
Mansura Khanam
mansura@icddrb.org

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Effects of *Moringa oleifera* leaves on hemoglobin and serum retinol levels and underweight status among adolescent girls in rural Bangladesh

Mansura Khanam[1]*, Kazi Istiaque Sanin[1], Gulshan Ara[1], Razia Sultana Rita[1], Anika Bushra Boitchi[1], Fahmida Dil Farzana[1], Md. Ahshanul Haque[1] and Tahmeed Ahmed[1,2,3]

[1]Icddr, b, Nutrition and Clinical Services Division, Dhaka, Bangladesh, [2]Department of Global Health, University of Washington, Seattle, WA, United States, [3]Department of Public Health Nutrition, James P. Grant School of Public Health, Bangladesh Rehabilitation Assistance Committee University, Dhaka, Bangladesh

Objectives: *Moringa oleifera* has been used for centuries due to its medicinal properties and health benefits. The plant has antifungal, anti-viral, and anti-inflammatory properties. We aimed to evaluate the effect of consumption of Moringa leaves, along with a regular diet on serum hemoglobin and retinol and underweight status among rural Bangladeshi adolescent girls.

Methods: This school-based quasi-experimental study involved 226 adolescent girls (12–14 years-old). Intervention group (n = 113) received a meal comprising rice, concentrated dal, and fried potato with Moringa pakora (oil-fried snack); the control group (at a different school in an adjacent area with similar population demographics) received calorie-matched meal without Moringa pakora for 6 months. We used generalized liner regression (GLM) analysis, to explore the effect of the intervention among the groups between baseline and endline.

Results: Mean age of the intervention and control groups were 12.7 ± 0.7 and 13.3 ± 0.8 years, respectively. After adjusting for maternal education, absenteeism, asset index, BMI-for-age Z-score, GLM regression showed significant positive changes in hemoglobin (intervention vs. control: coef = 0.41, P = 0.010) and serum retinol (coef = 0.27, P = 0.00). No significant changes in weight was observed between groups.

Conclusion: Consumption of Moringa leaves has the potential to improving hemoglobin and serum retinol level and should be encouraged as regular diet.

KEYWORDS
Moringa, hemoglobin, vitamin A, underweight, adolescent girls

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Introduction

Adolescence, a unique period of human growth linking childhood and adulthood, includes 10–19 year-olds and is further divided into early adolescence (10–14-years-old) and late adolescence (15–19-years-old) (1). This period is considered the second window of opportunity to mitigate or even reverse the ill effects of inadequate development and nutritional deficiencies that may have existed since early childhood (2). Adolescents have additional nutritional requirements compared to adults, as they gain about 40% of their adult weight and 15% of their adult height during this period (3). Moreover, adolescent girls have a greater need for nutrient-dense food, to fulfill the demands caused by the onset of menstruation (4). Hence, insufficient nutritional intake during such crucial period has grave consequences throughout the reproductive years and beyond. Unfortunately, this larger demand for nutritious food almost always remains unmet among vulnerable adolescent girls residing in low-and-middle income countries (5).

Bangladeshi adolescents aged 10–19-years-old account for over one-fifth of the country's total population, including 14.4 million girls (6, 7). Two common factors that underlie the poor nutritional status of Bangladeshi adolescent girls are poor diets and early childbearing. Nearly 1 in 3 adolescent girls are thin, and 11% of girls are moderately or severely thin. The majority of them are micronutrient deficient, including iodine, zinc, and iron (8). A World bank report stated the proportion of adolescent girls having inadequate dietary diversity increased to 64% between 2012 and 2014 (9). About 80% of the kilocalories consumed per day by adolescents are derived from micronutrient-poor foods (70% from rice alone), particularly among girls from poor families (10). To mitigate this crisis, that report highlighted six prioritized interventions targeted at adolescent boys and girls that are proven to reduce undernutrition, which included weekly iron-folic acid (IFA) supplementation, school-based nutrition education, and provision of mid-day meals or fortified snacks at schools (11).

Moringa oleifera leaves have been found to contain the majority of essential nutrients required to maintain good health (12–15). The powdered form of the leaf is rich in multiple minerals and vitamins including iron, vitamin A (carotenoid), and vitamin C. Moreover, Moringa may help to resolve multiple malnutrition problems as it contains all essential amino acids, the building blocks for the proteins crucial to cell growth and metabolism (12, 16, 17). Based on Moringa's nutritional value and availability, and the emphasis given to the provision of fortified meals at school, we aimed to assess the effect of *M. oleifera* leaves to improve hemoglobin and retinol levels and reduce underweight status among adolescent girls in rural Bangladesh.

Materials and methods

Study design

We implemented a school-based intervention using a quasi-experimental design to evaluate the effect of consumption of Moringa leaves (along with regular diet and nutrition education) on the micronutrient status of adolescent girls in rural Bangladesh. To implement the study in a school-based setting, random assignment of students was not possible as it would be unethical to include some children from one class and not include other children.

Study site

The study was conducted in Muktarpur union (the smallest rural administrative and local government units in Bangladesh) of Kaliganj sub-district, a semi-urban area located near to Dhaka, the capital of Bangladesh.

Randomization procedure

We listed the schools in the region, consulted with the headmasters and school committee members, visited the facilities, and obtained the student's list. Of the six high schools in Muktarpur Union, three were excluded as only limited numbers of adolescent girls attended there. We discussed the purpose and objectives of the study with the local stakeholders and chairman. After getting their approval, we randomly selected one school for the intervention and another school as a control group.

Study participants

Our intervention was focused on the early adolescent period, when the rate of human growth is the highest outside early infancy. In Bangladesh, children in our target age group of 12–14 years usually study at class VI-VIII. After the selection of participating schools, list of female students in these classes were obtained from the schools. Age of the students was verified through birth certificate/immunization cards (if available) or admission information from the school archives. All female students in classes VI-VIII were screened. A total of 180 girls from intervention schools and 156 girls from control schools was screened and 226 adolescent girls (113 in each schools) completed the trial and returned follow-up questionnaires (Figure 1). Before starting the intervention, we conducted meetings with the parents at both schools to inform them of the nature of the

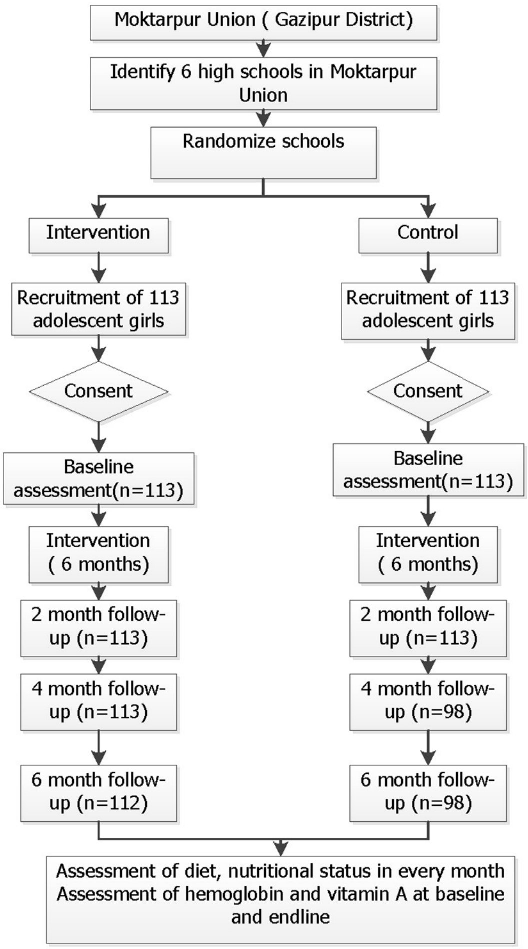

FIGURE 1
Study profile.

intervention and data collection procedures. We visited the houses of all selected students to obtain the parents' consent and the student's assent. Only adolescent girls who gave assent themselves with their parents' consent were enrolled in the study.

Inclusion and exclusion criteria

Unmarried adolescent girls aged 12–14-years-old who attended the selected high schools were eligible for the study. Participants were excluded if they were taking any other nutritional supplements (vitamins and minerals), as this may affect the levels of hemoglobin and other micronutrients that we intended to measure. Adolescent girls with documented medical records of chronic disease were also excluded. However, we provided the meal to every girl due to ethical reason but collected data from only the recruited participants.

Sample size

We assumed a mean hemoglobin level of 12.0 g/dL in the control group (18), mean hemoglobin level of 13.8 g/dL in the intervention group after the intervention, 80% power, 95% confidence interval, standard deviation (SD) of 4.50, and a 15% dropout rate. Based on the assumptions, the minimum sample size required was 226 individuals (113 in each arm). Furthermore, this sample size had 98% power to detect a change in serum retinol (control: 1.51; intervention: 1.74; SD: 0.42) and 87% power to detect a change in mean weight (control: 45.10; intervention: 48.10; SD: 7.0) between arms.

Intervention

The intervention package included (1) a school-based mid-morning meal containing Moringa leaves (150 g) cooked traditionally as pakora (oil-fried snack), and (2) behavior change communication (BCC) on nutrition and dietary habits, personal health, and hygiene issues that magnify the risk of malnutrition for 6 months.

Each adolescent girl from the intervention group received Moringa leaves cooked as pakora along with 30 g rice and 25 g concentrated dal, once daily, for 5 days/week at tiffin time. The control group received 30 g rice, 25 g concentrated dal and 25 g fried potato (*aluvaji*), once daily for 5 days/week. Each tiffin box was numbered so that leftover food could be measured daily for each participant. A standard food record form was used to measure food compliance. The tiffin meals provided to both arms supplied 411 kilocalories.

Preparation of the meals

We recruited two local cooks who were responsible for preparing the meals daily under direct supervision of the field staff. Two field staff monitored and measured the cooking procedure and placed the meals in the food boxes using measuring cups to measure 30 g of rice and 25 g of concentrated dhal. To prepare Moringa pakora, 150 g granules of fresh *sajna* (Moringa) leaves were mixed with mashed lentils, and then onion, chili and salt were added and mixed to make a paste. A portion of ∼50 g paste was fried as pakora. Each student received 3 pakora/ day. Three pakoras provided 282 kilocalories/person/day.

Behavior change communication (BCC)

Two locally recruited health workers conducted bi-monthly counseling on nutrition and dietary habits, personal health, and menstrual hygiene, targeting the female adolescents from both arms in small groups after the school day had ended. The duration of each session was usually 30–40 min.

Data collection

A team of field staff was responsible for implementing the study under the guidance of the Investigator(s). Before starting the field activities, 5 days of intensive training was provided to the field staff. The emphasis of the training was interview techniques and understanding the questionnaire. Field staff also received training on anthropometric measurements following the standard WHO guidelines (19).

Before the survey, the questionnaire was thoroughly discussed, extensive field-testing was conducted, and necessary modifications were made. The structured questionnaire was used to collect information on socioeconomic status and demographics, health and morbidity, food consumption patterns, and other relevant information.

Household demographics

Information on ethnicity, religion, level of education of household head, occupation of household head, number of family members, ownership of the house, number of dwelling rooms, household construction materials, toilet facilities, sources of drinking water, household assets, land ownership, and household monthly expenditure were collected as key indicators of socioeconomic status.

Feeding history of adolescent girls

Data on food items were collected using an adapted version of FANTA's Minimum Dietary Diversity for Women. The categories are: (1) grains, white roots, tubers, and plantains; (2) pulses (beans, peas, and lentils); (3) nuts and seeds; (4) dairy; (5) meat, poultry, and fish; (6) eggs; (7) oils and fats; (8) fruits; (9) vegetables; and (10) condiments and seasonings, etc. (20).

Weighed food record

Consumption of the provided mid-morning meals was measured daily using a standard food record form to measure compliance to the food.

Anthropometric measurements

Trained field staff was collected anthropometric measurements (weight and height) monthly using established methods (21) and record these measurements on the questionnaire. The weight of each adolescent in school uniform without shoes were measured in kilograms using a portable Tanita Scale with an accuracy of 100 g. Height was recorded with the adolescents' head level with a horizontal Frankfurt plane (below the imaginary line from the lower border of the eye orbit to the auditory meatus) without shoes using a wooden height measuring board with a sliding head bar to the nearest 0.1 cm. All measurements had taken twice, unless the difference between the two readings is beyond acceptable accuracy. All instruments were calibrated every morning against a standard weight and a height stick.

Morbidity questionnaire

Trained field staff asked all participants standard questions about recent morbidity within the previous 15 days using pre-coded questionnaires designed for recording specific morbidity symptoms. The morbidity recall period was 2 weeks. Urinary tract infections and symptoms of menstrual problems and experiences regarding school absenteeism was also collected monthly.

Assessment of hemoglobin

Anemia assessment was done by considering the hemoglobin concentration of capillary blood using HemoCue 301 device (HemoCue AB, Angleholm, Sweden). Trained research staff was conducted the assessments. After asepsis by chlorhexidine gluconate at 0.5%, the disposable lancet on the fingertip (middle or ring or index) made a puncture. The first drop of blood was discarded. The second drop made to form by gentle pressure. Once the sample is formed, the micro cuvette was dipped into it to fill it up with the blood sample by capillary action.

Assessment of serum retinol

Peripheral blood samples were collected from all participants in the intervention and control groups at baseline, 3 months and endline. The blood samples were labeled using bar-coded identification labels specifically created for this study that correspond to the subject's identification number. Thus, the laboratory had easily identified which particular cluster scan been tested in a batch and thus minimize repeated freeze/thaw cycles. A sample record/handover form, including the name of the participant, ID number, sample ID number and type of analysis, was completed. Samples were transported to the nutritional biochemistry laboratory in Dhaka in a temperature-controlled cool box and stored in a −70°C freezer at the laboratory until blood parameters were quantified by high-performance liquid chromatography (HPLC).

Delivery of the intervention

Trained staff were responsible for delivering the food in the classrooms with the help of two locally recruited field staff. They went to the classroom during tiffin time, provided the meals to the students, and informed the students not to throw food out as the leftover food was measured. Each tiffin box had an identifier number for each participant to measure the remaining food. Every class also had male students, and we also offered them the food, if they wanted it. However, their intake was not measured or monitored. Total intervention period was 6 months.

Ethical approval

This study (PR-19060) was approved by the Research Review Committee and Ethical Review Committee, the two compulsory components of the institutional review board of the International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b). Written informed consent was obtained from all study participants (>18-years-old) and/or assent (<18-years-old) from their parents/guardians prior to enrolment.

Study outcomes

The primary outcomes were the differences in the mean changes in the adolescent girls' hemoglobin and retinol levels from baseline to endline between the intervention group and control group. The secondary outcome was the difference in weight gain between the intervention group and the control group.

Data management

A senior research officer was responsible for regular observations at the schools and checking the data for validity and completeness. The staff independently repeated the data collection for 3–5% of the study participants on the same day using a field-tested format.

After completion of data collection, data were entered into Microsoft (MS) Access software. Maximum validation rules were set in the data system to prevent errors during data entry. After completing the entry, data were transferred to Stata (Release 14, College Station, Texas 77845, USA: StataCorp LP) software.

Data analysis

Descriptive analysis

Statistical plots such as histograms, scatter plots were used for data visualization. Descriptive statistics were used to compare frequencies and proportions for categorical variables, and means and standard deviations for symmetric quantitative variables.

TABLE 1 Household characteristics of the participants by group.

Household characteristics	Intervention [$N = 113$]	Control [$N = 113$]
Sex of household head		
Male	79.7 (90)	85.8 (97)
Female	20.3 (23)	14.2 (16)
Religion		
Islam	111 (98.2)	108 (95.6)
Hinduism	2 (1.8)	5 (4.4)
Number of rooms used for sleeping		
1–2	65 (57.5)	66 (58.4)
>2	48 (42.5)	47 (41.6)
Mother's occupation		
Service holder	14 (12.4)	11 (9.7)
Housewife	99 (87.6)	102 (90.3)
Father's occupation		
Agricultural laborer	21 (18.5)	27 (23.9)
Service	14 (12.4)	9 (7.9)
Business	14 (12.4)	21 (18.6)
Factory worker	9 (8.0)	7 (6.2)
Construction laborer	7 (6.2)	9 (8.0)
Unemployed	48 (42.5)	40 (35.4)
Mother's education		
Illiterate	15 (13.3)	8 (7.08)
Primary completed	49 (43.36)	70 (61.9)
Secondary and higher	49 (43.36)	35 (30.9)
Father's education		
Illiterate	27 (23.9)	8 (7.08)
Primary completed	42 (37.1)	81 (71.7)
Secondary and higher	44 (38.9)	24 (21.2)
The main source of drinking water		
Own tube well	83 (73.4)	82 (72.6)
Other's tube well	2 (1.8)	6 (5.3)
Community tube well	1 (0.9)	0 (0)
Supply water (piped)	0 (0)	1 (0.9)
Deep tube well	27 (23.9)	24 (21.2)
Toilet facility of household members		
Sanitary with flush	4 (3.6)	17 (15.1)
Sanitary without flush	47 (41.6)	58 (51.3)
Pucca/pit	57 (50.4)	37 (32.7)
Kutcha/Hanging	5 (4.4)	1 (0.9)
Toilet facility used for children		
Sanitary with flush	4 (3.6)	17 (15.1)
Sanitary without flush	47 (41.6)	58 (51.3)
Pucca/pit	55 (48.7)	34 (30.1)
Kutcha/Hanging	6 (5.2)	1 (0.9)
Others	1 (0.9)	3 (2.6)
Share of toilet facility with other households		
Yes	11 (9.7)	27 (23.9)

(Continued)

TABLE 1 Continued

Household characteristics	Intervention [$N = 113$]	Control [$N = 113$]
No	102 (90.3)	86 (76.1)
Ownership of the house		
Owns the house	102 (90.3)	110 (97.3)
Rented	2 (1.8)	1 (0.9)
In kind	9 (7.9)	2 (1.8)
Wealth quintile*		
Poor	20 (17.7)	26 (23.0)
Poorer	24 (21.2)	21 (18.6)
Middle	20 (17.7)	25 (22.1)
Richer	22 (19.5)	23 (20.4)
Richest	27 (23.9)	18 (15.9)
Respondent characteristics		
Age (Y) (mean ± SD)	12.7 ± 0.7	13.3 ± 0.8
Year of schooling (mean ± SD)	6.52 ± 0.50	7.43 ± 1.09
Weight (kg)	42.4 ± 9.7	42.6 ± 8.3
Height (cm)	148.8 ± 7.5	149.7 ± 5.7
Hemoglobin (g/dL)	12.0 ± 0.7	11.8 ± 0.9
Serum retinol (μmol/l)	1.3 ± 0.3	1.4 ± 0.9

*Wealth quintile: The household wealth quintile was constructed using household asset data obtained from the Socioeconomic Status questionnaire. From these asset-related dichotomous variables, a common factor score for each household was generated using polychoric principal components analysis in STATA software. After ranking based on their score, we divided first principal component score into quintiles to create five categories where the first category represents the poorest household, and the fifth category represents the wealthiest household.

Exploratory analysis

We used the Student's t-test and the chi-square test to compare means and explore the associations among categorical variables. Coefficients were generated by generalized linear regression modeling (GLM), in which a dependent variable is regressed on the set of hemoglobin and retinol levels. Effect of intervention was adjusted for variables those were associated with the outcome during univariate regression such as maternal age, sex of household head, maternal education, BMI for age, wealth index and absentism of school. P-values < 0.05 were considered significant for all tests.

Results

Table 1 compares the household characteristics of the participating girls in the intervention and control groups. More than 90% of the household heads were male, and their main religion was Islam. The households in both groups had a similar number of rooms that were used for sleeping. More parents of participants from the control group had completed primary education, whereas more parents in the intervention group had completed secondary education. A higher proportion of mothers worked in the intervention group (12.39%) than in the control group (9.73%). Around 35.4% of the participants' fathers were unemployed in both groups; farming and business were the main occupations of the majority of the working fathers. About 73.4 and 72.6% of households in the intervention and control group used personal tube wells as the main source of drinking water. A higher percentage of households in the control group used sanitary latrines than in the intervention group.

The mean age of the adolescent girls in the intervention and control groups was 12.7 and 13.3 years, respectively; this difference was not statistically significant. The mean weight and height of the girls were similar in both groups. The mean hemoglobin level was 12.0 and 11.8 g/dL for the intervention and control groups, respectively. Serum retinol was similar in both groups (1.3 μmol/l).

Figures 2A,B presents the mean weight and height of the adolescent girls at baseline and endline. Increases in both height and weight were observed during follow-up in both the intervention and control groups; however, the changes in height and weight between baseline and endline were greater in the intervention group than the control group. The mean weight of the adolescent girls was 42.0 kg at baseline. At endline, the mean weight of the intervention group increased more than that of the control group (46.64 vs. 45.28 kg).

At baseline, the girls in the intervention group (148.85 cm) were marginally shorter than the girls in control group (149.70 cm). However, at the end of the follow-up, the height of the girls in the intervention group had increased more than the height of the girls in the control group (153.43 vs. 152.87 cm). On average, participants in the intervention group became 0.56 cm taller than the girls in the control group, however, the association was not statistically significant.

The primary outcomes were mean hemoglobin and serum retinol levels, as presented in Table 2. We performed generalized linear regression modeling to assess the effect of the intervention by adjusting for (i) differences between the control and intervention groups (potential confounding factors) and (ii) temporal trends in the outcome unrelated to the intervention. After adjusting for maternal education, household head sex, absenteeism, asset index, and BMI-for-age Z-score, GLM analysis showed a significant positive change in the hemoglobin level (intervention compared to control: coef = 0.41; 95% CI: 0.14, 0.76; $P = 0.010$). A significant positive change in the retinol level was also observed between the intervention group compared to the control group (coef = 0.27; 95% CI: 0.14, 0.36; $P = 0.00$). We did not observe any significant impact of the intervention on weight gain among the study participants.

Discussion

This study aimed to assess the effect of consumption of Moringa leaves (alongside normal staple foods) on the nutritional status of adolescent girls in Bangladesh. To our

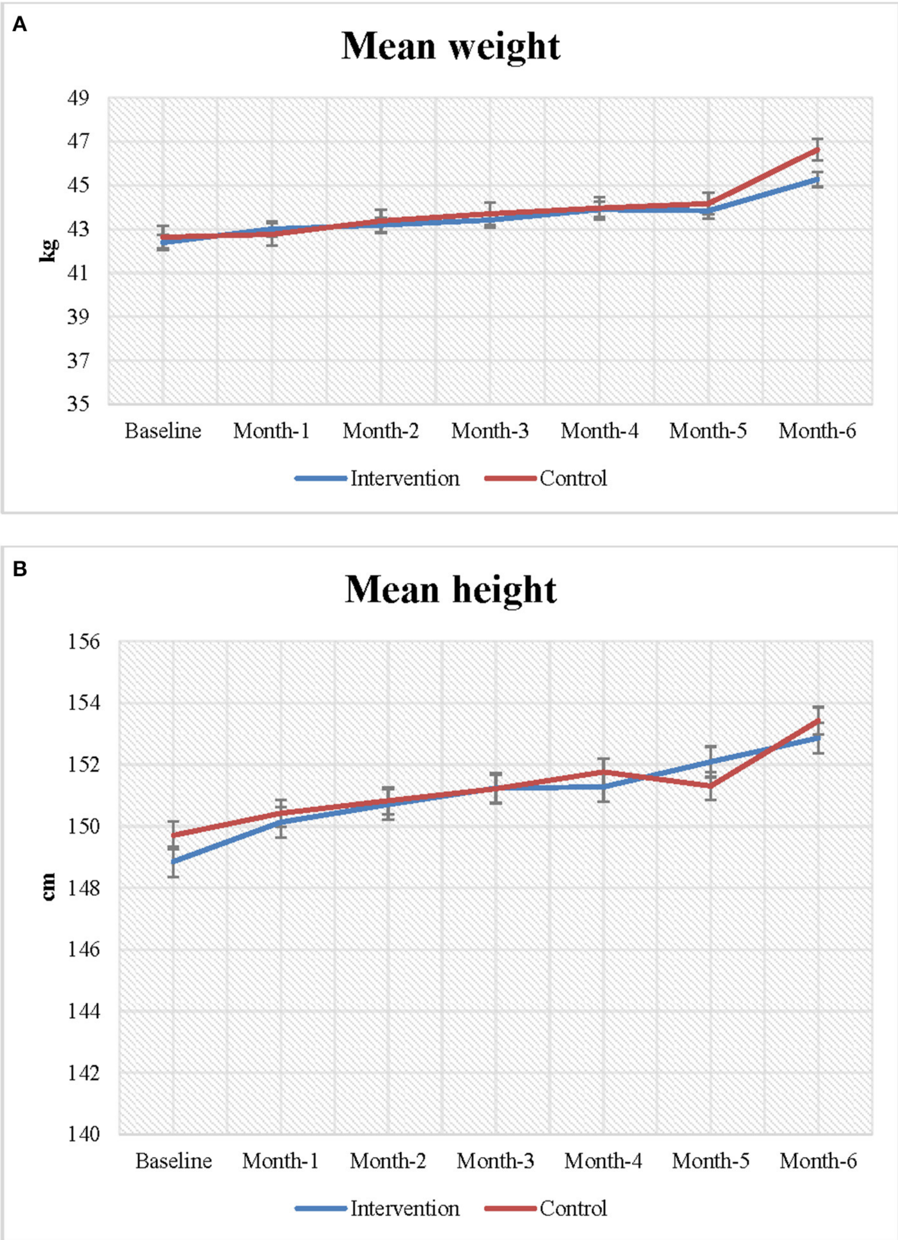

FIGURE 2
(A,B) Changes in nutritional status among the study participants.

best knowledge, this is the first study to assess the nutritional effects of Moringa in Bangladesh, which is widely available in the country and traditionally used to treat fever and diarrhea. However, there is limited scientific evidence to confirm the benefits of this potential plant-based food. Our school-based, quasi-experimental study demonstrates the beneficial effects of regular consumption of Moringa leaves on Bangladeshi female adolescents. Consumption of Moringa leaves as part of a daily nutritious snack, combined with nutrition BCC, significantly improved the average hemoglobin and retinol levels of the female adolescents aged 12–14 years.

The measurement of average hemoglobin level from our study echoes with the result of school-going children from the last National Micronutrient Survey done in 2011–12. At baseline, average hemoglobin level was higher in the intervention group compared to the control group, though, the differences were not statistically significant. In our study, although both groups had an increment of the hemoglobin

TABLE 2 Changes in biomarkers between the intervention and control groups.

Indicators	Baseline			Endline			Coef[b]	P-value
	Intervention ($n = 113$)	Control ($n = 113$)	Diff	Intervention ($n = 112$)	Control ($n = 99$)	Diff[a]		
Haemoglobin[b] (g/dL)	12.04	11.78	0.31	13.31	12.59	0.72	0.41 (0.14, 0.76)	0.009
Retinol (µmol/l)[b]	1.32	1.40	−0.07	1.38	1.19	0.19	0.27 (0.14, 0.36)	0.000
Weight (kg)[c]	42.39	42.64	0.25	46.64	45.28	−1.36	1.41 (−1.91, 4.72)	0.406
BMI for age[c]	−0.09	−0.24	−0.16	0.20	−0.05	−0.25	0.09 (−0.34, 0.51)	0.674

[a]Difference between control and Intervention at baseline and endline.
[b]Effects of the intervention over 6 months of follow-up using GLM with adjustment for maternal age, sex of household head, maternal education, BMI for age, wealth index, and absentism of school.
[c]Effects of the intervention over 6 months of follow-up using GLM with adjustment for maternal age, sex of household head, maternal education, wealth index, and absentism of school.

level at endline, the intervention group experienced a significant improvement. These results are in agreement with previous studies that showed consumption of Moringa leaves increased the mean hemoglobin level from 11.43 to 12.36 g/dL (22) and 10.43 g/dL to 10.85 gm/dl among women of reproductive age (15–45-years-old) from a poor segment of the Indian population (23). Moringa leaves have a high vitamin C content, which increases the bioavailability of iron (24). Vitamin C has also been shown to improve the absorption of iron from non-haem sources by up to 4-fold (25). As vitamin C and iron combine to form ferrous-ascorbate complexes that are soluble and easily absorbed, fresh vegetables and fruits high in vitamin C are particularly effective in improving hemoglobin level. Several studies showed that different side dishes made from Moringa also increase the absorption of non-haem iron from foods consumed; for instance, Suzana et al. found that side dishes and fruits and vegetables affected the haematocrit values among school aged-children that consumed Moringa in Ghana (26). Based on our positive finding; fresh Moringa leaves could potentially be promoted as a natural food-based supplement for improving hemoglobin level among women of reproductive age.

Our study demonstrates regular consumption of Moringa leaves significantly improved the serum retinol of school-going adolescent girls. Serum retinol is required for effective utilization of iron and to maintain normal hemoglobin levels (27). Significant correlations have been explored between the serum retinol concentration and hemoglobin, indicating a possible relationship between vitamin A status and the use of iron for haematopoiesis (28). *Moringa* leaves have a total carotene content of 40,000 µg and beta carotene content of 19,000 µg/100g, thus having equivalent bioavailability as synthetic vitamin A (29, 30). At the baseline, serum retinol was higher in our control group. However, with intervention, the serum retinol level significantly increased in the intervention group. A study conducted among 35 young Mexican children aged 17–35 months old demonstrated that consumption of moringa leaves improved the storage of retinol in the body (31). Another study conducted in Ghana found that supplementation of a cereal-legume blended flour with Moringa leaves increased mean vitamin A levels among children aged 4–12-years-old; however, this population was deficient in vitamin A at baseline (32). Glover-Amengo et al. (32) showed that the vitamin A status of school-age children could be improved by supplementing their diets with Moringa leaf powder. About 53.3% of school-age-children in Bangladesh have mild vitamin A deficiency (0.35–0.70 µmol/l). Our findings suggest that regular consumption of moringa leaves may be effective for the vitamin A deficient population in Bangladesh or in other vitamin A-deficient populations. As locally available food material, Moringa leaves may represent a cost-effective strategy to combat the prevalent problem of nutritional deficiencies and underweight status among adolescent girls in Bangladesh. Incorporating recipes with Moringa leaves in the daily diet could be employed as a preventive and maintenance strategy for better health outcomes.

A major strength of this study was the high response rate (98%) in each group, which enabled a fair statistical comparison. The Hemocue devices used to measure hemoglobin level were calibrated every day; the retinol samples were transported to the nutritional biochemistry laboratory at the icddr,b and analyzed in a blinded manner. Nevertheless, our work has some limitations. A limitation of the study was its quasi-experimental design, as it was not possible to mask the fieldworkers responsible for delivering the meals to the participants and recoding the data, or the participants to their group allocation.

Conclusion

Our school-based intervention showed that addition of Moringa leaves to the diet significantly improved the hemoglobin and retinol levels, among adolescent girls in Bangladesh. Incorporating recipes with Moringa leaves in the daily diet may provide a simple preventive and maintenance strategy to ameliorate micronutrient deficiency during this critical period of female growth and development, in achieving better health outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study (PR-19060) was approved by the Research Review Committee and Ethical Review Committee, the two compulsory components of the Institutional Review Board of the International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b). Written informed consent was obtained from all study participants (>18-years-old) and/or assent (<18-years-old) from their parents/guardians prior to enrolment. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MK and KIS conceptualized the study, drafted the original manuscript, and revised the final version of the manuscript. KIS contributed to drafting the manuscript and result interpretation. MK, KIS, GA, RSR, ABB, FDF, MAH, and TA had contributed to data analyses, interpretation, and write-up of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cardiovascular risk among 6-8-year-old children living in urban and rural communities in Ecuador: A cross-sectional analysis

Signe Vargas-Rosvik[1†], Nelly Lazo-Verdugo[1†], Samuel Escandón[1], Cristina Ochoa-Avilés[1], Lucy Baldeón-Rojas[2*] and Angélica Ochoa-Avilés[1*]

[1]Departamento de Biociencias, Universidad de Cuenca, Cuenca, Ecuador, [2]Instituto de Investigación en Biomedicina, Universidad Central del Ecuador, Quito, Ecuador

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EDITED BY
Mainul Haque,
National Defence University
of Malaysia, Malaysia

REVIEWED BY
Kona Chowdhury,
Gonoshasthaya Samaj Vittik Medical College, Bangladesh
Zakirul Islam,
Eastern Medical College & Hospital, Bangladesh

*CORRESPONDENCE
Lucy Baldeón-Rojas
lybaldeon@uce.edu.ec
Angélica Ochoa-Avilés
angelica.ochoa@ucuenca.edu.ec

†These authors have contributed equally to this work and share first authorship

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Cardiovascular diseases have their origins in childhood. At least 20% of children and adolescents in Latin America are overweight or obese. However, little is known regarding the cardiovascular risk of young children living in the region. This paper aims to identify associations between socio-demographics, adiposity, and dietary intake with cardiometabolic risk among children between 6- and 8-years old living in urban and rural Andean regions of Ecuador. A cross-sectional study was conducted among 267 children attending elementary schools between February and August 2018. Sociodemographic data were collected using a structured interview. Bodyweight, height, and waist circumference were measured in duplicate; blood samples were taken after overnight fasting to determine blood lipids, hepatic enzymes, and adipokines; food intake data was assessed by two 24-h recalls administered to the guardians. Associations between cardiometabolic risk (i.e., blood lipids, hepatic enzymes, and adipokines) with sociodemographic characteristics, dietary intake, and waist circumference were tested using multiple hierarchical regression models. Twenty-nine percent of the children were overweight or obese, 12% had low HDL levels, and over 18% had high levels of LDL and triglycerides. Children living in the urban region had lower levels of HDL (β −4.07 mg/dL; 95% CI: −7.00; −1.15; P = 0.007) but higher levels of LDL cholesterol (β 8.52 mg/dL; 95% CI: 1.38; 15.66; P = 0.019). Hepatic enzymes were also higher among urban children (SGOT: β% 22.13; 95% CI: 17.33; 26.93; $P < 0.001$; SGPT: β 0.84 U/L; 95% CI: 0.09; 1.59; P = 0.028). Leptin blood levels were higher (β% 29.27; 95% CI: 3.57; 54.97; P = 0.026), meanwhile adiponectin plasma concentrations were lower among urban children (β%−103.24; 95% CI: −58.9; −147.58; P = < 0.001). Fiber intake was inversely associated with total cholesterol (β−9.27 mg/dL; 95% CI −18.09; −0.45; P = 0.040) and LDL cholesterol blood levels (β−9.99 mg/dL; 95% CI: −18.22; −1.75; P = 0.018). Our findings demonstrate that young children are at high cardiovascular risk; if no actions are taken, the burden of non-communicable diseases will be substantial. The differences in risk between rural and urban areas are evident; urbanization might predispose children to a different reality and, in most cases, result in poor habits.

KEYWORDS

children, cardiovascular risk, dietary intake, anthropometry, Ecuador

Introduction

Cardiovascular diseases (CVD) are the leading causes of death worldwide, responsible for around 31% of global deaths. Although CVDs have their onset during adulthood, their pathogenic process begins during childhood and adolescence, a critical period for detecting CVD risk factors such as obesity, dyslipidemia, high blood pressure, metabolic syndrome, non-alcoholic fatty liver disease, atherogenic diet, and physical inactivity (1, 2).

Evidence demonstrates that the burden of CVD risk factors among children and adolescents is high. In Latin America, over 20% of children and adolescents are overweight or obese, a situation which often coexists with other cardiovascular risk factors (3, 4). The American Heart Association data shows that the fraction of children and adolescents in the United States with atherogenic dyslipidemia has increased in the last decade. About 25% of adolescents have high triglycerides and low high-density lipoprotein (HDL) blood levels (5), and dyslipidemia is seven times higher among obese children than their lean counterparts (6). Several factors play a role in dyslipidemia development among obese children; insulin resistance and visceral adiposity are the most important factors (5). Pediatric non-alcoholic fatty liver disease is the most common chronic liver disorder in children and adolescents with obesity (5, 7). Worryingly, children with non-alcoholic fatty liver disease often have dyslipidemia, and the severity of the disease is linked to an increased prevalence of CVD risk in children (7).

Molecular factors produced by adipose tissue play a critical role in cardiovascular risk among obese populations. Obesity is a chronic state of inflammation related to adipokines imbalance (i.e., high blood levels of leptin and low levels of adiponectin), which is a critical factor for cardiovascular disease (8–10). Leptin prevents lipid accumulation in peripheral tissues and stimulates the metabolism of fatty acids and glucose in skeletal muscle (11, 12). However, leptin's stimulatory effect on fatty acid oxidation is absent in obese people, and leptin resistance is one of the causal factors of cardiovascular complications in obesity (11, 12). Adiponectin regulates energy homeostasis, glucose, and lipid metabolism. Blood levels of adiponectin are decreased in patients with obesity, diabetes, and coronary heart disease (13, 14).

Inadequate dietary intake, physical inactivity, socioeconomic factors, and urbanization are important risk factors for dyslipidemia and cardiovascular diseases (15–17). In Latin America, the consumption of energy-dense, nutrition-poor foods has dramatically increased, while the intake of fruit, vegetables, whole grains, cereals, and legumes has decreased (3, 4). With food globalization, the correlation between income and dietary patterns has changed dramatically; lower-income countries consume higher percentages of calories from fat and sugars; this could predispose the population to a double burden of malnutrition, where undernutrition coexists with overweight and obesity (18). Chile, Mexico, and Argentina are the countries with faster development, the sharpest rise in processed foods and processed beverage sales and the highest prevalence of cardiovascular risk factors (3, 4).

Regarding cardiovascular risk status and its behavioral and social determinants, little is known among young children in Latin America. According to a systematic review, the available research has quantified overweight and obesity prevalence in the region (19). However, information regarding cardiovascular risk factors, such as abnormal blood lipids, hepatic profile, and adipokines, is scarce among young children. Furthermore, associations between the level of urbanization, sociodemographic factors, and eating behavior with cardiometabolic risk are poorly understood among young Latin American children (8, 20). Understanding the cardiovascular risk status and its influential factors in this specific population is essential to providing informed recommendations. Thus, this paper aims to: (i) determine weight status and abdominal adiposity; (ii) estimate cardiometabolic risk by measuring blood lipid profile, adipokines, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase levels (SGPT); (iii) characterize dietary intake; and (iv) identify associations between socio-demographics, adiposity, and dietary intake with cardiometabolic risk among 6–8-year old children living in urban and rural areas in Ecuador's Andean region.

This paper is the first report of the project "The Andean Microbiome," which aims to determine the factors associated with microbiota patterns of children 6–7 years of age living in urban and rural areas of the Andean highlands in Ecuador.

Materials and methods

Study design, setting and sampling

A cross-sectional study was conducted between February and August 2018 with a convenient sample of 267 children aged 6–8 years living in the Andean region of Ecuador. The participants were recruited at three schools located at altitudes over 2.100 m.a.s.l; one was in the urban area, and two were in the rural area. The urban school was located in Cuenca, a city in the country's southern Andean region, where 20% of the population is classified as poor based on unsatisfied basic needs, and 2.5% of the inhabitants are illiterate (21). The rural schools were located in the northern Andean region (Quito) in parishes with poverty levels ranging between 40 and 57% and illiteracy rates of 5% (22–25). In each school, all the 6–8-year-old children were invited to participate; only children with signed informed consent by their parents/guardians were included. This study was approved by the Ethics Committee of Universidad San Francisco de Quito code: 2017-152-M.

Measurements

Sociodemographic data, blood sampling, and weight status measurements were taken at school during regular school hours with the parent/guardian present. Dietary intake data were collected at the participants' homes on dates arranged beforehand with the guardian. Dietary intake data could not be collected when the guardian/tutor was unavailable. Data were collected by trained staff under standardized procedures.

Sociodemographic data

Sociodemographic characteristics were collected using a structured interview applied to the guardian. The interview included questions from the National Institute of Statistics and Census, such as age, home address, time living in the current residence, child ethnicity and the guardian's education level (26).

Anthropometry

A trained researcher measured anthropometric variables in duplicate, considering a third measurement only if the difference between the first two was greater than 0.5 kg for weight and 0.5 cm for height, according to standardized procedures based on the INBIOMED Manual (27). During the measurements, children wore light clothes and no shoes. Weight was measured to the nearest Kg using a mechanical calibrated scale (SECA 760), and height was measured to the nearest mm, using a calibrated stadiometer SECA 213 (Seca, Hamburg, Germany). Waist circumference was measured to the nearest mm using a tape measure [SECA (28)]. Body mass index for-age Z-score was calculated was calculated using the World Health Organization's (WHO) macros for Stata [WHO (29)]. Subsequently, according to WHO cutoff points, children were classified as underweight, normal weight, overweight, and obese (29).

Cardiometabolic risk profile

Blood samples were taken in the morning after overnight fasting by venipuncture at the antecubital vein using anticoagulant-free tubes. All the samples were centrifuged at 3,400 rpm for 8 min to obtain blood serums and were transported on dry ice to the laboratory, where they were stored at −80°C until processing, which took no more than 15 days. Total cholesterol, triglycerides, SGOT, and SGPT, were measured using commercial kits (Human, Wiesbaden, Germany) in a spectrophotometer Eppendorf PCP6121 (Eppendorf, Hamburg, Germany). HDL cholesterol was quantified by precipitation of lipoproteins (Human, Wiesbaden, Germany). The Friedewald formula was used to calculate LDL-cholesterol (plasma LDL concentrations = plasma total cholesterol concentrations – plasma HDL concentrations – plasma TAG concentrations/5). Leptin and adiponectin were determined by the ELISA sandwich technique using DIAsource kits (DIAsource ImmunoAssays S.A., Belgium); readings were performed in a H.S. Human ELISA' lector equipment (Human, Wiesbaden, Germany). Blood lipid values were categorized according to reference values for children (30). SGPT and SGOT were classified in acceptable and high ranges according to Human SGPT and SGOT kits. Values < 37 U/L for men and < 31 U/L for women for SGOT, and < 42 U/L for men and < 32 U/L for women SGPT were classified as normal.

Dietary intake

Food intake data were assessed by two 24-h recalls administered using the multi-pass method (31, 32); different interviewers, randomly assigned by a principal investigator, applied the recalls on a weekday and a weekend day. Portion sizes were estimated by employing local standardized utensils (33).

A list of all the recipes reported in the 24-h recalls was constructed, and food ingredients and quantities were estimated using standardized recipes from previous studies (33, 34). In the case of unavailable recipes, these were prepared in duplicate following the details provided by the participant. The ingredients and total recipe weight were measured to obtain an average for each recipe.

In Ecuador, an up-to-date food composition database does not exist. For this reason, nutrient intake was calculated using a compiled food composition database (33). The database was constructed by searching the United States [USDA (35)], Mexican [INNSZ (36)], Central American [INCAP/OPS (37)], and Peruvian [CENAN/INS (38)] databases. Nutrient content of the processed and pre-packaged food was obtained from nutrition facts labels and was included in the compiled food composition database.

The data from the 24-h recalls were entered using *MikunaSoft*, a software developed by this paper's authors. The standardized recipes and the compiled food composition database were uploaded to the software to estimate the participants' dietary intake. Total energy intake (in kilocalories/day), carbohydrates, total fat, protein, and fiber intake (in grams/day) were estimated using the average of the two 24-h recalls. Macronutrients and fiber intake are reported as the percentage of energy intake per day (E%/day). In addition, nutrient intake was categorized according to the dietary reference intake cutoffs as insufficient, adequate, and high. Dietary reference intake for 4 to 8-year-old children is 45–65 E%/d for carbohydrates, 10–30 E%/d for protein, and 25–35 E%/d for total fat; finally, the adequate intake for fiber is 25 g/d (39).

All the recipes and food items reported in the 24-h recalls were categorized into four groups according to the NOVA food framework: (i) unprocessed or minimally processed foods, (ii) culinary ingredients, (iii) processed foods, and (iv) ultra-processed foods (40). The E%/day was calculated from each NOVA food group.

Data analysis

Data were analyzed using Stata (Stata Statistical Software: Release 13. College Station, TX, United States: Stata Corp LLC), and figures were obtained using RStudio [RStudio Team (41). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, United States].[1] A significance level of 5% was considered for the statistical tests. Continuous variables were reported as mean with standard deviation, while categorical variables were displayed in frequency tables and bar charts. The distribution of continuous variables (and their possible transformations) was assessed using the ladder and gladder commands in Stata.

Differences in continuous variables between urban and rural areas for descriptive tables were tested using the Student's *T*-Test (with unequal variances when appropriated) or Wilcoxon Rank Sum test depending on the variables' distribution. Chi-square tests were applied to compare frequency distributions of categorical variables between urban/rural areas.

Multiple hierarchical regression models adjusted for age and sex with three steps were applied to identify predictors significantly associated with cardiometabolic risk outcomes (i.e., blood lipids, hepatic enzymes, and adipokines). Step 1 included residence (urban/rural) and de education level of the guardian as independent variables. In Step 2, BMI for age z-score and waist circumference were introduced; finally, macronutrients and fiber intake were included as independent variables in Step 3. Firstly, bivariate models were built with each cardiometabolic risk outcome as a dependent variable and sociodemographics, BMI for age z-score, waist circumference and nutrients as independent variables. Only independent variables significantly associated ($P < 0.10$) with the outcomes in bivariate models were included in the hierarchical adjusted model. For each model, regression diagnoses were evaluated (i.e., residuals versus fitted values plots); when unequal error variances or outliers were detected, the dependent variables were log-transformed, and the corresponding Beta coefficients were back-transformed and expressed as percentage differences. Multicollinearity between the independent variables was analyzed using the variance inflation factor (VIF), which showed a small risk of multicollinearity. The final models were tested for heterogeneity and properly corrected using robust standard deviation.

Results

A total of 267 children were recruited; the participants' average age was 6.7 ± 0.7 years, 36.3% lived in the urban area, and 47% were female (**Table 1**). Most guardians identified their children as mestizos (92%); 53% of the guardians completed secondary education, while 29% completed primary education only. There were no differences in age, sex or parental level of education between urban and rural children (**Table 1**).

Anthropometry

The mean BMI Z-score was 0.5 ± 1.1, 19% of the children were overweight, and 10% were obese. Bodyweight, height, waist circumference, and BMI Z-score were significantly higher among children living in the urban area ($P < 0.01$) (**Table 2**). Likewise, overweight and obesity prevalence was significantly higher among children in the urban area than those in the rural area (26 vs. 16% and 16 vs. 7%, respectively; $P = 0.005$) (**Figure 1**).

1 http://www.rstudio.com/

TABLE 1 Sociodemographic characteristics of the study participants.

	Total *n* = 267		Urban *n* = 97		Rural *n* = 170		
	n	%	*N*	%	*n*	%	*P**
Sex							0.336
Female	126	47.2	42	43.3	84	49.4	
Male	141	52.8	55	56.7	86	50.6	
Ethnicity *n* = 259							0.011
Mestizo (European and Indigenous ancestry)	238	91.9	81	86.2	157	95.2	
Other[a]	21	8.1	13	13.8	8	4.8	
Educational level of the guardian *n* = 260							0.109
None/Primary education	81	31.1	25	26.0	56	34.2	
Secondary education	138	53.1	51	53.1	87	53.1	
Higher education/Master's degree	41	15.8	20	20.8	21	12.8	

* Differences were tested using the Pearson's Chi-square non-parametric test.
[a] Other ethnic groups: white, Afro-descendant and Indigenous.

Cardiometabolic risk profile

The mean values of blood lipids, SGOT, SGPT and adipokines are shown in Table 2. Mean triglycerides (86.8 ± 42.8 mg/dL) and total cholesterol blood levels (175.3 ± 29.1 mg/dL) were above the adequate reference values. Blood levels of total cholesterol, LDL cholesterol, SGOT, SGPT, and leptin were significantly higher among children living in the urban area ($P < 0.01$). On the other hand, the mean HDL cholesterol and adiponectin blood concentrations were lower among urban children ($P < 0.01$).

A substantial proportion of the children showed marginally high or high levels of total cholesterol (56%), triglycerides (49%), and LDL cholesterol (38%). Nearly a quarter of the participants (23%) had marginally low or low levels of HDL cholesterol (Figure 2). SGPT values were between the normal ranges for all children, and 4.2% of the participants showed high values of SGOT. A higher proportion of children in the urban area had low levels of HDL cholesterol in comparison with children from the rural area (18.5 vs. 8.4%, $P = 0.003$).

Dietary intake

Dietary intake data were available for 145 children ($n = 90$ from the urban area and $n = 55$ from the rural area). Total energy intake (total sample mean 10757.1 ± 461.4 Kcal) in the urban area was significantly higher than in the rural area (1961.5 kcal/day vs. 1422.6 kcal/day; $P < 0.001$).

Carbohydrate intake provided, on average, 60% of the daily energy intake, followed by fat (26%) and proteins (12.5%). The percentage of carbohydrate consumption doubled in the rural area compared to the urban area (31 vs. 14% $P = 0.028$) (Table 3). Total fat intake was within the recommended range for 43% of the children, and 47% percent had an insufficient fat intake. Most of the children had an adequate protein intake (88%). Ninety-four percent of the participants had insufficient fiber intake, with no significant difference between areas (Figure 3).

Fifty percent of daily energy was obtained from minimally processed or unprocessed food/ingredients, followed by ultra-processed foods (21% E/day). Culinary ingredients and processed foods contributed 14 and 15% E/day, respectively. There was no significant difference in NOVA groups intake between urban and rural areas (Table 3).

Associations between blood lipid, hepatic and adipokine profile and sociodemographic characteristics, BMI z-score, and food intake variables

Table 4 displays the results of the hierarchical models. Sex was associated with cardiometabolic risk after adjustment for anthropometrics. Female children had higher levels of triglycerides (β 16.13 mg/dL; 95% CI: 5.96; 26.30; $P = 0.002$); and leptin serum concentration was 62% higher among female children in comparison with males (β% 62.32; 95% CI: 39.19; 85.44; $P < 0.001$). Living in the urban area was associated with a higher cardiometabolic risk (after adjusting for anthropometric variables; Step 2). Children living in the urban region had lower blood levels of HDL cholesterol (β−4.07 mg/dL; 95% CI: −7.00; −1.15; $P = 0.007$) but higher levels of LDL cholesterol (β 8.52 mg/dL; 95% CI: 1.38; 15.66; $P = 0.019$). Hepatic enzymes were also higher among urban children in comparison with their rural counterparts (SGOT β% 22.13; 93% CI: 17.33; 26.95; $P < 0.001$. SGPT β 0.84 U/L; 95% CI: 0.09; 1.59; $P = 0.028$). Leptin blood levels were 29% higher (β% 29.27; 95% CI: 3.57; 54.79; $P = 0.026$), meanwhile adiponectin plasma concentrations were 103% lower among urban children (β%−103.24; 95% CI:

TABLE 2 Blood lipid, hepatic profile and weight status of the study participants.

	Total n = 264		Urban n = 97		Rural n = 167		
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***	***P***
Body weight (Kg) (n = 267)	23.8	4.7	25.3 (n = 97)	5.2	23.0 (n = 170)	4.1	<0.001[a]
Body height (cm) (n = 267)	118.9	5.5	120.6	5.7	118.0	5.1	<0.001[a]
BMI for age z-score (n = 263)	0.5	1.1	0.8	1.3	0.4 (n = 166)	1.0	0.008[b]
Waist circumference (cm)	58.67	6.69	60.8	7.44	57.46	5.92	<0.001[a]
Triglycerides (mg/dL)	86.8	42.8	92.0	47.9	83.8	39.3	0.254[a]
Total Cholesterol (mg/dL)	175.3	29.1	180.2	30.1	172.5	28.3	0.041[a]
HDL Cholesterol (mg/dL)	53.0	11.4	50.2	11.3	54.6	11.2	0.003[a]
LDL Cholesterol (mg/dL)	105.0	27.1	111.5	27.9	101.2	26.0	0.003[a]
SGOT (U/L)	23.9	5.0	27.3	5.0	21.9	3.8	<0.001[b]
SGPT (U/L)	10.4	3.0	11.3	3.7	9.8	2.3	0.001[a]
Leptin (ng/ml) (n = 129)	1.7	2.4	2.6 (n = 40)	3.5	1.4 (n = 89)	1.7	0.005[b]
Adiponectin (μg/ml) (n = 129)	7.4	6.9	3.8 (n = 40)	5.8	9.1 (n = 89)	6.7	<0.001[b]

SD, standard deviation; HDL, high density lipid; LDL, low density lipid; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; BMI, body mass index.
[a] Differences were estimated using the parametric student's test.
[b] Differences were estimated using the Wilcoxon Rank-sum non-parametric test.

−147.58; −58.9; P = < 0.001). Abdominal adiposity measured by waist circumference was positively associated with blood triglycerides (β 2.68 mg/dL; 95% IC 0.74; 4.61; P = 0.007), SGPT (β 0.17 U/L; 95% CI: 0.05; 0.28; P = 0.004), and leptin plasma concentrations (β% 7.05; 95% CI: 2.52; 11.58; P = 0.003).

Fiber was the only nutrient associated with cardiometabolic risk after adjustment for sociodemographic and anthropometric variables (Step 3). Every additional percentage of daily energy intake obtained from fiber was associated with a lower concentration of total cholesterol (β−9.27 mg/dL; 95% CI −18.09; −0.45; P = 0.040) and LDL blood levels (β 9.99 mg/dL; 95% CI: −18.22, −1.75; P = 0.018).

Discussion

This study found that young Ecuadorian children living in urban and rural areas are at high cardiovascular risk. Three out of ten children were overweight or obese. A quarter of the participants had low HDL values, and an important proportion of the children showed high triglycerides, total cholesterol, and LDL blood levels. Regarding dietary intake, carbohydrates were the primary energy source, and 20% of participants with available data consumed an excess of carbohydrates. Worryingly, refined carbohydrates seem to be an essential constituent of young children's diet. The energy obtained from dietary fiber did not even reach 2% per day. Children living in urban areas appear to be at higher cardiovascular risk. Overweight and obesity were twice as prevalent among urban children; unfavorable blood lipid profiles were detected more frequently in children from urban areas; hepatic enzymes and leptin blood levels were higher, and adiponectin was lower among urban children when compared with their rural counterparts. Furthermore, living in urban areas was associated with having higher values of LDL cholesterol, SGOT, SGPT, and adiponectin blood levels but lower HDL cholesterol levels. Finally, visceral fat seems to be a critical risk factor associated with high triglycerides SGPT and leptin blood levels among young children.

Anthropometry

Our overweight/obesity estimate (29%) is in line with the one reported in the Ecuadorian health survey conducted in 2012 (29.9%) (21) but lower than the estimate of the national survey conducted in 2018 (35.4%) (42). In any case, the overweight/obesity burden in the studied area lies within the Latin American prevalence rate (18.9 to 36.9%) among school-age children (19). It is a matter of concern since childhood overweight and obesity are associated with an increased risk of cardiovascular diseases, type 2 diabetes, and high blood pressure (43, 44).

Blood lipids profile

Our study's faction of children with low HDL cholesterol levels is in line with reports among children in the United States (12 vs. 12.8%) (45). However, the prevalence of elevated levels of total cholesterol, triglycerides, and LDL cholesterol

TABLE 3 Dietary intake of the study participants.

	Total n = 145		Urban n = 90		Rural n = 55		
Dietary intake	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***P***
Total energy (kcal/day)	1757.1	461.4	1961.5	378.9	1422.6	384.0	<0.00[a]
Total fat intake (%E/day)	26.1	6.4	26.6	5.9	25.2	7.2	0.229[a]
Total protein (%E/day)	12.5	2.4	12.4	2.3	12.7	2.5	0.622[b]
Total carbohydrate (%E/day)	59.8	7.0	59.5	6.3	60.3	8.2	0.542[a]
Total fiber (%E/day)	1.6	0.6	1.5	0.5	1.8	0.7	0.037[a]
NOVA[c]							
Minimally processed food (%E/day)	49.6	11.7	48.2	10.6	51.8	13.2	0.071[a]
Culinary ingredients (%E/day)	14.6	6.7	14.9	6.8	14.0	6.5	0.306[b]
Processed food (%E/day)	15.3	7.3	15.0	7.3	15.6	7.3	0.646[a]
Ultra-processed food (%E/day)	20.6	11.9	21.0	12.2	20.1	11.5	0.675[a]

SD, standard deviation; %E/day, energy percentage per day.
[a] Differences were estimated using the parametric student's test.
[b] Differences were estimated using the Wilcoxon Rank-sum non-parametric test.
[c] NOVA: NOVA food framework: (i) unprocessed or minimally processed foods, (ii) culinary ingredients, (iii) processed foods, and (iv) ultra-processed foods (40). The E%/day was calculated from each NOVA food group. The difference in sample size among the study variables is explained by the fact that not all parents in the rural area were able to schedule a meeting for the 24-recall.

is higher in our study population than in reports from the United States (45). Unfortunately, we did not find relevant studies in Latin America on the general pediatric population. Our data highlights the need to conduct population-based studies in the region on larger samples to quantify the risk; the evidence suggests that 40 to 50% of children with elevated blood lipid levels would continue this trend in adulthood and, consequently, have a higher cardiovascular risk (46). A possible explanation for the alterations in the lipid profile could be an unbalanced diet. We identified an inverse correlation between fiber intake and total and LDL cholesterol levels, a result in line with a systematic review that reported that the consumption of whole grains (a source of fiber) has the potential to lower LDL and total cholesterol (47). Our data and reports on Ecuadorian children and adolescents have shown that Ecuadorians' diet is poor in whole grains and fiber (21, 33). Adequate fiber intake has several health benefits, especially when it starts during childhood. The benefits include prevention and treatment of obesity, maintenance of normal serum lipid values, and a lower risk of developing cardiovascular diseases (48, 49). The effect of fiber is mediated, in part, by the phytosterols present in whole grains that compete with the fat for absorption

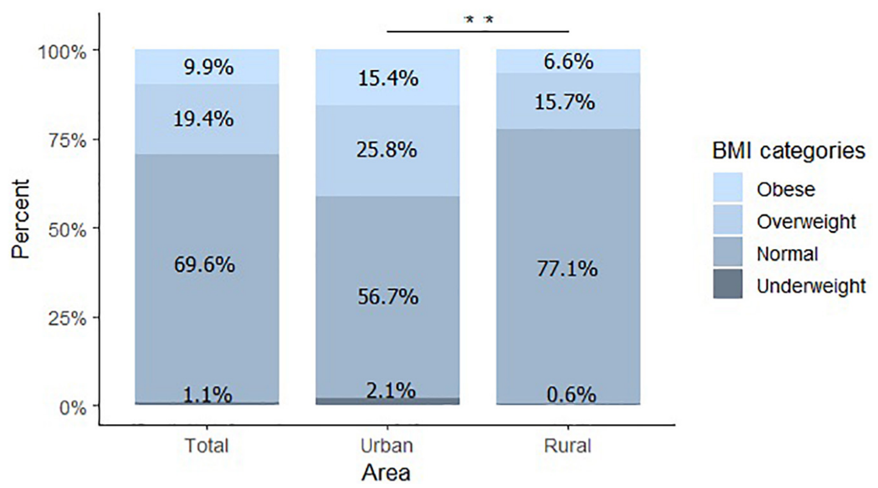

FIGURE 1
Body mass index classification. Percentage of children obese, overweight, normal, and underweight. Total n = 263, Urban n = 97, Rural n = 166. $^{**}P$ < 0.01.

TABLE 4 Associations between blood lipids, hepatic enzymes and adipokines with sociodemographic, anthropometrics, and nutrient intake data*.

Step	*Predictors*	Triglycerides[b]			Total cholesterol			LDL cholesterol			HDL cholesterol[b]		
		β	*95% CI*	*P*	β	*95% CI*	*P*	β	*95% CI*	*P*	β	*95% CI*	*P*
1	Age (years)	2.87	−3.70; 9.44	0.390	4.05	−1.09; 9.20	0.122	1.31	−3.45; 6.07	0.589	1.93	−0.06; 3.93	0.058
	Sex (0 male, 1 female)	**15.55**	**4.93; 26.17**	**0.004**	4.82	−2.27; 11.92	0.182	1.86	−4.72; 8.44	0.579	−1.73	−4.49; 1.03	0.218
	Residence (0 rural, 1 urban)	–	–	–	5.08	−2.42; 12.57	0.184	**9.90**	**2.95; 16.85**	**0.005**	**−5.27**	**−8.18;−2.35**	**<0.001**
	Educational level of the guardian[a]	–	–	–	4.49	−0.90; 9.87	0.102	–	–	–	–	–	–
2	Age (years)	−2.24	−9.49; 5.00	0.543	4.45	−1.16; 10.05	0.120	1.72	−3.48; 6.92	0.516	**2.78**	**0.65; 4.91**	**0.011**
	Sex (0 male, 1 female)	**16.13**	**5.96; 26.3**	**0.002**	4.28	−2.81; 11.38	0.236	1.43	−5.16; 8.03	0.669	−1.85	−4.55; 0.86	0.180
	Residence (0 rural, 1 urban)	–	–	–	3.48	−4.19; 11.15	0.372	**8.52**	**1.38; 15.66**	**0.019**	**−4.07**	**−7.00;−1.15**	**0.007**
	Educational level of the guardian[a]	–	–	–	4.08	−1.29; 9.45	0.136	–	–	–	–	–	–
	BMI Z-score	−0.90	−10.78; 8.98	0.857	1.70	−5.67; 9.06	0.651	1.60	−5.32; 8.51	0.650	0.14	−2.69; 2.98	0.921
	Waist circumference (cm)	**2.68**	**0.74; 4.61**	**0.007**	0.12	−1.15; 1.39	0.855	0.07	−1.12; 1.27	0.904	−0.46	−0.95; 0.03	0.064
3	Age (years)	–	–	–	2.86	−5.02; 10.75	0.474	0.62	−6.67; 7.91	0.866	–	–	–
	Sex (0 male, 1 female)	–	–	–	9.06	−0.76; 18.89	0.070	5.96	−3.21; 15.13	0.201	–	–	–
	Residence (0 rural, 1 urban)	–	–	–	−0.26	−10.94; 10.42	0.961	4.72	−5.14; 14.58	0.345	–	–	–
	Educational level of the guardian[a]	–	–	–	5.44	−1.89; 12.78	0.144	–	–	–	–	–	–
	BMI Z-score	–	–	–	2.02	−8.43; 12.48	0.702	2.72	−7.03; 12.48	0.582	–	–	–
	Waist circumference (cm)	–	–	–	0.18	−1.57; 1.92	0.841	0.13	−1.50; 1.76	0.874	–	–	–
	Fiber (%E/day)	–	–	–	**−9.27**	**−18.09;−0.45**	**0.040**	**−9.99**	**−18.22;−1.75**	**0.018**	–	–	–

(Continued)

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TABLE 4 (Continued)

Step	*Predictors*	SGOT^{b,c}			SGPT^{b}			Leptin^{b,c}			Adiponectin^{b,c}		
		B%	*95% CI*	*P*	β	*95% CI*	*P*	B%	*95% CI*	*P*	B%	*95% CI*	*P*
1	Age (years)	−0.74	−3.93; 2.45	0.648	0.44	−0.04; 0.92	0.070	4.13	−17.36; 25.62	0.705	14.12	−15.76; 44.00	0.351
	Sex (0 male, 1 female)	−0.65	−5.05; 3.75	0.773	0.19	−0.54; 0.92	0.607	**66.25**	**37.55; 94.95**	**<0.001**	−0.77	−40.39; 38.85	0.969
	Residence (0 rural, 1 urban)	**22.29**	**17.64; 26.94**	**<0.001**	**1.36**	**0.50; 2.23**	**0.002**	**49.42**	**18.02; 80.82**	**0.002**	**−110.11**	**−153.58;−66.65**	**<0.001**
	Educational level of the guardian[a]	3.01	−0.33; 6.35	0.077	–	–	–	–	–	–	–	–	–
2	Age (years)	−0.68	−4.19; 2.84	0.705	0.14	−0.37; 0.65	0.586	−5.98	−24.89; 12.93	0.533	23.18	−9.72; 56.08	0.166
	Sex (0 male, 1 female)	−0.64	−5.08; 3.80	0.777	0.22	−0.45; 0.90	0.517	**62.32**	**39.19; 85.44**	**<0.001**	−0.05	−39.75; 39.66	0.998
	Residence (0 rural, 1 urban)	**22.13**	**17.33; 26.93**	**<0.001**	**0.84**	**0.09; 1.59**	**0.028**	**29.27**	**3.57; 54.97**	**0.026**	**−103.24**	**−147.58;−58.9**	**<0.001**
	Educational level of the guardian[a]	3.03	−0.33; 6.40	0.077	–	–	–	–	–	–	–	–	–
	BMI Z-score	0.92	−3.70; 5.53	0.695	0.16	−0.44; 0.77	0.594	7.66	−17.71; 33.03	0.551	18.85	−24.64; 62.35	0.393
	Waist circumference (cm)	−0.07	−0.87; 0.72	0.858	**0.17**	**0.05; 0.28**	**0.004**	**7.05**	**2.52; 11.58**	**0.003**	−5.82	−13.63; 2.00	0.143
3	Age (years)	–	–	–	–	–	–	–	–	–	–	–	–
	Sex (0 male, 1 female)	–	–	–	–	–	–	–	–	–	–	–	–
	Residence (0 rural, 1 urban)	–	–	–	–	–	–	–	–	–	–	–	–
	Educational level of the guardian[a]	–	–	–	–	–	–	–	–	–	–	–	–
	BMI Z-score	–	–	–	–	–	–	–	–	–	–	–	–
	Waist circumference (cm)	–	–	–	–	–	–	–	–	–	–	–	–
	Fiber (%E/day)	–	–	–	–	–	–	–	–	–	–	–	–

*Analysis performed using hierarchical regression models with blood lipids, hepatic enzymes and adipokines as dependent variables; Age, Sex, Place of residence and Education level of the guardian as independent variables in the first step; BMI Z-score and waist circumference in step 2; and nutrients in Step 3. Only variables significantly associated with the dependent variables in bivariate linear regression models were included in the hierarchical regressions.

[a] Education level of the guardian: 0 = None/primary education, 1 = Secondary education, 2 = Higher education/Master's degree.

[b] Step 3 is not shown as no significant association was found in the bivariate analysis with any nutrient.

[c] Dependent variables log-transformed, the results are presented as B% to enhance interpretability. –Variables not significantly associated with the dependent variables in bivariate linear regression models.

Bold: Significant associations in the hierarchical models.

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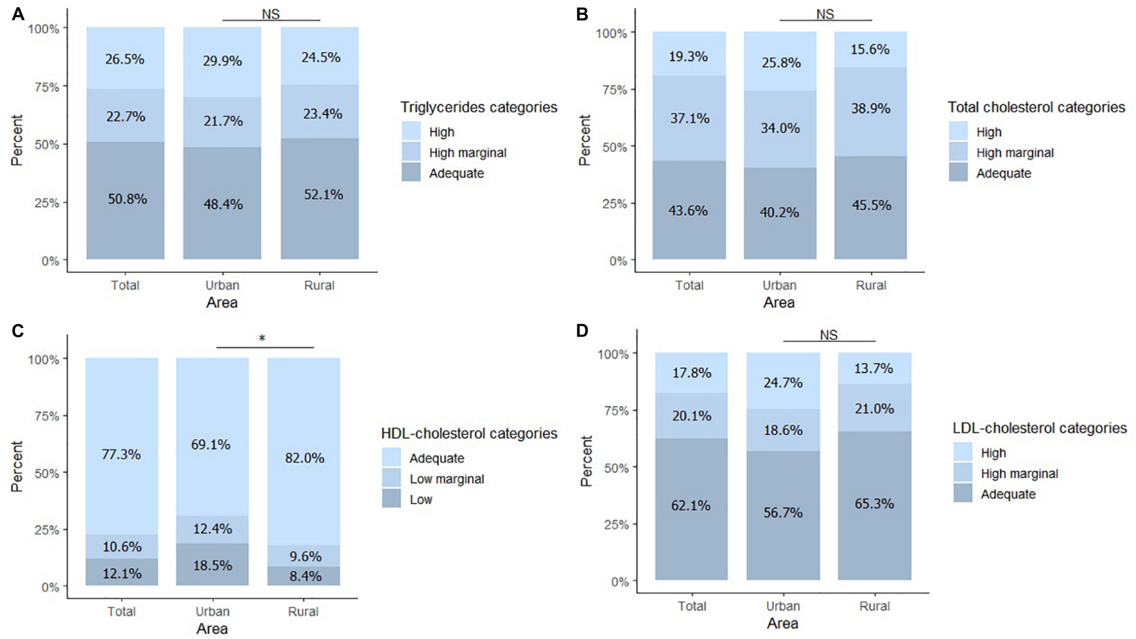

FIGURE 2
Blood lipid profile. **(A)** Percentage of children within high, marginal high, and adequate values for triglycerides. **(B)** Percentage of children within high, marginal high, and adequate values for total cholesterol. **(C)** Percentage of children within low, marginal low, and adequate values for HDL-cholesterol. **(D)** Percentage of children within high, marginal high, and adequate values for LDL- cholesterol. Total n = 264, Urban n = 97, Rural n = 167. *P < 0.05. NS, no significant differences.

in the small intestine (48). Other key factors related to alterations in lipid profile comprise sedentary behaviors and physical fitness; longitudinal studies have suggested positive associations between television viewing and screen time with cardiometabolic risk in children and adolescents (50) and inverse associations between cardiorespiratory fitness with blood lipids (51). The available data have shown that sedentary behavior and poor physical fitness are problems with a high prevalence in the Ecuadorian pediatric population (52).

Another aspect to consider is the need to perform blood lipid screening among children. Some authors suggest blood lipid screenings with this population to diminish cardiovascular risk later. However, there is no consensus on the parameters to test or the age to perform routine blood lipid screening. One approach is routine screening among children with a family history of cardiovascular diseases, while other authors support universal screening. However, the available evidence on blood lipid screening has been generated using data from high-income countries; research needs to be extended to other regions with a high prevalence of cardiovascular disease and lower access to the health system (i.e., Latin America) (53, 54).

Abdominal adiposity

Waist circumference was positively associated with blood levels of triglycerides, SGPT, and leptin. Previous reports have found a clear positive relationship between triglycerides and waist circumference (55, 56). Excess abdominal fat causes an overflow of lipids to visceral and non-adipose tissues, a phenomenon known as lipotoxicity (57, 58). The relationship between waist circumference and SGOT among young children demonstrates an advanced inflammatory state; worryingly, the available evidence has established that the association between waist circumference-SGPT values represents a strong risk factor for pediatric non-alcoholic fatty liver disease (59, 60). Therefore, our data suggest that the children studied are already at risk of developing non-alcoholic fatty liver disease.

Differences between urban and rural settings

Our data prove that children living in urban areas in Ecuador are at a higher risk. Dietary intake seems not to explain the differences in cardiovascular risk between urban and rural children; although the net daily energy intake was higher in the urban area, energy density estimated as E%/day did not differ between the study regions. Furthermore, the energy obtained from processed and ultra-processed foods rich in added sugar and saturated fat between urban and rural children is similar, a result in line with a previous study performed among urban and rural adolescents living in Ecuador (33); and, insufficient fiber intake is similar in both settings. Therefore,

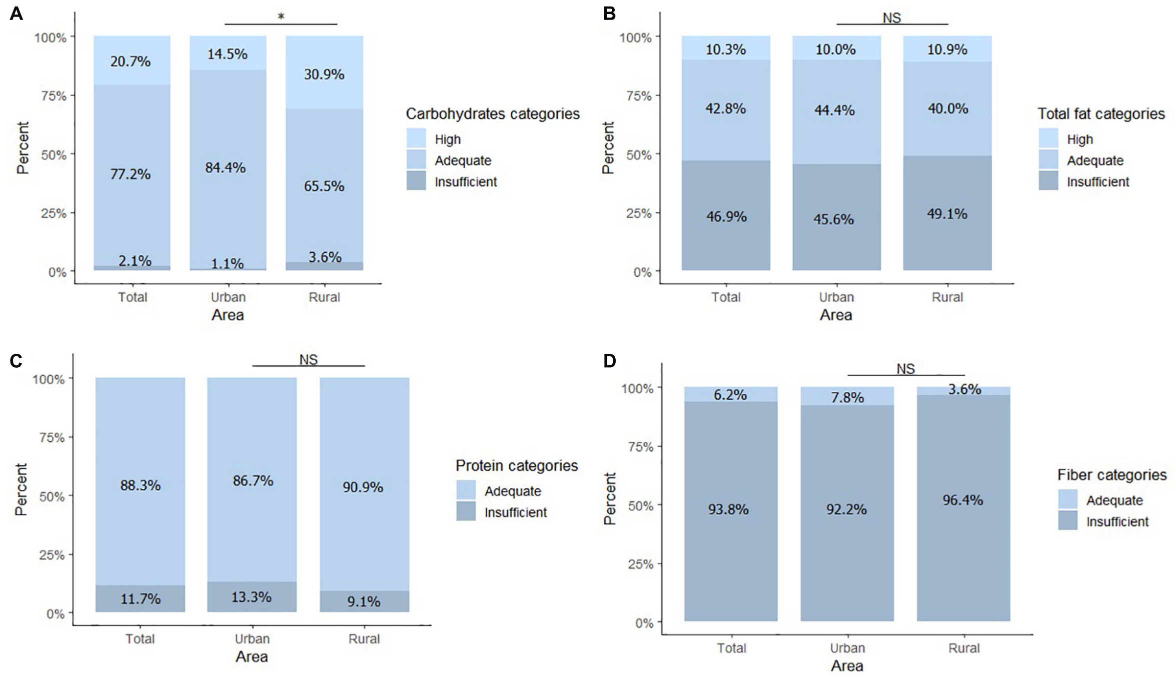

FIGURE 3
Dietary intake according to recommendation. **(A)** Percentage of children within high, adequate, and insufficient carbohydrate consumption category. **(B)** Percentage of children within the high, adequate, and insufficient total fat consumption category. **(C)** Percentage of children within the adequate and insufficient protein consumption category. **(D)** Percentage of children within the adequate and insufficient fiber consumption category. Total *n* = 145, Urban *n* = 90, Rural *n* = 55. The difference in sample size among the study variables is explained by the fact that not all parents in the rural area were able to schedule a meeting for the 24-recall. $^{*}P < 0.05$. NS, no significant differences.

the differences might be explained by sedentary behavior, physical activity, or cardiorespiratory fitness differences. The Ecuadorian health survey performed in 2012 showed how 22% of children in the urban Andean region spent more than 2 h per day viewing television, while 15% of rural children reported more than 2 h.

Similarly, the fraction of children classified as active was lower in the urban region (21). Data regarding differences in urban and rural settings in Latin America are scarce. A recent report from Brazil shows how rural children perform better in cardiorespiratory fitness tests and have lower cardiometabolic risk (54). The lower cardiorespiratory fitness in urban settings might result from living conditions. For example, rural children and adolescents in Latin America spend more time in agriculture-related activities (54, 61). Other possible explanations involve crime concerns and distances to green spaces secondary to inadequate urban planning (54). Our data demonstrate how cardiovascular risk affects a considerable proportion of young children with a higher impact in urban settings. Formative research is needed to design effective strategies aimed at reverting the problems according to each setting; one might consider that although the risk is lower among rural children, the risk's magnitude is important in both settings.

Adiponectin was significantly lower among children living in urban areas. Considering that urban children have higher BMI, waist circumference, and more unfavorable lipid profiles, it is reasonable that adiponectin levels are lower in this group (11). Interventions promoting physical activity among children have effectively increased adiponectin levels among obese children. Once again, this highlights the need to undertake preventive strategies to revert the children's inflammatory state in the region (62).

This study was designed to determine cardiovascular risk factors among young children. Our findings demonstrate that young children are at high cardiovascular risk; if actions are not taken, the burden of non-communicable diseases will be substantial. The differences in risk between rural and urban areas are evident; urbanization might predispose children to a different reality and, in most cases, result in poor health habits. Adipokines, hepatic enzymes, and lipid profiles were strongly correlated with waist circumference and urbanization. Several combined factors are responsible for the current health status of the children studied. The findings highlight the need to implement preventive strategies to increase fiber intake and prevent overweight, obesity, and cardiovascular risk. Urbanization is critical when developing effective strategies tailored to the local context. This study highlights a significant problem in an understudied population (i.e., 6–8-year-old children living in Latin America) and demonstrates the need to implement comprehensive policies.

The study has some limitations. The participants were selected by convenience. Nevertheless, the results are comparable with previous reports, and this study has the strength to analyze several risk factors among young children living in urban and rural Latin America. Future studies should extend the research to larger samples. We did not measure some behaviors, such as physical activity and sedentary behavior; our data suggest that such behavior might be an influential factors.

Data availability statement

The data that support the findings of this study are available from the corresponding authors LB-R, lybaldeon@uce.edu.ec and AO-A, angelica.ochoa@ucuenca.edu.ec, upon reasonable request. The data from the urban area used in this article formed part of a Bachelor thesis (63).

Ethics statement

The studies involving human participants was reviewed and approved by the Comité de Ética de Investigacón en Seres Humanos de la Universidad San Francisco de Quito "CEISHUSFQ." Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LB-R acquired the funding, processed the blood samples, and collected the 24-h recall data from rural areas. LB-R and AO-A designed the research. NL-V and SV-R supported the field work and collected the 24-h recall data from urban areas. SE, SV-R, NL-V, and AO-A conceived statistics analyses. AO-A, SV-R, NL-V, SE, LB-R, and CO-A were involved in interpreting results, drafting, editing the manuscript, and approving the submitted and published versions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Mainul Haque,
National Defense University of Malaysia, Malaysia

REVIEWED BY
Parinaz Poursafa,
Tampere University, Finland
Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh
Adekunle Rowaiye,
National Biotechnology Development Agency, Nigeria

*CORRESPONDENCE
Mehdi Ebrahimi
m_ebrahimi49@yahoo.com
Ramin Heshmat
rheshmat@tums.ac.ir

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Association of zinc serum level with metabolic syndrome in iranian children and adolescents: The CASPIAN-V study

Mostafa Qorbani[1,2], Negar Movasaghi[2], Nami Mohammadian Khonsari[3], Elnaz Daneshzad[1], Gita Shafiee[2], Haleh Ashraf[4,5], Leily Sokoty[1,6], Armita Mahdavi-Gorabi[1], Mehdi Ebrahimi[7]*, Ramin Heshmat[2]* and Roya Kelishadi[8]

[1]Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran, [2]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute Tehran University of Medical Sciences, Tehran, Iran, [3]Dietary Supplements and Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran, [4]Research Development Center, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran, [5]Cardiac Primary Prevention Research Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran, [6]Social Determinants of Health Research Center, Alborz University of Medical Sciences, Karaj, Iran, [7]Department of Internal Medicine, Faculty of Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran, [8]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease Isfahan University of Medical Sciences, Isfahan, Iran

Introduction: Metabolic syndrome comprises a set of metabolic risk factors associated with cardiovascular disease and type 2 diabetes. Zinc plays an essential role in numerous enzyme functions that may be associated with metabolic dysfunctions. The relationship between serum zinc levels and metabolic syndrome in adolescents has not been specifically studied. Therefore, this study was performed to determine the relationship between serum zinc levels and metabolic syndrome in Iranian children and adolescents.

Materials and methods: This cross-sectional study was performed using data collected in the CASPIAN-V study. In this project, data were collected using interviews, examinations, biochemical assessments, anthropometric studies, and the nutritional status of participants. The variables considered in this study included serum zinc levels, triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood sugar, height, weight, abdominal circumference, and systolic and diastolic blood pressure.

Results: A total of 1371 participants were included in this study, with a mean age of 12.24 ± 3.23 years. In total, 12.40% ($n = 170$) of the study population had metabolic syndrome, of which 55.7% were boys and 44.3% were girls. Mean zinc levels (μg/dL) in patients with and without metabolic syndrome were 107.03 and 110.6, respectively (p-value = 0.211) and 111.8 for boys and 109.10 for girls (p-value = 0.677).

Conclusion: This cross-sectional study showed no association between serum zinc levels and metabolic syndrome in children. Further similar studies and cohort studies with large sample sizes are needed to reveal the exact relationship between serum zinc levels and metabolic syndrome.

KEYWORDS

metabolic syndrome, zinc, adolescents, children, CASPIAN-V

Introduction

Metabolic syndrome is a set of metabolic risk factors associated with cardiovascular diseases and type 2 diabetes (1). Numerous definitions of components and their diagnostic boundaries have been proposed for this syndrome, all of which are associated with metabolic disorders such as elevated blood pressure, impaired glucose and insulin metabolism, dyslipidemia, and central obesity (Measured parameters include: abdominal obesity or waist circumference equal to or more than 90th percentile of the age and sex; Systolic or diastolic blood pressure (SBP or DBP) equal to or greater than 90th percentile by height, age, and sex; Serum triglyceride (TG) level greater than 110 mg/dL, High-density lipoprotein (HDL) equal to or less than 40 mg/dL, fasting glucose level equal to or more than 100 mg/dL) (1–3). Metabolic syndrome is one of the main health hazards worldwide, resulting in a significant number of years lost (DALY) due to its associated morbidity and mortality (3, 4). Although many studies have been conducted on the prevalence of this syndrome in adults based on different definitions and its relationship with cardiovascular diseases (2, 3), there is no precise definition for it in childhood and adolescence. As nutrition plays a major role in growth and development in children, and deficiencies in various nutrients could result in metabolic defects (5), it seems that deficiencies in trace elements such as zinc which plays an essential role in numerous enzyme functions could result in metabolic dysfunction as well (6).

Zinc is a rare and essential element in the body involved in the metabolism of nucleic acids and their stability in protein synthesis, cell division, and gene expression. Furthermore, zinc plays an essential role in the activity of more than 300 enzymes in the body. Its deficiency can result in many skin diseases, mental disorders, pregnancy, lactation, growth disturbances, and susceptibility to infections (7). Hence, in theory, zinc deficiency can result in metabolism defects and metabolic disorders. Since the body does not have a proper zinc reserve, nutrition plays a significant role in providing this micronutrient (8).

Although severe zinc deficiency is rare, studies have shown that mild to moderate zinc deficiency occurs on a large scale in unbalanced diets (9). In Iran, due to the calcareous nature of agricultural soils, bicarbonate water, and the lack of zinc-containing fertilizers, the amount of zinc absorbed by plants is minimal (10–12).

The relationship between serum zinc levels and the incidence of metabolic syndrome in adolescents has not been specifically studied, and there has been controversy regarding the effects of zinc on metabolic syndrome (13). Therefore, this study was performed to determine the relationship between serum zinc levels and metabolic syndrome in children and adolescents.

Materials and methods

Study design

This cross-sectional study was performed using data collected in the Caspian-V study. (Caspian-V study, was a care system for health-related behaviors and risk factors for diseases in students in Iran).

Data collection

Sampling was done by multi-stage using cluster and stratified sampling method. Class sampling was performed in each province of the country according to the student's residence (city or village) and educational level (primary and secondary) in a manner commensurate with the size with an equal sex ratio. This means that the number of boys and girls in each province was equal, and their ratio in urban and rural areas was also proportional to the number of urban and rural students. Similarly, the number of samples was divided between the educational levels in the city and the village in proportion to the number of students studying at each level. In this study, 480 students were selected from each province (i.e., 48 clusters of 10 people in each province). In total, according to the study in 31 provinces, 14,880 people were surveyed using the standard questionnaire "WHO-GSHS," which has been translated into Persian, and its validity has been evaluated and approved in previous studies (14). Trained professionals collected information about health-related behaviors and risk factors for diseases; and assessed anthropometric measurements, including height, weight, waist circumference, hip, neck, wrist circumferences, and blood pressure, for all participating students. One-third of the number of clusters from each province were randomly selected for blood sampling, and a skilled blood sampler took six ccs of their venous blood with consideration of all health issues to measure blood glucose indices, lipid profile, liver enzymes, and serum zinc level. It should be noted that the waist circumference was measured as a waist from the tangent and above the iliac crest to the ground with a metal meter. Metabolic syndrome was defined based on NHANES III (Third National Health And Nutrition Examination Survey)(15) as the presence of 3 out of 5 criteria for the diagnosis of this syndrome, including abdominal obesity or waist equal to or more than 90th percentile in terms of age and sex; SBP or DBP equal to or greater than 90th percentile by height, age, and sex; serum TG level greater than 110 mg/dL, HDL serum equal to or less than 40 mg/dL, fasting serum glucose levels equal to or greater than 100 mg/dL.

Inclusion and exclusion criteria

The study population was children and adolescents studying in primary or secondary school whose information was recorded in the Caspian Cohort. Participants with incomplete data, according to the studied variables, as well as individuals with reduced renal function (glomerular filtration rate; GFR < 30), Chronic liver diseases, and glucocorticoids were excluded from the study.

Data analysis

The SPSS software version 21 was used for data analyzes. Descriptive analysis results on quantitative variables are presented as mean and standard deviation, and qualitative variables as frequency and relative frequency. Furthermore, the correlation of coefficients was calculated. A p-value less than 0.05 was considered statistically significant.

Ethical considerations

No information about the identities of individuals entered the study process; hence, the data were anonymous, and at no stage of the study, the individuals' information was recorded or mentioned. Furthermore, this study was approved by the ethics committee of the Alborz University of Medical Sciences.

Results

A total of 1,371 participants were included in this study, with a mean age of 12.24 ± 3.22 years. In total, 6.41% ($n = 88$) of the study population had metabolic syndrome, of which 55.68% were boys, and 44.32% were girls. The means of height, weight, waist circumference, SBP, DBP, TG and HDL were 147.24 ± 18.13 cm, 42.64 ± 16.5 kg, 67.7 ± 11.72 cm, 101.33 ± 13.46 mmHg, 65.45 ± 10.76 mmHg, 88.08 ± 44.58 mg/dL, and 46.88 ± 9.24 mg/dL, respectively. Serum zinc level mean was 107.23 ± 25.81 μg/dL. The presence or absence of metabolic syndrome based on demographic parameters has been categorized in **Table 1**. As shown in this table, no significant difference was observed between zinc levels in children and adolescents with or without metabolic syndrome (p-value = 0.211). Among the different variables among children with metabolic syndrome and others, only a significant difference in their TG levels can be seen. Participants with metabolic syndrome had greater TG and FBS compared to those without metabolic syndrome (109.29 ± 68.25 vs. 86.62 ± 41.18; p-value < 0.0001 and 99.26 ± 8.65 vs. 92.95 ± 8.32; p-value < 0.0001, respectively).

Furthermore, there was no significant difference between zinc levels and sex in participants with and without metabolic syndrome. (p-value = 0.34). Similarly, there was no significant relationship between serum zinc levels and the age of children in children without metabolic syndrome (p-value = 0.184).

In **Table 2**, the association between metabolic syndrome components and dyslipidemia with serum zinc levels based on linear logistic regression analysis can be seen. No significant association was found between serum zinc levels and any metabolic syndrome components. **Table 3** illustrates the same data but is based on serum zinc tertiles. As can be seen in **Tables 2**, **3**, no significant relationship between serum zinc levels and the aforementioned variables was observed.

Discussion

This study investigated the serum level of zinc in children and adolescents and the factors affecting metabolic syndrome. Metabolic syndrome is one of the most significant risk factors associated with cardiovascular disease and type 2 diabetes (3). Studies estimate that more than 100 million children worldwide are obese (16), highlighting the importance of paying attention to metabolic syndrome and its factors in this age group. Moreover, studies also suggest that serum zinc and manganese levels may be essential factors in controlling and synthesizing insulin and controlling fat profile in individuals (17).

This cross-sectional study, based on the population of the Caspian cohort, showed no significant difference in the overall picture between children and adolescents with metabolic syndrome in terms of serum zinc levels. Also, in subgroup analysis, there was no significant correlation between serum zinc levels and age, abdominal obesity, or different fat profiles, and in all evaluations, the numbers did not differ significantly in children with metabolic syndrome or others. However, based

TABLE 1 Demographic status of the study population according to the presence or absence of metabolic syndrome ($n = 1371$).

Variables	Total	Metabolic syndrome		*P*-value
		Yes $N = 88$	No $N = 1283$	
Gender; n (%)				
Female	675 (49.2)	39 (5.8)	636 (94.2)	0.340
Male	696 (50.8)	49 (7.0)	647 (93.0)	
Residential region n (%)				
Rural	370 (27)	19 (5.1)	351 (94.9)	0.238
Urban	1001 (73.0)	69 (6.9)	932 (93.1)	
Age (year)	12.24 (3.22)	11.81 (3.23)	12.29 (3.24)	0.184
Weight (kg)	42.64 (16.50)	42.69 (15.90)	42.54 (16.41)	0.934
BMI (kg/m^2)	18.99 (4.82)	19.23 (4.21)	18.96 (4.89)	0.618
WC (cm)	67.70 (11.72)	69.13 (12.79)	67.54 (11.76)	0.225
NC (cm)	30.23 (3.71)	30.01 (3.51)	30.26 (3.73)	0.531
Wrist Circumference (cm)	15.12 (2.11)	15.39 (2.36)	15.12 (2.11)	0.247
Hip Circumference (cm)	78.89 (14.99)	79.44 (15.77)	78.91 (14.96)	0.748
WHtR	0.46 (0.06)	0.47 (0.06)	0.46 (0.06)	0.136
SBP (mmHg)	101.33 (13.46)	101.45 (16.29)	101.35 (13.36)	0.947
DBP (mmHg)	65.45 (10.76)	64.81 (11.85)	65.46 (10.78)	0.589
TG (mg/dl)	88.08 (44.58)	109.29 (68.25)	86.62 (41.18)	**<0.0001**
Cholesterol (mg/dl)	152.95 (26.57)	154.27 (24.88)	152.51 (26.70)	0.550
LDL (mg/dl)	88.77 (22.60)	88.21 (21.10)	88.59 (22.62)	0.880
HDL (mg/dl)	46.88 (9.24)	45.78 (11.27)	46.88 (9.08)	0.283
FBS (mg/dl)	93.16 (8.64)	99.26 (8.65)	92.95 (8.32)	**<0.0001**
Serum Zinc (μ g/dL)	107.23 (25.81)	110.60 (29.84)	107.02 (25.59)	0.211
ST n (%)				
Low	1044 (76.1)	70 (6.7)	974 (93.3)	0.440
High	327 (23.9)	18 (5.5)	309 (94.5)	
PA level n (%)				
Low	471 (34.4)	33 (7.0)	438 (93.0)	0.327
Moderate	490 (35.7)	25 (5.1)	465 (94.9)	
High	410 (29.9)	30 (7.3)	380 (92.7)	
SES n (%)				
Low	370 (27.0)	23 (6.2)	347 (93.8)	0.732
Moderate	569 (41.5)	34 (6.0)	535 (94.0)	
High	432 (31.5)	31 (7.2)	401 (92.8)	

BMI, Body Mass Index; WC, Waist Circumference; WHtR, waist-to-height ratio; NC, Neck Circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, Triglyceride; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; FBS, Fasting Blood Sugar; ST, screen time (above 2 h per day are regarded as high, otherwise as low); PA, physical activity; SES, socioeconomic status.
Data presented as mean (SD) and number (%) for quantitative and qualitative variables, respectively.
SES,PA and other abbreviations are listed under the table or their definition can be found in the methods, or under the bolded variable.

on the findings of this study, it seems that healthy girls with metabolic syndrome have lower serum zinc levels than boys. This difference, In addition to biological factors, can also be attributed to the different eating habits of boys and girls. In addition, the studies showed a slight difference between serum zinc levels and blood pressure status in children with metabolic syndrome. Among children with metabolic syndrome, serum zinc levels were significantly lower in children with elevated blood pressure than in others. Compared to this study, few studies have reported a more significant zinc effect than what was seen in this study. For example, in the study of the relationship between serum zinc levels and metabolic syndrome in Korea in 2014, 1,926 people were studied and analyzed. Serum zinc levels were negatively correlated with elevated fasting blood sugar and positively correlated with elevated TG levels in a statistically significant manner. It was also found that in women, serum zinc levels are associated with an increase in the incidence of metabolic syndrome (18). Although, some studies report an association between zinc levels and blood pressure (19), and in theory, zinc could potentially affect blood

TABLE 2 Association between metabolic syndrome components and dyslipidemia with serum zinc level in children: linear regression analysis.

Variables	β	Standard error	*P*-value
FBS (mg/dl)			
Crude model	0.30	0.29	0.291
Adjusted model	0.23	0.29	0.419
Adjusted + BMI	0.23	0.29	0.417
SBP (mmHg)			
Crude model	0.08	0.47	0.853
Adjusted model	0.14	0.46	0.751
Adjusted + BMI	0.14	0.46	0.748
DBP (mmHg)			
Crude model	0.07	0.37	0.850
Adjusted model	0.17	0.38	0.649
Adjusted + BMI	0.17	0.37	0.640
HDL (mg/dl)			
Crude model	−0.13	0.31	0.666
Adjusted model	−0.07	0.31	0.804
Adjusted + BMI	−0.07	0.31	0.804
LDL (mg/dl)			
Crude model	−0.27	0.75	0.716
Adjusted model	−0.15	0.76	0.836
Adjusted + BMI	−0.15	0.76	0.839
TG (mg/dl)			
Crude model	1.09	1.49	0.463
Adjusted model	0.87	1.50	0.561
Adjusted + BMI	0.87	1.50	0.562
TC (mg/dl)			
Crude model	−0.10	0.89	0.907
Adjusted model	0.07	0.90	0.937
Adjusted + BMI	0.07	0.90	0.936
WC (cm)			
Crude model	0.16	0.41	0.692
Adjusted model	0.004	0.37	0.991

FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WC, waist circumference.
Adjusted model: Variables were controlled for age, gender, socioeconomic status, physical activity, residential region, and screen time. Moreover, MetS components except for WC were adjusted for one more confounder (BMI).

pressure, due to the effects of zinc on the endothelial cells and vasodilation/constriction through its interactions with various enzymes and proteins (further explained by Tubek) (20); in this study, serum zinc levels were not significantly correlated with blood pressure.

However, it should be noted that the findings on this subject are not entirely consistent. For example, a study by Ghasemi et al. in 2014 in Tehran that was performed on 2401 participants, indicated that there is a significant difference between the genders of participants regarding the relationship between serum zinc levels and metabolic syndrome;(21).

The difference in the populations being studied. (children, adults, specific groups of patients), different adjustments, different settings, confounding variables, and most importantly serum zinc level differences across studies could be the cause of the observed controversial findings. As stated zinc plays a part in many metabolic functions, some of these functions are opposite in nature and outcome (20, 22); Thus many metabolic factors, could potentially impact the results of studies (e.g., mean levels of serum zinc, mean age, sex, ethnicity and other related factors of the population). Hence, more detailed studies are recommended to determine the role of serum zinc levels in the progression of metabolic disease.

It should be noted that in these studies, adults were studied, while in this study, the target population was focused on children and adolescents. Therefore, differences in the final findings are to be expected. In this regard, a study was performed on 60 obese Iranian children by giving zinc and placebo supplements. This intervention showed that zinc supplementation reduces LDL, Total Cholesterol, C-reactive protein (CRP), markers of insulin resistance, fasting blood sugar, insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in children. It should be noted that this study was interventional and prospective, not a cross-sectional one (23).

Our study showed no significant association between serum zinc levels, Mets, and its components. In a similar study conducted on Chinese children and adolescents regarding the association of serum zinc level and metabolic syndrome alongside its components, similarly, no association between serum zinc levels and MetS was found, However serum zinc levels were inversely associated with low-HDL levels and elevated fasting blood glucose with a significant trend (24).

Recommendation for future research

Further research is needed on the need, deficiency, and biological effects of these supplements to further determine the factors affecting the usefulness of zinc supplementation in children with metabolic syndrome. Furthermore, this study shows that there is no significant difference between children with metabolic syndrome and others in terms of weight; however, the fat profile significantly affected the incidence of metabolic syndrome. Thus, studies need to be conducted, not focusing on obesity but on the global standards of metabolic syndrome in children and adolescents.

Limitations and strength

To the best of our knowledge, it is the first study that assessed the relationship between serum zinc levels and

TABLE 3 Association between metabolic syndrome components and dyslipidemia with tertiles of serum zinc in children: logistic regression analysis.

Variables	Serum Zinc tertiles			P trend
	1 (< 94)	2 (94–113)	3 (113 <)	
MetS ($n = 88$)				
Crude model	1	0.75 (0.43; 1.30)	1.08 (0.64; 1.80)	0.751
Adjusted model	1	0.73 (0.42; 1.27)	1.01 (0.60; 1.70)	0.938
FBS ≥ 100 mg/dl ($n = 54$)				
Crude model	1	1.87 (0.89; 3.91)	1.91 (0.91; 4.02)	0.097
Adjusted model	1	1.78 (0.84; 3.74)	1.61 (0.76; 3.43)	0.253
Adjusted + BMI	1	1.80 (0.85; 3.78)	1.62 (0.76; 3.45)	0.249
SBP ≥ 90th ($n = 77$)				
Crude model	1	1.15 (0.66; 1.98)	0.81 (0.45; 1.48)	0.526
Adjusted model	1	1.05 (0.60; 1.84)	0.76 (0.41; 1.41)	0.400
Adjusted + BMI	1	1.08 (0.61; 1.90)	0.77 (0.41; 1.43)	0.417
DBP ≥ 90th ($n = 209$)				
Crude model	1	1.17 (0.81; 1.68)	1.19 (0.82; 1.73)	0.347
Adjusted model	1	1.13 (0.78; 1.64)	1.19 (0.81; 1.74)	0.364
Adjusted + BMI	1	1.14 (0.78; 1.65)	1.19 (0.81; 1.74)	0.371
HDL < 40 mg/dl ($n = 335$)				
Crude model	1	0.99 (0.73; 1.35)	1.19 (0.88; 1.62)	0.241
Adjusted model	1	1.00 (0.73; 1.36)	1.19 (0.88; 1.62)	0.246
Adjusted + BMI	1	0.99 (0.73; 1.35)	1.19 (0.88; 1.62)	0.247
LDL ≥ 130 ($n = 224$)				
Crude model	1	1.17 (0.83; 1.66)	1.03 (0.71; 1.48)	0.878
Adjusted model	1	1.18 (0.83; 1.68)	1.04 (0.72; 1.50)	0.812
Adjusted + BMI	1	1.19 (0.83; 1.69)	1.05 (0.72; 1.51)	0.794
TG ≥ 150 mg/dl ($n = 369$)				
Crude model	1	0.91 (0.67; 1.22)	1.16 (0.87; 1.56)	0.295
Adjusted model	1	0.89 (0.66; 1.19)	1.12 (0.83; 1.50)	0.440
Adjusted + BMI	1	0.89 (0.66; 1.20)	1.12 (0.83; 1.50)	0.435
TC ≥ 200 mg/dl ($n = 48$)				
Crude model	1	1.02 (0.52; 1.99)	0.68 (0.32; 1.45)	0.337
Adjusted model	1	1.03 (0.53; 2.02)	0.70 (0.33; 1.51)	0.389
Adjusted + BMI	1	1.03 (0.53; 2.02)	0.70 (0.33; 1.51)	0.389
Abdominal obesity ($n = 333$)				
Crude model	1	1.30 (0.96; 1.78)	1.30 (0.95; 1.78)	0.106
Adjusted model	1	1.22 (0.89; 1.67)	1.20 (0.87; 1.66)	0.261

MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBS, fasting blood sugar.

Adjusted model: Variables were controlled for age, gender, socioeconomic status, physical activity, residential region, and screen time. Moreover, MetS components except for abdominal obesity were adjusted for one more confounder (BMI).

-High blood pressure and abdominal obesity cut-offs are based on the 90th percentile or higher based on height, weight, age, and gender. TG, TC, LDL, HDL, and FBS cutoffs were 150, 200, 130, 40, and 100 mg/dL, respectively.

MetS components, especially with consideration of confounder variables and impressive sample size. However, there are probably some other unknown confounders that are effective in the exact association. Moreover, this study was cross-sectional and due to its natural cause and effect relationship, could not distinguish.

Conclusion

This cross-sectional study showed no association between serum zinc levels and metabolic syndrome in children. Hence it seems that zinc supplementation in children without zinc deficiency who suffer from Mets or any of its components is redundant. Nonetheless, clinicians must keep racial and age aspects in mind since conflicting findings across different races, sexes, and ages were seen.

Further studies similar studies and cohort studies are needed to reveal the exact relationship between serum zinc levels and metabolic syndrome and warrant our findings.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Alborz University of Medical Sciences. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MQ and NM conceived the study. NMK and ED substantially contributed to the conception and design, data analysis and interpretation, drafted the manuscript, and revised it critically. RK, HA, and LS participated in preparing the manuscript. AM-G, ME, and RH participated in the study design and data acquisition. MQ carried out the analysis of the data. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Mainul Haque,
National Defence University of Malaysia, Malaysia

REVIEWED BY
Iffat Jahan,
Eastern Medical College and Hospital, Bangladesh
Susmita Sinha,
Khulna City Medical College and Hospital, Bangladesh

*CORRESPONDENCE
Khadijeh Mirzaei
mirzaei_kh@tums.ac.ir;
mirzaei_kh@sina.tums.ac.ir

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The relationship between ultra-processed food intake and cardiometabolic risk factors in overweight and obese women: A cross-sectional study

Dorsa Hosseininasab[1], Farideh Shiraseb[2], Sahar Noori[1], Shahin Jamili[3], Fatemeh Mazaheri-Eftekhar[1], Mahshid Dehghan[4], Alessandra da Silva[5], Josefina Bressan[5] and Khadijeh Mirzaei[2]*

[1]Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran, Iran, [2]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran, [3]Department of Surgery, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada, [5]Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, MG, Brazil

Background: Cardiovascular diseases (CVDs) are the leading cause of death globally. Based on recent studies, one of the factors that can have detrimental effects on CVD is the consumption of ultra-processed foods (UPFs). The current study investigated the relationship between UPF intake and cardiometabolic risk factors among Iranian women.

Methods: The current cross-sectional study was conducted on 391 women aged 18–65 years with a body mass index (BMI) $\geq$ 25 kg/m^2. Dietary intake was assessed using a 147-item food frequency questionnaire (FFQ). Anthropometric and biochemistry parameters were also collected. UPFs were identified using the NOVA classification.

Results: In the present study, women had a mean (standard deviation) age of 36.67 (9.10) years and the mean BMI of 31.26 (4.29) kg/m^2. According to our findings, there was a significant association between UPF consumption and transforming growth factor (TGF) (β: 0.101, 95% CI: 0.023, 0.180, p = 0.012), atherogenic coefficient (AC) (β: 0.011, 95% CI: 0.001, 0.032, p = 0.034), visceral fat level (VFL) (β: 0.006, 95% CI: −0.017, 0.029, p = 0.076), and the quantitative insulin sensitivity check index (QUICKI) (β: −3.775, 95%CI: 0.001, 0.001, p = 0.042).

Conclusion: In conclusion, an increase in consumption of one gram of UPFs is associated with an increase in TGF, AC, and VFL but with a decrease in QUICKI. Despite this, further experimental studies are necessary to draw a more definite conclusion and disentangle the mechanisms by which UPFs may affect health.

KEYWORDS

ultra-processed food, cardiovascular diseases, obesity, overweight, cardiometabolic risk

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally; an estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths (1). About 85% of the deaths were due to heart attack and stroke (1). According to previous studies conducted in 2016 and 2017, CVD has been the major cause of mortality in Iran, accounting for 46% of all deaths and 20–23% of the disease burden (2, 3).

The global consumption of ultra-processed foods (UPF) has risen exponentially. UPFs account for between 25 and 60% of total daily energy consumption, according to the Nationwide Food Surveys (4–14). According to the NOVA classification system, UPFs are defined as foods made up entirely or predominantly from unhealthy components containing higher levels of total fat, saturated fat, added sugar, energy density, and salt, and lower quantities of fiber and vitamin density (15). UPF packaging contains materials that come into contact with food, such as Bisphenol A, which, according to a meta-analysis of observational studies, may increase the risk of cardiometabolic disorders, even though prospective cohort studies are still limited (16, 17). Some studies reported that consumption of UPF is associated with adverse health outcomes, including CVDs, and obesity (18–20). Srour et al. reported a higher risk of CVD associated with the consumption of ultra-processed foods (21).

Given the high prevalence of CVDs in Iran, it is necessary to find dietary factors that may associate with the disease (22). The main objective of this study was to investigate the relationship between UPF intake and cardiometabolic risk factors among Iranian women, and the secondary objectives were to exhibit the association between UPF consumption, food groups, and demographic variables.

Methods

Study population

The research was conducted in Tehran, Iran, using a multi-stage cluster random sampling procedure on 391 overweight and obese women with a body mass index (BMI) ranging from 25 to 40 kg/m^2 and aged 18–48 years, recruited from the community health center of the Tehran University of Medical Sciences (TUMS) in 2018. We used the sample size formula $N = ([(Z_{1-\alpha} + Z_{1-\beta}) \times \sqrt{1-r^2}]/r)^2 + 2)$, $\beta = 95\%$, and $\alpha = 0.05$, $r = 0.25$. Participants were excluded from the study if they reported a total daily energy intake outside of 800–4,200 kcal (17,556–3,344 kJ) (23) or if they reported a history of diseases such as CVD, diabetes, cancer, kidney disease, thyroid disease, menopause, pregnancy, and breastfeeding. In addition, individuals on lipid-lowering agents, individuals on blood glucose-lowering agents, and those who consumed alcohol or smoked were excluded from the study. Furthermore, the food frequency questionnaire (FFQ) did not include individuals who did not respond to more than 70 questions and had significant fluctuations in their weight over the past year. After learning about the study's objectives, all the participants signed an informed consent form. The Human Ethics Committee of Tehran University of Medical Sciences approved the study protocol (Ethics number: IR.TUMS.VCR.REC.1398.142, Date of reference number: 5 April 2019).

Dietary assessment and NOVA calculation

To evaluate the food consumption of participants during the previous year, we used a validated semi-quantitative FFQ, whose validity and reliability have already been authorized (24, 25). Trained dietitians were responsible for applying the FFQ. In total, one hundred forty-seven food items were included in this FFQ with a standard serving size, and participants assessed their consumption frequency according to four categories: daily, weekly, monthly, and infrequent. Using home measures, the portion sizes of the consumed foods were converted to grams (23). Nutrient and energy intakes were calculated using NUTRITIONIST IV software (version 7.0; N-Squared Computing, Salem, OR). The following food and beverage items are classified as UPFs in the NOVA food group classification, which is the subject of this research, and are grouped into the FFQ into seven food groups (daily intake was calculated as grams): (1) Non-dairy beverages (coffee, cola, nectar, and industrial sweet drink), (2) dairy beverages (ice cream, pasteurized and non-pasteurized, chocolate milk, and cocoa milk), (3) cakes and cookies (cookies, biscuits, pastries (creamy and non-creamy), cake, pancake, industrial bread, toasted bread, noodles, and pasta), (4) fast food and processed meat (burger, sausage, pizza, and bologna), (5) salty snacks (chips, crisps, crackers, and cheese puff), (6) oil and sauce (mayonnaise, margarine, and ketchup), (7) sweets (Gaz, Sohan, Noghl, sesame halva, chocolate, candies, rock candies, jam, and sweets) (26). All the NOVA components were adjusted for energy intake.

Anthropometry and body composition

Participants were advised to fast for 12 h the night before the assessment and avoid unusual physical activity for 72 h before the anthropometrics and body composition assessments. A digital stadiometer (Seca) was used to measure height (m) with a precision of 0.5 cm. The waist circumference (WC) (cm) and hip circumference (HC) (cm) with an accuracy of 0.5 cm were measured within the largest and the littlest circumference separately. The waist-to-hip ratio (WHR) was computed as WC (cm)/HC (cm).

A multi-frequency bioelectric impedance analyzer (BIA) (Inbody Co., Seoul, Korea) scanner evaluated body composition. This electrical impedance analyzer measures the resistance of body tissues to the passage of an electrical signal given through the feet and hands. The body composition analyzer was used to assess the individuals' weight, BMI, fat mass (FM), fat-free mass (FFM), body fat percentage (%), and the others, according to a predetermined methodology. The participants were instructed to urinate before measuring their body composition according to the fabricant recommendations.

Biochemical assessment

The blood samples were obtained between 8:00 and 10:00 a.m. at the Nutrition and Biochemistry lab of the School of Nutritional Sciences and Dietetics, TUMS, after an overnight fast and deposited in tubes containing 0.1 percent ethylenediaminetetraacetic acid (EDTA). The serum was centrifuged, aliquoted, and stored at −70°C. The glucose oxidase phenol 4-aminoantipyrine peroxidase (GOD/PAP) technique determined fasting blood glucose levels (FBG). To evaluate blood triglyceride (TG) levels, enzyme colorimetric assays with GPO–PAP were utilized. Total cholesterol was assessed using phenol 4-aminoantipyrine peroxidase (CHOD–PAP), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured using the direct approach and immunoinhibition. The serum high-sensitivity C-reactive protein (hs-CRP) was measured using an immunoturbidimetric method. The Enzyme-Linked Immunosorbent Assays (ELISA) technique was used to evaluate the levels of IL-1β and PA-I (Human PAI-1*96 T ELIZA kit Crystal Company). The serum insulin concentrations were determined using the enzyme-linked immunosorbent assay (ELISA kit). The ELISA kit was also used to quantify serum MCP-1 levels (Zell Bio GmbH, Germany, assay range:5 ng/L—1,500 ng/L, sensitivity:2.4 ng/L, CV10 percent inter-assay variability). All of the kits were given by Pars Azmoon (Pars Azmoon Inc. Tehran, Iran). Insulin resistance was assessed using a homeostasis model (HOMA–IR). The index was computed using the algorithm (plasma glucose mmol/ l / × fasting plasma insulin mIU/ l)/22.5 (27). The quantitative insulin sensitivity check index (QUICKI) was also used to evaluate insulin resistance through the formula 1/[log (fasting insulin) + log (fasting glucose)] (27). From biochemical parameters, FBG, TG, HDL, LDL, hs-CRP, and IL_1β variables are considered as CVD risk factors in this study.

The atherogenic index of plasma (AIP) was calculated using the logarithmic of (TG/HDL-C). TC/HDL, LDL/HDL, and (TC-HDL) /LDL were used to determine castelli's risk index 1 (CRI-I), castelli's risk index 2 (CRI- II), and atherogenic coefficient (AC), respectively. The following formula was used to compute CHOLIndex: CHOLIndex = LDL-C – HDL-C (TG <400) = LDL-C – HDL-C + 1/5 TG (TG >400). (28). Ln (FBG (mg/dl) * TG (mg/dl)/2) was used to determine triglyceride–glucose index (TyG index) (29). The terms triglyceride glucose-waist circumference (TyG–WC) and triglyceride glucose–body mass index (TyG–BMI) were obtained through the formulas: [Ln (FBG (mg/dl) * TG (mg/dl)/2)] * WC and [Ln (FBG (mg/dl) * TG (mg/dl)/2)] * BMI), respectively (30).

Blood pressure assessment

Blood pressure was measured using an automated sphygmomanometer according to standard procedures (OMRON, Germany).

Other collected data

General information about the participants, such as their age, job status (employed, unemployed), education level (illiterate, under diploma, diploma, and bachelor and higher) (what are the categories? Detail the methodology here, as well as the other variables), marital status (single and married), economic status (low, middle, and high class), standard questionnaires, were collected. The physical activity status was obtained using the validated International Physical Activity Questionnaire (IPAQ). Afterward, metabolic equation hours per day (MET-min/week) were calculated for each subject. After that, each subject's metabolic equation hours per day score (MET-min/week) was calculated. Trained professionals were responsible for applying the questionnaires (31, 32).

Statistical analyses

The Kolmogorov–Smirnov test was used to check the quantitative variable's normality ($P > 0.05$). Categorical data were reported as absolute and relative frequencies, and quantitative data were reported as means and standard deviation (SD). According to the NOVA score, the participants were categorized into tertiles of UPF consumption in grams. To compare the mean difference of quantitative and frequency of categorical variables across UPF tertiles, a one-way analysis of variance (ANOVA) and Pearson chi-square (χ^2) tests were performed, respectively. Analysis of covariance (ANCOVA) adjusted for potential confounders (age, BMI, energy intake, and physical activity) and considering BMI as a collinear variable for anthropometrics and body composition variables were performed. The Bonferroni *post-hoc* test was used to detect the statistically significant difference among UPF tertiles. Linear regression was performed to evaluate the association of the UPF consumption (independent variable) with cardiometabolic risk factors (dependent variable). Model 1 was adjusted for age, BMI, physical activity, total energy

TABLE 1 General characteristics among tertiles of NOVA score in obese and overweight women ($n = 391$).

Quantitative variables	NOVA tertiles			P-value	P-value*
	T1	T2	T3		
	<383.681	383.681–467.713	>467.713		
	N = 131	N = 130	N = 130		
	Mean ± SD				
Age (year)[a]	36.480 ± 9.138	38.759 ± 8.77	34.860 ± 9.352	**0.003**	**0.004**
PA (MET-min -week)	1,465.171 ± 231.881	834.995 ± 235.775	1,353.665 ± 254.709	0.098	0.154
Weight (kg)	81.958 ± 12.382	79.884 ± 10.975	81.669 ± 13.320	0.337	0.365
Height (cm)	161.574 ± 5.888	160.115 ± 5.881	161.763 ± 5.796	**0.047**	0.869
BMI (kg/m^2)	31.141 ± 0.440	30.847 ± 0.449	30.459 ± 0.483	0.946	0.576
WC (cm)	113.163 ± 8.516	113.638 ± 7.477	116.295 ± 13.637	0.247	0.592
BMC (Kg)	2.676 ± 0.376	2.622 ± 0.342	2.661 ± 0.330	0.445	0.643
SMM (Kg)	25.954 ± 3.281	25.347 ± 3.300	25.333 ± 3.4205	0.247	0.311
SLM (Kg)	44.083 ± 5.759	43.585 ± 5.126	43.587 ± 5.317	0.693	0.454
Categorical variables					
Supplementation intake *n* (%)[b]				0.311	**0.057**
Yes %	58 (36.7)	47 (29.7)	53 (33.5)		
No %	51 (29.0)	61 (34.7)	64 (36.4)		
Income status *n* (%)				0.582	0.185
Low class	33 (37.5)	31 (35.2)	24 (27.3)		
Middle class	60 (33.0)	61 (33.5)	61 (33.5)		
High class	35 (32.7)	31 (29.0)	41 (38.3)		
Marital status *n* (%)				0.275	0.880
Single	35 (32.1)	31 (28.4)	43 (39.4)		
Married	92 (33.6)	96 (35)	86 (31.4)		
Job status *n* (%)				0.137	**0.073**
Unemployed	2 (100)	0 (0)	0 (0)		
Employed	128 (33.2)	129 (33.5)	128 (33.2)		
Educational status *n* (%)				0.753	0.744
Illiterate	1 (25)	1 (25)	2 (50)		
Under diploma	12 (26.1)	17 (37)	17 (37)		
Diploma	46 (30.9)	54 (36.2)	49 (32.9)		
Bachelor and higher	68 (37)	55 (29.9)	61 (33.2)		

PA, physical activity; BMI, body mass index; WC, waist circumference; BMC, bone mineral content; SMM, skeletal muscle mass; SLM, soft lean mass.
Values are represented as means and SD and number (%) for categorical variables.
ANCOVA (P-value*) was performed to adjust potential confounding factors; age, energy intake, PA, BMI. BMI consider as the collinear variable for body composition, and anthropometric measurements.
$p < 0.05$ were considered as significant.
[a]significant difference was seen between T3 and T2.
[b]significant difference was seen between T2 and T3.
A $p < 0.05$ were considered as significant and p-values of 0.05, 0.06, and 0.07 were considered as marginally significant.

intake, supplements intake, and job status. Model 2 was further adjusted for legumes and vegetables. This analysis was presented as the β-value and a confidence interval of 95% (CI). SPSS v.26 software (SPSS Inc., IL, USA) was used for statistical analysis. The significance level was set at $p < 0.05$.

Results

A total of 391 participants were included in the present study. Women had a mean (SD) age of 36.67 (9.10) years and a mean BMI of 31.26 (4.29) kg/m^2. The majority of women were employed (97%), 47% were highly educated (bachelor's degree and higher), and 45.5% had a middle income. The mean of UPF intake in our sample was 442.47 (127.91) g or 96.8 %.

The general characteristics of participants among UPF tertiles are presented in Table 1. The average UPF consumption in tertile 1 was <383,681 g, in tertile 2 was from 383,681 g to 467,713 g, and in tertile 3 was >467,713 g. The mean of age ($P = 0.003$) was statistically different between UPF tertiles in the crude model and after controlling for confounding variables. The mean height ($P = 0.047$) was statistically different between UPF tertiles in the crude model. According to the Bonferroni's *post-hoc* test, the significant mean difference in age was between T2 and T3, and the mean difference was higher in T2 than in T3.

In the categorical variables, the supplementation intake ($P = 0.057$) and job status ($P = 0.073$) were marginally significant between UPF tertiles after controlling for cofounders. There was no significant difference for other variables (Table 1).

Dietary intakes among the UPF tertiles

Dietary intakes of all the participants among tertiles of UPF consumption are presented in Table 2. The mean of non-dairy beverages ($P = 0.001$), dairy beverages ($P = 0.001$), cookies (cakes) ($P = 0.001$), potato chips (salty) ($P = 0.001$),

TABLE 2 Dietary intakes among tertiles of the NOVA score in obese and overweight women ($n = 391$).

	Total	UPF consumption tertiles			*P*-value	*P*-value*
		T1 ($n = 131$) <383.681	T2 ($n = 130$) 383.681-467.713	T3 ($n = 130$) >467.713		
NOVA score components						
Nondairy beverages (g/d)	177.351 ± 93.223	124.069 ± 25.540	157.152 ± 27.648	251.242 ± 126.711	**0.001**	**0.001**
Cookies-cakes (g/d)	98.913 ± 44.205	75.570 ± 25.626	97.288 ± 28.007	124.061 ± 57.167	**0.001**	**0.001**
Dairy beverages (g/d)	47.833 ± 27.952	37.472 ± 18.4894	46.629 ± 22.117	59.479 ± 35.795	**0.001**	**0.001**
Potato chips- salty	22.106 ± 13.893	17.354 ± 9.094	22.652 ± 10.166	26.348 ± 18.853	**0.001**	**0.001**
Processed meat- fast food (g/d)	41.138 ± 25.424	28.402 ± 12.600	40.230 ± 14.202	54.881 ± 35.167	**0.001**	**0.001**
Oil_ Sause (g/d)	18.269 ± 8.727	16.764 ± 8.5494	17.861 ± 7.4184	20.194 ± 9.766	**0.005**	**0.005**
Sweet (g/d)	36.861 ± 24.0635	30.679 ± 15.1176	36.916 ± 17.1858	43.037 ± 33.8778	**0.001**	**0.001**
Food groups						
Refined grains (g/d)	432.348 ± 220.133	474.142 ± 191.103	380.801 ± 207.529	444.129 ± 253.5120	**0.008**	0.969
Whole grains (g/d)	7.586 ± 10.410	9.144 ± 11.2396	6.769 ± 9.0196	6.746 ± 10.831	0.177	0.361
Fruits (g/d)	528.904 ± 338.1681	605.778 ± 317.153	466.287 ± 317.377	513.252 ± 370.044	**0.011**	0.340
Vegetables (g/d)	433.577 ± 263.259	526.618 ± 264.203	382.927 ± 226.814	385.498 ± 275.073	**0.001**	**0.003**
Nuts (g/d)	14.370 ± 16.1868	17.821 ± 17.786	11.449 ± 14.354	13.795 ± 15.697	**0.018**	0.518
Legumes (g/d)	52.691 ± 41.2788	63.432 ± 49.5718	45.834 ± 35.7690	48.313 ± 34.0807	**0.005**	**0.045**
Dairy (g/d)	387.451 ± 246.357	438.192 ± 267.952	330.196 ± 224.147	394.927 ± 233.413	**0.007**	0.769
Eggs (g/d)	21.687 ± 14.174	22.105 ± 12.3656	21.235 ± 12.394	21.732 ± 17.7520	0.909	0.569
Fish and seafood (g/d)	11.408 ± 12.1569	12.086 ± 11.932	10.743 ± 11.2257	11.399 ± 13.4774	0.735	0.990
Meats (g/d)	64.571 ± 50.1758	67.371 ± 40.9762	54.081 ± 41.6793	73.518 ± 65.0100	**0.022**	0.250
Red meat (g/d)	21.479 ± 18.5197	24.003 ± 20.368	17.760 ± 15.8117	22.894 ± 18.722	**0.038**	0.947
Macronutrients and energy						
Energy intake (kcal/d)	2633.280 ± 809.432	2916.675 ± 654.474	2267.608 ± 712.433	2713.37 ± 904.867	**0.001**	-
Micronutrients						
SFA (mg/d)	28.409 ± 11.545	30.861 ± 11.417	24.761 ± 10.291	29.587 ± 12.033	**0.001**	0.628
MUFA (mg/d)	32.008 ± 12.917	35.155 ± 13.593	27.591 ± 10.563	33.253 ± 13.241	**0.001**	0.817
PUFA (mg/d)	20.082 ± 9.568	22.589 ± 10.515	17.403 ± 8.316	20.235 ± 9.087	**0.001**	0.717
Trans fat (g/d)	0.0007 ± 0.002	0.001 ± 0.003	0.0006 ± 0.001	0.0005 ± 0.001	0.097	0.120
Total fiber (g/d)	47.344 ± 21.360	57.263 ± 21.377	40.359 ± 19.203	44.333 ± 19.795	0.078	**0.001**

pro, protein; Cho, carbohydrate; SAFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
Values are represented as means (SD).
ANCOVA (P-value*) was performed to adjust potential confounding factors (energy intake).
A P-value under 0.05 is considered significant.

TABLE 3 CVD risk factors consist of anthropometric measurements and body composition, biochemical variables, and inflammatory factors among tertiles of NOVA score in obese and overweight women ($n = 391$).

Variables		UPF consumption tertiles			*P*-value
		T1 <383.681	T2 383.681– 467.713	T3 >467.713	
Body Composition					
FFM (Kg)	Crude	47.019 ± 5.938	46.217 ± 5.444	46.263 ± 5.616	0.440
	Model 1	46.402 ± 0.982	47.858 ± 1.037	46.017 ± 1.332	0.513
	Model 2	46.286 ± 1.014	47.917 ± 1.058	46.121 ± 1.347	0.499
FFMI	Crude	18.977 ± 1.618	17.977 ± 1.443	17.672 ± 11.450	0.266
	Model 1	17.801 ± 0.246	18.153 ± 0.260	17.838 ± 0.334	0.625
	Model 2	17.729 ± 0.252	18.202 ± 0.263	17.882 ± 0.33	0.479
FMI	Crude	13.422 ± 3.163	13.318 ± 3.235	13.610 ± 3.799	0.784
	Model 1	12.214 ± 0.590	12.903 ± 0.623	12.217 ± 0.800	0.716
	Model 2	12.168 ± 0.612	12.929 ± 0.638	12.255 ± 0.813	0.700
BF (%)	Crude	42.238 ± 5.016	41.890 ± 5.255	42.550 ± 6.196	0.629
	Model 1	40.208 ± 1.026	41.033 ± 1.084	39.571 ± 1.392	0.725
	Model 2	40.174 ± 1.066	41.058 ± 1.112	39.588 ± 1.416	0.726
BFM (Kg)	Crude	34.936 ± 8.395	33.830 ± 7.801	35.421 ± 9.887	0.325
	Model 1	31.494 ± 1.421	33.926 ± 1.501	31.150 ± 1.927	0.450
	Model 2	31.387 ± 1.471	33.978 ± 1.535	31.251 ± 1.955	0.450
TF (kg)	Crude	16.965 ± 3.489	16.5070 ± 3.411	17.103 ± 4.086	0.393
	Model 1	15.609 ± 0.624	16.608 ± 0.660	15.450 ± 0.847	0.493
	Model 2	15.571 ± 0.648	16.630 ± 0.676	15.479 ± 0.861	0.492
TF (%)	Crude	320.916 ± 65.872	317.959 ± 68.968	322.384 ± 75.379	0.875
	Model 1	298.070 ± 12.616	312.018 ± 13.326	297.691 ± 17.107	0.736
	Model 2	297.023 ± 13.092	312.746 ± 13.660	298.300 ± 17.394	0.712
Anthropometric measurements					
WC (cm)	Crude	97.281 ± 16.058	97.138 ± 12.693	97.951 ± 17.058	0.933
	Model 1	92.021 ± 3.239	98.703 ± 3.421	89.857 ± 4.391	0.259
	Model 2	91.161 ± 3.329	99.287 ± 3.473	90.382 ± 4.423	0.207
WHR	Crude	0.939 ± 0.054	1.637 ± 8.018	0.936 ± 0.051	0.372
	Model 1	0.931 ± 0.009	0.940 ± 0.010	0.911 ± 0.013	0.236
	Model 2	0.931 ± 0.010	0.939 ± 0.010	0.911 ± 0.013	0.233
VFA (CM^2)	Crude	168.858 ± 36.720	176.087 ± 150.293	168.733 ± 42.799	0.764
	Model 1	154.422 ± 6.889	161.912 ± 7.276	147.917 ± 9.341	0.526
	Model 2	154.298 ± 7.155	161.986 ± 7.465	148.012 ± 9.506	0.536
VFL	Crude	17.122 ± 12.037	15.612 ± 3.307	17.514 ± 17.260	0.423
	Model 1	14.815 ± 0.605	15.404 ± 0.639	14.262 ± 0.820	0.576
	Model 2	14.826 ± 0.628	15.397 ± 0.656	14.252 ± 0.835	0.589
NC [a] (cm)	Crude[a]	38.338 ± 12.042	36.958 ± 2.702	37.430 ± 3.942	0.537
	Model 1[b]	36.130 ± 0.421	37.791 ± 0.445	36.420 ± 0.571	**0.036**
	Model 2[a]	36.233 ± 0.433	37.723 ± 0.452	36.354 ± 0.575	**0.068**
Biochemical variables					
SBP (mmHg)	Crude	113.000 ± 15.0006	112.227 ± 12.386	108.333 ± 17.190	0.083
	Model 1	113.074 ± 1.661	111.479 ± 1.691	108.975 ± 1.734	0.231
	Model 2	113.374 ± 1.4497	110.824 ± 1.504	119.552 ± 1.164	0.222
DBP (mmHg)	Crude	77.969 ± 9.586	77.930 ± 9.454	76.547 ± 12.418	0.590
	Model 1	77.745 ± 1.194	77.736 ± 1.216	77.931 ± 1.247	0.992
	Model 2	78.237 ± 1.064	76.992 ± 1.069	78.117 ± 1.172	0.677

(Continued)

TABLE 3 Continued

Variables		UPF consumption tertiles			*P*-value
		T1 <383.681	T2 383.681– 467.713	T3 >467.713	
HOMA-IR	Crude	3.240 ± 1.346	3.585 ± 1.388	3.142 ± 1.007	**0.073**
	Model 1	2.941 ± 0.190	3.770 ± 0.189	3.143 ± 0.204	0.011
	Model 2[a]	3.031 ± 0.196	3.738 ± 0.189	3.078 ± 0.207	**0.024**
Insulin (mIU/ ml)	Crude	1.205 ± 0.245	1.240 ± 0.234	1.194 ± 0.197	0.415
	Model 1	1.229 ± 0.035	1.235 ± 0.034	1.190 ± 0.037	0.636
	Model 2[a]	1.227 ± 0.036	1.237 ± 0.035	1.189 ± 0.038	0.629
FBG (mg/dL)	Crude	87.569 ± 9.927	88.912 ± 10.343	85.536 ± 7.919	0.089
	Model 1	84.834 ± 1.382	88.262 ± 1.372	84.393 ± 1.482	0.126
	Model 2	85.057 ± 1.439	88.199 ± 1.388	84.209 ± 1.516	0.136
TC (mg/dL)	Crude	182.383 ± 37.483	189.395 ± 33.851	183.000 ± 37.733	0.371
	Model 1	177.717 ± 4.406	179.295 ± 4.417	184.293 ± 466	0.569
	Model 2	177.026 ± 4.583	179.669 ± 4.472	184.648 ± 4.741	0.514
TG (mg/dL)	Crude	118.267 ± 55.944	120.022 ± 59.970	116.144 ± 64.776	0.922
	Model 1	115.533 ± 8.472	126.502 ± 8.494	118.257 ± 8.966	0.666
	Model 2	114.907 ± 4.583	179.669 ± 8.609	118.752 ± 9.126	0.653
HDL (mg/dL)	Crude	47.267 ± 10.965	47.340 ± 11.662	45.536 ± 9.567	0.518
	Model 1	48.039 ± 1.328	45.996 ± 1.331	47.130 ± 1.405	0.584
	Model 2	48.149 ± 1.383	45.941 ± 1.350	47.068 ± 1.431	0.561
LDL (mg/dL)	Crude	95.244 ± 23.856	97.109 ± 24.795	92.029 ± 23.850	0.420
	Model 1	98.986 ± 3.071	98.070 ± 3.078	99.803 ± 3.249	0.931
	Model 2	98.176 ± 3.186	98.486 ± 3.109	100.248 ± 3.296	0.890
GOT (mg/dL)	Crude	17.720 ± 7.441	18.604 ± 8.179	16.927 ± 5.976	0.358
	Model 1	18.502 ± 1.037	18.579 ± 1.021	16.154 ± 1.104	0.202
	Model 2	18.365 ± 1.064	18.675 ± 1.022	16.194 ± 1.112	0.221
GPT (mg/dL)	Crude	19.209 ± 14.249	20.373 ± 13.793	17.478 ± 9.842	0.378
	Model 1	21.013 ± 1.886	21.034 ± 1.857	16.240 ± 2.008	0.144
	Model 2	21.125 ± 1.945	21.047 ± 1.868	16.093 ± 2.033	0.131
AIP	Crude	0.366 ± 0.236	0.362 ± 0.240	0.361 ± 0.272	0.990
	Model 1	0.343 ± 0.034	0.403 ± 0.034	0.353 ± 0.036	0.449
	Model 2	0.339 ± 0.035	0.404 ± 0.034	0.356 ± 0.036	0.434
CRI-I	Crude	4.029 ± 1.206	4.194 ± 1.209	4.294 ± 2.100	0.542
	Model 1	3.778 ± 0.118	3.998 ± 0.118	4.025 ± 0.125	0.292
	Model 2	3.755 ± 0.122	4.010 ± 0.119	4.038 ± 0.127	**0.062**
CRI-II	Crude	2.075 ± 0.531	2.132 ± 0.642	2.075 ± 0.580	0.765
	Model 1	2.114 ± 0.080	2.191 ± 0.080	2.187 ± 0.085	0.760
	Model 2	2.091 ± 0.083	2.202 ± 0.081	2.200 ± 0.086	0.593
AC	Crude	3.029 ± 1.206	3.194 ± 1.209	3.294 ± 2.100	0.542
	Model 1	2.778 ± 0.118	2.998 ± 0.118	3.025 ± 0.125	0.292
	Model 2	2.755 ± 0.122	3.010 ± 0.119	3.038 ± 0.127	**0.072**
CHOLIndex	Crude	47.976 ± 21.460	49.769 ± 23.040	46.492 ± 23.306	0.657
	Model 1	50.947 ± 3.040	52.074 ± 3.048	52.674 ± 3.218	0.925
	Model 2	50.027 ± 3.151	52.545 ± 3.075	53.180 ± 3.260	0.775
TyG index	Crude	8.446 ± 0.478	8.466 ± 0.486	8.377 ± 0.494	0.516
	Model 1	8.404 ± 0.068	8.517 ± 0.068	8.402 ± 0.072	0.434
	Model 2	8403 ± 0.070	8.517 ± 0.069	8.404 ± 0.73	0.449

(Continued)

TABLE 3 Continued

Variables		UPF consumption tertiles			*P*-value
		T1 <383.681	T2 383.681– 467.713	T3 >467.713	
TyG-BMI	Crude	261.876 ± 40.206	261.827 ± 41.224	255.425 ± 46.928	0.571
	Model 1	253.760 ± 7.272	246.303 ± 7.625	254 ± 337 ± 8.691	0.586
	Model 2	252.295 ± 7.491	265.151 ± 7.716	255.342 ± 8.813	0.510
TyG-WC	Crude	810.989 ± 177.111	812.087 ± 135.178	791.246 ± 132.359	0.76
	Model 1[b]	718.567 ± 26.978	838.143 ± 28.287	754.874 ± 32.243	**0.057**
	Model 2[b]	741.185 ± 27.740	842.278 ± 28.573	760.139 ± 32.637	**0.026**
Inflammatory biomarkers					
PAL-1 (mg/dl)	Crude	20.265 ± 39.585	14.200 ± 24.731	13.319 ± 20.377	0.405
	Model 1	31.411 ± 12.591	23.991 ± 15.100	5.875 ± 12.168	0.429
	Model 2	47.091 ± 17.465	20.579 ± 18.555	9.139 ± 12.762	0.255
MCP1 (mg/dl)	Crude	57.514 ± 94.785	54.332 ± 109.983	36.967 ± 54.657	0.389
	Model 1	83.110 ± 28.588	52.148 ± 34.285	25.798 ± 27.629	0.301
	Model 2	117.021 ± 40.136	57.515 ± 42.640	25.996 ± 29.328	0.224
TGF (ng/ml)	Crude	74.436 ± 39.046	80.671 ± 61.1695	80.775 ± 41.250	0.733
	Model 1	55.998 ± 10.530	78.067 ± 12.628	88.626 ± 10.177	0.295
	Model 2[c]	49.350 ± 15.871	78.440 ± 16.862	88.086 ± 11.597	**0.077**
IL_1β (ng/ml)	Crude	2.585 ± 0.895	2.745 ± 1.022	2.843 ± 0.927	0.647
	Model 1	2.625 ± 0.274	3.010 ± 0.328	2.715 ± 0.264	0.538
	Model 2	2.307 ± 0.418	3.052 ± 0.445	2.708 ± 0.306	0.580
hs_CRP (mg/l)	Crude	4.300 ± 4.624	4.219 ± 4.641	4.480 ± 4.773	0.942
	Model 1[b]	3.905 ± 0.727	1.385 ± 0.871	6.109 ± 0.702	**0.001**
	Model 2 [b]	3.972 ± 1.006	0.566 ± 1.069	6.390 ± 0.735	**0.001**

AC, atherogenic coefficient; BFM, body fat mass; BF, body fat; FFM, fat-free mass; FMI, fat mass index; FFMI, fat-free mass index; WC, waist circumference; WHR, Waist-to-Hip Ratio; NC, Neck circumference; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; CRI, Cardiac risk index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; FBS, Fasting Blood Sugar; TG, Triglyceride; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; GPT, Glutamic-pyruvic transaminase; GOT, Glutamic-oxaloacetic transaminase; PAI-1, plasminogen activator inhibitor- 1, TF, Trunk Fat, VFA, Visceral fat area, VFL, Visceral fat level, SD Standard deviation; hs-CRP, high sensitive- C reactive protein; TC, Total cholesterol; AIP, Atherogenic index of plasma; TyG, Triglyceride-glucose; TGF, Transforming growth factor.

Quantitative variables were shown by means ± SD and categorical variables were shown by number (%).

P-values resulted from one-way ANOVA analysis and thechi-squared test. A p-value < 0.05 was considered significant and p-values equal to 0.05, 0.06, and 0.07 were considered marginally significant.

*P-values resulted from ANCOVA analysis and were adjusted.

Model 1: Adjusted for age, BMI, physical activity, total energy intake, supplements intake, and job status (BMI consider as a collinear variable).

Model 2: Additionally controlled for the effect of vegetables and legumes.

The Bonferroni *post-hoc* test was used to investigate differences between tertiles, significant difference between two means with p <0.05. 0.05, and 0.06 considered as marginally significant.

[a]Significant difference was seen between T1 and T2.

[b]Significant difference was seen between T2 and T3.

[c]Significant difference was seen between T1 and T3.

processed meat (fast food) ($P = 0.001$), oil (sauce group) ($P = 0.005$), sweet ($P = 0.001$) were statistically different among UPF tertiles, with it being higher in the third tertile. With increasing UPF consumption, non-dairy beverages, cookies (cakes), dairy beverages, potato chips (salty), processed meat (fast food), oil, sauce, and sweet have increased in the crude and adjusted model.

CVD risk factors among the UPF tertiles

The association of CVD risk factors among UPF consumption tertiles is shown in Table 3. UPF consumption was associated with the HOMA–IR index ($P = 0.024$), hs-CRP ($P = 0.001$), and TYG–WC ($P = 0.026$). On the contrary, it was marginally associated with the markers TGF ($P = 0.077$), AC ($P = 0.072$), CRI-1 ($P = 0.062$), and NC ($P = 0.068$).

Association between UPF consumption and CVD risk factors, anthropometric measurements, body composition, biochemical variables, and inflammatory factors

Association between UPF consumption and CVD risk factors, anthropometric measurements, body composition,

TABLE 4 Association between NOVA score and CVD risk factors, anthropometric measurements, body composition, biochemical variables, and inflammatory factors in obese and overweight women ($n = 391$).

Variables		NOVA score		*P*-value	*P*-value*
		β (SE)	CI (95%)		
Body composition					
FFM (Kg)	Crude	−0.001 (0.002)	−0.005, 0.003	0.682	-
	Model 1	−0.004 (0.004)	−0.011, 0.003	-	0.278
	Model 2	−0.004 (0.004)	0.001, 0.001	-	**0.056**
FFMI	Crude	−0.004 (0.003)	−0.009, 0.001	0.115	-
	Model 1	−0.001 (0.001)	−0.003, 0.001	-	0.201
	Model 2	−0.001 (0.001)	−0.003, 0.001	-	0.376
FMI	Crude	−0.004 (0.001)	−0.014, 0.006	0.427	-
	Model 1	0.001 (0.002)	−0.005, 0.004	-	0.878
	Model 2	−5.286 (0.002)	−0.004, 0.004	-	0.981
BF (%)	Crude	0.003 (0.002)	−0.001, 0.007	0.148	-
	Model 1	0.001 (0.004)	−0.006, 0.008	-	0.768
	Model 2	0.001 (0.004)	−0.006, 0.008	-	0.768
BFM (Kg)	Crude	0.006 (0.003)	−0.001, 0.013	0.084	-
	Model 1	−0.002 (0.006)	−0.013, 0.009	-	0.719
	Model 2	−0.002 (0.006)	−0.014, 0.009	0.658	
TF (kg)	Crude	0.002 (0.001)	0.001, 0.005	0.097	-
	Model 1	−0.001 (0.002)	−0.005, 0.004	-	0.812
	Model 2	−0.001 (0.002)	−0.006, 0.004	-	0.709
TF (%)	Crude	0.035 (0.028)	−0.020, 0.089	0.213	-
	Model 1	0.001 (0.044)	−0.086, 0.088	-	0.988
	Model 2	−0.005 (0.045)	−0.094, 0.083	-	0.904
VFA (CM^2)	Crude	0.028 (0.037)	−0.044, 0.100	0.442	-
	Model 1	−0.005 (0.082)	−0.168, 0.157	-	0.951
	Model 2	−0.007 (0.085)	−0.174, 0.159	-	0.930
VFL	Crude	0.002 (0.005)	−0.007, 0.012	0.647	-
	Model 1	0.005 (0.011)	−0.017, 0.028	-	0.651
	Model 2	0.006 (0.012)	−0.017, 0.029	-	**0.076**
Biochemical variables					
Insulin (mIU/ml)	Crude	−6.160 (0.001)	0.001, 0.001	0.617	-
	Model 1	0.001 (0.001)	−0.001, 0.000	-	0.230
	Model 2	0.001 (0.001)	0.001, 0.001	-	0.273
HOMA_IR	Crude	0.001 (0.001)	−0.0002, 0.001	0.671	-
	Model 1	−2.096 (0.001)	−0.002, 0.002	-	0.981
	Model 2	0.001 (0.001)	0.001, 0.033	-	**0.055**
QUICKI (mg/lit)	Crude	−1.731 (0.001)	0.001, 0.001	0.205	-
	Model 1	−4.306 (0.001)	−0.001, 0.001	-	0.720
	Model 2	−3.775 (0.001)	0.001, 0.001	-	**0.042**
hs-CRP (mg/l)	Crude	0.001 (0.003)	−0.005, 0.005	0.962	-
	Model 1	0.001 (0.003)	−0.006, 0.007	-	0.875
	Model 2	0.001 (0.003)	−0.006, 0.007	-	0.916
FBG (mg/dL)	Crude	−0.004 (0.005)	−0.014, 0.006	0.427	-
	Model 1	−0.004 (0.006)	−0.017, 0.009	-	0.506
	Model 2	−0.006 (0.007)	−0.020, 0.007	-	0.335
SBP (mmHg)	Crude	−0.012 (0.007)	−0.027, 0.002	0.102	-

(Continued)

TABLE 4 Continued

Variables		NOVA score		*P*-value	*P*-value*
		β (SE)	CI (95%)		
	Model 1	−0.015 (0.008)	−0.032, 0.002	-	0.032
	Model 2	0.017 (0.008)	−0.001, 0.020	-	0.148
DBP (mmHg)	Crude	−0.008 (0.005)	−0.018, 0.002	0.134	-
	Model 1	−0.004 (0.086)	−0.016, 0.008	-	0.503
	Model 2	−0.007 (0.006)	−0.019, 0.005	-	0.236
TC (mg/dL)	Crude	0.003 (0.019)	−0.036, 0.041	0.893	-
	Model 1	0.012 (0.022)	−0.032, 0.055	-	0.598
	Model 2	0.020 (0.022)	−0.024, 0.064	-	**0.073**
TG (mg/dL)	Crude	0.003 (0.032)	−0.060, 0.067	0.916	-
	Model 1	0.031 (0.042)	−0.052, 0.115	-	0.456
	Model 2	0.041 (0.043)	−0.044, 0.126	-	0.344
HDL (mg/dL)	Crude	−0.005 (0.006)	−0.016, 0.006	0.391	-
	Model 1	−0.004 (0.007)	−0.017, 0.010	-	0.588
	Model 2	−0.002 (0.007)	−0.016, 0.011	-	0.720
LDL (mg/dL)	Crude	−0.010 (0.013)	−0.036, 0.015	0.433	-
	Model 1	−6.043 (0.015)	−0.030, 0.030	-	0.997
	Model 2	0.007 (0.016)	−0.024, 0.038	-	0.662
GOT (mg/dL)	Crude	−0.004 (0.004)	−0.012, 0.0003	0.274	-
	Model 1	−0.007 (0.005)	−0.017, 0.003	-	0.167
	Model 2	−0.006 (0.005)	−0.017, 0.004	-	0.245
GPT (mg/dL)	Crude	−0.006 (0.007)	−0.020, 0.008	0.391	-
	Model 1	−0.016 (0.009)	−0.034, 0.003	-	0.097
	Model 2	−0.015 (0.010)	−0.034, 0.004	-	0.117
PAI-1 (mg/dL)	Crude	−0.019 (0.022)	−0.063, 0.025	0.401	-
	Model 1	−0.012 (0.033)	−0.077, 0.053	-	0.705
	Model 2	−0.005 (0.033)	−0.071, 0.061	-	0.883
MCP1 (mg/dL)	Crude	−0.047 (0.052)	−0. 15, 0.055	0.363	-
	Model 1	−0.041 (0.072)	−0.184, 0.102	-	0.570
	Model 2	−0.039 (0.073)	−0.184, 0.107	-	
TGF (mg/dL)	Crude	0.034 (0.036)	−0.038, 0.106	0.106	
	Model 1	0.092 (0.038)	0.016, 0.167	-	**0.018**
	Model 2	0.101 (0.040)	0.023, 0.180	-	**0.012**
IL-1 β (mg/dL)	Crude	0.001 (0.001)	−0.001, 0.003	0.250	-
	Model 1	0.001 (0.001)	−0.002, 0.003	-	0.596
	Model2	0.001 (0.001)	−0.001, 0.003	-	**0.060**
AIP (mg/dL)	Crude	2.472 (0.001)	0.001, 0.01	0.853	-
	Model 1	0.001 (0.001)	0.001, 0.001	-	0.482
	Model2	0.001 (0.001)	−0.001, 0.011	-	0.072
CRI-I	Crude	0.001 (0.001)	−0.001, 0.002	0.476	-
	Model 1	0.001 (0.001)	−0.001, 0.002	-	0.277
	Model2	0.001 (0.001)	−0.001, 0.002	-	**0.064**
CRI-II	Crude	−3.679 (0.001)	−0.001, 0.001	0.907	-
	Model 1	0.001 (0.001)	−0.001, 0.001	-	0.574
	Model2	0.001 (0.001)	0.001, 0.001	-	0.431
AC	Crude	0.001 (0.001)	−0.001, 0.002	0.476	-

(Continued)

TABLE 4 Continued

Variables		NOVA score		*P*-value	*P*-value*
		β (SE)	CI (95%)		
	Model 1	0.001 (0.001)	−0.001, 0.002	-	0.277
	Model2	0.011 (0.001)	0.001, 0.032	-	**0.034**
CHOlIndex	Crude	−0.005 (0.012)	−0.029, 0.019	0.688	-
	Model 1	0.004 (0.015)	−0.026, 0.033	-	0.811
	Model2	0.009 (0.015)	−0.021, 0.040	-	0.547
TyG	Crude	−6.963 (0.001)	−0.001, 0.001	0.794	-
	Model 1	0.001 (0.001)	0.001, 0.001	-	0.610
	Model2	0.001 (0.001)	0.001, 0.001	-	0.501
TyG-BMI	Crude	0.010 (0.023)	−0.035, 0.055	0.648	-
	Model 1	−0.012 (0.028)	−0.67, 0.044	-	0.685
	Model 2	−0.003 (0.029)	−0.060, 0.054	-	0.917
TyG-WC	Crude	0.061 (0.105)	−0.146, 0.267	0.563	-
	Model 1	−0.056 (0.177)	−0.408, 0.296	-	0.752
	Model 2	0.048 (0.188)	−0.324, 0.421	-	0.797

AC, atherogenic coefficient; BFM, body fat mass; BF, body fat; FFM, fat-free mass; FMI, fat mass index; FFMI, fat-free mass index; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GPT, glutamic-pyruvic transaminase; GOT, glutamic-oxaloacetic transaminase; PAI-1, plasminogen activator inhibitor- 1, SD standard deviation; hs-CRP, high sensitive-C reactive protein; TF, trunk Fat; VFA, visceral fat area; VFL, visceral fat level; TC, total cholesterol; AIP, Atherogenic index of plasma; TyG, Triglyceride-glucose; TGF, Transforming growth factor; CRI: Cardiac risk index.
Model 1: Adjusted for age, BMI, physical activity, total energy intake, supplements intake, and job status (BMI considered as a collinear variable).
Model 2: In addition controlled for the role of vegetables and legumes.
*A P-value obtained from adjustment. All of the p-values obtained from the analysis of the linear regression.
A P < 0.05 was considered significant and p-values equal to 0.05, 0.06, and 0.07 were considered marginally significant.

biochemical variables, and inflammatory factors in crude and adjusted models present with β-value and a 95% CI is shown in Table 4. In the model 1, there was a significant association between UPF consumption and TGF (β: 0.101, 95% CI: 0.023, 0.180, $p = 0.012$). Also, there was a significant association between UPF consumption and AC (β: 0.011, 95%CI: 0.001, 0.032, $p = 0.034$), VLF (β: 0.006, 95% CI: −0.017, 0.029, $p = 0.076$), and ISQIUKI (β: −3.775, 95% CI: 0.001, 0.001, $P = 0.042$). With increasing one gram of UPF intake, AC increases to 0.011, VFL increases by 0.006, and QUICKI is significantly reduced by −3.775 mg/lit. The other variables in Table 3 had no significant association.

Discussion

To the best of our knowledge, this is the first study investigating the relationship between UPF intake and cardiometabolic risk in overweight and obese Iranian women.

In the current study, we found an inverse association between the NOVA score and FFM. In addition, we observed a positive association between the NOVA score and VFL, AC, the HOMA-IR-index, QUICKI, TC, TGF, IL-1B, and the CRI-I levels. In other words, participants who had higher NOVA scores and consumed higher amounts of UPF had higher levels of VFL, AC, the HOMA-IR-index, QUICKI, TC, TGF, IL-1B, and CRI-I. The positive association observed between UPFs and mentioned markers might be partly explained by their poorer nutritional quality compared with the NOVA scores' lower tertiles. In fact, UPFs tend to be higher in saturated fats, sugar, and energy, and poorer in dietary fiber (5, 9, 21, 33). The positive association between consumption of UPF and inflammatory markers that have been seen among women may be explained by the greater accumulation of body fat in women (34). In line with our study, in 2021, a systematic review and meta-analysis of 7 cohort studies (207,291 adults) showed a significant positive association between UPF consumption and the risk of CVDs among adults with a BMI of more than 25 kg/m^2 (35). Moreover, a recent narrative review study by Matos et al. (36) concluded that the consumption of UPFs is positively associated with the prevalence of chronic complications, including obesity, hypertension, CVDs, type 2 diabetes, and consequently the risk of all-cause mortality (36). The mechanism by which UPF is associated with CVD is summarized in Figure 1.

In our study, individuals at higher tertiles of NOVA (compared to tertile 1) had higher NC, AC, TyG-WC, HOMA-IR-INDEX, CRI-I, TGF, and hs-CRP levels. Beslay et al., in a large observational prospective study of 110,260 adults, indicated that higher consumption of UPF was associated with a gain in BMI and higher risks of overweight and obesity (37). Also, a prospective cohort of healthy subjects in Italy showed that adults in the highest quartile of UPF consumption

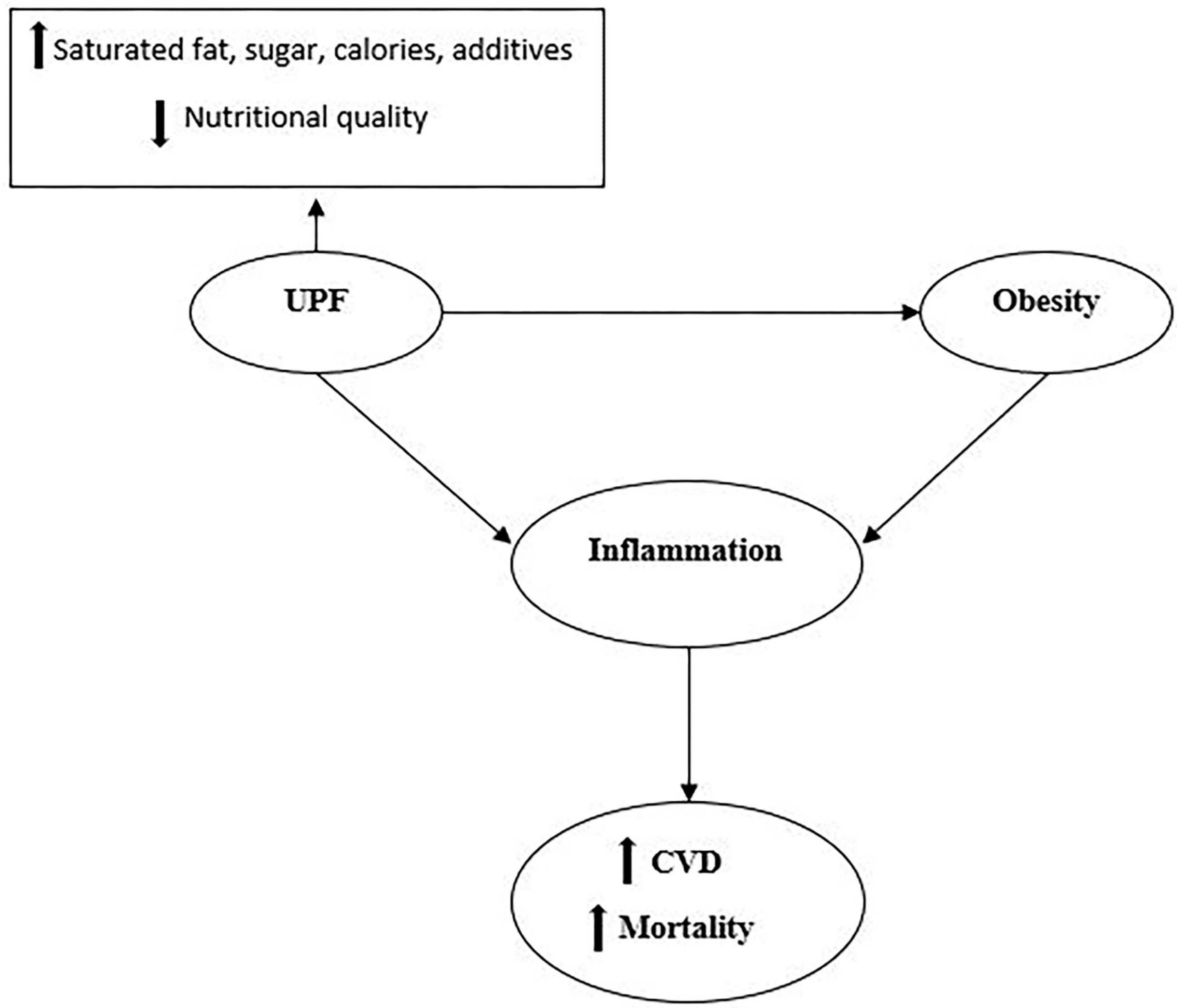

FIGURE 1
UPFs have higher levels of saturated fats, sugar, salt, additives, calories, and lower nutritional quality. Consumption of UPFs is suggested to have associations with obesity. Both obesity and consumption of UPFs could stimulate the whole chronic inflammation cascade and enhance the risk of CVD and all-cause mortality.

had a higher risk of CVD (38). It is well known that adipose tissue produces cytokines that induce inflammatory markers production (39). Thus, the association between the consumption of UPFs and the inflammatory response is expected to be mostly dependent on adiposity. A cross-sectional study displayed that there might be a direct association between consumption of ultra-processed foods and CRP levels, under the assumption that the high-glycemic index of these food products could stimulate the whole chronic inflammation cascade, along with an indirect association mediated by obesity. They suggest that decreased consumption of UPFs can reduce chronic low-grade inflammation, perhaps by reducing obesity (40).

In the present study, participants with higher NOVA scores had higher consumption of cakes and sweets, processed meats, and fast foods. Bonaccio et al., in 2021, indicated that a high proportion of UPF in the diet was associated with an increased risk of CVD and all-cause mortality, probably because of its high dietary content of sugar (38). Rising evidence suggests that the consumption of UPF products determined by the low-nutritional quality and high-calorie content adversely contribute to an unhealthy dietary pattern, which enhances the risk of all-cause mortality as a substantial risk factor (36). In addition, additives in such foods containing noncaloric artificial sweeteners, emulsifiers, and thickening agents cause numerous chronic disorders such as metabolic dysfunction, systemic inflammation, endothelial dysfunction, and disrupted immune response (41–43). More than that, synthetic compounds used in the packaging of UPFs, such as bisphenol A, can act as xenohormones. Particularly, bisphenol A has been indicated to impair reproductive function and augment the risk of cancer-cause mortality (44, 45). Recently, a study conducted in the US displayed that UPF consumption was related to increased exposure to phthalates (44), which has suggested associations with obesity (46). Some food additives specific to UPFs might be involved in obesity etiology. For instance, saccharin, an artificial sweetener, could potentiate glucose-stimulated insulin release from isolated pancreatic β-cells (47), leading to insulin resistance and possibly weight gain. Several emulsifiers (such as carboxymethyl cellulose and polysorbate-80) induced metabolic perturbations, alterations to the gut microbiota, and low-grade inflammation in mice (48). Carrageenan, in the top 20 used additives, might augment insulin resistance and inhibit insulin signaling in mouse liver and human HepG2 cells (49, 50), which might, in turn, induce weight gain (51). Trans fatty acids found in UPFs containing hydrogenated oils have been associated with cardiovascular disease (52) and obesity (53), apparently by altering nutrient handling in the liver, the adipose tissues, and the skeletal muscle (54). Acrylamide, a neo-formed compound created during thermal processing of food as a result of the Maillard reaction, was shown to induce adipocyte differentiation and obesity in mice (55).

The present study possesses some strengths and limitations. At first, to the best of our knowledge, this is the first study to have evaluated the association between processed food intake and CVD risk in overweight and obese Iranian women. Second, dietary intake was assessed using a validated questionnaire. Third, in the current study, we assessed several inflammatory markers, other biochemical parameters, and body composition as risk factors for CVD.

Nevertheless, despite these strengths, we must acknowledge some limitations in the present study. First, the cross-sectional nature of this study limited the ability to suggest a causal relationship between UPF intake and the risk of cardiovascular diseases. Second, some errors may be present in the dietary assessment, mostly due to recall bias and misclassification errors; to overcome such errors, we evaluated biomarkers such as vitamin C to better capture individuals' variability in intakes. Third, our result may not be generalizable to normal-weight women. At final, although we considered known potential confounders, residual confounding cannot be ruled out.

Conclusion

In conclusion, an increase of one gram of UPFs consumption is associated with an increase in TGF, AC, and VFL but with a decrease in QUICKI. Higher consumption of UPF is significantly associated with an enhanced risk of adult inflammation and cardiometabolic risk factors. Further large studies involving participants of different ages and genders are highly warranted, in addition to experimental studies, to draw a more definite conclusion and disentangle the mechanisms by which UPFs may affect health.

Data availability statement

Participants of this study disagreed on their data being shared publicly, so supporting data is not available. Further inquiries can be directed to the corresponding author KM, mirzaei_kh@tums.ac.ir; mirzaei_kh@sina.tums.ac.ir.

Ethics statement

The studies involving human participants were reviewed and approved by Tehran University of Medical Sciences, Tehran, Iran. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DH and SN wrote the paper. FS and FM-E performed the statistical analyses. SJ, MD, AS, and JB critically reviewed and revised the manuscript. KM had full access to all of the data in the study and took responsibility for the integrity and accuracy of the data. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Association Between the Risk of Hyperuricemia and Changes in Branched-Chain Amino Acids Intake Over Twelve Years: A Latent Class Trajectory Analysis From the China Health and Nutrition Survey, 1997–2009

Xiyun Ren[1†], Shasha Wu[2†], Wei Xie[1], Ying Liu[1,2] and Shucai Yang[3*]*

[1] *Experimental Center for Preventive Medicine Teaching, College of Public Health, Harbin Medical University, Harbin, China,*
[2] *Department of Nutrition and Food Hygiene, College of Public Health, Harbin Medical University, Harbin, China,*
[3] *Translational Medicine Research and Cooperation Center of Northern China, Heilongjiang Academy of Medical Sciences, Harbin, China*

Objective: This study aims to identify dietary branched-chain amino acids (BCAA) consumption trajectories in Chinese adults and to evaluate their association with the risk of hyperuricemia (HU).

Methods: Cohort data from the China Health and Nutrition Survey 1997–2009 were adopted in this research. A total of 6,810 participants aged ≥18 years were included in this study. Participants were designated into four subgroups on basis of the trajectories of dietary BCAA consumption. Cox proportional hazards models were performed to discuss the relationships between varied trajectories and the risk of HU after adjusting potential confounders. The intermediary effect of differential blood indexes between the trajectories and the risk of HU was explored with mediation analysis.

Results: Four distinct trajectory groups of dietary BCAA consumption were identified. Compared with the low stable trajectory group, high to low trajectory group was greatly related to an increased risk of HU (HR 1.35 (95% CI 1.03 to 1.79)) with modification for covariates. Total cholesterol (TC), hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and triglyceride (TG) partially regulated trajectories and HU.

Conclusion: Gradually decreasing dietary BCAA intake increased the risk of HU, which is, at least, partially mediated by TC, HbA1c, FBG, and TG levels.

Keywords: branched chain amino acids, hyperuricemia, latent class trajectory model, China health and nutrition survey, mediation analysis

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*Ruiyue Yang,
Peking University, China
Mevlude Kizil,
Hacettepe University, Turkey*

***Correspondence:**
*Ying Liu
liuying0223@sohu.com
Shucai Yang
yangshucai3@hrbmu.edu.cn*

†These authors have contributed equally to this work

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INTRODUCTION

Hyperuricemia (HU) is a disease, in which serum uric acid (UA) exceeds the normal range due to abnormal purine metabolism for various reasons (1). The pooled prevalence of HU was 13.3% in mainland China from 2000 to 2014 (2). HU is considered a risk factor for gout (3), cardiovascular disease (4), stroke (5), diabetes (6), and hypertension (7). HU is becoming a great health issue and is arousing more attention. Currently, most studies on HU have been limited to some regions or nationality, and the pathophysiology of HU has not yet been fully illustrated. Hence, nationally representative research based on the entire population on the epidemiology of HU is needed.

Dietary factor, which is an adjustable element, exerts significant effect on the occurrence and development of HU. Branched-chain amino acids (BCAAs), including Leucine, Isoleucine, and Valine, an important group of basic amino acids, are significant nutrition signals with important roles in protein synthesis, glucose homeostasis, and nutrient-sensitive signaling pathways (8). Previous research has shown that adequate BCAA supplementation can reduce body weight and promote fat metabolism (9, 10). Meanwhile, BCAA can also reduce oxidative stress by restoring mitochondrial function (11). Overweight, obesity, abnormal lipid metabolism, and oxidative stress are potential risk factors for HU (12). However, the association between dietary BCAA consumption and risk of HU are still unknown. Most studies about dietary BCAA intake adopted a single or limited number of measurements. However, little research has been designed to investigate the dynamic change of dietary BCAA levels and the risk of HU. It is necessary to use a time-varying measurement of dietary BCAA to explore the relationship between dietary BCAA trajectory and HU risk.

Therefore, this study firstly used latent class trajectory modeling (LCTM) to identify dietary BCAA consumption trajectories over 12 years in the Chinese adults and to evaluate their association with the risk of HU.

MATERIALS AND METHODS

Study Population

China Health and Nutrition Survey (CHNS), which stands for 47% of the Chinese population, is designed as prospective household-based research, including various ages and cohorts across different provinces, and five follow-up surveys between 1997 and 2009. Detailed information of CHNS has previously been provided (13). The Institutional Review Committees of the University of North Carolina at Chapel Hill, NC, United States approved the survey protocols, instruments, and process for acquiring informed consent, as well as the China National Institute of Nutrition and Food Safety at the Chinese Center for Disease Control and Prevention, Beijing, China. All participants offered survey data after written informed consent.

A total of 13,575 adults participated in CHNS from 1997 to 2009, with no missing value for BCAA intake were selected in this study. Individuals with missing serum UA information (n = 1,419) and data of demographic or total nutrient intakes dietary interview (n = 228) were excluded. Participates who took part in only one survey (n = 5,118) were excluded. After exclusion, a total of 6,810 adults, including 3,212 men and 3,598 women, with a mean age of 42.5 ± 13.4 years and a mean follow-up time of 9.98 years, met the study criteria and ranged from two to six measurement surveys (two visits, n = 807; three visits, n = 1,148; four visits, n = 1,550; five visits, n = 3,305).

Questionnaire Survey

Detailed in-person interviews were managed by trained personnel with a structured questionnaire, to collect data of demographic features, dietary habits, lifestyle, physical condition, and anthropometric features. In CHNS, the collection of individual dietary intake for three consecutive days was made for every household member. Dietary measurements included total energy (kcal/day), dietary fat (g/day), dietary protein (g/day), dietary carbohydrate (g/day), dietary fiber (g/day), and vitamin C (VC, mg/day), which were calculated by three versions of Chinese food composition table (FCT) according to CHNS project requirements. The 1991 FCT version was adopted in 1997 and 2000. The 2002/2004 (two books integrated) FCT versions were adopted in 2004, 2006, and 2009. Present smoking was defined as a positive answer to the question "do you still smoke now?". Participants who gave the answer of "never smoker" to the question "Have you ever smoked (such as hand-rolled or device-rolled)?" were categorized into the group of never smoked, and who positively answered the questions "Have you ever smoked (such as hand-rolled or device-rolled)?" and negatively answered "do you still smoke now?" as ex-smoker. Drinks and a standard drink was any drink that contained about 0.6 fluid ounces or 14 grams of pure alcohol were adopted to measure the amount of alcohol consumed (14). Physical activity level (PAL) mainly contained occupational activity, transportation activity, domestic activity, and leisure activity (15). The calculation of total metabolic equivalents (METs) of physical activity MET-h per week was made (15).

In 2009, 12 ml of blood (in three 4-ml tubes) were collected from all individuals on an empty stomach. The measurement of serum UA and fasting blood glucose (FBG) was made by enzymatic colorimetric and glucose oxidase (GOD-PAP) method (Hitachi 7600, Randox, United Kingdom). Total cholesterol (TC) and triglyceride (TG) were measured by cholesterol oxidase (CHOD-PAP) method and glycerol-phosphate oxidase (GPO-PAP) method (Hitachi 7600, Kyowa, Japan). The measurement of HDL-cholesterol (HDL-C) was made by enzymatic approaches (Hitachi 7600, Kyowa, Japan). The measurement of hemoglobin A1c (HbA1c) and high-sensitivity C reactive protein (hs-CRP) was made by high performance liquid chromatography method (HLC-723 G7/D10/PDQ A1c, Japan) and immunoturbidimetric (Hitachi 7600, Denka Seiken, Japan). HU was defined as serum UA ≥7 mg/dl in males and ≥6 mg/dl in females. Hypertension was defined as persistent systolic blood pressure measurements of ≥140 mmHg and/or 90 mmHg of diastolic blood pressure. The calculation of body mass index (BMI) as weight in kilograms divided by the square of height in meters was made. Self-report of a history of diabetes diagnosis, and/or FBG ≥ 7 mmol/L, and/or HbA1c ≥40 mmol/mol (6.5%), and/or receiving treatment for diabetes were adopted to identify Type 2 diabetes (T2D). Details of treating diabetes included special diet, weight control, oral medication, insulin injection, Chinese traditional medicine, and home remedies.

Statistical Analysis

All statistical analyses were conducted with R 4.1.3[1]. A two-sided p-value <0.05 was of statistical significance. Dietary nutrient intake and anthropometric measurements were shown as mean ± standard deviation (SD) for continuous variables and percentage for categorical variables. General linear models and baseline features were compared with Chi-square tests.

The LCTM is a relatively new methodology in epidemiology to describe life-course exposures, which simplifies heterogeneous populations into homogeneous patterns or classes. Model fit was assessed using both the Bayesian information criterion and entropy measures in conjunction with Vuong-Lo-Mendell-Rubin likelihood ratio test. The LCTM has three general advantages. First, it better informs etiological associations by deeply phenotyping certain "at risk" subpopulations. Second, LCTM offers a public health strategy to identify early divergent adverse trajectories as potential intervention targets. Third, the trajectory approach allows a better understanding of the causes of between-individual variation in certain features.

Dietary BCAA consumption trajectories were identified with LCTM, a censored normal model applying the R package lcmm. The best fit and each trajectory class included at least 3% of the sample population, which were decided with statistically rigorous Bayesian information criteria. Once trajectories of dietary BCAA consumption were decided, and a nominal categorical variable was generated to illustrate the trajectory classes of every participant, which was then adopted in Cox multivariate regression models.

After calculating the follow-up time of non-HU and HU, Cox proportional-hazards model was adopted to assess the relationship between dietary BCAA consumption trajectories and the risk of HU. A set of potential confounders and effect modifiers, which were age, sex, smoking, education, PAL, urban index, total dietary energy, fat, protein, carbohydrate, VC intake, BMI, and disease state of hypertension and T2D, were controlled.

After categorizing participants into varied dietary BCAA consumption trajectories, the association between acquired dietary BCAA consumption trajectories and blood indexes modified with the above co-variables was determined with subgroup analyses by generalized linear models, which could recognize HU-associated blood indexes that were statistically different in varied trajectories.

At last, the R package lavaan was adopted to make mediation analysis models, to investigate whether these biomarkers with modification for the above covariates were adopted to mediate the relationship between dietary BCAA consumption trajectories and risk of HU.

[1] www.r-project.org/

Sensitivity Analysis

Two sets of sensitivity analyses were made below: in set 1, blood samples from the participants were first collected in 2009, the relationship between dietary BCAA intake and the risk of HU for participants in 2009 was analyzed using logistic regression model; and in set 2, the association between mean dietary BCAA intake during follow-ups and the risk of HU from 1997 to 2009 was analyzed with logistic regression models.

RESULTS

Trajectories of Dietary Branched-Chain Amino Acids Intake

In this cohort of 6,810 Chinese adults, the trajectories of BCAA intake were displayed in **Figure 1**. Every trajectory group was named based on dynamic variations of the BCAA intake levels. **Figure 1** corresponded with the first trajectory, labeled "T1: Low stable," to participants who kept low BCAA intake throughout the survey period. The second trajectory, "T2: High to low," corresponded to participants whose BCAA intake gradually decreased from high to low by comparing with T1. The third trajectory, "T3: Moderate stable," corresponded to participants whose BCAA intake remained in moderate level by comparing with T1. The fourth trajectory, "T4: Moderate to high then decline," corresponded to participants whose intake of BCAA gradually increased to moderate level and then decreases. It was estimated that the trajectories from T1 to T4 include 12.1, 7.8, 76.1, and 4% of participants.

Baseline Features by Varied Trajectories of Dietary Branched-Chain Amino Acids Intake

The baseline characteristics of different dietary BCAA intake trajectories were displayed in **Table 1**. There

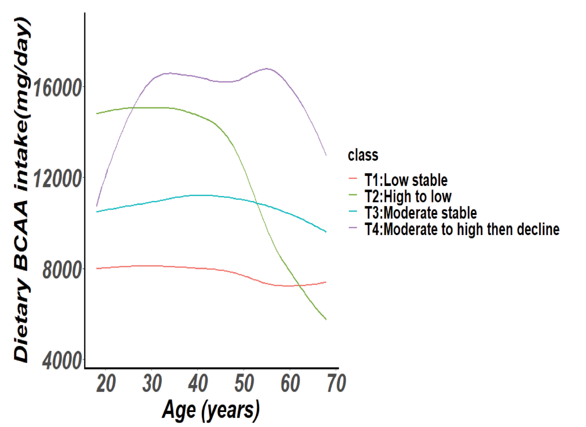

FIGURE 1 | Trajectories of dietary branched-chain amino acids (BCAA) consumption (n = 6,810) in the Chinese adults from the CHNS by LCTM. BCAA, Branched chain amino acids; CHNS, China Health and Nutrition Survey; LCTM, Latent class trajectory modelling.

TABLE 1 | Baseline characteristics of study variables by different trajectories of dietary branched-chain amino acids (BCAA) consumption (*N* = 6,810).

Trajectory	Low stable (*n* = 821)	High to low (*n* = 528)	Moderate stable (*n* = 5,188)	Moderate to high then decline (*n* = 273)	*P*-value
Age (years)	40.7(10.4)	34.4(14.8)	43.6(13.5)	41.9(8.0)	<0.001
Men (*n*,%)	157(19.1)	344(65.2)	2505(48.3)	206(73.8)	<0.001
High school education or above (*n*,%)	110(13.4)	126(23.9)	1,035(19.9)	59(21.1)	<0.001
Hypertension (*n*,%)	127(15.5)	77(14.6)	968(18.7)	48(17.2)	0.026
Current smoking (*n*,%)	152(18.5)	207(39.2)	1,620(31.2)	134(48.0)	<0.001
T2D (*n*,%)	117(14.2)	72(13.6)	977(18.8)	60(21.5)	<0.001
Total energy intake (kcal/day)	1,976.4(594.9)	2,692.2(884.8)	2,295.5(627.6)	2,764.9(991.3)	<0.001
Total fat intake (g/day)	53.7(28.2)	78.4(41.4)	68.9(35.7)	77.2(38.7)	<0.001
Total carbohydrate intake (g/day)	319.5(118)	411.7(150.5)	353.4(122.3)	424.5(173.5)	<0.001
Total protein intake (g/day)	55.6(33.3)	88.6(63.2)	68.5(24.2)	94.3(81.2)	<0.001
Total VC intake (mg/day)	81.4(53.1)	99.3(86.5)	88.3(70.5)	96.5(62.3)	0.033
Drinking (Drinks/week)	2.1(7.9)	5(10.6)	5.1(13.6)	8.5(15.7)	<0.001
Uric acid (mg/dL)	4.6(1.5)	5.5(1.8)	5.2(1.8)	5.6(1.7)	<0.001
Urban index	50.3(17.9)	54.6(20.5)	55.8(19.4)	54.9(20.5)	<0.001
BMI (kg/m^2)	22.5(3.2)	22.8(3.0)	22.7(3.2)	22.3(3.0)	<0.001
PAL (Mets-h/week)	63.1(98.5)	85.5(116.7)	68.4(100.5)	95.1(120)	0.060

Continuous data are expressed as mean (SD); where shown, data are n (%); SD, standard deviation.
Generalized linear models and Chi-square test were used to probe for differences in continuous variables and dichotomous variables.
PAL, Physical activity level; VC, Vitamin C; T2D, Type 2 diabetes; BMI, Body mass index.

were great diversities in age, gender, smoking, drinks, education levels, total energy, fat, protein, carbohydrate, VC intake, BMI, T2D, and hypertension among the four trajectories ($p < 0.05$). There was no great diversity in PAL among the different dietary BCAA intake trajectories ($p > 0.05$).

Association Between Dietary Branched-Chain Amino Acids Intake Trajectories and Risk of Hyperuricemia

The relationships between dietary BCAA intake trajectories and risk of HU were displayed in **Table 2**. By comparing with "T1," the trajectory labeled "T2" was greatly related to growing risk of HU (HR 1.35 (95% CI 1.03, 1.79)) with adjustment for covariates.

TABLE 2 | Association between dietary branched-chain amino acids (BCAA) consumption trajectories and hyperuricemia (HU) by Cox regression models.

Trajectory	Case/*N*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Low stable (T1)	118/821	1(Ref.)	1(Ref.)	1(Ref.)
High to low (T2)	97/528	1.43(1.09,1.87)	1.39(1.06,1.83)	1.35(1.03,1.79)
Moderate stable (T3)	974/5,188	1.19(0.84,0.98)	1.17(0.96,1.42)	1.14(0.94,1.39)
Moderate to high then decline (T4)	61/273	1.25(0.80,0.91)	1.24(0.90,1.70)	1.20(0.88,1.66)
P for trend		0.540	0.710	0.800

Model 1 Adjusted for age, sex, smoking, drinking, education, urban index, and PAL.
Model 2 was further adjusted by total energy, fat, protein, carbohydrate, and VC intake.
Model 3 was further adjusted by BMI, hypertension, and T2D status.
PAL, Physical activity level; VC, Vitamin C; T2D, Type 2 diabetes; BMI, Body mass index.

Trajectories of Dietary Branched-Chain Amino Acids Intake and Biomarkers of Hyperuricemia

The biomarkers across different dietary BCAA intake trajectories were shown in **Table 3**. TG, TC, FBG, and HbA1c in the T2 trajectory were higher than the other three trajectories (T1, T3, and T4) (all p for trend <0.05). HDL-C and hs-CRP in the T2 trajectory were not statistically different from the other trajectories.

Mediation Analysis

Figure 2 demonstrates mediation results of TC, HbA1c, FBG, and TG in the relationship between dietary BCAA trajectory (T2) and risk of HU. The total effect of dietary BCAA intake trajectories was estimated at 7.5%. The total indirect role for four factors was calculated with β1 to β8. It was estimated that the percentages of the total effect mediated by TC, HbA1c, FBG, and TG are 10.2%, 4.2%, 10.2%, and 12.7%, respectively.

TABLE 3 | Difference for hyperuricemia (HU)-related factors across dietary branched-chain amino acids (BCAA) consumption trajectories in 2009.

Variables	T1	T2	T3	T4	*P*-value
HDL-C (mmol/L)	1.43(0.38)	1.41(0.54)	1.45(0.49)	1.42(0.34)	0.232
hs-CRP (mg/L)	2.90(13.19)	3.44(22.77)	2.61(6.43)	2.43(5.05)	0.177
TC (mmol/L)	4.83(0.99)	4.94(0.91)	4.74(1.01)	4.92(0.97)	< 0.001
TG(mmol/L)	1.64(1.39)	1.75(1.50)	1.73(1.31)	1.68(1.50)	0.007
FBG (mmol/L)	5.32(1.41)	5.47 (1.38)	5.34(1.50)	5.44(1.21)	0.004
HbA1c (%)	5.58(0.79)	5.69(0.82)	5.66(0.95)	5.58(0.82)	0.005

Generalized linear model was used to probe for the HU-related factors differences across different trajectories. Data are mean (SD).
HDL-C, High density lipoprotein cholesterol; TC, Total cholesterol; TG, triacylglycerol; hs-CRP, High sensitivity C reactive protein; HbA1c, Hemoglobin A1c FBG, Fasting blood glucose; SD, standard deviation.

Sensitivity Analysis

Sensitivity analyses demonstrated that compared to the lowest quintile, the highest quintile of dietary BCAA intake was not greatly related to the risk of HU in 2009 (OR, 1.16, 95%CI (0.76, 1.33)) in **Table 4**. Similarly, the highest quintile of mean dietary BCAA intake during follow-ups was also not significantly associated with the risk of HU from 1997 to 2009 (OR, 1.18, 95%CI (0.94, 1.49)) in **Table 5**.

DISCUSSION

In this prospective cohort of Chinese adults with five surveys, four unique dietary BCAA intake trajectories were identified, in which the high to low trajectory group was greatly related to increased risk of HU. In addition, high to low trajectory has higher TC, HbA1c, FBG, and TG than other trajectories, which may explain the association between trajectory and HU.

Obesity is considered as an independent risk factor for HU. Obesity can cause HU by increasing UA synthesis and inhibiting its excretion. Changes in obesity measure indices levels are independently associated with subsequent changes in UA concentrations. Previous studies have shown a strong association between obesity and HU (16–18). Higher dietary BCAA intake was related to lower prevalence of overweight and obesity in Asia (19). BCAA contributes to the oxidation of fat, and decreases fat in the body (20). Increased dietary leucine intake significantly reduced body weight and improved

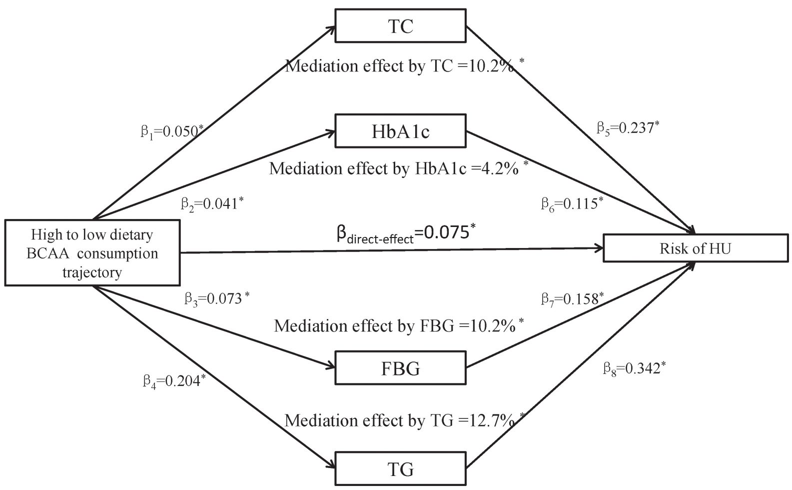

FIGURE 2 | Mediation effects of TC, HbA1c, FBG, and TG on the association between dietary branched-chain amino acids (BCAA) consumption trajectories and risk of HU. Data were standardized regression coefficients with adjustment for covariates; *$p < 0.05$ for coefficients different from 0. TC, Total cholesterol; HbA1c, Hemoglobin A1c; FBG, Fasting blood glucose; TG, Triglyceride; BCAA, Branched chain amino acids; HU, Hyperuricemia.

TABLE 4 | Association between dietary branched-chain amino acids (BCAA) consumption and hyperuricemia (HU) by Logistic regression models in 2009 (*N* = 6,810).

BCAA intake	Q1 ≤ 7,579.6	Q2 (7,579.7-9,299.3)	Q3 (9,299.4-11,088.9)	Q4 (11,089.0-13,531.9)	Q5 ≥ 13,531.9	*P* for trend
Case/N	222/1,362	249/1,362	227/1,362	273/1,362	279/1,362	
Model 1	1(Ref.)	1.16(0.93,1.45)	1.04(0.81,1.33)	1.31(0.98,1.76)	1.32(0.88,2.00)	0.150
Model 2	1(Ref.)	1.17(0.96,1.44)	1.04(0.84,1.28)	1.33(1.09,1.39)	1.37(1.12,1.68)	0.001
Model 3	1(Ref.)	1.11(0.89,1.39)	1.00(0.78,1.30)	1.21(0.90,1.63)	1.16(0.76,1.33)	0.390

Model 1 Adjusted for age, sex, smoking, drinking, education, urban index, and PAL.
Model 2 was further adjusted by total energy, fat, protein, carbohydrate, and VC intake.
Model 3 was further adjusted by BMI, hypertension and T2D status.
PAL, Physical activity level; VC, Vitamin C; T2D, Type 2 diabetes; BMI, Body mass index.

TABLE 5 | Association between Mean dietary branched-chain amino acids (BCAA) intake during follow-ups and hyperuricemia (HU) by Logistic regression model (*N* = 6,810).

BCAA intake	Q1 ≤ 6,203.3	Q2 (6,203.4-8,172.8)	Q3 (8,172.9-9,674.6)	Q4 (9,674.7-11,324.6)	Q5 ≥ 11,324.6	*P* for trend
Case/*N*	241/1,362	234/1,362	254/1,362	256/1,362	265/1,362	
Model 1	1(Ref.)	0.96(0.77,1.19)	1.15(0.93,1.43)	1.12(0.90,1.39)	1.24(0.99,1.39)	0.020
Model 2	1(Ref.)	0.98(0.80,1.21)	1.16(0.95,1.42)	1.18(0.96,1.44)	1.30(1.06,1.60)	0.002
Model 3	1(Ref.)	0.92(0.73,1.15)	1.00(0.78,1.30)	1.12(0.90,1.40)	1.18(0.94,1.49)	0.060

Model 1 Adjusted for age, sex, smoking, drinking, education, urban index, and PAL.
Model 2 was further adjusted by total energy, fat, protein, carbohydrate, and VC intake.
Model 3 was further adjusted by BMI, hypertension and T2D status.
PAL, Physical activity level; VC, Vitamin C; T2D, Type 2 diabetes; BMI, Body mass index.

glucose and cholesterol metabolism (21). It has been found that adenosine monophosphate-activated protein kinase (AMPK) is involved in the basic control of whole-body energy balance by controlling food intake and energy expenditure in response to hormonal and nutritional signals in the central nervous system and peripheral tissues (22). Negative AMPK expression in the hypothalamus is clearly enough to decrease food intake and body weight (23). Mammalian target of rapamycin (mTOR), which is a serine/threonine kinase, takes part in a lot of cellular processes, such as protein synthesis, cell metabolism, and growth (24). Studies have shown that activation of mTOR can inhibit food intake (25). However, dietary leucine intake can lead to weight loss by reducing AMPK or increasing mTOR activity (26). Meanwhile, the BMI of the high to low trajectory group was greatly higher than the other trajectory groups in this research, which confirmed the results of previous studies.

The systemic inflammatory response index (SIRI), a potent indicator of HU, is independently associated with the risk of HU (27). Studies have also shown that decreasing the intake of proinflammatory diet decreases the incidence of HU in women (28). However, BCAA plays an anti-inflammatory role in the body or indirectly regulates inflammatory states (29). Reducing the intake of BCAA may increase inflammation in the body and lead to the occurrence of HU. The hs-CRP is widely used laboratory markers of systemic inflammation. Previous studies demonstrated no correlation between hs-CRP levels and valine (30), and there was no statistical difference in hs-CRP between different trajectories in this study, which was consistent with previous research result.

Insulin resistance (IR) is closely associated with the occurrence and growth of HU by inhibiting UA excretion and increasing sodium reabsorption in renal tubules (31, 32). It is well-known that increased glucose content in the liver is a major characteristic of IR. Elevated liver glucose content is due to the activation of c-Jun N-terminal kinase (JNK) caused by the produced reactive oxygen species (ROS), leading to phosphorylation of FoxO1 and nuclear accumulation of FoxO1, and ultimately leading to increased liver glucose content (33). Intake of BCAA can improve IR by activating antioxidant mechanisms and can reduce ROS production in the liver by improving albumin metabolism (34). A cross-sectional study has demonstrated that higher intakes of BCAA were associated with lower IR, inflammation, blood pressure, and adiposity-related metabolites (35). Therefore, the risk of HU might be reduced by BCAA intake.

Blood glucose control is of great significance for the prevention of HU (36). Studies have shown that increased isoleucine intake can stimulate the uptake of glucose by skeletal muscle, leading to a reduction in blood glucose (37). Growing leucine intake can enhance glucose metabolism, decrease the insulin resistance induced by diets, and lower levels of plasma glucagon and the expression of hepatic glucose 6 phosphatase, which is the key enzyme for regulating hepatic glucose production (38). In addition, previous studies have shown that UA levels increase significantly with the increase of FBG in the non-diabetic phase (39). Leucine levels were inversely correlated with FBG, and FBG increased when leucine intake was reduced (40). Reduced BCAA intake will lead to increased FBG, which can increase UA levels in the body.

The alteration of blood lipid may be another mechanism to explain our observations. Higher TG and TC levels were significantly correlated with the increase of serum UA (41). The risk of HU in patients with hypertriglyceridemia was higher than those in patients with normal TG (42). High TG may disrupt the metabolism of free fatty acids and accelerate the breakdown of adenosine triphosphate, which ultimately results in a growth in UA (43). Isoleucine reduces TG accumulation by affecting fatty acid oxidation (44), which decreases the incidence of HU. Animal studies have shown that compared to the control group, when mice consumed more isoleucine, the adiposity of liver and skeletal muscle was less, which indicated that the TG levels in both tissues were lowered. Several studies have shown that higher intake of BCAA presents lower occurrence of hypertriglyceridemia (45).

There are several strengths in this study. Primarily, this is the first research in this subject area that was made with a relatively great cohort size and long follow-up duration. Secondly, this research firstly explored the association between the dynamic trajectory of dietary BCAA intake and the risk of HU by using LCTM in Chinese adults. Thirdly, results of this study using dietary trajectory analysis were not presented in cross-sectional data, which meant that the study using dietary trajectory method to discuss the association between dietary BCAA intake, and the incidence of HU might provide additional information in cohort study and emphasized the significance of utilizing LCTM to scientific research. Nevertheless, it was recognized that there were several restrictions in this research. First, the dietary data were acquired by questionnaires in CHNS, and the respondents might have misreported the mount and kinds of food intake, leading to inaccurate mean value for BCAA measurement in three consecutive days. Secondly, several confounding elements, which were not measured or recognized, might have affected the outcomes.

CONCLUSION

Gradually decreasing dietary BCAA intake increased the risk of HU, which is, at least, partially mediated by TC, HbA1c, FBG, and TG levels.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YL and SY conceived the concept. XR designed the research and prepared the original manuscript. WX researched and explained data. SW made the validation analyses. All authors have read and agreed to the published version of the manuscript.

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EDITED BY
Mainul Haque,
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Aqil M. Daher,
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Keerti Singh,
The University of the West Indies, Cave Hill, Barbados
Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh

*CORRESPONDENCE
Huaqing Liu
lhqbbmc@163.com
Min Zhang
zmbbmc@163.com

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Long-term tea consumption reduces the risk of frailty in older Chinese people: Result from a 6-year longitudinal study

Tianjing Gao[1], Siyue Han[1], Guangju Mo[1], Qing Sun[1], Min Zhang[2]* and Huaqing Liu[1]*

[1]School of Public Health, Bengbu Medical College, Bengbu, China, [2]School of Health Management, Bengbu Medical College, Bengbu, China

Background: Vast accumulative evidence suggests that the consumption of tea and its components have various potential health benefits. This study used a longitudinal study to examine the causality between tea consumption and frailty in older Chinese people.

Methods: This study employed the longitudinal data from 2008 to 2014 of the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which were systematically collected through face-to-face interviews. Two thousand six hundred and thirty participants completed six-follow-up surveys in 2014 and were analyzed in this study. The frailty index recommended by Searle and co-authors, including 44 health deficits, was used. A Generalized Estimating Equation (GEE) was applied to determine the risk ratio (RR) with a 95% confidence interval (CI) for frailty, and further subgroup analyses were conducted to investigate whether the risk differed stratified by age, sex, and socioeconomic status. Additionally, the interaction between tea consumption with sex and frailty was tested.

Results: Of the 2,630 participants, 15.3% were consistent daily tea drinkers, and 22.6% reported frailty at the 6-year follow-up. Compared to non-tea drinkers, consistent daily tea drinkers reported a significantly lower ratio of having frailty [risk ratio (RR) = 0.51, 95% confidence interval (CI): 0.36–0.71], adjusting for sociodemographic characteristics, health behavior, socioeconomic status, and chronic illnesses. In further subgroup analyses, consistent daily tea consumption significantly reduced the risk of frailty for males (RR = 0.51, 95% CI: 0.32–0.81) but not females (RR = 0.61, 95% CI: 0.36–1.04); informal education (RR = 0.39, 95% CI: 0.23–0.67) but not formal education (RR = 0.63, 95% CI: 0.39–1.02); financial dependence (RR = 0.40, 95% CI: 0.24–0.65) but not financial independence (RR = 0.66, 95% CI: 0.39–1.12). Tea consumption was associated with a lower risk of frailty in both the young (RR = 0.36, 95% CI: 0.20–0.64) and the oldest (aged ≥ 80) (RR = 0.63, 95% CI: 0.40–0.98). Additionally, females showed a lower tea-mediated risk of frailty in occasional tea consumers (RR = 0.51, 95% CI: 0.29–0.89) and inconsistent tea drinkers (RR = 0.58, 95% CI: 0.37–0.93).

Conclusions: Habitual tea consumption can reduce the risk of frailty in older Chinese, and the benefit varied by age, sex, education, and financial support.

KEYWORDS

tea consumption, frailty, China, older people, CLHLS

Introduction

Frailty has become one of the most severe challenges in global public health. A previous study has found that the prevalence of frailty and prefrailty in older adults was 24 and 49%, respectively (1). The rapid expansion of the aging population has caused an increase in the amount of frail older people, which, in turn, has put more pressure on healthcare systems worldwide (2). The prevalence of frailty is higher in older adults but is not considered a part of normal aging (3). Frailty is a complex geriatric syndrome characterized by low resistance and response to stressors, resulting from a general decline in multiple systems and organs (4). Older people who are frail are at risk of increased exposure to adverse outcomes, such as falls, disability, delirium, morbidity, and death (5). Frailty is considered an early stage of disability. Additionally, it has reversible nature, suggesting that appropriate interventions at the right time can prevent, delay, or even reverse this phenomenon (6).

The causes of frailty can be multifaceted and include environmental, physical, and nutrient factors (7). Well-known determinants of frailty are older age, sex (female), lower education, and living without a partner (8). An unhealthy lifestyle is also an essential determinant of frailty, such as smoking, excessive alcohol consumption, poor dietary habits, and low physical activity (9). Previous studies have shown that co-morbidities increase the risk of frailty in older patients (10). Tea is one of the favorite beverages consumed worldwide (11). Vast accumulative evidence suggests that the consumption of tea and its components have various potential health benefits (12), including the prevention of cardiovascular diseases and cancer and its antibacterial, antiangiogenic, antiarthritic, anti-inflammatory, antioxidative, cholesterol-lowering, neuroprotective, and antiviral effects (13). Previous studies have indicated that tea consumption is correlated with a lower risk of stroke, depressive symptoms, and cognitive impairment (14, 15). Additionally, the benefits of tea increase progressively with the frequency of consumption (16). Although many studies have presented the health benefits of tea consumption, others have found the opposite. Different compounds derived from tea, such as caffeine, increase the risk of hypertension (17). Tea drinkers tend to smoke and drink alcohol, while the protective effect of tea consumption is only present in non-smokers or non-alcohol drinkers (18). A previous study has suggested that the positive association between tea consumption and the risk of type 2 diabetes might be caused by pesticide residue in tea leaves (19). Although pesticide residues and mycotoxins could be detected in some tea samples, they are usually below the maximum residue levels. Therefore, tea consumption can be recommended to the public for chronic disease prevention and treatment (20). Although a cross-sectional study has investigated the relationship between green tea consumption and comprehensive frailty in Japanese (21); however, the causality remains unclear.

Drinking tea is a lifestyle and even a culture among Chinese people (22). In China, tea is usually classified as different types according to different manufacturing processes and properties (23), e.g., green tea, black tea and white tea. Green tea is often processed by heating, which inactivates the polyphenol oxidase, oxidative enzymes, and peroxidase ubiquitous in tea leaves (24), and the processes in black tea generally includes four steps, i.e., withering, rolling, fermentation and drying, among which drying plays an important role in fragrance formation and quality fixation of famous high-quality tea (25). Generally, white tea is only processed by prolonged withering and drying processes without any process in enzyme deactivation or fermentation (26). The method of processing and degree of fermentation also affect active ingredients and pro-health properties in tea (27).

This study investigated the causal relationship between tea consumption and frailty among Chinese older adults and the heterogeneity in the association by age groups, sex, and socioeconomic status by using longitudinal data from 2008 to 2014 from the Chinese Longitudinal Healthy Longevity Survey (CLHLS).

Materials and methods

Study sample

The data were sourced from the CLHLS, a nationally representative survey jointly conducted by the Center for Healthy Aging and Development Studies at Peking University

Abbreviations: CLHLS, Chinese Longitudinal Healthy Longevity Survey; FI, Frailty Index; RR, Risk Ratio; CI, Confidence Intervals; SD, Standard Deviation; GEE, Generalized Estimating Equation.

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and Duke University. It was designed to identify the range of environmental, behavioral, social, and biological risk factors impacting healthy longevity; hence, this survey provides detailed information on the family constitution, marriage status, activities of daily living, social activities, health status, and lifestyle for older adults aged $\geq$ 65 years. More than half of China's counties and cities were selected for the survey (23 out of 31 provinces). The surveyed provinces were Tianjin, Liaoning, Heilongjiang, Jiangsu, Anhui, Jiangxi, Shandong, Hubei, Guangdong, Chongqing, Shanxi, Beijing, Hebei, Shanxi, Jilin, Shanghai, Zhejiang, Fujian, Henan, Hunan, Guangxi, Sichuan, and Hainan (28). The survey area represented 85.3% of the overall population of the country and may be a nationally designated sample (29). The CLHLS systematically collected data from older adults through face-to-face interviews by trained staff (30). The data quality was validated as acceptable, and a more detailed method has been depicted elsewhere (28). The CLHLS study was approved by the Ethics Committee of Peking University (IRB00001052–13074). All participants or their representatives legally signed written consent.

Our study used the 2008–2014 datasets of the CLHLS, which were surveyed from 1 January 2008 to 10 July 2009 and from 10 April 2014 to 23 November 2014, respectively. Of 16,954 respondents in the 2008 baseline interview, 8,881 respondents aged $\geq$ 65 years had completed data about frailty and had no frailty, with 8,073 being excluded (391 aged <65 years, 3799 had missing data about frailty, and 3,883 had frailty). A total of 4,905 participants were excluded between the two assessments in 2008 and 2014. Of these, 3,172 died or were lost in the 2011 survey, 397 were lost in the 2014 survey, and 1,336 died before the 2014 survey. Finally, 2,630 participants completed a six-follow-up survey in 2014 and were analyzed in this study. The screening procedure is described in Figure 1.

Definition of frailty

Following the criteria procedure recommended by Searle and co-authors (31), our study used 44 health deficits to form the frailty index (FI), including daily living activities (basic and instrumental), psychological functions, and chronic diseases. The scale of a frailty index in this study has a Cronbach's alpha of 0.870. Each deficit variable was dichotomized or multichotomized and then mapped to a 0–1 interval (e.g., daily task-bathing, where "without assistance" was conferred as 0, "partial assistance" as 0.5, and "need assistance" as 1) to reflect its seriousness. For each participant, the FI scores were measured as the sum of deficit scores divided by the amount of deficit included, ranging from 0 to 1. The participants with a score of >0.21 were referred to as frail (32), while those with a score of $\leq$0.21 were referred to as not frail. Detailed deficits of the frailty index are shown in Supplementary Table 1.

Definition of tea consumption

Tea consumption was defined by the answer to the question, "how often do you drink tea at present?" The responses included daily, occasionally, rarely, or never (33). We classified tea consumption into four types based on the information in both 2008 baseline and 2014 follow-up surveys to further capture the uniformity of tea consumption in subsequent years. Participants were defined as "non-tea drinkers" if they reported rarely or never drinking tea both in the baseline and 2014 follow-up surveys, which was the reference classification in the regression analyses; "consistent daily tea drinkers" if they daily drank tea both in the baseline and 2014 follow-up surveys; "consistent tea drinkers" if they daily or occasionally drank tea both in the baseline and 2014 follow-up surveys, but not daily for both; or "inconsistent tea drinkers" if they rarely or never drank tea either in the baseline survey or 2014 follow-up survey but not in both (30).

Covariates measurement

Some potential covariates were analyzed, including sociodemographic characteristics, socioeconomic status, and health behavior. Sociodemographic characteristics included age group (ages 65–79 years *vs.* ages 80+ years), sex (male *vs.* female), marital status (married *vs.* others), and residence (urban *vs.* rural). Socioeconomic status included education, occupation, and financial support. Education was classified into formal education and informal education, according to $\geq$1 and <1 year of education, respectively. Occupation before 60 years old was dichotomized into "agricultural work" (coded as 0) and "non-agricultural work" (coded as 1). Financial support has defined as the answer to the question "what is your main source of financial support?," including financial dependence (coded as 0) and financial independence (coded as 1). Health behavior was measured by current drinking (yes *vs.* no), current smoking (yes *vs.* no), and current exercise (yes *vs.* no). Chronic illnesses were classified as yes and no and included hypertension, diabetes, heart disease, stroke or cardiovascular disease, bronchitis, emphysema, pneumonia, asthma, tuberculosis, cataract, cancer, glaucoma, gastric or duodenal ulcer, Parkinson's disease, bedsore, arthritis, and dementia.

Statistical analysis

The number and percentage were used to describe the characteristics of tea consumption and frailty, and the difference was verified by the Chi-square test. Mean and standard deviation (SD) were used to describe age and frailty index. The frailty index recommended by Searle and co-authors, including 44 health deficits, was used. A histogram was

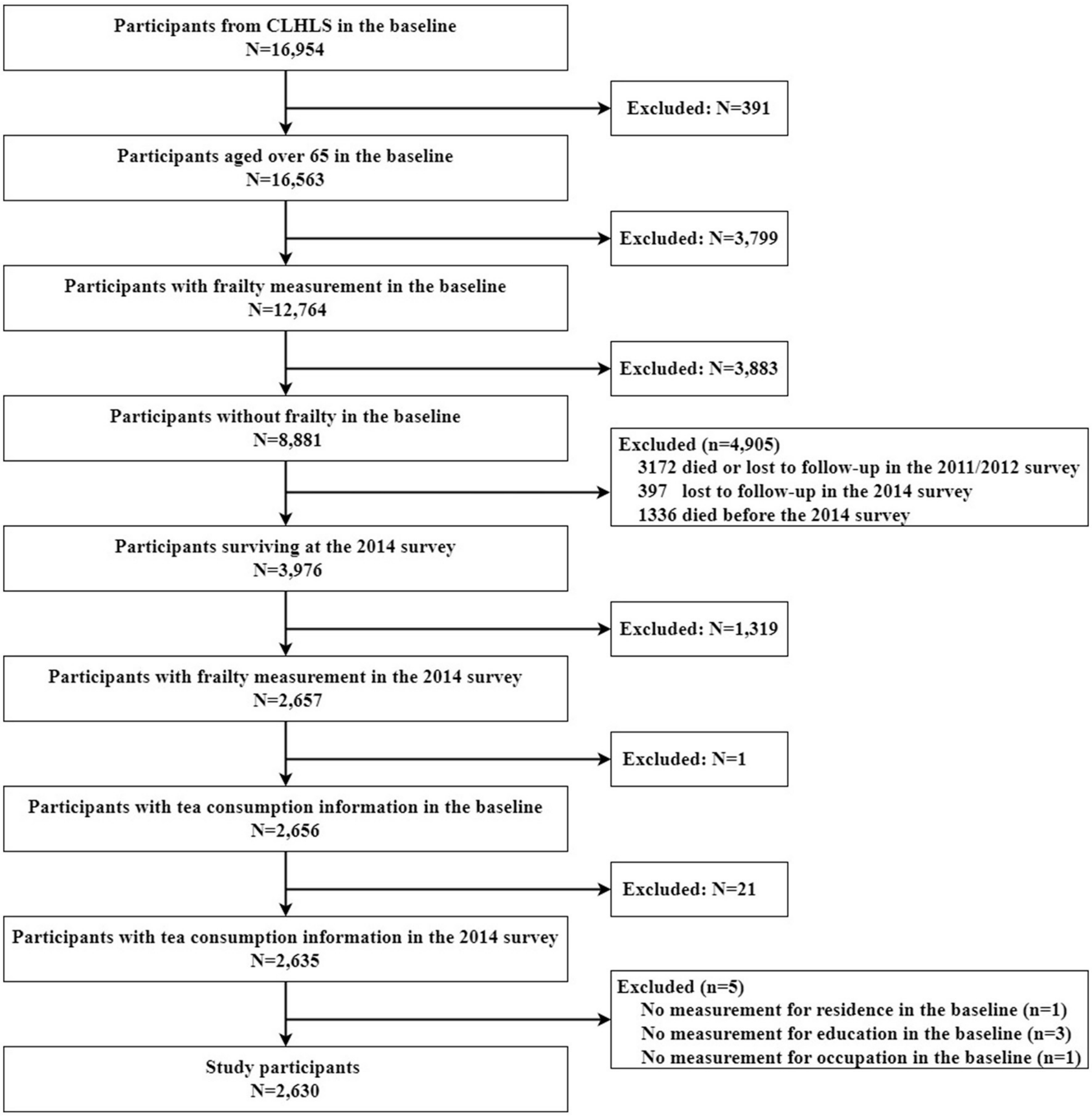

FIGURE 1
Flow chart of sample selection.

used to describe the frequency change of the frailty index. A Generalized Estimating Equation (GEE) was applied to determine the risk ratio (RR) with a 95% confidence interval (CI) for frailty, and further subgroup analyses were conducted to investigate whether the risk differed stratified by age, sex, and socioeconomic status. Additionally, the interaction between tea consumption with sex and frailty was tested. All statistical analyses were performed with SPSS 26.0 (Chicago, IL, USA). Statistical significance was considered when P was $<$ 0.05 (two-sided).

Results

Characteristics of the participants at baseline are summarized in Table 1. The sample was composed of 2,630 participants, with 1,353 males (51.4%) and 1,277 females (48.6%). The participants' mean age was 76.84 (SD = 8.5) years. Of these participants, 63.5% were aged 65–79 years, and 36.5% were aged $\geq$ 80 years; 56.8% were married, 89.1% resided in rural areas, 49.8% had informal education, 68.1% did agricultural work, 57.9%

TABLE 1 Characteristics of older adults by tea consumption, tea consumption status in 2008 baseline, and frailty in the 2014 follow-up.

Characteristics	*n* (%)	Tea consumption				χ^2	Tea consumption status at baseline			χ^2	Frailty	χ^2
		Consistent daily tea drinkers	Consistent tea drinkers	Inconsistent tea drinkers	Non-tea drinkers		Daily	Occasionally	Rarely or never			
Age group (years)						3.219				0.630		183.863***
65–79	1,671 (63.5)	258 (15.4)	224 (13.4)	605 (36.2)	584 (34.9)		650 (38.9)	273 (16.3)	748 (44.8)		238 (14.2)	
80+	959 (36.5)	144 (15.0)	107 (11.2)	355 (37.0)	353 (36.8)		368 (38.4)	148 (15.4)	443 (46.2)		357 (37.2)	
Sex						167.154***				91.247***		28.348***
Female	1,277 (48.6)	103 (8.1)	119 (9.3)	481 (37.7)	574 (44.9)		379 (29.7)	213 (16.7)	685 (53.6)		346 (27.1)	
Male	1,353 (51.4)	299 (22.1)	212 (15.7)	479 (35.4)	363 (26.8)		639 (47.2)	208 (15.4)	506 (37.4)		249 (18.4)	
Marital status						57.635***				27.961***		50.101***
Married	1,495 (56.8)	281 (18.8)	220 (14.7)	518 (34.6)	476 (31.8)		637 (42.6)	245 (16.4)	613 (41.0)		263 (17.6)	
Others	1,135 (43.2)	121 (10.7)	111 (9.8)	442 (38.9)	461 (40.6)		381 (33.6)	176 (15.5)	578 (50.9)		332 (29.3)	
Residence						11.628**				4.458		1.543
Rural	2,344 (89.1)	344 (14.7)	292 (12.5)	850 (36.3)	858 (36.6)		892 (38.1)	375 (16.0)	1,077 (45.9)		522 (22.3)	
Urban	286 (10.9)	58 (20.3)	39 (13.6)	110 (38.5)	79 (27.6)		126 (44.1)	46 (16.1)	114 (39.9)		73 (25.5)	
Education						53.757***				20.429***		40.655***
Formal education	1,319 (50.2)	254 (19.3)	196 (14.9)	452 (34.3)	417 (31.6)		564 (42.8)	210 (15.9)	545 (41.3)		230 (17.4)	
Informal education	1,311 (49.8)	148 (11.3)	135 (10.3)	508 (38.7)	520 (39.7)		454 (34.6)	211 (16.1)	646 (49.3)		365 (27.8)	
Occupation						50.936***				39.163***		1.430
Agricultural work	1,790 (68.1)	226 (12.6)	200 (11.2)	672 (37.5)	692 (38.7)		622 (34.7)	293 (16.4)	875 (48.9)		393 (22.0)	
Non-agricultural work	840 (31.9)	176 (21.0)	131 (15.6)	288 (34.3)	245 (29.2)		396 (47.1)	128 (15.2)	316 (37.6)		202 (24.0)	
Financial support						51.951***				27.456***		33.642***
Financial dependence	1,523 (57.9)	173 (11.4)	177 (11.6)	584 (38.3)	589 (38.7)		525 (34.5)	258 (16.9)	740 (48.6)		406 (26.7)	
Financial independence	1,107 (42.1)	229 (20.7)	154 (13.9)	376 (34.0)	348 (31.4)		493 (44.5)	163 (14.7)	451 (40.7)		189 (17.1)	
Smoking						75.999***				43.123***		14.482***
Yes	646 (24.6)	148 (22.9)	113 (17.5)	222 (34.4)	163 (25.2)		315 (48.8)	106 (16.4)	225 (34.8)		111 (17.2)	
No	1,984 (75.4)	254 (12.8)	218 (11.0)	738 (37.2)	774 (39.0)		703 (35.4)	315 (15.9)	966 (48.7)		484 (24.4)	
Drinking						67.410***				46.404***		13.991***
Yes	590 (22.4)	144 (24.4)	91 (15.4)	202 (34.2)	153 (25.9)		298 (50.5)	86 (14.6)	206 (34.9)		100 (16.9)	
No	2,040 (77.6)	258 (12.6)	240 (11.8)	758 (37.2)	784 (38.4)		720 (35.3)	335 (16.4)	985 (48.3)		495 (24.3)	
Exercise						17.238**				7.937*		0.331
Yes	1,030 (39.2)	191 (18.5)	134 (13.0)	372 (36.1)	333 (32.3)		433 (42.0)	157 (15.2)	440 (42.7)		227 (22.0)	
No	1,600 (60.8)	211 (13.2)	197 (12.3)	588 (36.8)	604 (37.8)		585 (36.6)	264 (16.5)	751 (46.9)		368 (23.0)	
Chronic illnesses						3.310				2.732		6.385*
Yes	1,361 (51.7)	212 (15.6)	156 (11.5)	500 (36.7)	493 (36.2)		515 (37.8)	209 (15.4)	637 (46.8)		335 (24.6)	
No	1,269 (48.3)	190 (15.0)	175 (13.8)	460 (36.2)	444 (35.0)		503 (39.6)	212 (16.7)	554 (43.7)		260 (20.5)	

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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were financially dependent on others, and 51.7% had chronic illnesses.

Table 1 summarizes the characteristics of respondents by the types of tea drinkers and tea consumption status at baseline of CLHLS. Of the 2,630 participants, 35.6% were non-tea drinkers, 36.5% were inconsistent tea drinkers, 12.6% were consistent tea drinkers, and 15.3% were consistent daily tea drinkers. Categorized by tea drinking status at baseline, 45.3% were non-tea drinkers, 16.0% were occasional tea drinkers, and 38.7% were daily tea drinkers. Compared to non-tea drinkers, a high frequency of tea drinking was more prevalent among those who were younger, male, married, living in the urban area, doing non-agricultural work, financially independent, doing exercise, and had a formal education. Moreover, tea drinkers tended to smoke and drink. There was no significant difference in tea consumption across age groups and chronic illnesses.

Table 1 also shows the association of participants' characteristics with frailty. The mean frailty index for participants was 0.15 (SD = 0.11) (Figure 2). The prevalence of frailty was 22.6% among older people, higher in the ≥ 80 years group (37.2%) than in the 65–79 years group (14.2%). Older people with frailty were likely to be female, have another marital status, have informal education, not smoke, not drink, be financially dependent on others, and have chronic illnesses. There was no significant difference in residence (P = 0.214), occupation (P = 0.232), and exercise (P = 0.565).

Compared to non-tea drinkers, consistent daily tea drinkers had a significantly lower ratio of frailty (RR = 0.34, 95% CI: 0.29–0.39) in the crude and (RR = 0.51, 95% CI: 0.36–0.71) adjusted models (Table 2). However, daily tea drinkers had a lower ratio of frailty (RR = 0.78, 95% CI: 0.64–0.96) in the crude model, but the difference became small and not statistically significant (RR = 0.86, 95% CI: 0.69–1.07) in the adjusted final model. Additionally, we investigated whether tea benefits differ by age, sex, and socioeconomic status. As shown in Table 3, consistent daily tea consumption resulted in a significantly reduced risk of frailty in males (RR = 0.51, 95% CI: 0.32–0.81) but not in females (RR = 0.61, 95% CI: 0.36–1.04); in informal education (RR = 0.39, 95% CI: 0.23–0.67) but not in formal education (RR = 0.63, 95% CI: 0.39–1.02); in financial dependence (RR = 0.40, 95% CI: 0.24–0.65) but not in financial independence (RR = 0.66, 95% CI: 0.39–1.12). Tea consumption was associated with a lower risk of frailty in both the young (RR = 0.36, 95% CI: 0.20–0.64) and the oldest (aged ≥ 80)

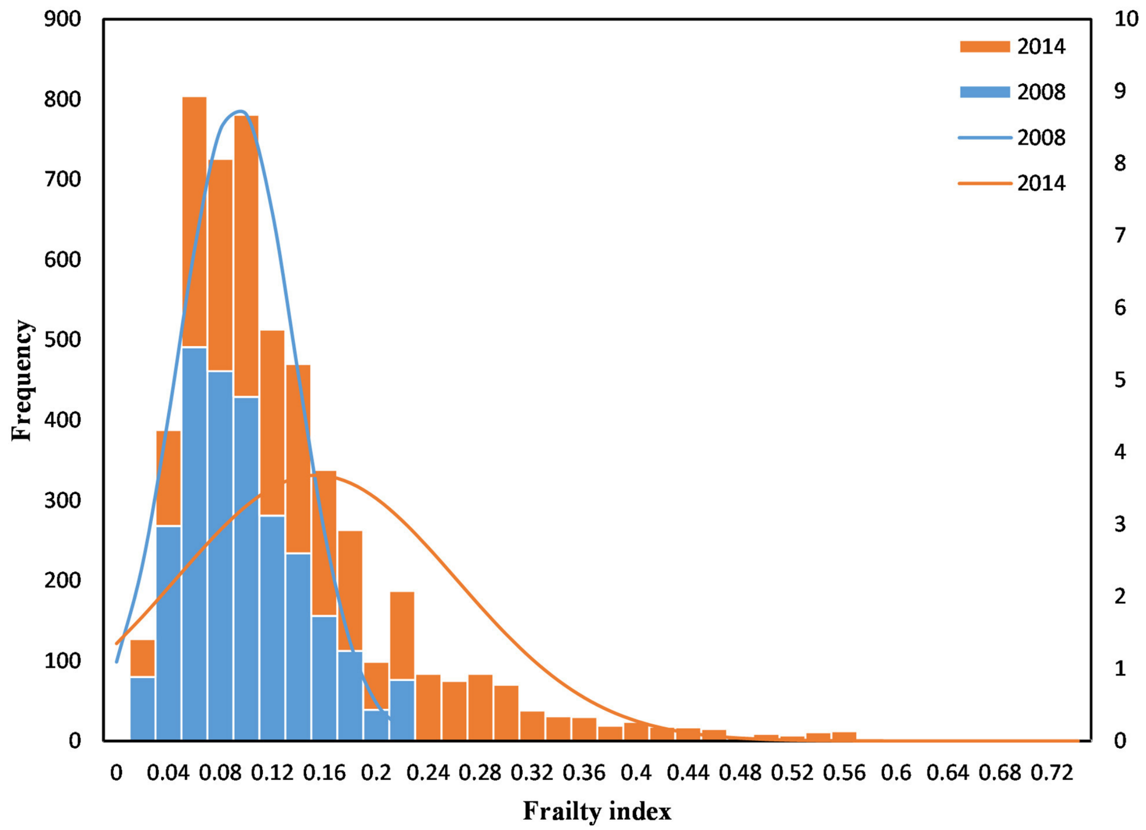

FIGURE 2
Histogram of the frailty index.

TABLE 2 Associations between tea consumption and frailty among older Chinese people.

Characteristics	Crude model RR (95% CI)	Final model RR (95% CI)
Tea consumption (ref.= non-tea drinkers)		
Consistent daily tea drinkers	0.34 (0.29, 0.39)***	0.51 (0.36, 0.71)***
Consistent tea drinkers	0.44 (0.32, 0.62)***	0.99 (0.72, 1.37)
Inconsistent tea drinkers	0.85 (0.63, 1.14)	1.01 (0.81, 1.26)
Tea consumption status at baseline (ref.= rarely or never)		
Daily	0.78 (0.64, 0.96)*	0.86 (0.69, 1.07)
Occasionally	1.03 (0.80, 1.33)	1.11 (0.84, 1.46)

RR represents the risk ratio, 95% CI represents 95% confidence intervals, and Ref. represents reference. *P < 0.05, ***P < 0.001. The R2 value for the final model of tea consumption was 0.144. Multiple logistic regression analysis was applied to estimate the RR and 95% CI for frailty. The final model is adjusted for age, sex, marital status, residence, education, occupation, financial support, smoking, drinking, exercise, and chronic illnesses.

TABLE 3 The association between tea consumption and frailty stratified by age, sex, and socioeconomic status.

Characteristics	Consistent daily tea drinkers	Consistent tea drinkers	Inconsistent tea drinkers
Stratified by age group			
65–79	0.36 (0.20, 0.64)**	0.97 (0.63, 1.51)	0.91 (0.66, 1.25)
80+	0.63 (0.40, 0.98)*	1.06 (0.66, 1.68)	1.07 (0.79, 1.46)
Stratified by sex			
Female	0.61 (0.36, 1.04)	0.95 (0.59, 1.51)	0.81 (0.61, 1.08)
Male	0.51 (0.32, 0.81)**	1.18 (0.74, 1.88)	1.38 (0.96, 1.99)
Stratified by education			
Formal education	0.63 (0.39, 1.02)	1.17 (0.72, 1.89)	1.21 (0.84, 1.74)
Informal education	0.39 (0.23, 0.67)**	0.91 (0.59, 1.42)	0.90 (0.68, 1.19)
Stratified by occupation			
Agricultural work	0.53 (0.33, 0.83)**	0.82 (0.54, 1.25)	0.91 (0.70, 1.18)
Non-agricultural work	0.48 (0.28, 0.82)**	1.33 (0.77, 2.27)	1.24 (0.82, 1.89)
Stratified by financial support			
Financial dependence	0.40 (0.24, 0.65)***	0.94 (0.63, 1.40)	0.86 (0.66, 1.12)
Financial independence	0.66 (0.39, 1.12)	1.20 (0.68, 2.12)	1.46 (0.98, 2.18)

RR represents the risk ratio, 95% CI represents 95% confidence intervals. *P < 0.05, **P < 0.01, ***P < 0.001. The final model is adjusted for age, sex, marital status, residence, education, occupation, financial support, smoking, drinking, exercise, and chronic illnesses.

(RR = 0.63, 95% CI: 0.40–0.98); agricultural work (RR = 0.53, 95% CI: 0.33–0.83) and non-agricultural work (RR = 0.48, 95% CI: 0.28–0.82).

We tested the interaction between tea consumption and sex to further determine whether tea consumption was differently related to frailty between the sexes (Table 4). The results showed that the effects of tea consumption on frailty were partially mediated by sex. Females showed a lower tea-mediated risk of frailty in occasional tea consumers (RR = 0.51, 95% CI: 0.29–0.89) and inconsistent tea drinkers (RR = 0.58, 95% CI: 0.37–0.93).

Discussion

Our study showed that daily tea consumption was associated with a significantly lower risk of frailty over a 6-year follow-up, and the findings provide new evidence for the protective role of tea consumption in frailty among older people, especially among those who kept regularly drink tea.

The antioxidant status of older people is often poor, and there is evidence that frailty probably results from tissue damage due to oxidative stress and inflammatory processes (34). Tea has been an active component linking anti-inflammatory and antioxidative processes (35); moreover, this anti-inflammatory and antioxidant effect is to inhibit signaling in the inflammatory process by scavenging reactive oxygen species (36). Additionally, tea polyphenols can significantly reduce the pro-inflammatory cytokine tumor necrosis factor, interleukin 6, and interleukin 1β expression, thereby reducing inflammation and achieving the goal of anti-inflammatory (37). A diet with high antioxidant capacity has been strongly inversely correlated with frailty prevalence (38). Tea consumption has been one of the major contributors to dietary antioxidant capacity (39). This beneficial effect on frailty is related to bioactive compounds (21); for example, tea is rich in flavonoids, e.g., epicatechin, catechin,

TABLE 4 Effect of interaction between tea consumption and sex on frailty.

Characteristics	Crude model RR (95% CI)	Final model RR (95% CI)
Sex (Ref.= Male)		
Female	1.65 (1.37, 1.98)***	1.24 (0.97, 1.59)
Tea consumption× Female		
Consistent daily tea drinkers		1.17 (0.58, 2.37)
Consistent tea drinkers		0.76 (0.40, 1.47)
Inconsistent tea drinkers		0.58 (0.37, 0.93)*
Tea consumption status at baseline × Female		
Daily		0.84 (0.54, 1.31)
Occasionally		0.51 (0.29, 0.89)*

RR represents the risk ratio, 95% CI represents 95% confidence intervals, and Ref. represents reference. *$P < 0.05$, ***$P < 0.001$. The final model for the interaction between tea consumption and sex had an R2 value of 0.148. Multiple logistic regression analysis was applied to estimate the RR and 95% CI for frailty. The final model is adjusted for age, sex, marital status, residence, education, occupation, financial support, smoking, drinking, exercise, and chronic illnesses.

and epigallocatechin gallate. Lakshmi et al. (40) identified that epigallocatechin gallate inhibits activation of nuclear factor-κB, the key inflammatory transcription factor, and performs anti-inflammatory properties. A previous study showed that these bioactive ingredients can relieve inflammation, reduce oxidative stress, and enhance endothelial and cardiomyocyte function (41). Drinking tea is complex as different types of tea have different constitutions and contaminations (42). A previous study has shown that habitual tea consumption is associated with a slightly higher risk of hypertension (43). Although tea has therapeutic properties, it can be a major source of fluoride exposure, and excessive intake of fluoride can lead to health problems, such as fluorosis and skeletal fluorosis (44). Anti-nutritional factors, such as tannins, are often considered responsible for the high incidence of iron deficiency, especially among vulnerable groups (45). A previous study has indicated that tea needs to be consumed frequently enough to reach some cumulative amount to contribute to the health of older adults; however, excessive consumption of tea is not healthy for older adults (46).

Tea consumption is traditionally considered to be a promising non-pharmacological strategy for supplementing the management of hypertension, obesity or diabetes, especially where tea drinking is a widely accepted cultural practice (47). Long-term tea consumption may be necessary to confer health benefits (48). Tea and its components are also extensively used as cardiomyocyte functional foods or dietary supplements for the preventing and treatment of various chronic diseases (49, 50), including preventing cardiovascular disease, Parkinson's disease, metabolic syndromes, osteoporosis, diabetes, obesity, stroke, dementia, and certain cancers (47, 51). Previous studies have shown a negative association between tea consumption and the risk of depression (15). Tea and its bioactive compounds help older people maintain better mental health (52). Tea consumption has been associated with better physical functional performances in older adults (10). Hence, tea consumption may play an essential role in preventing frailty. Habitual tea consumption has been correlated with better health-related quality of life among older Chinese people (53). These results support our data findings of an association between tea consumption and frailty. Tea consumption habits may change over time (54). Perhaps only long-term but not short-term tea drinking behavior plays a beneficial role in frailty.

The prevalence of frailty increases with age (55). The inverse relationship between consistent daily tea consumption and frailty has been statistically significantly different in the young-old people aged 65–79 but not the oldest-old people aged $\geq$ 80. Tea consumption varied to some extent by age and sex (56). Males and younger older adults tend to drink more tea each day or strong tea with a high concentration of beneficial ingredients; thus, the benefits of tea for these groups may increase (30). The sex gap in frailty increases with advancing age (57). Women have a higher prevalence of frailty than men (58), and it reflected the fact that women suffer a more significant loss of physical reserves and are more likely to experience worse socioeconomic and health conditions than men, indicating a higher chance of fragility (59). Consistent daily tea consumption significantly lessened the risk of having frailty in males but not in females. Previous studies have suggested that women were less likely to be habitual tea drinkers than men (47); the proportion of male and female tea consumers was 72.7 and 55.4%, respectively. Additionally, the balance of daily tea consumers, the duration, and the amount of tea consumption in men were significantly higher than in women (60). Inconsistent tea drinkers and female sex resulted in a reduced risk of frailty. A previous study has shown that women who drank 1–2 cups of tea daily and men who drank $\geq$ 3 cups of tea daily had a lower prevalence of frailty. Females become frail at a time when they are younger than males. Habitually drinking tea has a powerful antioxidant effect and can prevent frailty in women early (21).

The prevalence of frailty varies among socioeconomic groups (61). Lower economic status, lower levels of education, and multimorbidity have been identified as risk factors for frailty (62). Occupation reflected education, salary, and social status; thus, it has been strongly associated with frailty (63). People with lower income had significantly higher chances of frailty (64).

Indeed, the prevalence of smoking and poor diet has already been reported as significantly higher in lower socioeconomic groups (65). Socioeconomic conditions can also influence dietary choices and eating patterns and, therefore, nutritional status (66). Drinking tea may be one of the characteristics of a healthy dietary pattern. Tea consumers have a more nutritious diet with higher protein levels, minerals, and vitamins and fewer added sugars (53). Additionally, tea consumption may also be positively associated with health behavior. For instance, people with higher tea consumption tend to be more health-conscious (67). Health behavior, including regular physical work and exercise, has been significantly associated with a lower risk of frailty (68). Consistent daily tea consumption significantly lessened frailty in those with informal education, agricultural work, and financial dependence. From an economic point of view, a household's budget may not impact the quantity of daily tea consumption (69). Indeed, higher levels of cultural achievement promote an overall healthier lifestyle through good practice derived from regular physical activity, sustained cognitive stimulation, and better social integration (70).

Strengths and limitations

Tea-drinking behavior may be altered in later years, and the advantages of tea drinking may be long-term. This measurement based on two-time points in the longitudinal study may help capture the role of tea consumption on frailty. We used data from long-term, reliable longitudinal studies to establish that tea consumption was inversely associated with frailty. The study used a simple self-reported screening tool to assess frailty in the older population.

There are several limitations to our study. First, the data for the study came primarily from interviews, which might have had recall bias. Although tea consumption is usually a long-term personal habit, recall bias may be comparatively low. Second, we did not assess the effect of the specific type of tea and its interaction with prescription medication because the relative information was not available in the baseline survey. Finally, there may be other uncontrolled confounders that affected the results.

Conclusions

Habitual tea consumption can reduce the risk of frailty in older Chinese, and long-term persistence of the habit provides robust protection. In addition, there are age, sex, education, and financial support specific differences in the protective role. Our findings give a further insight into the beneficial role of tea consumption, and have great public health implications for preventing frailty. Future well-designed observational studies on the type of tea and tea intake are needed to fully characterize this association. Additionally, the potential mechanisms, active ingredients in tea, and drug history that may be responsible for the association await further elucidation.

Recommendations

Tea drinking should be recommended as one of ongoing healthy lifestyle, and is an affordable, cost-effective, and easily adoptable prevention intervention for frailty in older people, especially in males and low socioeconomic status.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052–13074), and all participants provided written informed consent. All methods were performed in accordance with the relevant guidelines and regulations (e.g., the Declaration of Helsinki).

Author contributions

MZ and TG: conceptualization. HL, TG, and SH: methodology. HL, QS, and MZ: investigation and data management. TG: original draft preparation. HL, SH, TG, and GM: review and editing. MZ, QS, and SH: supervision. HL, MZ, and GM: project administration. HL and MZ: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.916791/full#supplementary-material

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Farhana Akter,
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Addis Ababa University, Ethiopia
Sidikiba Sidibe,
Gamal Abdel Nasser University
of Conakry, Equatorial Guinea

*CORRESPONDENCE
Melkamu Aderajew Zemene
melmahman3m@gmail.com

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Trends and factors associated with thinness among late adolescent girls in Ethiopia: Multivariate decomposition and multilevel analysis

Melkamu Aderajew Zemene[1]*, Netsanet Worku Mengistu[2] and Solomon Gedlu Nigatu[3]

[1]Department of Public Health, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia, [2]Department of Human Nutrition, College of Medicine and Health Sciences, Institute of Public Health, University of Gondar, Gondar, Ethiopia, [3]Department of Epidemiology and Biostatistics, College of Medicine and Health Sciences, Institute of Public Health, University of Gondar, Gondar, Ethiopia

Background: Undernutrition among adolescent girls is still a major public health problem in low- and middle-income countries (LMICs). Even though the global prevalence of thinness among adolescent girls declined over time, it remains steady in LMICs including Ethiopia. Therefore, this study aimed to assess the trends and factors associated with thinness.

Methods: A logit-based multivariate decomposition analysis for a non-linear response model was fitted to identify factors that contributed to the change in thinness over time. For the associated factors, a multilevel binary logistic regression model was employed. The intra-class correlation coefficient (ICC) and likelihood ratio (LR) test were used to assess the presence of the clustering effect, and deviance was used for model comparison. Statistical significance was declared at $p < 0.05$.

Results: Thinness among late adolescent girls declined significantly from 34.4% (95% CI: 32.8%, 36.0%) in 2000 to 24.9% (95% CI: 23.4%, 26.5%) in 2016 with an annual average reduction rate of 1.73%. About 84% of the decrement in thinness was attributed to the change in the effect of the characteristics. The place of residence and marital status were significantly associated with a change in thinness due to the change in coefficients. The compositional changes in the age of the adolescents, religion, and types of toilet facilities were also significantly associated with the change in thinness. From the multilevel binary logistic regression, higher age of adolescents (AOR = 0.83; 95% CI: 0.77, 0.90), improved toilet facility (AOR = 0.45; 95% CI: 0.31, 0.65), middle wealth index (AOR = 1.45; 95% CI: 1.10, 1.90), and female head of the household (AOR = 0.77; 95% CI: 0.61, 0.98) were significantly associated at an individual level, whereas being from Somali (AOR = 2.14; 95% CI:1.76, 3.10) and

SNNP region (AOR = 0.35; 95% CI: 0.18, 0.68), they had a statistically significant association with thinness at community level.

Conclusion: Thinness among late adolescent girls declined substantially, but it remains a major public health concern. Nutritional interventions targeting thinness reduction among late adolescent girls should base on the identified factors. Age, residence, marital status, type of toilet facility, religion, wealth index, sex of head of the household, and region were all associated with thinness in this study.

KEYWORDS

thinness, adolescent girls, Ethiopia, multivariate decomposition, multilevel

Introduction

Adolescence is a phase of the human lifecycle extending from 10 to 19 years of age. Adolescents within this age group are in a critical transition period from childhood to adulthood (1). It is further classified as; early adolescence (10–14 years) and late adolescence (15–19 years) (2). Globally, the adolescent population represents 1.8 billion, where the majority (90%) of them reside in low and middle-income countries (LMICs). Yet, adolescents have been largely neglected from the public health agenda in LMICs (3). The global prevalence of thinness among adolescent girls decreased from 10% by the year 2014 to 8.4% in 2018. This shows that thinness in this age group remained fairly steady over the past decade (4). There is a significant disparity in the prevalence of thinness across the globe. For instance, adolescence thinness in South Asia and Sub-Saharan Africa is higher with a magnitude ranging from 32–65% to 15–58%, respectively, (5) compared to Northern America, Europe and Oceania, Latin America, and the Caribbean (6, 7). The lowest mean BMI among adolescent girls was from South East Asia followed by East Africa (Ref). Particularly, the lowest age-standardized mean BMI in girls was 16.8 kg/m^2 which is from Ethiopia (4, 8). Growth and development of the body brought a hormonal change in adolescents which in turn leads to a change in body composition, macro, and micronutrient requirements. More than half of the adult body weight is gained during adolescence (9).

Undernourished adolescent girls grow slowly and sometimes if they get pregnant, they may not even finish growing before their first pregnancy. When energy intake in adolescents is constrained due to pregnancy, they will start to use their calories for the privilege of reproductively valuable adipose tissue formation at the expense of investing in their growth (4). In times of adolescent pregnancy, there is increased competition for nutrients with the fetus and there is a high risk of the mother becoming thin and the fetus becoming stunting (10).

Previous studies conducted on adolescent thinness revealed that rural residence, early marriage, and subsequent pregnancy, low educational status, poor access to safe water and sanitation, lack of health services targeted for adolescents, and low utilization of family planning were factors significantly associated with thinness among adolescent girls (11–17).

Despite countries having a range of nutrition programs and strategies, there is an implementational problem leaving thinness among adolescent girls still a major public health problem in LMICs, including Ethiopia (18). Thinness has short- and long-term consequences in adolescents. It has an impact on physical growth, mental development, and poor birth outcome that adversely affects cognitive development and school achievements, lowers productive capacity, and increases the risk of infections (19).

When the undernourished mother becomes pregnant, the next generation may also suffer from malnutrition and poor health (20).

Even though there have been different local studies on the prevalence and factors associated with thinness among adolescent girls in Ethiopia, there is limited evidence on the trends of thinness and factors that contributed to the change in thinness over time.

Therefore, this study has aimed to assess trends, the factors that are either positively or negatively contributing to the change in thinness prevalence, and the individual and community-level factors associated with thinness among late adolescent girls in Ethiopia. Thus, findings from this study will help policymakers, program managers,

Abbreviations: BAZ, body mass index for age; BMI, body mass index; DHS, demographic and health survey; EAs, enumeration areas; EDHS, Ethiopia Demographic and Health Survey; ICC, intra-class correlation coefficient; IRB, Institution Review Board; LMIC, lower- and middle-income countries; MOR, median odds ratio; PCV, proportional change in variance; SNNP, Southern Nations and Nationalities Region.

scholars, and healthcare providers in evaluating and designing strategies targeting influential factors for improving nutritional status in adolescents.

Materials and methods

Study design, area, and period

Secondary data analysis was conducted based on the four consecutive Ethiopian Demographic and Health Survey (EDHS) datasets (EDHS 2000, EDHS 2005, EDHS 2011, and EDHS 2016). EDHS is a community-based cross-sectional study conducted every 5 years to generate updated health and health-related indicators.

Source and study population

The source population was all adolescent girls aged (15–19 years) in Ethiopia at the time of the survey years 2000, 2005, 2011, and 2016 EDHS. All late adolescent girls aged 15–19 years in Ethiopia at the time of the survey years of 2000, 2005, 2011, and 2016 EDHS in the selected Enumeration Areas (EAs) were the study population.

EDHS uses a two-stage stratified cluster sampling technique. In the first stage, a sample of EAs was selected independently from each stratum with proportional allocation stratified by residence (urban and rural) and region. In the second stage, from the selected EAs, a fixed number of households was taken by systematic sampling in each survey year. From the selected households, measurements of weight and height were taken from children aged 0–59 months, women 15–49 years, and men 15–59 years. A total weighted sample of 11,783 adolescent girls was included in this study. Of which, 3,456, 1,516, 3,724, and 3,087 weighted adolescent girls were screened in the 2000, 2005, 2011, and 2016 survey years, respectively. The detailed sampling procedures are available in the full EDHS reports (11–14).

Eligibility criteria

The study included adolescent girls aged 15–19 years who were in the selected enumeration areas (EAs) in Ethiopia's Demographic and Health Survey 2000, 2005, 2011, and 2016. Moreover, the study excluded adolescent girls who were pregnant or who gave birth in the last 2 months preceding the date of the interview. Additionally, adolescent girls who were not weighed/measured and whose values for weight and height were not recorded were excluded.

Variables and data collection procedure

The outcome variable was thinness taken as a binary response; 0 coded for "not thin" and 1 coded for "thin." The independent variables considered for this study were from two sources; individual-level variables (socio-economic and socio-demographic related factors, environmental factors, behavioral related factors) and community-level factors. The data were accessed and downloaded from the webpage of the international DHS program after subscribing as an authorized user. From EDHS, 2000, 2005, 2011, and 2016, we used the women dataset (IR recode) for this study.

Operational definitions

Thinness (total underweight)

WHO classifies thinness as mild, moderate, and severe when the adolescent BMI for age z-score is < -1SD, < -2SD, and < -3SD, respectively, as compared with the median value of the world health organization reference point (21). In this study, thinness included mild, moderate, and severe. This operational definition is made to make it in line with DHS reports, where the data were taken from.

Wealth index

It is a composite measure of a household's cumulative living standard divided into five quantiles using the wealth quantile data derived from principal component analysis (14).

Community poverty

It is defined as the proportion of late adolescent girls who resided in poor or poorest households in the cluster categorized as 0 for "low" (0–0.16) and 1 for "high" (0.161–1).

Community mass media exposure

It is defined as the proportion of late adolescent girls who had mass media exposure within the cluster categorized as 0 for "poor" (0–0.6) and 1 for "good" (0.61–1).

Community adolescent girls' literacy

It is defined as the proportion of late adolescent girls who attended primary, secondary, or higher education within the cluster categorized as 0 for "low" (0–0.84) and 1 for "high" (0.85–1).

Data management and analysis

The data were extracted, edited, coded, and verified by using STATA version 16/MP software. The analysis was conducted by using STATA, Microsoft Excel, and WHO Anthro Plus software accordingly. The overall analysis in this study was carried out on weighted data to restore representativeness and complex sampling procures were also considered during the testing of statistical significance.

Data analysis

Trends of thinness among late adolescent girls

First, a descriptive analysis was done to observe the trends with a 95% confidence interval (CI) of thinness among adolescent girls in the four survey years. Similarly, the proportion of thinness for each factor in all periods was explored. The trends were explored separately for the periods 2000–2005, 2005–2011, 2011–2016, and 2000–2016.

Then, a logit-based multivariate decomposition analysis for a non-linear response model was implemented to determine the extent to which factors contributed to the observed change in thinness prevalence among adolescent girls.

Initially, a *p*-value of less than 0.25 was used to select candidate variables for multivariate decomposition analysis. A *p*-value of less than 0.05 with 95% CI was used to declare statistical significance after fitting to multivariate decomposition analysis in the overall decomposition and factors that contribute to the endowment and coefficient components.

Multivariate decomposition analysis is a non-linear model used to split the difference in a distribution statistic between two groups, or its change over time, into various explanatory factors. This statistical approach uses the output from regression models to partition the components of a group difference in a statistic, such as a mean or proportion, into a component attributable to compositional differences between groups; differences in characteristics (endowments), and a component attributable to differences in the effects of characteristics (differences in coefficients). This analysis technique is equally applicable for partitioning change over time into components attributable to changing composition and changing effects (22).

The dependent variable is the function of the linear combination of predictors and regression coefficients.

$$Y = F(X\beta)$$

where Y is the N × 1 dependent variable vector, X is an N × K matrix of independent variables, and β is a K × 1 vector of coefficients. F (·) is any once-differentiable function mapping a linear combination of X(Xβ) to Y. The overall differences in components that reflect compositional differences between groups (endowments) and differences in the effects of characteristics (coefficients) between two groups A and B can be decomposed as:

$$YA - YB = F(XA\beta A) - F(XB\beta B)$$

$$\text{Logit}(Y_A) - \text{logit}(Y_B) = F(X_A\beta_A) - F(X_B\beta_B)$$

$$= \underbrace{F(X_A\beta_A) - F(X_B\beta_B)}_{E} + \underbrace{F(X_B\beta_A) - F(X_B\beta_B)}_{C}$$

The component labeled "E" refers to the part of the differential attributable to differences in endowments or characteristics, usually called the explained component or characteristics effect. The "C" component is the difference attributable to coefficients (behavioral change) usually called the unexplained component. We have chosen group A as the comparison group and group B as the reference group. Thus, E reflects a counterfactual comparison of the difference in outcome from group A's perspective (i.e., the expected difference if group A were given group B's distribution of covariates). C reflects the counterfactual comparison of the difference in outcome from group B's perspective (i.e., the expected differences if group B were experienced in group A's behavioral response to X).

In this study, we applied a decomposition analysis to account for changes in thinness among adolescent girls between 2000 and 2016. The model for decomposition analysis was: Logit (A)-Logit (B) = [β0A-β0B] +ΣβijA [XijA-XijB] +ΣxijB[βijA-βijB], (22)
where,

- → β0A is the intercept in the regression equation for EDHS 2016.
- → β0B is the intercept in the regression equation for EDHS 2000.
- → βijA is the coefficient of the jth category of the ith determinant for EDHS 2016.
- → βijB is the coefficient of the jth category of the ith determinant for EDHS 2000
- → XijA is the proportion of the jth category of the ith determinant for EDHS 2016.
- → XijB is the proportion of the jth category of the ith determinant for EDHS 2000.

Factors associated with thinness among late adolescent girls

Finally, due to the hierarchical nature of the DHS data where individuals are nested in the community, multilevel binary logistic regression analysis was employed to identify the factors associated with thinness among late adolescent girls. In this analysis, four models were fitted for EDHS 2016: (1) a null model (**model I**) with no exposure variables to check the variability of thinness in the cluster, (2) the second model (**model II**) containing individual-level variables, (3) the third model (**model III**) containing community-level variables, and (4) the fourth model (**model IV**) containing both individual and community-level variables with the outcome variable.

The fixed effects (a measure of association) were used to estimate the association between thinness and explanatory variables for both individual and community-level factors.

Explanatory variables with a $p < 0.25$ were selected for multivariable analysis. In the multivariable analysis, adjusted odds ratio (AOR) with 95% confidence interval (CI) was reported and statistical significance was declared at a $p < 0.05$. Multicollinearity was checked using correlation coefficient and variance inflation factor where variables with correlation coefficient less than 0.8 and VIF less than 10% were considered for the analysis.

Random effects (a measure of variation) were estimated by intra-class correlation coefficient (ICC), median odds ratio (MOR), and proportional change in variance (PCV).

Intra-class correlation coefficient (ICC) was the proportion of total variance in the outcome variable that was attributed to the area level. ICC of greater than 5% in the null model was used as a cut-off point to say there was a clustering or dependence (23).

$$\text{ICC} = \text{VA}/(\text{VA} + \text{VI}),\ \text{where VA is the area}-$$
$$\text{level variance and VI corresponds to individual}-$$
$$\text{level variance } (\text{VI} = \pi^2/3 = 3.29).$$

Median odds ratio (MOR) was defined as the median value of the odds ratio between the area at highest risk and the area at lowest risk when randomly picking out two areas. MOR shows the median probability of being thin determined by resident area. It aims to translate the area-level variance into a widely used odds ratio that has a consistent and intuitive interpretation. It showed unexplained heterogeneity between clusters (23).

$$\text{MOR} = \exp.[\sqrt{}(2 \times \text{VA}) \times 0.6745], \text{ or MOR } e^{0.95\sqrt{\text{VA}}}$$

The proportional change in variance (PCV) measures the total variation attributed to individual and community-level factors in the multilevel model.

$$\text{PCV} = (\text{VA} - \text{VB})/\text{VA}^{*}100$$

where VA = variance of the initial model and VB = variance of the model with more terms. The model performance was assessed using deviance information criteria (DIC) to select the best-fitted.

Result

Background characteristics of the study population

In this study, a total weighted sample of 11,783 adolescent girls was included. They had a mean ± standard deviation (SD) of age of 16.8 ± 1.39 years. The proportion of urban adolescent girls increased from 22.3% in 2000 to 26.8% in 2011 and slightly decreased to 23.6% in 2016. Regarding educational status, about 60% of adolescent girls were not educated in 2000 but significantly decreased to 13.4% in 2016. Besides, the proportion of adolescent girls who had primary education increased from 27.2% in 2000 to 63.6% in 2016 (**Table 1**).

Trends in thinness among late adolescent girls in the four survey years

The trend period was divided into four phases 2000–2005, 2005–2011, 2011–2016, and 2000–2016. In the overall trend, thinness among late adolescent girls has shown a significant decrement of 9.5% changing from 34.4% (32.8, 36.0) to 24.9% (23.4, 26.5) in the period 2000–2016 with an annual average reduction rate of 1.73%. The prevalence of mild, moderate, and severe thin late adolescent girls in EDHS 2000 was 23.9, 8.7, and 1.8% which declined to 19.8, 4.2, and 0.9% in EDHS 2016, respectively (**Figure 1**), indicating 50% or more reduction in moderate and severe forms of thinness within the 16 years of the data collection period.

Trends of thinness in adolescent girls' characteristics

The trend in thinness among late adolescent girls over the study period (2000–2016) varied in terms of different factors. For example, among rural residents, the overall change in thinness was 11.6%. The largest decrement was in the third phase (2011–2016) with an 8.1%point change, while the lowest was 3.4 in the second phase (2005–2011). Regarding marital status, adolescent girls who were not married showed a 7.8% point decrement in thinness in the period from 2011 to 2016 (**Table 2**).

Based on region, Benishangul-Gumuz showed the largest decrement of 32.2% change in thinness in the period 2000–2016 **Figure 2**.

Factors associated with a change in thinness

Decomposition analysis

Differences due to characteristics (endowments)

After controlling the role of changes due to coefficients, 16% of the decrement in thinness among late adolescent girls in Ethiopia in the last one and a half-decade was due to differences in characteristics (endowments). Among the compositional factors; age, religion, and types of toilet had a statistically significant contribution to the change in thinness. Thus, as compared to 15 years old, there was an increase in

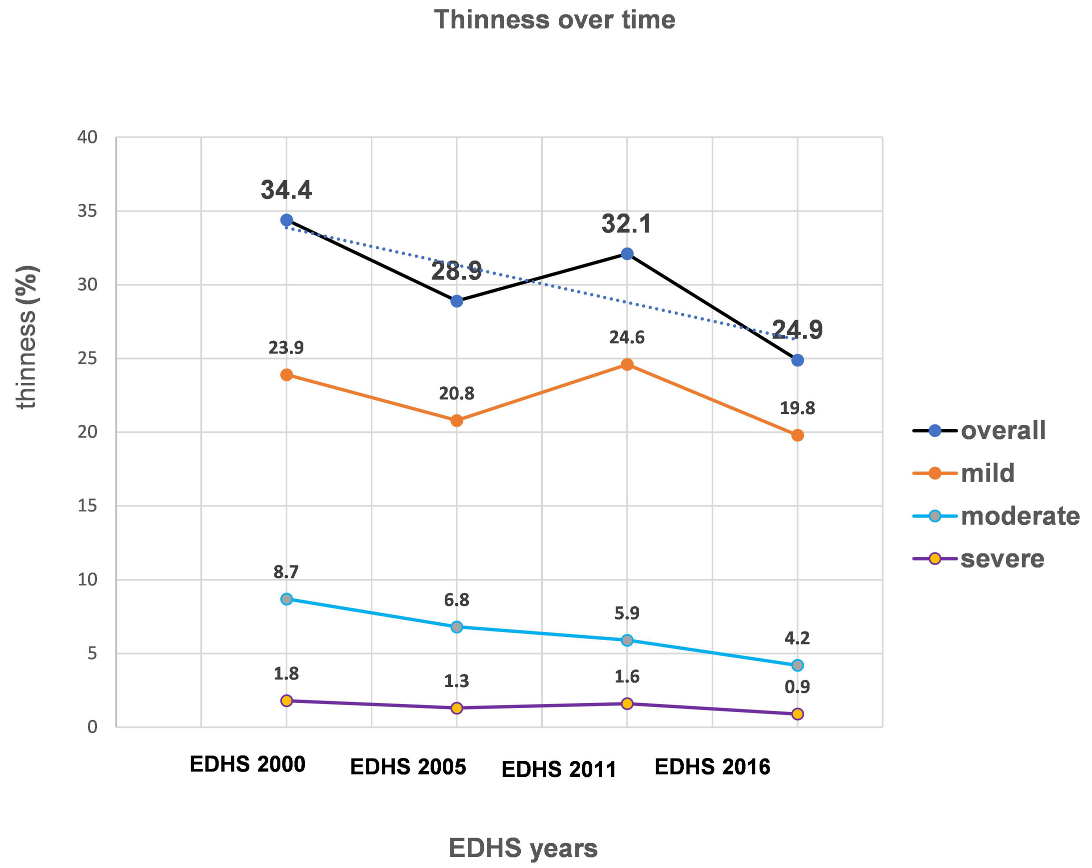

FIGURE 1
Trends of thinness among late adolescent girls in Ethiopia from EDHS 2000 to 2016.

the proportion of adolescent girls who were 17 and 18 years old in the study period positively attributed to the change in thinness. But the decrement in the composition of 19-years-old adolescent girls in the sample showed a significant impact on the overall change in thinness (Table 3).

Regarding religion, a result of an increase in the proportion of protestant followers from 14.8% in 2000 to 24.6% in 2016 had an important compositional contribution of 16% in the change in thinness. However, the proportion of adolescent girls from households that had improved toilets declined from 24.0% in 2000 to 16.5% in 2016. This change in the composition of the survey population resulted in a significant negative impact on the decrement of thinness (Table 3).

Difference due to the effect of coefficients

Controlling the role of changes in compositional characteristics, 84% of decrement in thinness among late adolescent girls in Ethiopia in the study period was attributed to change in the effect of the characteristics (coefficient). Residence and marital status were the most important factors that had a statistically significant contribution to the observed change in thinness (Table 3).

By keeping all the compositional change factors controlled, thinness significantly declined due to behavioral changes toward nutrition among rural residents during the study period. Furthermore, controlling all the compositional change factors, late adolescent girls who were not married had significantly contributed to the change in thinness as compared with those who were married as shown below (Table 3).

In the multivariate decomposition model fitted above, it should be noted that the intercept (0.13558) accounts for -144.83% of the overall decrement in thinness. This suggested that the model fit had some limitations in explaining the change in thinness between 2000 and 2016. Therefore, to reduce thinness, other factors could exist in nutrition programs and interventions targeting late adolescent girls.

Multilevel logistic regression analysis

Random effect and model comparison results

As shown in Table 4, the intra-class correlation coefficient (ICC) in the null model was 0.16, which means about 16% of the variations of thinness among late adolescent girls were

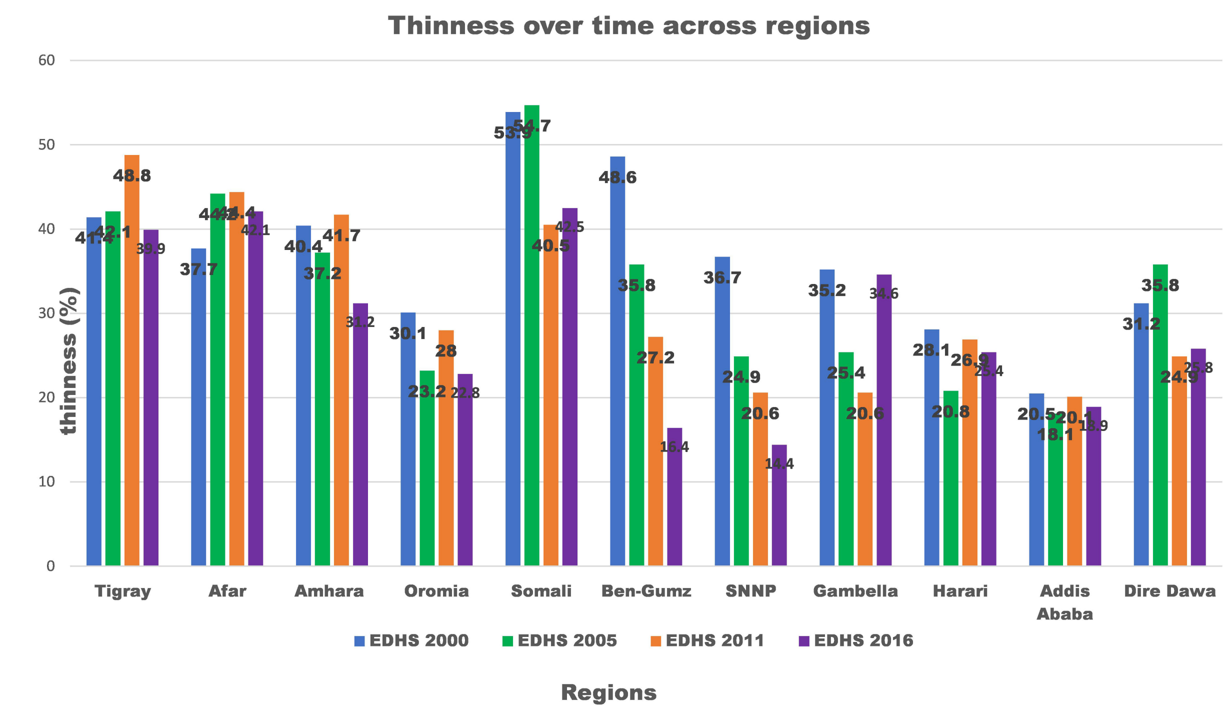

FIGURE 2
Trends of thinness among late adolescent girls over time across regions of Ethiopia from 2000 to 2016.

attributed to the difference at cluster level or community-level factors. This suggests the need for multilevel logistic regression rather than the standard flat model.

The median odds ratio (MOR) value of 2.12 (1.87, 2.46) in the null model also revealed that there was unexplained heterogeneity among clusters since MOR was 2.12 times more than the reference (MOR = 1). The unexplained community variation in thinness declined to MOR of 1.89 (1.68, 2.2) when the model was adjusted to both individual and community-level factors in the final model. This showed that after all factors were considered, the effect of clustering was still statistically significant in the full model.

After adjusting for individual and community-level factors in the full model, the proportional change in variance (PCV) revealed that about 26% of variations of thinness among late adolescent girls were attributed to both individual and community-level factors in the multilevel model.

Regarding model comparison/fitness statistics, we used deviance information criteria (DIC). Then, the model with the lowest deviance information criteria (DIC), that is the one that had the highest likelihood ratio value (**model IV**) was the best-fitted model (Table 4).

Fixed effect results; multilevel logistic regression analysis

In the bi-variable analysis, variables like the source of drinking water, educational status, history of chat chewing, anemia status, and community-level literacy had a *p*-value of > 0.2. So, they were omitted from further analysis.

From the final model (model IV) results, the age of the respondent, sex of head of the household, age of head of the household, types of toilets, wealth index, and region had a statistically significant association with thinness among late adolescent girls.

But all the remaining independent individual and community-level variables had no statistically significant association with the outcome variable at a *p*-value of 0.05.

Individual-level factors

As shown in Table 5, for a 1-year increase in ages of late adolescent girls, the odds of being thin decreased by 17% (AOR = 0.83; 95% CI: 0.77,0.90), given that all the other variables held constant. Late adolescent girls from female-headed households were 23% (AOR = 0.77; 95% CI: 0.61, 0.98) less likely to be thin as compared to male-headed households keeping all other variables constant.

The odds of being thin was 2.2 times (AOR = 0.45; 95% CI: 0.31, 0.65) higher for late adolescent girls from households that had unimproved toilets as compared to households that had improved toilet keeping other factors constant. Based on EDHS 2016 household wealth index classification, late adolescent girls from households with a middle wealth index had 45% higher odds of being thin as compared to late adolescent girls from the

TABLE 1 Percentage distribution of characteristics of adolescent girls in 2000, 2005, 2011, and 2016 Ethiopian demographic and health surveys.

Variables	Category	Weighted frequency (%)			
		EDHS 2000 (*N* = 3,456)	EDHS 2005 (*N* = 1,516)	EDHS 2011 (*N* = 3,724)	EDHS 2016 (*N* = 3,087)
Age	15	876 (25.4)	307 (20.2)	968 (26)	663 (21.5)
	16	763 (22.1)	318 (21)	778 (20.9)	668 (21.6)
	17	618 (17.9)	267 (17.6)	591 (15.8)	581 (18.8)
	18	733 (21.2)	403 (26.5)	874 (23.5)	790 (25.6)
	19	466 (13.4)	221 (14.7)	513 (13.8)	385 (12.5)
Residence	Urban	771 (22.3)	327 (21.6)	997 (26.8)	730 (23.6)
	Rural	2,685 (77.7)	1,189 (78.4)	2,727 (73.2)	2,357 (76.4)
Region	Tigray	217 (6.3)	112 (7.4)	286 (7.7)	252 (8.1)
	Afar	31 (0.9)	11 (0.7)	28 (0.7)	25 (0.8)
	Amhara	789 (22.8)	351 (23.2)	1,062 (28.5)	737 (23.9)
	Oromia	1,465 (42.3)	549 (36.2)	1,380 (37.0)	1,119 (36.2)
	Somali	38 (1.1)	34 (2.2)	57 (1.5)	86 (2.8)
	Ben-Gumz	38 (1.1)	12 (0.8)	36 (0.9)	29 (0.9)
	SNNP	652 (18.9)	341 (22.5)	637 (17.1)	601 (19.5)
	Gambela	7 (0.2)	3 (0.2)	16 (0.4)	8 (0.3)
	Harari	8 (0.2)	5 (0.3)	9 (0.3)	6 (0.2)
	Addis Ababa	193 (5.6)	90 (6.0)	196 (5.3)	206 (6.7)
	Dire dawa	17 (0.5)	7 (0.5)	14 (0.4)	17 (0.5)
Marital status	Not married	2,827 (81.8)	1,248 (82.3)	3,175 (85.3)	2,660 (86.2)
	Married	629 (18.2)	268 (17.7)	549 (14.7)	427 (13.8)
Religion	Orthodox	1,760 (51.0)	774 (51.0)	1,875 (51.2)	1,337 (43.3)
	Muslim	1,011 (29.2)	406 (27.0)	972 (26.6)	948 (30.7)
	Protestant	512 (14.8)	287 (18.9)	739 (20.2)	760 (24.6)
	Others*	173 (5.0)	48 (3.1)	72 (1.9)	42 (1.4)
Educational status	No education	2,072 (60)	596 (39.3)	604 (16.2)	415 (13.4)
	1^0	943 (27.2)	665 (43.9)	2,643 (71.0)	1,963 (63.6)
	2^0 and above	442 (12.8)	255 (16.8)	477 (12.8)	709 (23.0)
Wealth index	Poorest	–	230 (15.2)	613 (16.5)	423 (13.7)
	Poorer	–	265 (17.4)	645 (17.3)	501 (16.2)
	Middle	–	284 (18.7)	634 (17.0)	579 (18.8)
	Richer	–	271 (18.0)	831 (22.3)	670 (21.7)
	Richest	–	466 (30.7)	1,001 (26.9)	913 (29.6)
Occupation status	Not working	1,535 (44.4)	1,073 (70.8)	1,882 (50.5)	1,807 (58.5)
	Working	1,921 (55.6)	443 (29.2)	1,842 (49.5)	1,280 (41.5)
Family size	<6	1,914 (55.4)	859 (56.6)	2,137 (57.4)	1,878 (60.8)
	=6	1,542 (44.6)	658 (43.4)	1,587 (42.6)	1,209 (39.2)
HH head	Male	2,660 (77.0)	1,150 (75.9)	2,691 (73.3)	2,293 (74.3)
	Female	796 (23.0)	366 (24.1)	1,033 (27.7)	794 (25.7)
Age of HH head	<46	1,770 (51.2)	699 (46.1)	1,867 (50.1)	1,423 (46.1)
	=46	1,686 (48.8)	817 (53.9)	1,857 (49.9)	1,664 (53.9)
Toilet type	Unimproved	2,624 (76)	1,321 (87.1)	3,027 (81.3)	2,578 (83.5)
	Improved	832 (24)	195 (12.9)	697 (18.7)	509 (16.5)
Drinking water source	Unimproved	2,526 (73)	1,084 (71.5)	2,521 (67.7)	1,465 (47.5)
	Improved	930 (27)	432 (28.5)	1,203 (32.3)	1,622 (52.5)
Ever drink alcohol	No	–	–	2,193 (58.9)	2,111 (68.4)
	Yes	–	–	1,531 (41.1)	976 (31.6)

(Continued)

TABLE 1 Continued

Variables	Category	Weighted frequency (%)			
		EDHS 2000 (N = 3,456)	EDHS 2005 (N = 1,516)	EDHS 2011 (N = 3,724)	EDHS 2016 (N = 3,087)
Ever chew chat	No	–	–	3,528 (94.7)	2,865 (92.8)
	Yes	–	–	196 (5.3)	222 (7.2)
Media exposure	No	1,980 (57)	623 (41.1)	839 (22.5)	1,461 (47.3)
	Yes	1,476 (43)	893 (58.9)	2,885 (77.5)	1,626 (52.7)
Anemia status	Anemic	–	333 (21.9)	475 (12.9)	590 (19.5)
	Normal	–	1,183 (78.1)	3,183 (87.1)	2,438 (80.5)

*Catholic/traditional/other. HH, household.

rich wealth index (AOR = 1.45; 95% CI: 1.10,1.90) assuming all other variables keep constant.

Community-level factors

As shown in **Table 5**, the region showed a statistically significant association ($p < 0.05$) with thinness among late adolescent girls in Ethiopia from EDHS 2016. The odds of being thin were 2.14 (AOR = 2.14; 95% CI: 1.0, 4.10) times higher for late adolescent girls from the Somali region as compared to their counterparts from Addis Ababa, keeping other factors constant. Moreover, late adolescent girls who were from South Nations Nationalities and people of Ethiopia region had 65% (AOR = 0.35; 95% CI: 0.18, 0.68) fewer odds of being thin as compared to late adolescents from Addis Ababa, held other variables constant (**Table 5**).

Discussion

In this study, thinness among late adolescent girls has shown a significant decrement of 9.5% point change from 34.4% (32.8, 36.0) in 2000 to 24.9% (23.4, 26.5) in 2016. This could be attributed to the progress in the nutritional status of women of reproductive age and adolescent girls in the national nutrition program. Besides, the school health nutrition strategy and program in some parts of Ethiopia might be attributed to the observed change in thinness. Even though thinness in the study period showed a significant decrement, based on World Health Organization Nutrition Landscape Information System (NLIS) cut-off, it is still in the range of a high public health problem (24).

The multivariate decomposition analysis revealed that the contribution of behavioral (coefficients) changes was more important than that of the characteristic (endowments) changes in the decrement of thinness among late adolescent girls in Ethiopia in the last one and half-decade. Keeping the role of changes in compositional characteristics constant, about 84% of the decline in thinness among late adolescent girls in Ethiopia in the study period was attributed to a change in the effect of the characteristics (coefficient). Behavioral changes in nutrition among rural residents had a significant effect on the observed change in thinness. This finding is supported by evidence from a systematic- and meta-analysis in South and Southeast Asia (25), Dehradun district, India (26), Lay Gaynet district, Northwest Ethiopia (17), and Mizan district, Southwestern Ethiopia (27), where rural residents were undernourished than their counterparts and cultural and behavioral changes in feeding habits of rural society showed a positive effect in thinness reduction. Rural adolescents had poor access to safe water, and toilet facilities relatively lower educational attainment, and poor access and utilization of healthcare services than urban dwellers (28). Therefore, positive behavioral changes in rural adolescent girls might contribute to the decrement of thinness.

Another important factor that positively contributed to the decrement in thinness was marital status. Late adolescent girls who were not married significantly contributed to the decrement in thinness as compared with those who were married. The possible reason might be when adolescent girls get married before physical growth and developmental maturity, they will become pregnant with macro and micronutrient deficiencies or insufficiencies which in turn have negative nutritional and health status implications for them and their children (20).

After controlling the role of changes due to coefficients, 16% of the decrement in thinness among late adolescent girls in Ethiopia was due to differences in characteristics (endowments). Among the compositional factors; age, religion, and types of toilet had a statistically significant contribution to the change in thinness.

Regarding the age of adolescent girls, there was an increase in the proportion of adolescent girls who were 17 and 18 years old in the study period (**Table 1**) that positively attributed to the decrement in thinness. But the decrement in the composition of 19 years old adolescent girls in the sample showed a significant negative impact on the overall change in thinness. Similarly, the multilevel logistic regression analysis of this study indicated that the age of the adolescent girls had a statistically significant association with thinness. This finding is consistent with a study done among adolescent girls in Sub-Saharan Africa (29), a systematic review and meta-analysis done in

TABLE 2 Trends in thinness among late adolescent girls in Ethiopia by the selected characteristics of 2000, 2005, 2011, and 2016 Ethiopian demographic and health surveys in percent (%).

Variables	2000 *N* = 3,456	2005 *N* = 1,516	2011 *N* = 3,724	2016 *N* = 3,087	Point difference in thinness rate			
					2005–2000	2011–2005	2016–2011	2016–2000
Residence								
Urban	20.6	19.5	24.4	18.9	−1.1	4.9	−5.5	−1.7
Rural	38.4	31.5	34.9	26.8	−6.9	3.4	−8.1	−11.6
Marital status								
Not married	35.7	29.7	32.2	24.4	−6	2.5	−7.8	−11.3
Married	28.6	25.4	31.3	28.5	−3.2	5.9	−2.8	−0.1
Religion								
Orthodox	34.2	29.6	37.2	28.7	−4.6	7.6	−8.5	−5.5
Muslim	36.5	29.9	29.1	26.4	−6.6	−0.8	−2.7	−10.1
Protestant	29.3	26.2	23.8	17.0	−3.1	−2.4	−6.8	−12.3
Others*	39.3	24.4	20.3	15.7	−14.9	−4.1	−4.6	−23.6
Educational status								
No education	35.9	28.0	25.3	26.6	−7.9	−2.7	1.3	−9.3
1^0	36.7	31.6	35.2	25.8	−5.1	3.6	−9.4	−10.9
2^0 and above	22.4	24.0	23.2	21.6	1.6	−0.8	−1.6	−0.8
Wealth index								
Poorest	–	36.0	39.1	32.1	–	3.1	−7	–
Poorer	–	28.1	39.5	21.6	–	11.4	−17.9	–
Middle	–	36.6	30.9	32.7	–	−5.7	1.8	–
Richer	–	32.5	32.6	22.7	–	0.1	−9.9	–
Richest	–	19.1	23.3	20.1	–	4.2	−3.2	–
Occupation								
Not working	36.9	29.9	32.4	26.1	−7	2.5	−6.3	−10.8
Working	32.4	26.6	31.8	23.3	−5.8	5.2	−8.5	−9.1
Family size								
<6	32.9	26.6	29.5	23.8	−6.3	2.9	−5.7	−9.1
=6	36.2	32.0	35.6	26.7	−4.2	3.6	−8.9	−9.5
HHhead								
Male	35.7	29.1	33.8	26.3	−6.6	4.7	−7.5	−9.4
Female	30.2	28.1	27.7	21.0	−2.1	−0.4	−6.7	−9.2
Toilet type								
Unimproved	37.8	30.5	32.9	26.5	−7.3	2.4	−6.4	−11.3
Improved	23.7	18.4	28.5	17.2	−5.3	10.1	−11.3	−6.5
Water source								
Unimproved	37.4	32.6	37.3	26.1	−4.8	4.7	−11.2	−11.3
Improved	33.3	27.4	29.6	23.6	−5.9	2.2	−6	−9.7
Media exposure								
No	38.1	34.7	34.7	27.7	−3.4	0	−7	−10.4
Yes	29.5	24.8	31.3	22.5	−4.7	6.5	−8.8	−7
Anemia status								
Anemic	–	29.5	34.4	24.9	–	4.9	−9.5	–
Normal	–	28.7	31.8	25.1	–	3.1	−6.7	–
Overall	34.4	28.9	32.1	24.9	−5.5	3.2	−7.2	−9.5

*Catholic/traditional/other. HH, household.

TABLE 3 Detail decomposition of the change in thinness among late adolescent girls in Ethiopia, 2000–2016.

Variables	Differences due to characteristics (E)		Difference due to coefficients (C)	
	Coeff (95% CI)	Pct (%)	Coeff (95% CI)	Pct (%)
Age (years)				
15	1	1	1	1
16	0.00029 (−0.000044, 0.00006)	−0.33134	0.00415 (−0.01637, 0.02469)	−4.4428
17	−0.00087 (−0.00159, −0.00014)*	0.92801	0.00956 (−0.00883, 0.02796)	−10.223
18	−0.00492 (−0.0084, −0.00145)**	5.2616	0.00694 (−0.01353, 0.02742)	−7.4171
19	0.00121 (0.00023, 0.0022)*	−1.288	0.00964 (−0.00661, 0.02588)	−10.294
Residence				
Urban	1	1	1	1
Rural	−0.00029 (−0.00130, 0.00070)	0.31809	−0.09425 (−0.18726, −0.00125)*	100.68
Marital status				
Married	1	1	1	1
Not married	−0.00221 (−0.00557, 0.00115)	2.3633	−0.10228 (−0.18102, −0.02354)*	109.26
HH head				
Male	1	1	1	1
Female	−0.00117 (−0.00265, 0.00030)	1.2574	−0.00082 (−0.01917, 0.01753)	0.8769
Family size				
<6	1	1	1	1
=6	−0.00097 (−0.00362, 0.00168)	1.0374	0.00897 (−0.02201, 0.03996)	−9.5887
Religion				
Orthodox	1	1	1	1
Muslim	−0.00068 (−0.00152, 0.00016)	0.7292	−0.01584 (−0.03746, 0.00577)	16.924
Protestant	−0.01504 (−0.0221, −0.0079)***	16.075	−0.01303 (−0.02697, 0.00090)	13.922
Others$	0.00664 (−0.00709, 0.02037)	−7.0947	−0.01048 (−0.02787, 0.00690)	11.197
Toilet type				
Unimproved	1	1	1	1
Improved	0.00669 (0.00043, 0.01296) *	−7.1554	−0.01117 (−0.03584, 0.01349)	11.939
Media exposure				
No	1	1	1	1
Yes	−0.00369 (−0.01073, 0.00333)	3.9515	−0.00549 (−0.03322, 0.02222)	5.8747
Constants			0.13558 (−0.02601, 0.29718)	−144.83
Overall	−0.015092 (−0.02869, −0.0015)*	**16.121**	−0.07852 (−0.11172, −0.0453)***	**83.879**

$Catholic/traditional/other. *p < 0.05, **p < 0.01, ***p < 0.001. HH, household; 1, reference; CI, confidence interval. The bold values represent the overall values.

TABLE 4 Random effect and model fit statistics for thinness among late adolescent girls in Ethiopia by multilevel logistic regression analysis, EDHS 2016.

Parameters	Model I (Null)	Model II	Model III	Model IV
Coefficient variance	0.62	0.57	0.41	0.46
ICC (%)	16%	14.8%	11%	12%
MOR (CI)	2.12 (1.87, 2.46)	2.05 (1.78, 2.4)	1.84 (1.6, 2.1)	1.89 (1.68,2.2)
PCV (%)	Reff.	8%	34%	25.8%
Model fitness				
DIC (−2LL)	3,373	3,255	3,285	3,201
AIC	3,377	3,289	3,315	3,258
BIC	3,389	3,392	3,406	3,427

ICC, intra-class correlation coefficient; MOR, median odds ratio; PCV, proportional change in variance; DIC, deviance information criteria; AIC, Akaike's information criterion; BIC, Bayesian information criterion; Model I is the null model, a baseline model without any independent variable. Model II is adjusted for individual-level factors. Model III is adjusted for community-level factors. Model IV is the full model adjusted for both individual and community-level factors.

TABLE 5 Factors associated with thinness among late adolescent girls in Ethiopia by multilevel logistic regression analysis, EDHS 2016.

Variables	Model II AOR (95% CI)	Model III AOR (95% CI)	Model IV AOR (95% CI)
Individual-level factors			
Age of adolescents	0.84 (0.78, 0.90)***	–	0.83 (0.77, 0.90)***
Household head sex			
Male	1	–	1
Female	0.80 (0.63, 1.02)	–	0.77 (0.61, 0.98)*
Ever drink alcohol			
No	1	–	1
Yes	1.06 (0.79, 1.42)	–	0.95 (0.70, 1.28)
Occupation status			
Not working	1	–	1
Working	0.91 (0.69, 1.18)	–	0.87 (0.67, 1.15)
Family size			
Below 6	1	–	1
Six and above	1.19 (0.96, 1.46)	–	1.15 (0.93, 1.43)
Marital status			
Married	1	–	1
Not married	0.80 (0.59, 1.09)	–	0.82 (0.60, 1.11)
Religion			
Orthodox	1	–	1
Muslim	0.82 (0.59, 1.13)	–	0.87 (0.60, 1.28)
Protestant	0.43 (0.30, 0.62)***	–	0.71 (0.47, 1.06)
Others[#]	0.34 (0.11, 1.05)	–	055 (0.18, 1.71)
Media exposure			
No	1	–	1
Yes	0.84 (0.68, 1.03)	–	0.82 (0.65, 1.03)
Age of household head	0.97 (0.96, 0.99)**	–	0.96 (0.95, 1.07)
Toilet facility			
Unimproved	1	–	1
Improved	0.52 (0.38, 0.72)***	–	0.45 (0.31, 0.65)***
Wealth index			
Poor	0.97 (0.75, 1.26)	–	0.84 (0.62, 1.13)
Middle	1.46 (1.12, 1.89)**	–	1.45 (1.10,1.90) **
Rich	1	–	1
Community-level factors			
Residence	–		
Urban	–	1	1
Rural	–	1.76 (1.20, 2.57)**	1.18 (0.77, 1.80)
Region			
Addis Ababa	–	1	1
Tigray	–	2.08 (1.16, 3,72)*	1.61 (0.86, 2.98)
Afar	–	2.31 (0.86, 6.21)	1.83 (0.64, 519)
Amhara	–	1.39 (0.80, 2.41)	0.92 (0.51, 1.67)
Oromia	–	0.81 (0.47, 1.41)	0.60 (0.33, 1.08)
Somali	–	2.33 (1.14, 4.73)*	2.14 (1.0, 4.10) *
Benishangul-Gumz	–	0.53 (0.17, 1.68)	0.36 (0.11, 1.18)
SNNP	–	0.44 (0.25, 0.80)**	0.35 (0.18, 0.68) **
Gambelia	–	1.87 (0.39, 8.90)	1.36 (0.27, 6.85)
Harari	–	1.22 (0.17, 8.41)	0.92 (0.12, 6.70)
Dire Da'wa	–	1.36 (0.39, 4.68)	1.33 (0.37, 4.81)

(Continued)

TABLE 5 Continued

Variables	Model II AOR (95% CI)	Model III AOR (95% CI)	Model IV AOR (95% CI)
Community media exposure			
Low	–	1	1
High	–	0.99 (073, 1.33)	1.11 (0.80, 1.55)
Community poverty			
Low	–	1	1
High	–	1.02 (0.75, 1.35)	1.02 (0.73, 1.42)

#Catholic/traditional/other; *p < 0.05; **p < 0.01; ***p < 0.001 1 = reference; CI, confidence interval. Model I is an empty model. Model II is adjusted for individual-level factors. Model III is adjusted for community-level factors. Model Iv is the full model adjusted for both individual and community-level factors.

Ethiopia (15), Mirab Armachiho District, Northwest Ethiopia (30), and another study in Lay Gaynet district, Northwest Ethiopia (17), where thinness was more likely in early-stage and slightly decreases in late adolescence. This could be because as compared to older adolescence, young adolescence is a period of growth spurt by which a physiological demand for macro and micronutrient demand is high. Besides younger adolescents are prone to erratic feeding habits and time for the autonomy of food choice. But if they cannot get adequate food at this age, their body mass index tends to decrease and they will become thin (31).

As a result of an increase in the proportion of protestant followers among the survey population in the study period, being protestant had a positive compositional contribution to the decrement of thinness among late adolescent girls in Ethiopia. This might be partially explained by most of the protestant followers in Ethiopia being urban dwellers, and being urban is less likely to be thin (27, 28, 32). However, there is no evidence whether religion affects the nutritional status of individuals, it needs further investigation.

The proportion of adolescent girls from households that had improved toilets declined in the study period (2000–2016). This change in the composition of the survey population resulted in a significant negative impact on the decrement of thinness. Similarly, the multilevel logistic regression analysis showed that late adolescent girls who were from households with unimproved toilets had higher odds to be thin. This finding is consistent with a systematic- and meta-analysis conducted in Ethiopia (15). Hence, this can be explained by an individual who had improper latrine utilization will have a higher risk for contaminations, intestinal parasites, communicable diseases, and infections which causes poor nutritional status (18).

This study revealed that the wealth status of the respondents had a statistically significant association with thinness. This finding is supported by evidence from South and Southeast Asia (25), Ghana (33), and Southern Ethiopia (34). This might be because adolescent girls from households with middle and low wealth index had lower purchasing power which leads to the consumption of suboptimal quality and quantity of food (35). As a result, late adolescent girls from households with a middle wealth index were more likely to be thinner.

In this study, late adolescent girls from female-headed households were less likely to be thin as compared to male-headed households. This might be explained by increasing a mother's degree of autonomy at the household level which may impact the ability to make decisions in the best interest of the household members. When mothers have control over income, they tend to divert more toward health and nutrition-related expenditures than men. Therefore, empowering women and raising maternal autonomy is an important strategy for improving the nutritional status of children and adolescents to alleviate the global burden of malnutrition (36).

Residence by region showed a statistically significant association with thinness among late adolescent girls in Ethiopia from EDHS 2016. The odds of being thin were higher for late adolescent girls from the Somali region as compared to their counterparts from Addis Ababa. Moreover, late adolescent girls who were from Southern Nations Nationalities and people of the Ethiopian region had less odds of being thin as compared to late adolescents from Addis Ababa. This finding was consistent with a systematic review and meta-analysis study done in Ethiopia with a subgroup analysis by region which showed there was a high prevalence of thinness among adolescents in Eastern Ethiopia and lowest in Addis Ababa (15). This variety in adolescent thinness between regions could be due to recurrent drought, insufficient food production, household food insecurity differences, the difference in food culture, and genetic backgrounds, for example, Somali people as they are naturally taller and thinner with a minimal proportion of them are overweight and obese.

Strength and Limitation

As a strength, this study was conducted based on the nationally representative population-based study that gives a high statistical power to infer the characteristics of the study population. Additionally, this study used a multivariate decomposition analysis to identify influential factors that could help policymakers to design interventions for decreasing thinness among late adolescent girls in Ethiopia. However, this study has also limitations. For example, the EDHS IR dataset lacks many nutritionally important factors, such as dietary diversity score (DDS), household food insecurity status, meal frequency, feeding habits, and others that affect nutritional status and it is indicated in the decomposition analysis with a large percent contribution of the constant.

Conclusion

Thinness among late adolescent girls declined substantially, but it remains a high public health problem. The multivariate decomposition analysis revealed that more than 3/4th of the decrement in thinness among late adolescent girls in Ethiopia was attributed to the change in the effect of characteristics (coefficients) in the last one and half-decade. The place of residence and marital status were significantly associated with a change in thinness due to coefficients change. The compositional changes in the age of the adolescents, religion, and types of toilet facilities were also significantly associated with the change in thinness.

In this study, a multilevel logistic regression analysis identified a significant heterogeneity of thinness among clusters. From the fixed effect results, both individual and community-level factors had a significant association with thinness. Age of the adolescents, types of toilet facility, wealth index, and sex of head of the household were found significantly associated with thinness at an individual level, whereas being from Somali and Southern Nations Nationalities and people region had a statistically significant effect on the community level.

Therefore, we recommend to the government of Ethiopia, Ministry of Health, and Ministry of Education that nutrition programs and strategies targeting thinness reduction among late adolescent girls should base the identified factors like giving priority to rural and younger adolescents, enabling access and utilization of improved toilet facilities, improve the wealth status of households, empower women, and raise maternal autonomy through education. Regions identified with higher odds of thinness should be also prioritized for nutritional interventions. We recommend policymakers formulate and enforce laws and policies to prohibit the marriage of girls before 18 years of age. Furthermore, DHS lacks important nutritional variables like dietary diversity score (DDS), household food insecurity status, meal frequency, feeding habits, and others that affect the nutritional status of adolescents. So, we recommend the DHS program consider such variables for the next survey years. Besides, researchers need to further explore thinness from a religious perspective.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: www.measuredhs.com.

Author contributions

MZ, NM, and SN made the conceptualization, data curation, analysis, investigation, methodology, visualization, writing, review, and editing of the entire manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Kona Chowdhury,
Gonoshathaya Samaj Vittik Medical College, Bangladesh

*CORRESPONDENCE
Chalobol Chalermsri
Chalobol.chalermsri@kbh.uu.se

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Dietary diversity associated with risk of cardiovascular diseases among community-dwelling older people: A national health examination survey from Thailand

Chalobol Chalermsri[1,2]*, Shirin Ziaei[1], Eva-Charlotte Ekström[1], Weerasak Muangpaisan[2], Wichai Aekplakorn[3], Warapone Satheannopakao[4] and Syed Moshfiqur Rahman[1]

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden, [2]Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Department of Community Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [4]Department of Nutrition, Faculty of Public Health, Mahidol University, Bangkok, Thailand

Background: Cardiovascular diseases (CVD) are the common comorbidities in older people. Healthy diet is an essential strategy to alleviate the risk of developing CVD. Dietary diversity (DD) is an indicator of diet quality. Currently, limited research exists regarding DD and CVD in older people in developing countries, such as Thailand, despite rapid growth of older population. Therefore, this study aims to determine associations of DD with the risk of CVD and the cardiometabolic risk factors among Thai older people.

Methods: This cross-sectional study used the sub-sample of the fifth Thai National Health Examination Survey conducted from 2013 to 2015. A total of 6,956 older people aged 60 years and older and no pre-existing CVD were included.

Dietary diversity score (DDS) was assessed the consumption of eight food groups using food frequency questionnaires. Each food group was scored from 0 to 4. The DDS was calculated as the sum of the scores (0–32). The risk of CVD was calculated by using a Thai cardiovascular (CV) risk score. The cardiometabolic risk factors included hypertension, diabetes mellitus (DM), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels. Data were adjusted for a complex survey design and analysed using linear and logistic regression models.

Results: In the adjusted model, DDS had a significant negative association with log-Thai CV risk score, with adjusted β (95% CI) values of −0.01 (−0.01, −0.01). Regarding the cardiometabolic risk factors, DDS had a significant negative association with hypertension, DM and log-TG levels, with adjusted OR (95% CI) values of 0.97 (95% CI 0.97, 0.98) for hypertension, 0.94 (0.93, 0.95) for DM, and adjusted β (95% CI) values of −0.002 (−0.004, −0.001) for log-TG level. DDS was positively associated with TC and LDL-C, with adjusted β (95% CI) values of 0.59 (0.38, 0.80) for TC and 0.59 (0.38, 0.79) for LDL-C levels, while DDS was not associated with HDL-C level.

Conclusion: Higher DD was associated with a lower risk of CVD among Thai older people. The nutritional policies or interventions should encourage a diverse food intake for the prevention of CVD in this population.

KEYWORDS

dietary diversity, cardiovascular diseases, cardiometabolic risk factor, older people, Thailand

Introduction

Globally, the ageing population is continuing to increase. According to the World Health Organisation (WHO), the number of older people aged 60 years and above will increase significantly, from 12% in 2015 to 22% by 2050 (1). Due to biological degenerative processes and socioeconomic constraints, older people face greater risks of adverse health outcomes compared with younger populations (2). Cardiovascular diseases (CVD) accounted for the majority of comorbidities and are the leading cause of death in older people (3). Cardiometabolic risk factors, including hypertension, diabetes mellitus (DM) and dyslipidaemia, are influencing determinants for developing CVD (4). The degenerative changes due to the ageing process are one of the main causes of CVD too (5). In addition, inappropriate dietary intake, poor physical activity, smoking and excess alcohol consumption are common risk factors linked to these health conditions (6). Promoting a healthy lifestyle, such as healthy dietary practise and increased physical activity, is an essential strategy to control cardiometabolic risk factors and alleviate the risk of developing CVD (7, 8).

Dietary diversity (DD) is defined as the variety of food groups consumed over a reference period (9). DD is a convenient and affordable tool for assessing the variety of nutrient intake in larger population groups, particularly older people (10, 11). Although knowledge about DD and its adverse health outcomes is growing, there are still limitations. Previous studies have examined the relationship between DD and CVD; however, the results are still inconclusive (12). Although many previous studies have found the negative associations between DDS and the risk of CVD, diabetes mellitus (DM), and abnormal lipid profile (13–16), other studies could not show the significant associations (17). Furthermore, the majority of these studies have primarily focused on the middle-aged population rather than older people (12). Depending on the ageing process, the results in older people may differ from those in the middle-aged population. Additionally, the majority of past research on this topic have been conducted in high-income countries (HIC). Many socioeconomic factors have been found to be associated with DD and CVD, such as the equality of education and the health system, varying between HIC and lower- and middle-income countries (LMIC) (18). Therefore, this study focused on exploring the association between DD and CVD among older people in LMIC, adding to the body of knowledge on this topic.

Thailand is classified as an upper-middle-income country in the Southeast Asia region. By 2035, the older population in Thailand is estimated to reach 20 million, equal to more than one-third of the overall population (19). CVD, including coronary heart disease and cerebrovascular disease, are the leading causes of death in Thai older people (20). Identification of at-risk persons and promoting a healthy lifestyle, such as healthy eating, are essential strategies for primary prevention of CVD (21). To the best of our knowledge, there is no study determining the association between DD and the risk of CVD among Thai older people. Therefore, the primary objective of this study was to determine the association between DD and the risk of CVD in Thai older people. The secondary objective was to examine the association between DD and cardiometabolic risk factors, in terms of hypertension, DM and lipid profiles in Thai older people.

Materials and methods

Study design, setting and population

This study was a cross-sectional study of the fifth Thai National Health Examination Survey (NHES-V). NHES-V was a national survey conducted from 2013 to 2015 using a multistage, stratified sampling of the Thai population. The details of this survey have been previously described elsewhere (22). The inclusion criterion was age 60 years old or older. Older participants with pre-existing coronary artery disease or cerebrovascular disease, based on their history and physical examination, were excluded. A total of 7,365 older persons

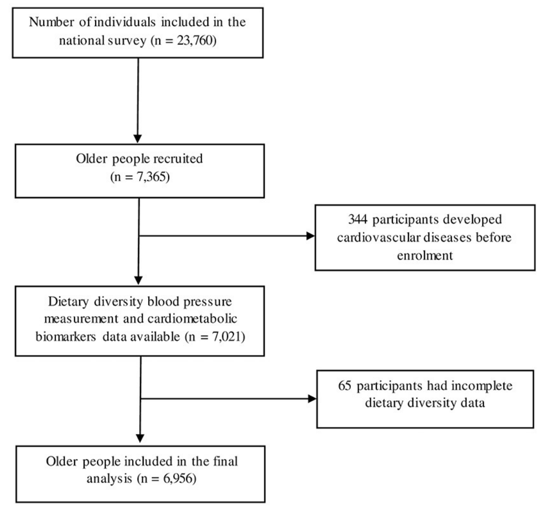

FIGURE 1
Flow diagram of study participants included in the analysis.

were recruited in this survey. Three hundred and forty-four older participants were excluded because of pre-existing CVD, such as symptomatic coronary heart disease and symptomatic cerebrovascular disease. Sixty-five older participants were excluded from the analysis because of incomplete dietary data. Thus, 6,956 older participants remained in the final analysis (Figure 1).

Data collection

Dietary diversity score

Individual-level DD was determined using a 34-item semi-quantitative food frequency questionnaire (FFQ) that represented participants' dietary intake during the 30 days prior to the survey. The FFQ was administered by trained interviewers. Food images were used to encourage participants' recall and response. If participants experienced physical or communication difficulties as a result of physical or cognitive impairment, data were collected *via* their caregivers. Dietary diversity score (DDS) was calculated by using an adapted combination of DDS established by the Food and Agriculture Organisation of the United Nations (FAO) (23) and the main food groups in the food-based dietary guideline (FBDG) in Thailand (24). Although the dietary guidelines recommended a small amount of fats and oils, it is still an essential food group, having health benefits such as helping the body to absorb fat-soluble vitamins (25). Therefore, we included fats and oils in the DDS for this study. The details of DDS development have been described elsewhere (1). In summary, the DDS included eight food groups, namely (1) grains; (2) pulse, beans, nuts and seeds; (3) dairy products; (4) meat, poultry or fish; (5) eggs; (6) vegetables; (7) fruits, and (8) fats and oils. Each food group was measured on a five-point scale, depending on the frequency of consumption: never eat or eat less than once per month (0 point), eat once to three times per month (1 point), eat once to three times per week (2 points), eat 4–6 times per week (3 points) and eat once or more per day (4 points). The DDS was calculated as the sum of the score obtained from each food group. DDS ranged from 0 to 32. The higher the DDS score, the more diverse the diet. DDS were calculated based on both the number of food group and the frequency of each food group consumption. The frequency of consumption is a proxy of diet quantity, and it will improve model fit due to the higher detail of information. The previous paper in Japan compared the performance of the different scoring systems of DDS in older people. It has showed that DDS which combined the frequency of each food group consumption, and the number of food groups has higher performance to diagnose malnutrition than the scoring system which used only the number of food group (26).

Risk of cardiovascular diseases and cardiometabolic risk factors

The risk of CVD was calculated by using the Thai CV risk score, which was constructed based on the population cohort in Thailand (27). The Thai CV risk score included sex, age, systolic blood pressure (SBP), the diagnosis of DM, current smoking status and total cholesterol (TC) level, while diastolic blood pressure (DBP), fasting plasma glucose (FPG), Low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) levels were not included in the score (28). This score was validated in the Thai population and used as the predictor of the percentage that would develop coronary artery disease, as well as fatal and non-fatal cerebrovascular disease in the next 10 years (27, 29). Thus, a higher score meant a higher risk of CVD.

Cardiometabolic risk factors, including hypertension, DM and lipid profiles, were collected through face-to-face interviews, blood pressure (BP) measurement and standard laboratory investigations. To get an accurate reading of the BP, participants were asked to rest in a sitting position for at least 5 min prior to the BP measurement. SBP and DBP were recorded using standard procedures by using an automatic BP monitoring device (Microlife model A100, Microlife AG, Switzerland). Each participant had three measurements of BP recorded at 1-min intervals. The first result was discarded, while the mean BP between the second and third results was used for the analysis. Hypertension was defined by the Eighth Joint National Committee (JNC 8) hypertension guidelines as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg (30), and/or self-reported use of antihypertensive medications within 2 weeks.

Venous blood samples were obtained from participants after overnight fasting for 12 h to measure the FPG and lipid profiles. Blood samples were frozen and transferred to a central laboratory at the Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. FPG was measured using a hexokinase enzymatic method. DM was defined by the WHO's definition as FPG ≥7.0 mmol/L (126 mg/dl) (31), and/or use of hypoglycaemic medication within 2 weeks. Serum TC and TG were analysed using enzymatic colorimetric methods. LDL-C was calculated based on the Friedewald formula for subjects with TG <4.5 mmol/L (400 mg/dl) (32) and was directly measured by the enzymatic method for those having TG ≥ 4.5 mmol/L (400 mg/dl). HDL-C was measured using homogeneous enzymatic colorimetric method. All lipid measurements were carried out using a Hitachi 917 biochemistry analyser (Roche Diagnostics, Switzerland).

Covariates

The following covariates were obtained during the interview: age, sex, education level, socioeconomic status (SES), place of residence, current smoking status, and current alcohol consumption. The educational level was categorised as no formal education, primary education, and secondary education and above. SES was quantified by using a wealth index, which has been described elsewhere (22). The wealth index was categorised into quintiles. The lowest quintile of the wealth index corresponded to the poorest group, and the highest corresponded to the richest group (22). The place of residence was divided into urban and rural areas. Current smoking status and current alcohol consumption were defined as smoke and alcohol consumption within 12 months before the survey date, respectively. The participant's body weight was measured in (kg) using a digital weighing scale (TANITA model HD316, Tanita Corporation, Japan). The height was measured in (cm.) using a standard metal tape. The body mass index (BMI, kg/m^2) was calculated using the participants' weight and height during the survey. BMI was categorised based on the Asia-Pacific cut-off values: BMI <18.5 kg/m^2 as underweight, 18.5–22.9 kg/m^2 as normal weight, 23.0–24.9 kg/m^2 as overweight, and ≥25.0 kg/m^2 as obese (33).

Data analyses

Statistical analyses were carried out using Stata17.0 (StataCorp LP, College Station, TX, USA). The analyses were adjusted for a complex survey design, which considered clustering and weighting of the data (34). This study was weighted based on the sampling probability against the 2014 registered Thai population. Descriptive statistics were presented as frequency and percentage (%) for categorical variables. The mean with standard deviation (SD) was presented for continuous variables with normal and abnormal distribution, while the median with range or interquartile range (IQR) was used for continuous variables with abnormal distribution. The association between DDS and continuous outcomes, including the Thai CV risk score and lipid profiles, was analysed using simple and multiple linear regression models and represented by beta co-efficients (β) and 95% CIs. The association between DDS and categorical outcomes, such as hypertension and DM, was evaluated using simple and multiple logistic regression models and represented by Odds ratio (OR) and 95% CI. The assumptions of linear regression were checked. The linearity was checked by using a scatter plot. The distribution of residuals was assessed visually using a histogram. The Thai CV risk score and TG level were $\log_{10}$-transformed to achieve an approximate normal distribution of residual for linear regression models. The homoscedasticity was also checked by using a scatter plot, and there was no heteroscedasticity. The potential confounders showing a P-value <0.2 in unadjusted models were entered in the adjusted model. Collinearity between categorical independent variables was checked with the chi-square test. When there was a substantial dependence between the two categorical variables, Goodman–gamma Kruskal's (G-K gamma) was used to determine the strength of the association. Sex was strongly associated with current smoking status and current alcohol consumption (P-value <0.05, G-K gamma −0.87 for smoking and −0.87 for alcohol consumption). Thus, these variables were not included in the final model. The generalised variance inflation factor (GVIF) with the R programme statistical software (35, 36) was also used to evaluate collinearity. The GVIF did not exceed 1.09 for any potential confounders. Therefore, there was no evidence of collinearity. The results were considered statistically significant at a level of P-value <0.05. Missing data accounted for 17.8% of the wealth index, while other variables such as education level accounted for <0.4% of the data. Participants with a missing wealth index were more likely to live in the urban area, abstain from alcohol consumption, have hypertension, as well as have a higher BMI and higher TC level (P-value <0.05). Therefore, a separate wealth index category of participants with missing wealth index data was included in all primary analyses. This method retained participants in the analysis and included their other features in the results (37). The sensitivity analyses were performed to test the robustness of the results by excluding fats and oils from the DDS.

Results

Median age of the participants was 68.0 years (range 60.0–99.0). The median DDS was 6.0 (IQR 2.0), and the median 10-year Thai CV risk score was 21.9% (IQR 24.5). Around 55% of the participants were female. More than 90% of the participants had primary education or higher. The proportion of people with hypertension was 38.6%. Almost 12% of the older participants had DM. In the aspect of BMI, ∼10% of the participants were underweight (BMI <18.5 kg/m^2), and 54.1% of the participants were overweight and obese (BMI 23.0 kg/m^2 and higher). The other characteristics of the participants are presented in Table 1.

The percentage of the frequency of the consumption of each food groups in DDS is presented in the Supplementary Table 1. Almost 95% of participants consumed grains once or more per day, while <2% of them consumed fats and oils once or more per day.

The association between DDS and Thai CV risk score

The simple and multiple linear regression analyses showed the inverse association between DDS and Thai CV risk score among older participants. After adjusting for the education level and the wealth index, DDS had a significant positive association with log-Thai CV risk score with adjusted β (95% CI) −0.01 (−0.01, −0.01) (Table 2).

The association between DDS and the prevalence of hypertension and DM

Table 3 demonstrates the simple and multiple logistic regression analyses for the association between each score of DDS and the diagnosis of hypertension and DM. DDS had a significant negative association with both hypertension and DM. In the adjusted models, the increase in each score of DDS was associated with a 3% lower risk of hypertension, with adjusted

TABLE 1 Characteristics of the study populations.

Characteristics	Unweighted frequency	Weighted frequency	Weighted % or mean ± SD or median (IQR)
Age (years, mean ± SD)	6,956	6,953	69.6 ± 7.6
Sex; %			
Male	3,010	3,010	44.5
Female	3,946	3,943	55.5
Education level; %			
No formal education	655	654	9.4
Primary education	5,247	5,245	79.2
Secondary education and above	1,029	1,135	11.3
Wealth index quintile; %			
Quintile 1 (poorest)	1,381	1,381	29.3
Quintile 2	879	879	17.4
Quintile 3	1,015	1,014	18.1
Quintile 4	1,137	1,136	18.7
Quintile 5 (richest)	1,306	1,306	16.5
Place of residence; %			
Urban	3,337	3,337	40.6
Current smoking; %			
Yes	1,028	1,028	15.8
Current alcohol consumption; %			
Yes	1,417	1,417	21.0
BMI (kg/m^2,mean ± SD)	6,861	6,858	23.7 ± 4.2
Hypertension; %			
Yes	2,774	2,774	38.6
Diabetes mellitus; %			
Yes	882	881	11.9
TC (mg/dl, mean ± SD)	6,721	6,720	200.8 ± 47.5
LDL-C (mg/dl, mean ± SD)	6,724	6,723	129.4 ± 40.1
HDL-C (mg/dl, mean ± SD)	6,715	6,714	47.6 ± 14.1
TG [(mg/dl, median (IQR)]	6,725	6,724	149.8 (85.1)

95% CI, 95% confidence interval; SD, standard deviation; IQR, interquartile range; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

TABLE 2 Linear regression analyses for the association between each score of DDS and log-Thai CV risk score among older participants ($n = 6,662$).

	Thai CV risk score[a]					
	Crude model			Adjusted model[b]		
	β	95% CI	*P*-value	β	95% CI	*P*-value
DDS	−0.01	−0.01, −0.01	<0.001	−0.01	−0.01, −0.01	<0.001

[a]Log-transformed.
[b]Adjusted for educational level and wealth index. The sample size was 6,639 due to the missing data.
DDS, dietary diversity score; Thai CV risk score, Thai cardiovascular risk score; β (95% CI), beta co-efficients and 95% confidence interval.

TABLE 3 Logistic regression analyses for the association between each score of DDS and cardiometabolic risk factors among older participants.

	Crude model				Adjusted model			
	Sample size	OR	95% CI	*P*-value	Sample size	OR	95% CI	*P*-value
Hypertension	6,826				6,801			
No			Reference				Reference	
Yes		0.98	9,97, 0.98	<0.001		0.97[a]	0.97, 0.98	<0.001
Diabetes mellitus								
No			Reference				Reference	
Yes		0.95	0.95, 0.96	<0.001		0.94[b]	0.93, 0.95	<0.001

[a]Adjusted for sex, age, educational level, wealth index, and place of residence.
[b]Adjusted for sex, age, wealth index, and place of residence.
DDS, dietary diversity score; OR (95% CI), odds ratio and 95% confidence interval.

TABLE 4 Linear regression analyses for the association between DDS and lipid profiles among older participants.

Lipid profiles	Crude model				Adjusted model			
	Sample size	β	95% CI	*P*-value	Sample size	β	95% CI	*P*-value
TC	6,720	0.66	0.45, 0.87	<0.001	6,697	0.59[a]	0.38, 0.80	<0.001
LDL-C	6,723	0.62	0.42, 0.82	<0.001	6,700	0.59[a]	0.38, 0.79	<0.001
HDL-C	6,714	0.05	−0.02, 0.11	0.130	6,691	0.00[b]	−0.06, 0.06	0.985
TG[c]	6,724	−0.002	−0.004, −0.001	<0.001	6,701	−0.002[a]	−0.004, −0.001	0.008

[a]Adjusted for age, sex, educational level, wealth index, and place of residence.
[b]Adjusted for sex, educational level, wealth index, and place of residence.
[c]Log-transformed.
DDS, dietary diversity score; β (95% CI), beta co-efficients and 95% confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

OR 0.97 (95% CI 0.97, 0.98). In addition, the increase in each score of DDS was associated with a 6% lower risk of DM, with adjusted OR 0.94 (95% CI 0.93, 0.95).

The association between DDS and lipid profiles

Table 4 shows the simple and multiple linear regression analyses for the association between DDS and lipid profiles. In the adjusted model, DDS had a significant positive association with TC, and LDL-C levels with adjusted β 0.59 (95% CI: 0.38, 0.80) for TC, adjusted β 0.59 (95% CI 0.38, 0.79) for LDL-C level. On the other hand, in the adjusted model, DDS had a significant negative association with log-TG, with adjusted β −0.002 (95% CI −0.001, −0.004). However, there was no association between DDS and HDL level in both univariate and multivariate models.

The robustness of the results was examined by excluding fats and oils from the DDS in sensitivity analyses. The sensitivity analyses showed similar results compared to the primary analyses.

Discussion

This population-based study among Thai older people indicated that DDS had a negative association with the 10-year risk of CVD. Regarding the cardiometabolic risk factors, DDS also had a negative association with the prevalence of hypertension, DM and TG levels, whereas a positive association was indicated with TC and LDL-C levels.

In this study, DDS was found to be a protective factor against developing CVD among older people. This finding was consistent with a previous study conducted among Italian older people. It shows that the increased DDS operates as a protective factor against coronary heart disease (13). Furthermore, another case-control study in Korean older patients confirms that the average DDS in cerebrovascular disease patients was significantly lower than in the control group (38). However, the result remained inconsistent. A cohort study in the US examined the association between three DDS measurement scores and the risk of ischemic heart disease. There was no association between DDS and ischemic heart disease when using the scores, which simply counted the number of food groups people consumed (39). However, the outcomes of this study included fatal myocardial infarction and non-fatal coronary disease, for which the information was self-reported from the participants themselves or their next of kin, and the vital registration. The accuracy of self-reported information might be less for diagnosis of myocardial infraction (40). Moreover, the difference in the participants' characteristics, lifestyle and dietary pattern might have affected the finding.

Because several risks factors contribute to the development of CVD, the multifactorial CV risk score provided a more comprehensive assessment of CVD than single risk factors (41). In this study, DDS had a negative association with the risk of CVD, hypertension, DM and TG level, whereas it had a positive association with TC and LDL-C levels. It demonstrated that the effect of DDS in decreasing the CVD risk through the pathway of hypertension, DM and TG level outweighed the increased CVD risk due to LDL-C.

Besides the risk of cardiovascular diseases, DDS also had a negative association with the diagnosis of hypertension. In line with our finding, there are previous studies in different settings that examine the negative relationship between DD and hypertension (42, 43). However, this association is inconsistent too. A recent study in Iran could not find such an association (44). However, there are several differences in terms of baseline characteristics and the measurement tool between the study in Iran and the current study. In the cited study, around 10% of the participants having a history of ischemic heart disease still remained in the analyses. Moreover, the prevalence of smoking and BMI in the cited study is higher than in the current study. With regard to DDS, the DDS in the cited study consists of five food groups including bread-grains, vegetables, fruits, dairy, and meat, whereas beans, eggs, and fats and oils were added as main food groups of DDS in our study. The different food groups might affect the results. Consumption of beans and eggs is negatively associated with blood pressure and the prevalence of hypertension (45, 46). Therefore, the characteristics and the component of DDS might modify the results.

Additionally, DDS demonstrated a negative association with the diagnosis of DM. These findings agreed with the findings of prior studies (15, 47). After a 10-year follow-up period, a previous population-based cohort study in the UK discovered that having a high DDS was related to a decreased chance of getting type 2 DM (15). Another prospective cohort study showed the interaction between DDS and cognitive function towards the prevalence of DM among older people in Taiwan. Older people with low DDS and cognitive impairment have a higher risk of being diagnosed with DM than those with high DDS and normal cognition (47). Evidence has shown that having a wide variety of foods has a positive effect on the diagnosis of DM (15).

In this study, DDS also had a negative association with the TG level. This association is consistent with the findings of previous studies in different settings (16, 48, 49). A study among older people residing in a rehabilitation centre found a negative association between DDS and TG levels (48). This association is also observed in people with at risk of diabetes or pre-diabetes (16, 49). However, the prior study conducted among Han and Tibetan older highlanders in China reveals a different conclusion. DDS shows a positive association with TG levels in Tibetan older people but not in Han older people (50). However, Tibetan highlanders have a unique dietary pattern that is distinguishable from mainland dwellers due to tradition and environment. Tibetan highlanders eat high amounts of meat and soybean, while they eat low amounts of fish and other aquatic products, fruits and vegetables (51). As a result, the finding might have been influenced by this dietary pattern.

This study found a positive association between the DDS with TC and LDL-C levels. Previous studies examined the association between DDS and these lipid profiles, showing the inconsistent findings. A previous study conducted among Japanese older people showed that older people with greater DDS have a higher prevalence of self-reported hyperlipidaemia (10), whereas another study conducted among frail older people in the US found no significant associations between DDS and TC or LDL-C levels (48). It is difficult to explain this finding. However, a noticeable characteristic of DDS in the US study was that whole foods were counted into the food variety score, not divided into separate food groups. Mixed dishes containing multiple main ingredients may contribute to the different results when compared with this current study. Additionally, the difference in food groups for the DDS and covariates, adjusted in the model, might affect the results. In the current study, fats and oils were included in DDS regardless of the type of fat. Moreover, the association between DDS and TC and LDL-C might be affected by fats and oils.

In this study, no association was examined between DDS and HDL-C level. Consistent with our findings, the previous studies in older Chinese people failed to discover the association between DDS and HDL-C level. In terms of the association between DDS and HDL-C level (50), it shows that there are several factors that affect this association, such as physical activities.

Several hypotheses may explain these findings. The first hypothesis involves biological processes. DDS has a relationship with gut microbiota. Although the gut microbiota may change as a result of ageing or chronic disease, the dietary component remains a critical determinant of the gut microbiota (52). High variety of food consumption has been found to be associated with a more diverse and healthier gut microbiota pattern (53). A recent review states the interaction between gut microbiota and coronary artery diseases (54). Additionally, the gut microbiota has been identified as a critical factor in the development of DM by affecting glucose metabolism, insulin resistance in multiple organs and inflammatory process (55). Thus, the diversity of food consumption might foster a healthy pattern of gut microbiota and reduce the chances of acquiring DM. The second hypothesis could be explained by the health consciousness behaviour. Older people have higher level of health consciousness behaviours, such as having a healthy lifestyle and attending health examination, compared with younger people (56). The previous qualitative study in Thai older people has shown that older people and their caregivers recognised the importance of food towards older people's health, and older people tend to follow the healthcare professional's recommendations. Thus, older people might adapt their lifestyle towards the healthier lifestyle than the younger population (57).

In Thailand, the concern about older people has been included in the twelfth nation economic and social development plan of Thailand. Currently, there are several policies aimed to enhance older people's health and wellbeing such as the national plan for older person (58). These policies focus on health promotion and diseases prevention among older people. In addition, the life-long education is encouraged in this population. Eating the variety of food is a component in Thai healthy eating index which is a tool to evaluate dietary quality and monitor the change of eating practise. Moreover, this index can be used as the tool for the nutritional educational program and health promotion program in the combination with the food based dietary guideline (24, 59).

Strengths and limitations

Strengths of this study included the use of data from a large cohort sample size of the older Thai population. Currently, knowledge about DD and CVD among older people in LMIC is still limited; therefore, the results from this study population of Thai older people can add additional comprehensive knowledge and help to reduce this gap. Moreover, this study used Thai CV risk score, which was the validated tool for estimating risk of CVD in Thailand. Ethnicity is a significant determinant of CVD. The screening tool for CVD in western and Asian countries should be established separately (60). Thus, the Thai CV risk score used in this study was a suitable tool for assessing the risk of CVD in the older Thai population. Additionally, this study had a high degree of data reliability since the dietary diversity data were collected on a personal level from the individuals themselves or their caregivers. To assist participants if they suffered memory loss in relation to their dietary intake, interviewers used photographs of food. Furthermore, older people were interviewed regarding their food consumption habits, which may reflect an individual's exact food intake rather than a snapshot in time. Finally, the analyses included a distinct category of participants with missing wealth index data. This method retained a greater number of participants in multivariate models than the complete case analysis.

However, it should be noted that the current study had limitations. Due to the cross-sectional nature of this investigation, temporal causation could not be established. In addition, the DDS was calculated using a semi-quantitative FFQ. As a result, it may not accurately display the amount of each food item consumed or food group. Moreover, DDS aimed to assess the variety of food group consumption. Thus, fats and oils were included in the DDS. It might not totally differentiate between healthy and unhealthy diet as well. Similar to other CV risk scores, Thai CV risk score did not validate for the extremely old age (61). Older participants might have a high Thai CV risk score due to their age alone. Moreover, the CV risk score accounted for only main CVD risk factors and not all risk factors. Another limitation was that many participants had missing data, especially on SES, and the missing pattern was not random. This might affect the results; however, we included a separate wealth index category of participants with missing wealth index data in order to retain these participants in the analyses. Finally, although we endeavoured to account for the potential confounders, a number of residual confounders, such as physical activities, the health system and the effect of caregivers, still persisted.

Recommendations

This study examined the negative association between DDS and the risk of CVD and the cardiometabolic risk factor among older Thai people. CVD is accounted as the most common NCD among older population. To prevent NCD among older people, the variety of food should be encouraged through the nutritional educational program (59). Furthermore, DD can be used as the tool for evaluating the lifestyle intervention strategies among older people with CVD or cardiometabolic risk factors.

Conclusions

This study demonstrated a negative association between DDS and risk factors of CVD. Thus, in this setting of older

Thai people, increases in dietary diversity may have a favourable effect on their risk of developing metabolic syndrome. Thus, this highlights the importance of nutritional interventions and strategies that promote healthy eating habits, characterised by a diversified diet in order to prevent CVD in this population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee for Research in Human Subjects, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand (COA Si 076- 2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CC, SZ, E-CE, SMR, WA, WS, and WM: conceptualisation and methodology and reviewing the paper. WA and WS: the data collection. CC and SMR: analysis of the data, drafting, and editing of the paper. All authors read, reviewed, and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1002066/full#supplementary-material

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Association between socioeconomic positions and overweight/obesity in rural Nepal

Sanju Bhattarai[1,2]*, Rikke Nerhus Larsen[2], Archana Shrestha[2,3,4], Biraj Karmacharya[2,3] and Abhijit Sen[1,5]*

[1]Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway, [2]Institute of Implementation Science and Health, Kathmandu, Nepal, [3]Department of Public Health, Kathmandu University School of Medical Sciences, Dhulikhel, Nepal, [4]Department of Chronic Disease Epidemiology, Center of Methods for Implementation and Prevention Science, Yale School of Public Health, New Haven, CT, United States, [5]Oral Health Services and Research Center, TkMidt, Trondheim, Norway

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Medical College for Women and Hospital, Bangladesh

*CORRESPONDENCE
Sanju Bhattarai
sanju.bhattarai@ntnu.no;
sanjuwagle@gmail.com
Abhijit Sen
abhijit.sen@ntnu.no

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Introduction: Obesity and its association with socioeconomic factors are well-established. However, the gradient of this relationship among rural populations in low- and middle-income countries such as Nepal is not fully understood. We sought to assess the association of socioeconomic factors (education, income, and employment status) with overweight/obesity.

Methods: This cross-sectional study analyzed data from 260 participants aged ≥18 years and attending a rural health center in Dolakha, Nepal. Self-reported data on demographic, socioeconomic, and lifestyle factors was collected, and weight and height were measured for all the study participants. Those with a body mass index of <25 kg/m2 were regarded as non-overweight/obese and those with ≥25 kg/m2 were regarded as overweight/obese. Poisson regression models were used to estimate prevalence ratios and corresponding 95% confidence intervals to assess the association between socioeconomic factors and overweight/obesity. In addition, we assessed the effect of modification by age and gender to study the effect of socioeconomic factors on overweight/obesity.

Results: The age-standardized prevalence of overweight/obesity was higher for individuals with higher education (23%) and high-income (32%) and those who were unemployed (42%). Compared to the low-income and no formal education groups, the prevalence ratio of overweight/ obesity was 1.69 and 2.27 times more for those belonging to the high-income and high school and above groups, respectively. No evidence of effect modification by gender and age was observed.

Conclusions: Socioeconomic factors, education, and income were positively associated with overweight/obesity prevalence in rural Nepal. Further large studies using longitudinal settings are necessary to replicate our findings.

KEYWORDS
obesity, epidemiology - descriptive, rural, Nepal, socioeconomic

Introduction

Obesity, a common risk factor for major non-communicable diseases (NCDs) has tripled in the last 4 decades (1–3). In 2016, more than 1.9 billion adults were overweight worldwide (4), and the number is still increasing. In Nepal, the prevalence of overweight and obesity (OWOB) also increased from 21% in 2013 to 29% in 2019 (5, 6). Therefore, understanding the burden of OWOB is important to develop effective strategies to halt obesity-associated several adverse health outcomes.

In low-income countries like Nepal, socioeconomic development drives food choices and diet pattern (7), and as a country progresses, obesity burden shifts from high to low income groups (8–10). Gradual economic prosperity has triggered nutrition transition shifting dietary patterns from home-produced food to easily available processed food contributing to the burden of OBOW and NCDs in Nepal (11).

Understanding the role of socioeconomic status (SES) in explaining food behavior that determines an individual's body weight is important (7). Individuals with low SES status is associated with increased risk of obesity in high-income nations (12, 13) while in LMICs (14, 15) results are mixed. For instance, findings from cross-sectional studies suggested that educated and affluent Nepalese (16), South Asian women (17), and Indians (18) were more likely to be overweight or obese. Likewise, being employed was positively associated with OWOB in Nepal (19), Mexico (20), and South India (21). On the other hand, obesity was reported to be inversely associated with education level and income in Argentina (22) and Iran (23). Furthermore, a national survey conducted in Nepal suggested that the prevalence of OWOB was more among affluent individuals living in urban hills (5), while a survey conducted among 341 Nepalese bureaucrats reported 33.4% of the participants to be either overweight or obese (24). The possible reason of higher OWOB prevalence in urban Nepal could be high consumption of energy-dense and cheap fatty foods as well as being physically less active (25, 26), whereas the lower prevalence of obesity seen among rural individuals might be due to engagement in physically demanding jobs (27).

Nepal has experienced considerable economic growth in recent years, and in 2015, the average income was $2,500 GDP per capita (gross domestic product per capita) (28). The impact of economic growth on obesity in different SES groups remains unclear. Compared to the rural women of Sherpa ethnicity, urban women had higher body mass index (BMI) (29), and this difference is the result of increase in income and less energy expenditure in the urban population (26). Therefore, a study to assess the association between SES and OWOB in rural Nepal, where 80% of the Nepalese population reside, is necessary. We recently published an article reporting a positive association between SES and hypertension (30). In this study, we used data from the same study (30) on individuals visiting a primary health center in rural Nepal to assess the association between SES and two other highly prevalent comorbid conditions, i.e., overweight and obesity.

Methods

The detail of the study design and the methodology used for this study are published elsewhere (30).

Study setting

The study was conducted in Kirnetar health center in Dolakha district in Nepal, providing primary health services to eight rural villages in its proximity. It was an opportunistic screening. The health center, established in 2012, provides primary-level health services 6 days a week including 24-h emergency services.

Study design and population

A cross-sectional study was conducted among 260 individuals who visited the health center for clinical examination or to purchase medicine from October to December 2016. Participants over 18 years were included in the study, but those who were pregnant were excluded.

Data collection

All the recruited participants were interviewed by trained enumerators. Self-reported data on demographic and socioeconomic factors, clinical history, lifestyle, and dietary factors were collected using a validated STEPS questionnaire (5). The participants were asked to stand (without footwear, jackets, and sweaters) on an instrument placed on a flat floor to measure weight (in kg) using BOSCH Electronic Scale PPWA4201. Similarly, the participants were asked to stand tall with heels and head against the measuring tape placed on the wall (without footwear, cap and hat) and the lineal measurement on the top point of the head was measured to the nearest 0.05 cm (5).

Outcome

BMI was computed by dividing the weight (in kg) by the squared value of height (in m) and categorized as underweight or normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/m^2) according to WHO recommendation. For analyses, we collapsed BMI categories into two groups, i.e., non-obese (BMI <25 kg/m^2) and overweight and obese (BMI ≥25 kg/m^2).

Exposures

Income

Per capita annual income was calculated by asking the total combined household income (in Nepalese rupee) in the year preceding the survey and dividing it by the total number of household members. Annual income was categorized into tertiles (low: 0–6,000, middle: 6,250–32,571, and high: 33,333–625,000 Nepalese Rupees).

Education

Participants who reported that they did not attend school were confined to the "*no formal education*" group; those who had at least 1 year of formal school including those who did not complete high school were confined to the "*less than high school*" group, and those who had completed high school or beyond were confined to the "*high school and above*" group.

Employment status: this variable was classified into three groups: farming (agricultural task), employed (government/non-government employees, self-employed people), or unemployed (retired, students, unpaid, unable to work, unemployed, homemakers).

Covariates

Sociodemographic variables include age (in years), gender (males, females), marital status (yes, no), and ethnicity (Dalit, Brahmin, Chettri, others). Lifestyle-related variables include both smoke or smokeless tobacco use (never-users, current, former users); alcohol intake (drinking <1 glass per week, 1–3 glasses/week, >3 standard drinks/week were categorized as "low drinkers," "moderate drinkers," or "heavy drinkers," respectively). Physical activity was assessed using Global Physical Activity Questionnaire (31) (≥ 600 metabolic equivalent minutes (MET) and < 600 MET were categorized as adequate and inadequate, respectively), as well as fruits and vegetables servings (<2, 2–4, and >4 servings per day).

Statistical analysis

The descriptive data were presented as frequencies and percentages for categorical variables and mean and SD for continuous variables. To assess the association between socioeconomic positions and prevalence of OWOB, we used modified Poisson regression models with robust standard errors (32) to estimate prevalence ratio (PR) with corresponding 95% CI. We fitted the Poisson regression models to estimate PR because odds ratio provides an overestimated approximation of the risk when the prevalence of outcome of interest is common (≥10%) (33). Two models were constructed. Model 1 was unadjusted, and model 2 was adjusted for age (in years), gender (male, female), marital status (married, unmarried), and ethnicity (Brahmin, Chettri, Dalits, Other). The analyses of the association between SES and OWOB was stratified by gender (male vs. female) and age (<50 vs. ≥50 years). The statistical interaction was assessed by likelihood ratio test incorporating product terms of (1) categories of SES × age and (2) categories of SES × gender in the model. All the statistical analyses were performed using Stata/IC 14 (Stata Corp, College Station, TX, United States).

Results

The sociodemographic and lifestyle characteristics of the 260 participants are presented in Table 1. The mean age of the study population was 45 years, 48.5% were women and 24.5% were OWOB. The prevalence of OWOB were higher among males, Dalit ethnicity, married, high level of education, high income and employed. Furthermore, the prevalence of OWOB were higher among those who consumed <2 servings of fruits and vegetables per day and those who were non-tobacco users, moderate drinkers, and less physically active.

The distribution of sociodemographic and lifestyle factors in relation to education and income are presented in Table 2. Sex and age group were significantly different across different levels of education and income categories. Alcohol consumption and tobacco use were significantly different across education categories.

In Table 3, the age-standardized prevalence of OWOB was higher among the high-income group, those who attained high school or had higher education, and the unemployed group. In the adjusted model, we observed that the prevalence of OWOB was 1.69 and 2.27 times greater in the high-income group and those with education of high school and above, respectively, compared to individuals in the low-income group and those with no formal education. Although the prevalence ratio was >1, there was uncertainty of the point estimates due to wide confidence interval. Furthermore, compared to the unemployed individuals, the farmers had significantly lower prevalence of OWOB (PR 0.5 and 95% CI 0.28–0.9). Furthermore, we found no evidence of effect modification on the outcome by age and sex. The *p*-value for interaction was not significant (results not shown).

Discussion

In this cross-sectional study, we assessed the effect of SES on OWOB among participants from rural Nepal. We

TABLE 1 Distribution of sociodemographic, lifestyle, and SES factors by obesity status.

	Total $N = 260$	Non-obese $N = 196$	Overweight and obese $N = 64$
Gender	N	N (%)	N (%)
Male	134	93 (73.81)	33 (26.19)
Female	126	103 (76.87)	31(23.13)
Age groups (categories)			
18–34 years	77	58 (75.32)	19 (24.68)
35–49 years	88	60 (68.18)	28 (31.82)
50–65 years	55	47 (85.45)	8 (14.55)
66 years and above	40	31 (77.50)	9 (22.50)
Age in years, Mean (±SD)	45 (±16.42)	45.83 (±16.98)	44.44 (±14.60)
Marital status			
Unmarried	38	34 (89.47)	4 (10.53)
Married	222	162 (72.97)	60 (27.03)
Ethnicity			
Brahmin Chettri	173	133 (76.88)	40 (23.12)
Dalits	35	25 (71.43)	10 (28.57)
Others	52	38 (73.08)	14 (26.92)
Education			
No formal education	113	92(81.42)	21 (18.58)
Less than high school	106	80 (75.47)	26 (24.53)
High school or more	41	24 (58.54)	17 (41.46)
Income			
Low income	87	73 (83.91)	14 (16.09)
Middle income	87	68 (78.16)	19 (21.84)
High income	86	55 (63.95)	31 (36.05)
Annual income median (IQR), NRS	16,733 (35,994)	15,833 (32,666)	30,000 (47,428)
Employment status			
Unemployed	59	42 (71.19)	17 (28.81)
Farming	128	108 (84.38)	20 (15.63)
Employed	73	46 (63.01)	27 (36.99)
Lifestyle factors			
Tobacco use			
Never	108	72 (66.67)	36 (33.33)
Current	60	52 (86.67)	8 (13.33)
Former	92	72 (78.26)	20 (21.74)
Alcohol intake			
Never	195	152 (77.95)	43 (22.05)
Low (<1 glass per week)	12	9 (75.00)	3 (25.00)
Moderate (1–3 glass per week)	14	9 (64.29)	5 (35.71)
High (>3 glass per week)	39	26(66.67)	13 (33.33)
Physical activity			
MET* <600 min/week	26	18 (69.23)	8 (30.77)
MET ≥600 min/week	234	178 (76.07)	56 (23.93)
Fruits and vegetables servings			
<2 servings per day	35	22 (62.86)	13 (37.14)
2–4 servings per day	204	157 (79.96)	47 (23.04)
>4 servings per day	21	17 (80.95)	4 (19.05)

* MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest.

TABLE 2 Distribution of socioeconomic position in relation to age, sex, and lifestyle factors.

	Education				Income			
	No formal education ($n = 113$)	Less than high school ($n = 106$)	High school or more ($n = 41$)	*P*-value	Low income ($n = 87$)	Middle income ($n = 87$)	High income ($n = 86$)	*P*-value
Sex								
Male	36 (31.9)	71 (67.0)	27 (65.8)	<0.001	51 (58.6)	41 (47.1)	34 (39.5)	0.041
Female	77 (68.1)	35 (33.0)	14 (34.2)		36 (41.4)	46 (52.9)	52 (60.5)	
Age group (years)								
18–34	12 (10.6)	41 (38.7)	24 (58.5)	<0.001	15 (17.3)	23 (26.4)	39 (45.3)	<0.001
35–49	33 (29.2)	41 (38.7)	14 (34.2)		24 (27.6)	36 (41.9)	28 (32.7)	
50–65	35 (31.0)	17 (16.0)	3 (7.3)		21 (24.1)	19 (21.8)	15 (17.4)	
66 and above	33 (29.2)	7 (6.6)	0 (0.0)		27 (31.0)	9 (10.3)	4 (4.6)	
Tobacco use								
Never	40 (35.4)	40 (37.8)	28 (68.3)	<0.001	33 (37.9)	31 (35.6)	44 (51.2)	0.219
Current	21 (18.6)	33 (31.1)	6 (14.6)		19 (21.8)	24 (27.6)	17 (19.8)	
Former	52 (46.0)	33 (31.1)	7 (17.1)		35 (40.2)	32 (36.8)	25 (29.1)	
Alcohol intake								
Never	95 (84.1)	71 (66.9)	29 (70.7)	0.023	71 (81.6)	63 (72.4)	61 (70.9)	0.363
Low (<1 glass per week)	2 (1.8)	6 (5.7)	4 (9.8)		4 (4.6)	4 (4.6)	4 (4.7)	
Moderate (1–3 glass per week)	7 (6.2)	6 (5.7)	1 (2.4)		4 (4.6)	7 (8.1)	3 (3.5)	
High (>3 glass per week)	9 (7.9)	23 (21.7)	7 (17.1)		8 (9.2)	13 (14.9)	18 (20.9)	
Physical activity								
MET* <600 min/week	14 (12.4)	10 (9.4)	2 (4.9)	0.377	12 (13.8)	4 (4.6)	10 (11.6)	0.107
MET ≥600 min/week	99 (87.6)	96 (90.6)	39 (95.1)		75 (86.1)	83 (95.4)	76 (88.4)	
Fruits and vegetables servings								
<2 servings per day	10 (8.8)	17 (16.0)	8 (19.5)	0.329	9(10.3)	11 (12.7)	15 (17.5)	0.567
2–4 servings per day	95 (84.1)	80 (75.5)	29 (70.7)		71 (81.6)	67 (77.0)	66 (76.7)	
>4 servings per day	8 (7.1)	9 (8.5)	4 (9.8)		7 (8.1)	9 (10.3)	5 (5.8)	

* MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest.

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TABLE 3 Multivariable modified Poisson regression analyses between socioeconomic positions and OWOB.

Socioeconomic factors	Overweight/obesity *N* (%)	Age standardized[a] prevalence (95%CI)	PR[b,c] (95% CI)	*P*-value
Income				
Low	14 (16.09)	18% (10–26%)	Ref (1.0)	
Middle	19 (21.84)	21% (12–29%)	1.26 (0.66–2.42)	0.487
High	31 (36.05)	32% (22%-41%)	1.69 (0.92–3.14)	0.093
Education				
No formal education	21 (18.58)	19% (12–27%)	Ref (1.0)	
Less than high school	26 (24.53)	21% (13–28%)	1.51 (0.77–2.94)	0.233
High school and above	17 (41.46)	23% (10–35%)	2.27 (1.00–5.13)	0.049
Employment status				
Unemployed	17 (28.81)	42% (30–55%)	Ref (1.0)	
Farming	20 (15.63)	11% (6–17%)	0.50 (0.28–0.90)	0.020
Employed	27 (36.99)	26% (16–36%)	1.21 (0.68–2.15)	0.516

[a]Standardized to the WHO Standard Population, [b]PR = prevalence ratio.
[c]Adjusted for age (continuous), gender (male, female), marital status (married, unmarried), and ethnicity (Brahmin, Chettri, Dalits, Other).

found that OWOB was predominant among men, young adults, those married, moderate alcohol drinkers, non-tobacco users, and those less physically active. We observed a positive association between SES (education, income, employment status) and prevalence of OWOB, while the group of farmers had significantly lower prevalence of being overweight or obese compared to the unemployed group. Furthermore, we found no evidence of effect modification by sex and age.

In line with our findings, nationally representative surveys from Nepal (6, 34) and studies from other low-income countries (35–38) reported a positive SES and OWOB association. The prevalence of OWOB was reported to be higher among affluent and educated individuals in Nepal (6), Bangladesh (39) and South Asia (40).

On the contrary, studies from developed countries reported an inverse association between SES (education level and income level) and obesity (8, 15, 41). Nevertheless, a meta-analysis of prospective cohort studies from high-income countries suggested that the inverse association observed between SES and obesity was inconclusive after correcting for publication bias and reverse causality (that obese people were less likely to earn) (42). A systematic review from a developing country reported mixed results by gender, i.e., positive association for men and inverse for women (43).

The positive association observed between SES and obesity might be explained by the high-SES group having access to surplus food (44), and change in dietary pattern to consumption of high-fat and sugar-containing foods (8, 14, 45–47). Occupation is related to physical activity, and many jobs in Nepal are still labor-intensive (27); however, those with high SES in rural Nepal seem more likely to be OWOB, as they are often engaged in sedentary jobs (48). The high prevalence of obesity can also be explained by preference for large body sizes in some countries (8, 49–51), including Nepal (24) where large body size is considered a sign of economic prosperity, thus high SES may gain weight to maintain a status quo. On the other hand, the lower prevalence of obesity among those with low SES might be explained by poor availability of nutritious food (44) and engagement in high energy-expending jobs (48, 52).

Furthermore, the inconsistent results observed between the studies might also be due to different categorizations of variables such as obesity, income and education, heterogeneity of the study population, variables included in the model, and, more importantly, the different economic development stages of the countries (43). As a country's economy progresses, SES and obesity associations might also tend to be reversed (15). Moreover, studies from high- and middle-income countries achieving economic prosperity have shown the reversal of obesity gradient with increase in income occurring more swiftly (43). The difference in obesity and SES association in high- and low-income countries is determined by lifestyle choices; high-SES individuals in LMICs consume high-calorie foods and avoid physically demanding tasks while high-SES individuals in high-income countries tend to eat a healthy diet and regularly exercise (53). Nepal has achieved a moderate reduction in poverty with a steady increase in gross domestic product (35). Evidence suggests obesity is rising in low-resource settings including Nepal, with a higher increase reported among the rural population (18, 54). Therefore, Nepal needs to understand that obesity is no longer confined to affluent populations in urban areas.

The government of Nepal monitors obesity trends through routine surveys and tackles it through broader NCD policies and programming (55). However, unclear implementation mechanisms and being under resourcing of these policies hamper effective implementation (56). Furthermore, the association of obesity with adverse events such as stroke, cardiovascular events, and diabetes (57, 58) makes it urgent to address modifiable risk factors by launching an obesity prevention and management program in rural Nepal where primary healthcare facilities are not well-equipped and are in a tattered state.

Our study has a few strengths. First, a validated questionnaire was used for the data collection. Second, we measured weight and height instead of relying on self-reported measures for computing BMI.

Our study also has some limitations. First, our analysis was based on a relatively small sample size with reasonable statistical power limiting our ability to perform further sub-group analyses. Second, due to the cross-sectional nature of the study design, we cannot rule out the possibility of reverse causality. Third, the self-reported questionnaire on physical activity, alcohol use, and income data might have introduced recall bias (59). Lastly, we cannot rule out the possibility of residual confounding because of some unmeasured and incorrectly specified adjusted confounders.

Conclusion

Overall, the findings from this study suggest that high-SES individuals had higher prevalence of OWOB. However, the results were based on participants who visited one health center in rural Nepal, limiting its generalizability even within regional Nepal.

Recommendation

We recommend studies to understand how the SES and obesity relationship changes with socioeconomic development in Nepal. Similarly, larger studies are required to replicate our findings, preferably a large prospective cohort study from rural Nepal to demonstrate the SES and OWOB association among different population groups, and needed for timely identification of high-risk groups that will allow for efficient use of scarce health resources to develop effective and personalized interventions to prevent obesity in rural Nepal.

Supplementary description

- The show cards shown to the respondents during data collection were same as the one used in the Non-Communicable Diseases Risk Factors: STEPS Survey Nepal 2013
    - to identify the type of tobacco the respondents used
    - to determine the amount of alcohol the respondents consumed
    - to identify the type of fruits the respondents ate
    - to identify the type of physical activity the respondents were engaged in.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon receiving request and approval to share from the ethics committee.

Ethics statement

Ethical approval from the Regional Ethical Committee in Central Norway and Institutional Review Committee of Kathmandu University School of Medical Sciences Nepal was obtained. Informed consent was obtained before the start of data collection. The enumerators were trained in ethical consideration of human subject research to minimize breach in confidentiality. The data were de-identified for analysis. The identifiers were stored for 5 years in a locked cabinet.

Author contributions

SB performed the analysis and drafted the manuscript. RN conceived the study, collected the data, and contributed to the draft. ASh and BK provided input during study design and on the drafting manuscript. ASe provided suggestions on data analysis and presentation, edited the draft of the manuscript, and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.952665/full#supplementary-material

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EDITED BY
Mainul Haque,
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REVIEWED BY
Stefan Kabisch,
Charité Universitätsmedizin Berlin, Germany
Ceren Gezer,
Eastern Mediterranean University, Turkey

*CORRESPONDENCE
Parvane Saneei
saneeip@yahoo.com;
saneei@nutr.mui.ac.ir

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Dietary insulin index and insulin load in relation to hypertriglyceridemic waist phenotype and low brain derived neurotrophic factor in adults

Zahra Hajhashemy[1,2], Keyhan Lotfi[3], Farnaz Shahdadian[2,4], Parisa Rouhani[1,2], Zahra Heidari[5] and Parvane Saneei[1]*

[1]Department of Community Nutrition, Nutrition and Food Security Research Center, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, [4]Department of Clinical Nutrition, Nutrition and Food Security Research Center, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Department of Biostatistics and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

Background: The evidence about the relation of the insulinemic potential of food with visceral obesity and brain-derived neurotrophic factor (BDNF) was limited. We aimed to investigate the relation of dietary insulin index (DII) and dietary insulin load (DIL) with hypertriglyceridemic waist phenotype (HTGW) and serum BDNF in Iranian adults.

Methods: This cross-sectional study included 528 middle-aged adults (45.6% women), using a multistage cluster random-sampling method. Dietary intakes were assessed using a validated semi-quantitative 168-item food frequency questionnaire. Blood samples were collected after 12 h of fasting for assessing the serum BDNF and triglyceride concentrations. HTGW was defined as triacylglycerol $\geq$ 150 mg/dL plus enlarged waist circumference. The values less than the first decile of serum BDNF were considered as the low level.

Results: Individuals in the top tertile of DIL, in comparison to those in the bottom tertile, had higher odds of HTGW in both crude (OR = 1.96, 95% CI: 1.14–3.37) and fully adjusted model (OR = 6.10, 95% CI: 1.58–23.53). However, the relation between DII and odds of HTGW was statistically insignificant in crude (OR = 1.30, 95% CI: 0.78–2.16) and maximally adjusted model (OR = 1.25, 95% CI: 0.65–2.40). After considering confounders, participants in the top tertile of DIL had marginally higher odds of having low BDNF values (OR = 2.00, 95% CI: 0.95–4.21). Nevertheless, the association between DII and odds of low BDNF values was statistically insignificant.

Conclusion: This population-based study demonstrated that adults with higher DIL had significantly higher chance of HTGW phenotype and slightly higher chance for low BDNF level. DII was not associated with HTGW phenotype or BDNF values.

KEYWORDS

dietary insulin load, brain-derived neurotrophic factor, dietary insulin index, hypertriglyceridemic waist phenotype, cross-sectional study, adults

Introduction

Abdominal obesity and visceral obesity became prevalent common public health problems worldwide, due to technological development, sedentary lifestyle, and dietary habits (1, 2). Visceral fat is strongly related to increased risk of non-communicable diseases (NCD) such as dyslipidemia, insulin resistance, type 2 diabetes, chronic inflammation, cardiovascular disease (CVDs), metabolic syndrome (MetS), some cancers, Alzheimer's disease, and mortality (3–7). Considering that visceral fat accumulation would lead to central adiposity and insulin resistance in adipose tissues, circulating free fatty acids in plasma would be increased and converted to triacylglycerol in the liver (8–11). Therefore, hypertriglyceridemic waist phenotype (HTGW), which is defined as abdominal obesity along with hypertriglyceridemia, is a practical index for predicting visceral fat accumulation (12, 13). Although magnetic resonance imaging and computed tomography (CT) scan are the gold standards for visceral fat measurement, because of applying radioactive rays and high expenses, these tools are not appropriate for epidemiologic studies. Also, waist circumference (WC) values cannot be used to distinguish between subcutaneous and visceral fat; so, it is not a proper tool for visceral obesity assessment (2, 14, 15).

Previous studies documented that brain-derived neurotrophic factor (BDNF), as a member of the neurotrophic factors family which is synthesized in neurons, endothelial cells, immune cells, adipocytes, and monocytes (16–18), plays an important role in regulating the growth, survival, and maintenance of neurons (19). Exercise is supposed to increase BDNF concentration, because the stored BDNF in the brain and platelets is released during the exercise (20). BDNF, as a novel contraction-induced muscle cell-derived protein, can enhance fat oxidation in skeletal muscle (21). In addition, more recent evidences have indicated interactions between serum BDNF and metabolic health status, the balance of energy expenditure, cardiovascular homeostasis, and control of lipid and glucose levels (22–24). It seems that insulin resistance and fat accumulation are related to low levels of serum BDNF (22). Therefore, low serum BDNF level is involved in the pathogenesis of both MetS and neurodegenerative diseases (NDD) like Huntington's disease, Parkinson's disease, Alzheimer's disease, and depression (22).

Regarding the motion pathways, insulin resistance is the key factor in the incidence of visceral obesity and low serum BDNF concentrations. Although there are several risk factors for insulin resistance and visceral fat accumulation, a diet with high insulin index or insulin load could be a main risk factor, because of its insulinemic potential and its direct effect on post-prandial insulin and consequent insulin resistance and visceral adiposity. The relations of several dietary patterns including posteriori-derived dietary patterns (25) and plant-based diet (26) with visceral adiposity have been investigated. Moreover, previous publications investigated the relation of dietary insulin index (DII) and dietary insulin load (DIL) with metabolic disorders such as general obesity (27) and MetS (28). On the other hand, multiple trials have assessed the effect of some dietary patterns such as the Mediterranean diet (29), reduced-calorie diet (30), and carbohydrate-restricted Paleolithic-based diet (31) on serum BDNF; however, the evidence about the relationship between usual long-term dietary intakes with serum BDNF levels in large representative populations was limited. As far as we know, there is no population-based study that investigated the relation of dietary insulin index (DII) and dietary insulin load (DIL) with HTGW or serum BDNF concentrations. Hence, we aimed to investigate these relationships in Iranian adults. The hypothesis of the current study was that DII and DIL were directly associated with odds of HTGW phenotype and low-BDNF level.

Abbreviations: FFQ, food frequency questionnaire; OR, odds ratios; 95% CI, 95% confidence interval; BMI, body mass index; MUFA, mono unsaturated fatty acids; PUFA, poly unsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides, ANOVA, analysis of variance; ANCOVA, analysis of covariance; SPSS, statistical package for the social sciences; SD, standard deviation; SE, standard error; FII, food insulin index; MetS, metabolic syndrome; CVD, cardiovascular disease; NCD, non-communicable diseases; CT, computed tomography; HTGW, hypertriglyceridemic waist phenotype; BDNF, brain-derived neurotrophic factor; NDD, neurodegenerative diseases; DII, dietary insulin index; DIL, dietary insulin load; WC, waist circumference; RCD, reduced-calorie diet; CRPD, carbohydrate-restricted Paleolithic-based diet.

TABLE 1 General characteristics and cardiometabolic factors of study participants across tertiles of DIL and DII[a].

	Tertiles of DIL				Tertiles of DII			
	T1 (n = 171)	T2 (n = 178)	T3 (n = 179)	P^b	T1 (n = 171)	T2 (n = 177)	T3 (n = 180)	P^b
Range	<79808.09	79871.39–107574.00	>107574.00		<40.61	40.63–44.21	>44.21	
Sex, (male) (%)	45.0	51.1	66.5	<0.001	40.9	50.3	71.1	<0.001
Age (year)	42.9 ± 10.8	43.2 ± 11.1	41.5 ± 11.4	0.31	43.9 ± 10.9	42.1 ± 10.3	41.7 ± 12.1	0.14
Weight (kg)	73.6 ± 12.8	74.1 ± 15.8	79.4 ± 14.0	<0.001	74.3 ± 14.5	75.8 ± 15.0	77.1 ± 13.9	0.18
Height (cm)	165 ± 8.6	167 ± 8.1	169 ± 8.4	<0.001	165 ± 8.2	167 ± 9.1	169 ± 7.8	<0.001
BMI[5] (kg/m^2)	26.7 ± 4.0	26.4 ± 5.0	27.4 ± 4.0	0.09	27.0 ± 4.7	26.9 ± 4.3	26.8 ± 4.1	0.93
Hip circumference (cm)	104 ± 7.2	104 ± 9.6	105 ± 7.2	0.81	104 ± 8.6	104 ± 8.0	104 ± 7.7	0.63
Waist circumference (cm)	91.1 ± 10.4	91.6 ± 12.1	95.1 ± 11.4	0.01	91.6 ± 11.5	92.5 ± 11.5	93.6 ± 11.3	0.25
TG (mg/dL)	149 ± 2.9	153 ± 2.9	156 ± 3.2	0.33	148 ± 2.8	151 ± 2.8	158 ± 3.4	0.06
BDNF (ng/mL)	1.18 ± 0.03	1.32 ± 0.16	1.11 ± 0.04	0.33	1.15 ± 0.03	1.36 ± 0.16	1.10 ± 0.04	0.15
Physical activity (MET. min/wk)	872 ± 85	828 ± 82	1077 ± 107	0.13	1043 ± 95	787 ± 81	947 ± 100	0.14
Education (University graduated) (%)	88.2	92.1	86.4	0.22	89.9	89.8	87.2	0.66
Marital status (Married) (%)	82.1	83.6	81.5	0.94	79.9	85.8	81.5	0.29
Smoking status (Smokers) (%)	2.0	4.3	3.2	0.27	1.3	5.1	3.0	0.14
Family size (>4) (%)	13.6	14.0	16.5	0.71	15.3	12.6	16.2	0.62
House ownership (yes) (%)	72.0	78.7	74.9	0.42	77.9	77.1	69.0	0.12
Hypertension (yes) (%)	21.3	24.2	28.5	0.29	22.4	22.7	28.9	0.27
History of type 2 diabetes (yes) (%)	5.9	3.9	6.1	0.59	6.5	5.1	4.4	0.68
Antihyperlipidemic drug use (yes) (%)	9.5	5.8	9.7	0.34	10.1	7.1	8.0	0.57

[a]For continuous variables, values are Mean ± SD, except for TG, BDNF and physical activity which are Mean ± SE. For categorical variables, values are percentage. [b]P-value obtained from one way ANOVA and χ^2 test for quantitative and categorical variables, respectively. BMI, Body Mass Index; TG, triglycerides; BDNF, brain derived neurotrophic factor.

Materials and methods

Study design and participants

This cross-sectional study was performed on a representative sample of adults in a large central city in Iran in 2021. Considering a prevalence of 17% for HTGW among Iranian adults (32), a confidence of 95%, and precision (d) of 4%, 339 individuals were approximately required for this study. However, considering the high prevalence of COVID-19 pandemic during data collection, a total of 600 eligible participants were invited to participate in the study. A multistage cluster random-sampling method was used to select 600 adults (both gender) aged 20–60 years from 20 schools in Isfahan city. In order to have a representative sample of the general adult population with different socioeconomic statuses, we included all adults who were working in the selected schools, including employees, teachers, school managers, assistants, and crews. However, subjects with the following criteria were not included: (1) being pregnant or lactating; (2) following a special diet; (3) having a prior history of cardiovascular disease, stroke, type 1 diabetes, and cancer. Among invited subjects, 543 of them agreed to participate in our investigation. In addition, we excluded individuals with the following criteria: (1) had left more than 70 items blank on the food frequency questionnaire (n = 4); (2) reported a total energy intake outside the range of 800–4,200 kcal/day (as under-reporters and over-reporters of energy intake) (n = 3); (3) did not have data of their waist circumference (WC) measurement (n = 7); and (4) did not accept blood draw (n = 1). Finally, 528 adults were included in the current analysis (response rate: 90.5%). Written informed consent was obtained from each participant. The protocol of the study was ethically approved by the local Ethics Committee of Isfahan University of Medical Sciences in 2021 (no. IR.MUI.RESEARCH.REC.1399.613).

Assessment of dietary intake

We assessed the usual dietary intake of individuals through a validated Willett-format semi-quantitative 168-item food

TABLE 2 Dietary intakes (energy, macro/micro nutrients and food groups) of study participants across tertiles of DIL and DII[a].

	Tertiles of DIL				Tertiles of DII			
	T1 ($n = 171$)	T2 ($n = 178$)	T3 ($n = 179$)	P^b	T1 ($n = 171$)	T2 ($n = 177$)	T3 ($n = 180$)	P^b
Range	<79808.09	79871.39–107574.00	>107574.00	–	<40.61	40.63–44.21	>44.21	–
Nutrient								
Energy, kcal	1570 ± 26	2205 ± 26	3015 ± 26	<0.001	2315 ± 52	2268 ± 50	2242 ± 51	0.61
Protein,% of energy	14.8 ± 0.2	14.1 ± 0.2	13.8 ± 0.2	0.01	15.1 ± 0.2	14.6 ± 0.2	12.9 ± 0.2	<0.001
Carbohydrate,% of energy	60.0 ± 0.6	60.6 ± 0.6	61.9 ± 0.6	0.08	55.6 ± 0.5	60.3 ± 0.5	66.3 ± 0.5	<0.001
Fat,% of energy	26.9 ± 0.5	27.1 ± 0.5	26.3 ± 0.5	0.45	31.2 ± 0.4	26.8 ± 0.4	22.5 ± 0.4	<0.001
Cholesterol, mg	337 ± 13	286 ± 8	209 ± 13	<0.001	321 ± 8	290 ± 8	220 ± 8	<0.001
SFA, gr	26.9 ± 0.8	23.3 ± 0.5	16.8 ± 0.8	<0.001	25.7 ± 0.5	22.9 ± 0.5	18.4 ± 0.5	<0.001
MUFA, gr	27.0 ± 0.7	22.4 ± 0.4	15.9 ± 0.7	<0.001	25.4 ± 0.4	21.9 ± 0.4	17.9 ± 0.4	<0.001
PUFA, gr	20.1 ± 0.8	16.9 ± 0.5	11.1 ± 0.8	<0.001	19.6 ± 0.5	15.4 ± 0.5	13.2 ± 0.5	<0.001
Fructose, gr	21.8 ± 1.3	20.9 ± 0.8	20.4 ± 1.4	0.80	20.3 ± 0.9	20.5 ± 0.8	22.3 ± 0.8	0.25
Calcium, mg	955 ± 43	909 ± 28	908 ± 44	0.64	999 ± 28	949 ± 27	826 ± 27	<0.001
Vitamin E, mg	7.93 ± 0.35	6.73 ± 0.23	5.98 ± 0.36	0.01	7.29 ± 0.24	6.96 ± 0.23	6.37 ± 0.23	0.02
Total fiber, gr	21.9 ± 0.7	21.0 ± 0.4	20.4 ± 0.7	0.49	21.6 ± 0.4	21.0 ± 0.4	20.7 ± 0.4	0.43
Food groups								
Whole grains, g/d	79.0 ± 9.1	96.6 ± 5.9	109 ± 9.3	0.16	94.7 ± 6.1	97.9 ± 5.9	93.1 ± 6.0	0.84
Refined grains, g/d	192 ± 18	262 ± 11	361 ± 18	<0.001	214 ± 12	273 ± 11	329 ± 11	<0.001
Fruits, g/d	605 ± 37	555 ± 23	507 ± 38	0.33	541 ± 24	549 ± 23	574 ± 24	0.62
Vegetables, g/d	379 ± 25	339 ± 16	281 ± 26	0.10	387 ± 16	329 ± 16	283 ± 16	<0.001
Red and processed meat, g/d	79.5 ± 5.2	71.0 ± 3.3	53.4 ± 5.3	0.01	71.8 ± 3.4	75.2 ± 3.3	56.7 ± 3.3	<0.001
Dairy, g/d	338 ± 30	306 ± 19	307 ± 31	0.65	368 ± 20	330 ± 19	254 ± 19	<0.001
Nuts, soy and legumes, g/d	52.1 ± 4.4	51.2 ± 2.8	49.8 ± 4.5	0.96	53.7 ± 2.9	50.5 ± 2.8	49.0 ± 2.8	0.50

[a]Values are Mean ± SE. Energy intake and macronutrients were adjusted for age and gender; all other values were adjusted for age, gender and energy intake. [b]*P*-value obtained from ANCOVA test for adjustment of energy intake. SFA, Saturated fatty acids; MUFA, Monounsaturated fatty acids; PUFA, Polyunsaturated fatty acids.

frequency questionnaire (FFQ) (33). A previous validation study of this FFQ on 132 middle-aged adults revealed reasonable correlations between dietary intakes assessed by FFQ and those obtained from multiple 24-h dietary recalls (33). The correlation coefficients between the dietary intakes obtained from the FFQ and those from the twelve 24-h dietary recalls were 0.55 for total energy, 0.65 for proteins, 0.59 for fat, 0.67 for fiber, and 0.65 for magnesium. The reliability of the FFQ was assessed by comparing nutrient intakes obtained from the FFQ on two occasions 1-year apart. Overall, these data supported that this FFQ could provide reasonably valid measures of the usual dietary intakes among Iranian adults (33). An expert dietitian instructed the study participants to complete the FFQ by reporting the frequency and amount of each food item that they have consumed in the preceding year. Then, the portion sizes of consumed foods were converted to g/day through the use of household measures (34). After that, we entered all food items into Nutritionist IV software, to obtain daily intake of energy and all nutrients.

Assessment of dietary insulin index and dietary insulin load

We used food insulin index (FII), which refers to the ratio of incremental insulin area under the curve over 2 h in response to the consumption of a 1000-kJ portion of the test food to the area under the curve after ingestion of a 1000-kJ portion of the reference food. The FII for each item was obtained from the previous publications of Holt et al. (35), Bao et al. (36), Bell et al. (37), and Sadeghi et al. (28) that provided a comprehensive list of FIIs. For food items that their FIIs were not reported in these studies, FIIs of similar foods were used.

The insulin load of each food was calculated by the following formula:

Insulin load of a given food = insulin index of that food × amount of that food consumed (g/d) × energy content per 1 g of that food (g/d) (38). DIL for each person was provided through the sum up of the insulin load of all food items consumed in the last year. Then, DII for each participant was computed by dividing DIL by total energy intake.

Assessment of hypertriglyceridemic waist phenotype and low serum brain-derived neurotrophic factor values

WC was measured to the nearest 0.1 cm through the use of a non-stretchable tape measure. WC was recorded after a normal expiration, by measuring halfway between the lower rib margin and the iliac crest and without any pressure on the body surface. WC measurement of each subject was repeated and the average of two measurements was considered in the analysis. Blood samples were collected after 12 h of fasting; blood samples were allowed to clot, and then were centrifuged to separate serum. Serum triglyceride concentration (TG) was determined by the enzymatic-colorimetric method. The ELISA kits were used to measure serum BDNF values (Zellbio, Veltlinerweg, Germany).

Based on a recently published study that has defined WC cut-off-points in Iranian adults (39), we considered the cut-point of 98 cm for men and 84 cm for women as the threshold for an enlarged WC. In addition, according to the NCEP ATP III, TG $\geq$ 150 mg/dL was considered as hypertriglyceridemia (40). Based on the mentioned cut-off-points, we categorized participants in to 4 phenotypes including: (1) HTGW (enlarged WC and high triglycerides) [triacylglycerol $\geq$ 150 mg/dL plus WC $\geq$ 98 cm (men) and $\geq$ 84 cm (women)]; (2) enlarged WC and normal triglycerides [triacylglycerol $\leq$ 150 mg/dL plus WC $\geq$ 98 cm (men) and $\geq$ 84 cm (women)]; (3) normal WC and high triglycerides [triacylglycerol $\geq$ 150 mg/dL plus WC $\leq$ 98 cm (men) and $\leq$ 84 cm (women)]; (4) normal WC and normal triglycerides [triacylglycerol $\leq$ 150 mg/dL plus WC $\leq$ 98 cm (men) and $\leq$ 84 cm (women)].

Based on a previous study (29), deciles of serum BDNF concentrations were computed and the bottom decile (D1) (with serum BDNF level of 0.074–0.466 ng/mL or <0.47 ng/mL) was considered as the low serum BDNF level.

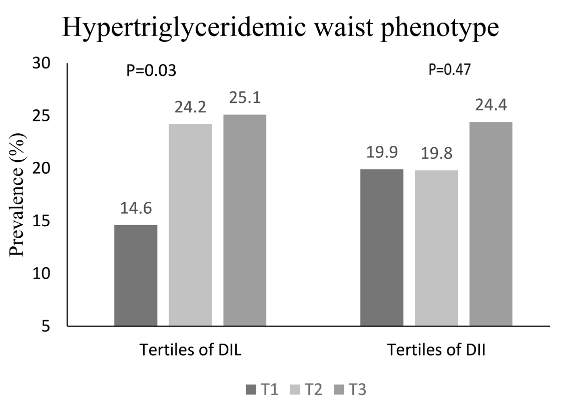

FIGURE 1
Prevalence of HTGW phenotype in tertiles of DIL and DII.

Assessment of other variables

Height and weight were measured while subjects stood with minimal clothing and without shoes. Height was measured to the nearest 0.1 cm through the use of a tape measure. Weight was measured using the body composition analyzer (Tanita MC-780MA, Tokyo, Japan). Weight (kg) divided by the height (m) squared to compute the body mass index (BMI). After 5 min of resting time, blood pressure was measured twice through the use of a digital sphygmomanometer (OMRON, M3, HEM-7154-E, Japan), with an accuracy of 0.5 mmHg, in a sitting position; the mean of two measurements was recorded for each participant.

Data of additional confounders such as age, sex, marital status, education, smoking habits, homeownership, medical history of diseases and medication use were gathered through the use of a self-reported questionnaire. Furthermore, physical activity was measured by the validated International Physical Activity Questionnaires (IPAQ) questionnaire (41). Depression was also assessed using the validated Hospital Anxiety and Depression Scale (HADS) for the Iranian population (42).

Statistical analysis

The Kolmogorov–Smirnov test was applied to examine the normality of quantitative variables. Mean ± SD/SE and percentage were respectively reported for continuous and categorical variables. First, individuals were distributed in tertiles of DIL and DII. Then, the categorical and continuous variables were compared across tertiles of DIL and DII, by the use of the chi-square test and one-way analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was applied to report age, sex, and energy-adjusted dietary intakes of participants across tertiles of DIL and DII. Using the binary logistic regression, the odds ratio (OR) of HTGW phenotype across tertiles of DIL and DII was calculated, in crude and multivariable-adjusted models. In the first model, the effects of age, sex, and energy intake were controlled. In addition, education, smoking, physical activity, marital status, history of diabetes, hypertension, use of anti-hyperlipidemic medication, family size and homeownership were adjusted in the second model. In the third model, the effect of BMI was additionally controlled. The first tertile of DIL or DII was considered as the reference category in all models. To determine trends, DIL or DII tertiles were treated as continuous variables in logistic regression models. Additionally, crude and multivariable-adjusted models were used to obtain odds of low BDNF values (<0.47 ng/mL) in tertiles of DIL and DII. The effects of age and sex were controlled in the first model. In the second model, depression, hypertension, hyperlipidemia, history of diabetes, and physical activity were adjusted. SPSS software version 20 was used for all statistical analyses. *P*-values less than 0.05 were considered statistically significant.

Results

The current population-based study was conducted on 528 adults with a mean age of 42.5 (±11.1) years and an average BMI of 26.92 (±4.41) kg/m^2; 45.6% of the study participants were female. Among study subjects, 21.4% of them had HTGW phenotype (n = 113) and the others belonged to the enlarged WC and normal triglycerides (33.9%, n = 179), normal WC and high triglycerides (15.1%, n = 80) and normal WC and normal triglycerides (29.5%, n = 156) phenotypes. The average serum BDNF was 1.20 (ng/mL) among the study population and 0.37 (ng/mL) among subjects with low BDNF levels or those in the first decile of serum BDNF.

General characteristics of study subjects across tertiles of DIL and DII are provided in Table 1. Those in the top tertile of DIL and DII were more likely to be male ($P < 0.001$). We observed significant increasing trends for the weight ($P < 0.001$), height ($P < 0.001$), and waist circumference ($P = 0.01$) across tertiles of DIL. Additionally, there was a significant increasing trend for height ($P < 0.001$) across tertiles of DII. Nevertheless, the distribution of other variables was not significantly different across tertiles of DIL and DII.

Dietary intakes of study participants across tertiles of DIL and DII are provided in Table 2. There were significant decreasing trends for intake of protein ($P = 0.01$), cholesterol ($P < 0.001$), saturated fatty acids (SFA) ($P < 0.001$), monounsaturated fatty acids (MUFA) ($P < 0.001$), polyunsaturated fatty acids (PUFA) ($P < 0.001$), vitamin E ($P = 0.01$) and red and processed meat ($P = 0.01$) across tertiles of DIL. Additionally, there were significant increasing trends for intake of energy ($P < 0.001$) and refined grains ($P < 0.001$) in DIL tertiles. Moreover, participants in the top tertile of DII in comparison to the bottom tertile had a significantly lower intake of protein ($P < 0.001$), fat ($P < 0.001$), cholesterol ($P < 0.001$), SFA ($P < 0.001$), MUFA ($P < 0.001$), PUFA ($P < 0.001$), calcium ($P < 0.001$), vitamin E ($P = 0.02$), vegetables ($P < 0.001$), red and processed meat ($P < 0.001$) and dairy ($P < 0.001$). However, subjects in the last tertile of DII had a higher intake of carbohydrates ($P < 0.001$) and refined grains ($P < 0.001$), compared with the first tertile.

The prevalence of HTGW in tertiles of DIL and DII is shown in Figure 1. In the first, second and third tertile DIL, 14.6, 24.2, and 25.1% of subjects respectively had HTGW phenotype; this increasing trend was statistically significant ($P = 0.03$). However, the prevalence of HTGW phenotype was not significantly different across tertiles of DII ($P = 0.47$).

The distribution of four different phenotypes based on serum triacylglycerol concentration and waist circumference across tertiles of DIL and DII is presented in Table 3. Although the prevalence of these phenotypes was slightly different in tertiles of DIL ($P = 0.06$), there was no significant difference in tertiles of DII ($P = 0.65$). Moreover, the prevalence of the second phenotype (enlarged waist circumference and normal triglyceride values) was higher than three other phenotypes across tertiles of both DIL and DII. The mean values of serum BDNF in four different phenotypes based on serum triacylglycerol concentration and waist circumference values are reported in Figure 2. Participants with the HTGW phenotype had the lowest serum BDNF values [1.15 ± 0.04 (SE)] and those with the third phenotype (normal WC and high triglyceride values) had the highest levels of serum BDNF [1.43 ± 0.35 (SE)]; however, these differences were not statistically significant ($P = 0.44$).

Multivariate adjusted odds ratio (OR) and 95% confidence interval (CI) for HTGW phenotype across tertiles of DIL and DII are presented in Table 4. Subjects in the highest tertile of DIL, in comparison to those in the lowest tertile, had 96% higher odds of HTGW (OR = 1.96, 95% CI: 1.14–3.37) in the crude model. After adjustment for potential confounders, this association became stronger; such that individuals in the third tertile of DIL had 6.10 times higher odds of HTGW, compared to those in the first tertile (OR = 6.10, 95% CI: 1.58–23.53). Additionally, there was a significant increasing trend for the odds of HTGW across tertiles of DIL ($P_{trend} = 0.01$). Nevertheless, there was no significant association between DII and HTGW, in the crude model (OR = 1.30, 95% CI: 0.78–2.16). After controlling potential confounders, this relation did not change (OR = 1.25, 95% CI: 0.65–2.40). Moreover, there was no significant trend for the prevalence of HTGW across tertiles of DII ($P_{trend} = 0.46$).

Multivariate adjusted odds ratio (OR) and 95% confidence interval (CI) for the prevalence of low BDNF values (<0.47 ng/mL) across tertiles of DIL and DII are provided in Table 5. Although the relation between DIL and odds of low BDNF values was statistically insignificant in the crude model (OR = 1.79, 95% CI: 0.87–3.66), after taking potential confounders into account, this relation became marginally significant; such that participants in the top tertile of DIL had marginally 2 times higher odds for low BDNF values (OR = 2.00, 95% CI: 0.95–4.21). Additionally, there was a marginally significant increasing trend for the odds of low BDNF values across tertiles of DIL ($P = 0.07$). Nevertheless, the association between DII and the prevalence of low BDNF values was statistically insignificant (OR = 1.42, 95% CI: 0.72–2.79), even after adjustment for potential confounders (OR = 1.49, 95% CI: 0.73–3.06). Also, no significant trend was found for low BDNF prevalence across DIL categories ($P = 0.25$).

Discussion

The current epidemiologic investigation illustrated that more adherence to a diet with higher DIL was related to elevated odds of HTGW phenotype in Iranian adults. Moreover, subjects who followed a diet with higher DIL had slightly higher odds for

TABLE 3 Distribution of different phenotypes of serum triacylglycerol concentration and waist circumference (WC) across tertiles of DIL and DII.

	Tertiles of DIL				Tertiles of DII			
	T1 (*n* = 171)	T2 (*n* = 178)	T3 (*n* = 179)	P[a]	T1 (*n* = 171)	T2 (*n* = 177)	T3 (*n* = 180)	P[a]
Range	<79808.09	79871.39–107574.00	>107574.00		<40.61	40.63–44.21	>44.21	
Phenotypes				0.06				0.65
Enlarged WC and high triglycerides[b] (%)	14.6	24.2	25.1		19.9	19.8	24.4	
Enlarged WC and normal triglycerides[c] (%)	40.4	27.5	34.1		37.4	35.6	28.9	
Normal WC and high triglycerides[d] (%)	17.0	14.6	14.0		13.5	14.7	17.2	
Normal WC and normal triglycerides[e] (%)	28.1	33.7	26.8		29.2	29.9	29.4	

[a]For differences among tertiles of DIL and DII (chi-square test). [b]Triacylglycerol ≥ 150 mg/dL plus WC ≥ 98 cm (men) and WC ≥ 84 cm (women). [c]Triacylglycerol ≤ 150 mg/dL plus WC ≥ 98 cm (men) and WC ≥ 84 cm (women). [d]Triacylglycerol ≥ 150 mg/dL plus WC ≤ 98 cm (men) and WC ≤ 84 cm (women). [e]Triacylglycerol ≤ 150 mg/dL plus WC ≤ 98 cm (men) and WC ≤ 84 cm (women).

low BDNF values. Nevertheless, there was no significant relation between DII and HTGW and serum BDNF concentrations.

The present population-based study indicated that a considerable percentage of Iranian adults (21.4%) had HTGW phenotype. This high-risk phenotype was more prevalent among participants with high adherence to a diet with high DIL and those with low serum BDNF values. Considering the role of visceral fat in metabolic disorders and the involvement of BDNF in metabolic health status, identification and management of HTGW and low serum BDNF values are crucial steps in preventing and decreasing the incidence rate of these disorders. Our findings have suggested that clinicians would advise people to adhere to a diet with lower insulinemic potential, in order to prevent these conditions.

Similar to our study, some recently published studies have investigated the relation of DII and DIL with metabolic disorders. Anjom-Shoae et al. investigated 8,691 Iranian middle-aged adults and found no significant association between DIL and general obesity, in contrast to the significant association between DIL and HTGW that was found in the present study. However, they found a straight relationship between DII and general obesity in females, while no significant association was observed in males (27). Moreover, Sadeghi et al. performed a cross-sectional analysis on 5,954 Iranian adults from the Shahedieh cohort study to investigate the relation of DIL and DII with metabolic syndrome. They reported that women in the highest quartile of DII and DIL in comparison to women in the lowest quartile had greater odds of MetS. Among male participants, the third quartile of DIL, compared with the first quartile, was significantly associated with higher odds of MetS (28); the last quartile of DIL as well as categories of DII were not related to MetS in men. Another cross-sectional study on 850 Iranian adults reported no significant association between DII and DIL and obesity, MetS or its components (43). Moreover, the data analysis of Nurses' Health Study and the Health Professionals Follow-Up Study revealed significant associations only between DII/DIL and two components of MetS (high-TG and low-HDL) (38). These observed differences might be due to tools applied for dietary assessment, the different age ranges of study participants, different variables considered as confounders, and various methods used to compute dietary insulin index and insulin load.

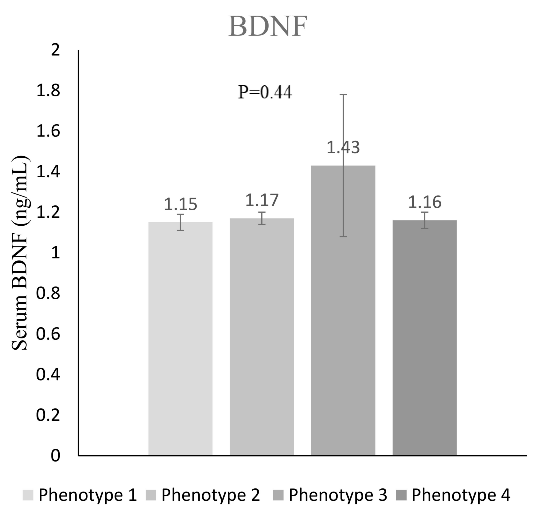

FIGURE 2
Serum BDNF values in different phenotypes of serum triacylglycerol concentration and waist circumference. Value of serum BDNF in phenotype 1 (enlarged waist circumference and high triglyceride concentrations) was 1.15 ± 0.04 (mean ± SE); in phenotype 2 (enlarged waist circumference and normal triglycerides) was 1.17 ± 0.03; in phenotype 3 (normal waist circumference and high triglyceride concentrations) was 1.43 ± 0.35; and in phenotype 4 (normal waist circumference and normal concentrations) was 1.16 ± 0.04.

TABLE 4 Multivariate adjusted odds ratio (OR) and 95% confidence interval (CI) for HTGW phenotype across tertiles of DIL and DII[a].

	Tertiles of DIL				Tertiles of DII			
	T1 (*n* = 171)	T2 (*n* = 178)	T3 (*n* = 179)	*P*-trend	T1 (*n* = 171)	T2 (*n* = 177)	T3 (*n* = 180)	*P*-trend
Cases	25	43	45		34	35	44	
Crude	1.00 (Ref)	1.86 (1.07, 3.21)	1.96 (1.14, 3.37)	0.02	1.00 (Ref)	0.99 (0.58, 1.68)	1.30 (0.78, 2.16)	0.29
Model 1	1.00 (Ref)	2.40 (1.22, 4.69)	3.61 (1.29, 10.13)	0.01	1.00 (Ref)	1.04 (0.61,1.78)	1.43 (0.84, 2.43)	0.18
Model 2	1.00 (Ref)	2.82 (1.26, 6.34)	3.94 (1.16, 13.35)	0.03	1.00 (Ref)	0.72 (0.38, 1.35)	1.17 (0.64, 2.16)	0.56
Model 3	1.00 (Ref)	4.30 (1.73, 10.69)	6.10 (1.58, 23.53)	0.01	1.00 (Ref)	0.67 (0.34, 1.34)	1.25 (0.65, 2.40)	0.47

[a]All values are odds ratios and 95% confidence intervals. P-trend was obtained by the use of DIL or DII tertiles as a continuous rather than categorical variable. Model 1, Adjusted for age, sex, and energy intake; Model 2, Additionally, adjusted for marital status, education, family size, smoking, hypertension, diabetes, physical activity and homeownership; Model 3, Additionally, adjusted for body mass index (BMI).

TABLE 5 Multivariate adjusted odds ratio (OR) and 95% confidence interval (CI) for very low BDNF (<0.47 ng/mL, 1st decile) across tertiles of DIL and DII[a].

	Tertiles of DIL				Tertiles of DII			
	T1 (*n* = 171)	T2 (*n* = 178)	T3 (*n* = 179)	*P*-trend	T1 (*n* = 171)	T2 (*n* = 177)	T3 (*n* = 180)	*P*-trend
Cases	13	18	23		16	15	23	
Crude	1.00 (Ref)	1.36 (0.64, 2.88)	1.79 (0.87, 3.66)	0.11	1.00 (Ref)	0.89 (0.43, 1.87)	1.42 (0.72, 2.79)	0.29
Model 1	1.00 (Ref)	1.39 (0.66, 2.95)	1.92 (0.92, 3.98)	0.08	1.00 (Ref)	0.92 (0.44, 1.93)	1.57 (0.77, 3.18)	0.24
Model 2	1.00 (Ref)	1.42 (0.66, 3.03)	2.00 (0.95, 4.21)	0.07	1.00 (Ref)	0.89 (0.42, 1.89)	1.49 (0.73, 3.06)	0.26

[a]All values are odds ratios and 95% confidence intervals. P-trend was obtained by the use of DIL or DII tertiles as a continuous rather than categorical variable. Model 1, Adjusted for age and sex; Model 2, Additionally, adjusted for depression, hypertension, hyperlipidemia, history of diabetes, and physical activity.

Several previous interventional studies indicated that dietary intakes could have important effects on circulating BDNF levels. The PREDIMED-NAVARRA randomized trial on 243 adults with depression has documented that the Mediterranean diet with virgin olive oil or nuts after 3 years of follow-up could slightly increase circulating BDNF concentrations (29). Another trial was conducted on 17 overweight and obese subjects to determine the effect of a reduced-calorie diet (RCD) on BDNF values. After 3-month adherence to this RCD, a significant increase in BDNF level was found and favorable changes in anthropometric and glycemic indices have occurred (30). Similarly, a cross-over randomized controlled trial with two 4-week phases and a 4-week washout period on 12 adults with MetS has indicated favorable changes in serum BDNF levels after following a carbohydrate-restricted Paleolithic-based diet (CRPD) with less than 50 g carbohydrates per day (31). These favorable changes were observed in both intervention groups with sedentary activity and high-intensity interval training (31). Although multiple clinical trials have investigated the effects of diet and physical activity interventions on serum BDNF levels, the relationship between usual dietary intakes of the general population with serum BDNF values was less studied so far. However, our population-based epidemiologic study on adults indicated that low serum BDNF values were marginally more prevalent among participants who followed a diet with higher DIL.

Some mechanisms have been suggested to explain the relationship between DIL and HTGW phenotype and serum BDNF levels. Adherence to a diet with higher insulinemic potential would lead to higher insulin secretion, carbohydrate oxidation and lower fat oxidation; therefore, following such a diet would promote fat storage, in particular in the abdominal area and increase the risk of visceral obesity (44). A diet with high insulinemic potential would also have a rapid process of digestion, absorption and transformation to glucose; so, such a diet would rapidly increase blood glucose and insulin and with a short interval decrease blood glucose (45). Blood glucose fluctuation would decrease satiety and elevate hunger sensation and calorie intake and consequently would increase the risk of obesity (45, 46). Additionally, higher DII and DIL are related to a higher risk of insulin resistance (47) and metabolic syndrome (28). Oxidative and nitrosative stresses due to elevated post-prandial glucose and visceral obesity would lead to decreased serum BDNF levels (48). Additionally, insulin resistance and raised post-prandial glucose would directly inhibit the BDNF secretion (49). Moreover, experimental studies suggested that the expression of BDNF mRNA was decreased because of stress and high levels of proinflammatory cytokines in the hippocampus (50). Therefore, due to the negative effect of insulin resistance and other mentioned metabolic disorders on serum BDNF levels (22), DII and DIL would be inversely related to serum BDNF levels.

BDNF serves as a neurotransmitter modulator and an anorexigenic factor that is related to the melanocortin-4 receptor gene, dopaminergic system and serotonin signaling (19, 22, 51, 52). Serotonin, which is decreased in depressed patients, is involved in psychological health, feeling, motivation, learning, appetite and sleep (22). Additionally, BDNF is involved in energy homeostasis through the secretion and function of pre-inflammatory cytokine, ghrelin, leptin, insulin and peptide neurotransmitters (53, 54). Therefore, low serum BDNF is related to both neurodegenerative diseases (NDD) such as Huntington's, Parkinson's, and Alzheimer's diseases, depression and metabolic disorders such as diabetes, obesity, dyslipidemia, inflammation and hypertension (22).

The current study has some strengths and weaknesses. We investigated the relation of DIL and DII with HTGW and serum BDNF levels for the first time among Iranian adults. Additionally, the effect of potential confounders was taken into account. Furthermore, the study sample was selected by the use of a multistage cluster random sampling method. Therefore, our population could be representative of the general adult population and the findings could be generalizable to the whole Iranian population. Nevertheless, some limitations should be considered, while interpreting these findings. Due to the cross-sectional design of the study, causality cannot be inferred; more prospective studies are required to find a causal relationship. Although dietary intakes were assessed by the use of a validated FFQ, recall bias along with other potential reporting biases were inevitable and might influence our findings. The range of DII among tertiles was too narrow (T3 vs. T1: 47.4 vs. 37.9), which made it difficult to find the associations with outcomes of interest. DII and DIL have some other restrictions that should be kept in mind while interpreting our findings. DII and DIL are somehow questionable parameters for describing food quality, because these indices cannot discriminate healthy from unhealthy fats. Additionally, fructose intake which is associated with the pathogenesis of metabolic diseases such as non-alcoholic fatty liver disease (NAFLD), obesity, hyperuricemia and hypertension, seems not to stimulate insulin secretion (55). Therefore, fructose rich foods would be considered healthy for being low-insulinogenic. Nevertheless, in the current study, there was no significant difference in fructose intake across tertiles of DII and DIL; therefore, our results might not be influenced by fructose intake. Moreover, besides DII and DIL, the energy and macronutrient intakes as well as energy density of foods, which are more dependent factors to the fat content of foods, would influence the results (56). Such that, in some previous studies on DII and DIL, different energy and macronutrient intakes across categories of DII or DIL might result in significant findings (28). However, in some other investigations with different energy and macronutrient intakes across categories of DII or DIL, no significant findings were found (38, 43). In the current study, we found a significant inverse relation between DIL and HTGW phenotype; while significant differences were found only in case of energy and protein intakes across tertiles of DIL; fat or carbohydrates were not different across DIL categories. Further investigations are needed to determine whether overall observed effects would be explained by energy or carbohydrate intake, irrespective of putative differential insulinemia, or not.

To conclude, this cross-sectional population-based study demonstrated that participants with higher DIL had significantly higher chance of HTGW phenotype. Additionally, subjects who followed a diet with higher DIL had slightly higher chance for low BDNF values. However, more prospective investigations should be conducted to confirm these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocol was approved by the Local Ethics Committee of Isfahan University of Medical Sciences in 2021 (no. IR.MUI.RESEARCH.REC.1399.613). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZHA, KL, FS, PR, ZHE, and PS contributed in conception, design, data collection, data interpretation, manuscript drafting, approval of the final version of the manuscript, and agreed for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Mainul Haque,
National Defence University of Malaysia, Malaysia

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Mitra Darbandi,
Kermanshah University of Medical Sciences, Iran
Minyi Zhang,
Southern Medical University, China

*CORRESPONDENCE
Deshi Dong
dongdeshi@dmu.edu.cn
Dong Shang
shangdong@dmu.edu.cn

†These authors have contributed equally to this work and share first authorship

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Contemporary Chinese dietary pattern: Where are the hidden risks?

Hong Xiang[1†], Xufeng Tao[2†], Xi Guan[1], Tianyi Yin[3], Junchen Li[3], Deshi Dong[2*] and Dong Shang[1,3*]

[1]Laboratory of Integrative Medicine, The First Affiliated Hospital of Dalian Medical University, Dalian, China, [2]Department of Pharmacy, The First Affiliated Hospital of Dalian Medical University, Dalian, China, [3]Department of General Surgery, The First Affiliated Hospital of Dalian Medical University, Dalian, China

Background: With the rapid improvement in economy and lifestyle, dietary risk-related diseases have become a public health problem worldwide. However, the health effects of dietary risk over time have not been fully clarified in China. Here, we explored the temporal trends in the death burden of unhealthy dietary habits in China and benchmark dietary risk challenges in China to G20 member states.

Method: Sex–age-specific burdens due to dietary risk in China were extracted from the Global Burden of Disease (GBD) Study 2019, including annual numbers and age-standardized rates (ASRs) of death, disability-adjusted life years (DALYs), and summary exposure values (SEVs) during 1990–2019. The variation trend of ASRs was evaluated by estimated annual percentage changes (EAPCs).

Result: Between 1990 and 2019, the number of dietary risk-based death and DALYs increased significantly in China with an overall downward trend of ASDR and ASR-DALYs. Ischemic heart disease was the first cause of death from diet, followed by stroke and colon and rectum cancers. Chinese men were at greater risk than women for diet-related death and DALYs. Further analysis showed that a high sodium diet has always been the "No. 1 killer" that threatens the health of Chinese residents. The death burden of dietary risk demonstrated an increasing trend with age, and the peak was reached in people over 75 years. Compared with other G20 countries, Japan and South Korea have the most similar dietary patterns to China with the character of high sodium intake. Notably, decreased whole grain intake, as the primary dietary risk attributable to death and DALYs burden in the United States and European countries, had already ranked second in China's dietary risks.

Conclusion: China's dietary burden cannot be ignored. Chinese residents should pay more attention to the collocation of dietary nutrients, especially men and 75+ years (elderly) people. Targeted dietary adjustments can significantly reduce deaths and DALYs in China.

KEYWORDS

dietary risk, China, death, disability-adjusted life years, summary exposure value, Global Burden of Disease Study

Introduction

Globally, in 2019, diet was the second leading risk attributed to deaths in women, and the third leading risk of deaths in men (1). Dietary patterns have been confirmed to be correlated with a variety of non-communicable diseases (NCDs), including cancers, cardiovascular disease, metabolic disease, etc. (2–4). A prospective cohort study reported that the intake of ultra-processed foods is positively associated with the risk of cardiovascular diseases (5). High consumption of preserved foods is linked to increased nasopharyngeal carcinoma risk in adolescence and adulthood (6). In addition, a dietary pattern with high consumption of plant foods but a minimal consumption of animal products has been recommended for dietary prevention and management of type 2 diabetes and related micro- and macrovascular complications (7).

With the rapid development in the economy and lifestyle, Chinese residents are presently undergoing unprecedented diversifications in their dietary patterns, and the focus is on high sugar and saturated fats intake (8). In order to prevent and manage diet-related diseases, a monitoring system for nutrition and risk factors covering the whole life course has been established in China, and the correlation between dietary patterns and diseases has been reported successively (9–12). However, there are still a lack of systematic national data covering the health impacts of dietary transitions and their trend variations as far as we know. In this report, we retrieve data from the Global Burden of Diseases Study (GBD) 2019 to examine the sex-age-specific burden of dietary risks-related death in China from 1990 to 2019, and benchmark dietary risk challenges in China to G20 member countries. In short, we found that the numbers of death and disability-adjusted life years (DALYs) at dietary risk increased significantly in China, while overall age-standardized rates (ASRs) of death (ASDR) and ASR-DALYs were on the decline from 1990 to 2019. The continued risk of a diet high in sodium and the dietary risk caused by the introduction of western dietary culture need more attention. In terms of individual differences, we found that male dietary risks were more serious than female ones, and age was positively correlated with most dietary risks. Therefore, this systematic investigation of unhealthy dietary habits may provide critical guidance for dietary consumption patterns to prevent and manage dietary risk-related diseases.

Methods

Data sources

Data on annual numbers and age-standardized rates (ASRs) of sex-age-specific death and DALYs due to dietary risk from 1990 to 2019 were collected *via* the GBD 2019 study using GBD Results Tool (https://ghdx.healthdata.org/gbd-results-tool). The GBD 2019 under the leadership of the Institute for Health Metrics and Evaluation (IHME) provides an open access tool to quantify the health burden from 369 diseases and injuries and 87 risk factors obtained from 204 countries and territories. Data coverage and statistical modeling methods for the GBD 2019 have been published in previous research (13).

Dietary risk factor definitions

A dietary risk factor is a behavior factor causally linked to an increased or decreased probability of getting a disease or injury. The decreased probability means the risk is a protective factor. In GBD 2019, dietary risks are classified as a secondary category under behavioral risks, with a total of 15 risks as follows: low fruits (≤200–300 g/day), vegetables (≤290–430 g/day), legumes (≤50–70 g/day), whole grains (≤100–150 g/day), nuts and seeds (≤16–25 g/day), milk (≤350–520 g/day), fiber (≤19–28 g/day), seafood omega-3 fatty acids (≤200–300 g/day), polyunsaturated fatty acids (≤9–13% of total daily energy), and calcium (≤1.00–1.50 g/day) intake; and high red meat (≥18–27 g/day), processed meat (≥ 0–4 g/day), sugar-sweetened beverages (≥ 50 kCal per 226·8 serving), trans fatty acids (≥ 0.0–1.0% of total daily energy), and sodium (≥ 1–5 g/day) consumption. The exposure definition and optimal level (or range) of intake have been reported in detail elsewhere (14). The inclusion of risk factors is mainly according to the association strength among dietary risks and diseases, evidence levels, and data availability.

Statistical analyses

All measures were reported as numbers and ASRs. An estimate of disability-adjusted life years (DALYs) is computed by summarizing the number of healthy years lost to disease, weighted for severity by disability weights (YLDs), and dividing that amount by the number of healthy years lost to the disease. Summary exposure value (SEV) measures the risk factor exposure of a population. SEV = 0, there is no excess risk for the population; and SEV = 1, the population is at the highest level of risk. According to GBD 2019, SEV is reported as a risk-weighted prevalence ranging from 0 to 100%. SEV decreases with decreasing exposure to a particular risk factor, while SEV increases with increasing exposure. Data were presented as values with a 95% uncertainty interval (UI). Moreover, we artificially divided these populations into four age groups: 25–44 years (young), 45–59 years (middle-aged), 60–74 years (middle-old aged), and 75+ years (old aged), and summed their data as the new age group (15, 16). In addition, to reflect the change trends of ASDRs from 1990 to 2019, we also calculated the estimated annual percentage change (EAPC) of ASDRs based on the formula $100 \times (\exp(\beta) - 1)$ ($Y = \alpha + \beta X + \varepsilon$, $Y = \ln$ (ASR), $X =$ calendar year, $\varepsilon =$ the error term), and the 95% confidence interval (CI) was obtained from the linear regression model. All data were analyzed by using the R program (Version 4.2.0) or GraphPad Prism (Version 6).

Results

Overall effects of dietary risks on health in China

The effects of dietary risks on health in China were presented as the numbers of death and DALYs, and these indexes all significantly increased from 1990 to 2019 (Table 1; Supplementary Table 1). In 2019, diet-related deaths accounted for 2.015 million deaths (95% UI 1.494–2.645), with an age-standardized death rate (ASDR) of 115.054 per 100,000 (95% UI 84.966–151.654) and an EAPC of −0.874 (−1.018– −0.730) (Table 1 and Figure 1A). Notably, dietary risk-related deaths increased dramatically in men in the last three decades, reaching 1.218 million (95% UI: 0.885–1.631) in 2019, which was 1.5 times that of women (Figure 1A). Moreover, as shown in Figure 1A and Supplementary Table 1, the loss of dietary factor-related DALYs reached 46.813 million (95% UI 35.645–60.012) person-years, and the ASR-DALYs of dietary risks was 2,393.995 per 100,000 (95% UI: 1,823.458–3,070.583) in 2019. The health burden in men was more severe than in women, with ASDR and ASR-DALYs of 157.902/100,000 and 3,203.180/100,000, respectively. In addition, the EAPC of dietary risks related ASR-DALYs were −1.254 (−1.285 – −1.223), −0.711 (−0.825 – −0.597), and −1.807 (−1.930 – −1.685) in both, men and women, respectively. Ischemic heart disease was the first cause of diet-related deaths [0.997 (0.766–1.227) million deaths] and DALYs [20.044 (15.603–24.457) million DALYs], followed by stroke [0.672 (0.436–0.937) million deaths and 16.729 (11.517–22.375) million DALYs] and colon and rectum cancer [0.090 (0.066–0.115) million deaths and 2.234 (1.610–2.831) million DALYs] (Figure 1B, Table 1, and Supplementary Table 1).

SEV and risk-specific trends of individual dietary risk factors

Age-standardized SEV rate of dietary risks declined in China (ARC = −0.055, 95% UI: −0.099– −0.019), falling from 81.860 per 100,000 people in 1990 (95% UI: 75.436–85.149) to 77.367 per 100,000 people in 2019 (95% UI: 69.577–81.933). Overall, men had a lower rate of change (ARC = −0.048, 95% UI: −0.089– −0.010) than women (ARC = −0.062, 95% UI: −0.122– −0.013). Based on the analysis of different individual risk factors of diet, the decreased age-standardized SEV rates of high trans fatty acids, sodium, and sugar-sweetened beverages consumption, as well as a diet low in calcium, legumes, fruits, nuts and seeds, fiber, seafood omega-3 fatty acids and polyunsaturated fatty acids in 2019 compared with those in 1990 have been reported, in particular, the biggest reduction was in the intake of low-vegetable diets. Conversely, the age-standardized SEV rates for four dietary risks in 2019 were higher than those in 1990, including a diet high in red meat and processed meat, but low in whole grains and milk. The details are integrated into Table 2.

Impact of individual factors of dietary risk on death burden

From 1990 to 2019, the impact of different dietary risks on the death burden varied widely. As shown in Figure 2A, deaths from a diet with high sodium and red meat, and low whole grains and legumes continued to climb, and the remaining dietary risk-related deaths have gradually plateaued, including high consumption of trans fatty acids, sugar-sweetened beverages, and diet with low calcium, fruits, nuts and seeds, milk, seafood omega-3 fatty acids and polyunsaturated fatty acids, etc. In China, high sodium intake-related deaths have long topped the list. In 1990, 0.554 million Chinese died from a high-sodium diet, but 0.855 million died in 2019. A high-sodium diet killed far more Chinese men than women.

Contrary to the rise in death cases, with the increase of the Chinese population, the majority of ASDR of dietary risks showed an overall volatile downward trend, 1990–2019, in which, the death burden due to a high sodium diet, and diets low in fruits, fiber and vegetables were significantly reduced (Figure 2B). There are gender differences in ASDRs of dietary risks in China, and the typical feature was that the ASDRs of high sodium, low fruit, fiber, and vegetable intake in Chinese men were higher than that of women (Figure 2B). Additionally, the ASDR percent change in women over the past 30 years decreased more significantly than in men (Figure 2C). From 1990 to 2019, the ratios of male ASDR to female ASDR were essentially maintained between 1.2 and 1.8 across 15 dietary risk factors. However, the ratio of sodium-rich and calcium-deficient diets reached over 2.0 (Figure 2D), indicating a further disparity between sexes in death burden due to high sodium and low calcium consumption. It is a relatively serious problem that the burden of dietary risks on health appears to be higher in men than in women.

As shown in Figure 2E, the dietary structure and eating habits of Chinese residents have undergone great changes over the study period with the improvement of living standards. The most significant improvement was the rank of death burden due to low fruits, fiber, and vegetable intake dropping from 2nd, 5th, and 6th in 1990 to 4th, 8th, and 15th in 2019, respectively. Under the influence of western animal-source diets, the death burden of Chinese residents due to a diet high in red meat has risen from the 4th in 1990 to the 3rd in 2019, and the ranking of other

TABLE 1 The death numbers and age-standardized death rates of dietary risks in China.

Characteristics	1990		2019		1990–2019
	Number of deaths (95% UI)	ASDR per 100,000 (95% UI)	Number of deaths (95% UI)	ASDR per 100,000 (95% UI)	EAPC of ASDR
China	1,134,883.502 (856,372.638–1,466,841.344)	161.523 (120.976–211.032)	2,015,169.973 (1,494,173.501–2,645,141.246)	115.054 (84.966–151.654)	−0.874 (−1.018– −0.730)
Sex					
Men	643,240.967 (478,196.989–837,808.740)	199.3180424 (148.896–259.249)	1,217,584.924 (884,975.215–1,631,263.425)	157.902 (116.2721–209.978)	−0.404 (−0.556– −0.251)
Women	491,642.535 (359,891.326–658,708.149)	133.796 (98.314–180.775)	797,585.049 (554,673.6788–1,110,938.342)	83.689 (58.012–116.222)	−1.382 (−1.547– −1.216)
Dietary risk-related diseases					
Rheumatic heart disease	12,491.670 (5,015.431–24,615.362)	1.497 (0.569–3.035)	5,529.203 (1,948.707–11,472.504)	0.287 (0.097–0.602)	−5.513 (−5.632– −5.394)
Ischemic heart disease	381,013.400 (310,915.419–448,758.930)	58.806 (47.864–70.269)	997,011.686 (766,215.915–1,227,448.978)	60.037 (46.276–74.239)	0.693 (0.430–0.957)
Hypertensive heart disease	71,590.602 (24,382.420–154,000.354)	10.830 (2.934–24.805)	77,818.671 (19,528.343–187,735.101)	4.582 (0.996–11.787)	−2.919 (−3.736– −2.095)
Atrial fibrillation and flutter	1,710.756 (593.410–3,226.251)	0.320 (0.092–0.645)	4,209.944 (1,250.690–8,718.238)	0.268 (0.069–0.579)	−0.657 (−0.773– −0.540)
Cardiomyopathy and myocarditis	705.917 (271.383–1,473.184)	0.081 (0.029–0.177)	1,331.259 (548.031–2,456.932)	0.069 (0.027–0.128)	−0.232 (−0.520–0.058)
Endocarditis	391.182 (175.613–688.914)	0.044 (0.019–0.080)	545.547 (234.071–985.726)	0.028 (0.012–0.051)	−2.141 (−2.415– −1.867)
Non-rheumatic valvular heart disease	239.849 (95.331–434.226)	0.026 (0.010–0.048)	421.215 (185.761–732.455)	0.020 (0.009–0.036)	−0.967 (−1.030– −0.904)
Aortic aneurysm	1,096.117 (467.719–1,966.616)	0.130 (0.053–0.239)	2,306.974 (983.398–4,095.032)	0.114 (0.048–0.207)	−0.419 (−0.493– −0.345)
Peripheral artery disease	54.730 (20.018–103.782)	0.008 (0.003–0.017)	169.980 (59.887–322.774)	0.009 (0.003–0.019)	0.504 (0.379–0.630)
Other cardiovascular and circulatory diseases	2,062.254 (924.023–3,619.849)	0.257 (0.107–0.477)	2,618.109 (1,056.149–4,654.357)	0.136 (0.051–0.248)	−2.161 (−2.287– −2.035)
Stroke	519,444.502 (365,946.892–684,456.414)	71.307 (49.378–95.394)	671,872.079 (436,354.759–937,093.269)	36.313 (23.549–50.850)	−2.311 (−2.478– −2.144)
Diabetes mellitus	16,985.751 (13,217.478–21,229.306)	2.282 (1.789–2.853)	41,951.856 (31,431.378–52,994.938)	2.269 (1.702–2.847)	0.121 (−0.118–0.360)
Chronic kidney disease	14,911.092 (6,753.376–25,100.603)	1.903 (0.800–3.346)	29,665.725 (11,330.585–54,546.973)	1.564 (0.557–2.956)	−0.312 (−0.455– −0.168)
Tracheal, bronchus, and lung cancer	13,486.463 (4,581.842–20,861.271)	1.640 (0.555–2.535)	27,187.203 (7,159.651–43,057.971)	1.402 (0.368–2.221)	−0.464 (−0.720– −0.207)
Breast cancer	1,302.360 (455.731–1,907.567)	0.144 (0.049–0.210)	4,483.464 (2,013.556–6,484.881)	0.223 (0.098–0.322)	1.672 (1.594–1.751)
Esophageal cancer	40,514.343 (17,910.852–66,618.102)	5.066 (2.230–8.319)	20,508.962 (4,338.342–52,320.932)	1.074 (0.237–2.733)	−5.744 (−6.224– −5.261)
Stomach cancer	27,226.500 (612.935–101,649.434)	3.343 (0.077–12.562)	37,131.477 (833.143–138,478.719)	1.900 (0.043–7.120)	−1.718 (−2.108– −1.328)
Colon and rectum cancer	29,656.014 (23,146.429–35,344.014)	3.839 (3.015–4.567)	90,406.618 (65,690.670–114,669.415)	4.761 (3.475–6.008)	1.112 (0.851–1.374)

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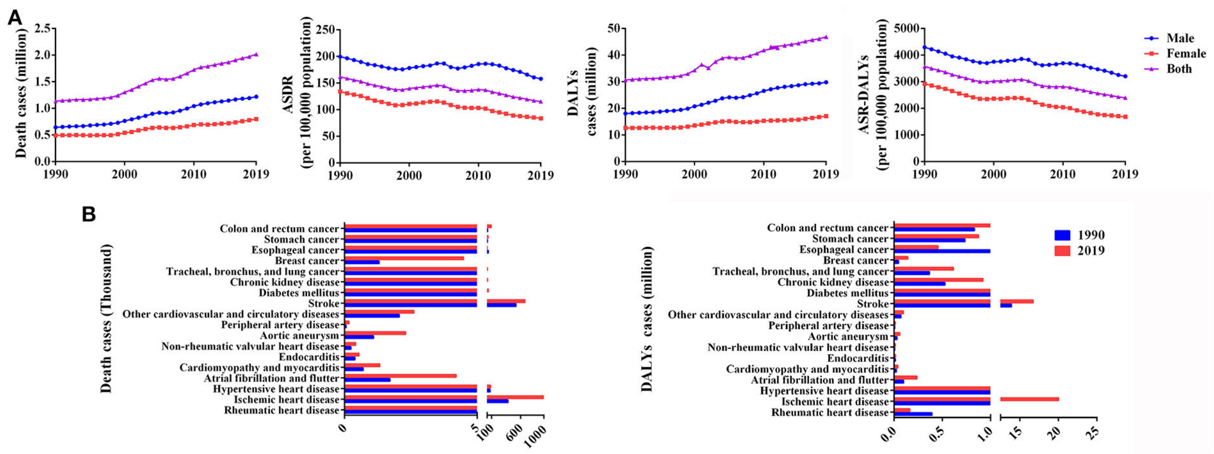

FIGURE 1
Overall effects of dietary risks on health in China from 1990 to 2019. **(A)** Deaths, ASDR, DALYs, and ASR-DALYs by sex from 1990 to 2019. **(B)** Deaths and DALYs in individual diseases in 1990 and 2019.

dietary risk factors all increased by varying degrees. From 1990 to 2019, the deaths due to a diet high in sodium have always ranked first, and it has become the "No. 1 killer" that threatens the health of Chinese residents.

Burden of dietary risk-related deaths in various age groups

As shown in Figure 3A, the Chinese death burden of dietary risks demonstrated age-related increases. Most dietary risk-related deaths occurred in the senior population, particularly those $\geq$ 75 years of age (old age). It was the old age group that had the highest absolute number of deaths in 2019 due to diets high in trans fatty acids, red meat, processed meat, sugar-sweetened beverages, and diets low in legumes, fruits, vegetables, whole grains, nuts, and seeds, fiber, seafood omega-3 fatty acids, polyunsaturated fatty acids, respectively; and the middle-old aged group had the highest absolute levels of deaths due to a diet high in sodium, and a diet low in calcium and milk. Comparatively to the other dietary risk factors, a sodium-rich diet led to the highest number of deaths at the end of the study period.

Next, the corresponding percent changes in death cases of each group for each dietary risk factor during 1990–2019 were examined and contrasted. Over the study period, the old-aged group in China experienced the greatest increase in deaths, followed by the young group (Figure 3B). All age groups showed marked increases in deaths due to a diet high in processed meat, while a diet low in fruits, vegetables, and fiber demonstrated a full-scale decline.

A trend toward older ages was observed in deaths due to dietary risks between 1990 and 2019. The middle-old aged group had the highest proportion of dietary risk-related deaths in 1990 until it was fully overtaken by the elderly individuals in 2019, with the contributions of the youth and middle-aged groups to total deaths due to decreased dietary risk (Figure 3C). A diet low in fiber had the youngest distribution among all dietary risk factors, as a fiber-deficiency diet in young and middle-aged groups accounted for as many as 39% of deaths in 1990 and 26% in 2019. In contrast, the distribution of diets poor in vegetables was the oldest, with middle-aged and elderly people accounting for 71% of deaths in 1990 and 90% in 2019.

Comparative view of dietary risk-related death burden across the G20 states

A comparison of the death burden caused by dietary risk in China and other G20 members is shown in Figures 4A,B. In China, the top three deaths and DALYs caused by dietary risk factors were due to eating too much sodium, eating few whole grains, and consuming too much processed meat. Compared with the G20 countries, Japan and Korea have the most similar dietary patterns to China. Traditional diets in East and South-East Asia have an obvious characteristic with dying high in sodium; therefore, high sodium intake-related dietary risks have always been associated with the highest deaths and DALYs in China, Japan, South Korea, and Indonesia. However, a diet low in whole grains is the major dietary risk associated with death, and DALYs in the United States and European countries had ranked second in China, only behind a diet high in sodium, suggesting that Chinese traditional eating habits are facing challenges from western diets.

TABLE 2 The age-standardized SEV rates of dietary risks in 1990 and 2019, and annualized rate of changes in China.

Factors	Sex	Age-standardized SEV rate (95% UI)		ARC (%) (95% UI)
		1990	2019	
Dietary risks	Male	83.875 (77.838–87.072)	79.849 (72.971–84.005)	−0.048 (−0.089– −0.010)
	Female	79.976 (72.903–84.025)	74.997 (65.946–80.617)	−0.062 (−0.122– −0.013)
	Both	81.860 (75.436–85.149)	77.367 (69.577–81.933)	−0.055 (−0.099– −0.019)
Diet high in trans fatty acids	Male	42.712 (34.609–58.711)	36.310 (28.414–52.930)	−0.150 (−0.267– −0.039)
	Female	43.229 (35.114–59.625)	37.092 (29.163–55.484)	−0.142 (−0.262– −0.037)
	Both	42.968 (35.388–58.614)	36.703 (29.400–53.605)	−0.146 (−0.239– −0.053)
Diet high in sodium	Male	96.270 (89.258–98.506)	95.227 (87.092–98.274)	−0.011 (−0.052–0.018)
	Female	91.123 (82.062–95.811)	88.888 (77.651–94.938)	−0.025 (−0.097–0.034)
	Both	93.570 (85.894–96.741)	91.959 (82.299–96.237)	−0.017 (−0.063–0.016)
Diet high in red meat	Male	40.009 (28.462–51.287)	70.206 (60.815–78.513)	0.755 (0.437–1.299)
	Female	40.771 (29.598–51.974)	71.187 (60.778–79.408)	0.746 (0.445–1.311)
	Both	40.381 (29.656–50.881)	70.696 (61.870–78.158)	0.751 (0.472–1.225)
Diet high in processed meat	Male	8.246 (3.869–18.999)	15.160 (6.528–32.013)	0.838 (0.169–1.513)
	Female	8.940 (4.043–19.284)	17.893 (8.077–35.478)	1.002 (0.317–1.775)
	Both	8.585 (3.978–19.220)	16.516 (7.344–33.916)	0.924 (0.211–1.577)
Diet high in sugar-sweetened beverages	Male	34.798 (23.186–56.595)	25.477 (17.310–40.130)	−0.268 (−0.479– −0.031)
	Female	30.751 (20.024–50.824)	23.801 (15.697–37.188)	−0.226 (−0.488–0.092)
	Both	32.804 (22.192–53.784)	24.609 (16.831–38.618)	−0.250 (−0.472– −0.020)
Diet low in calcium	Male	71.102 (59.686–85.775)	48.105 (34.432–67.585)	−0.323 (−0.444– −0.167)
	Female	65.386 (53.300–81.907)	44.725 (31.127–64.809)	−0.316 (−0.435– −0.161)
	Both	68.279 (56.874–83.824)	46.380 (32.989–65.969)	−0.321 (−0.439– −0.164)
Diet low in legumes	Male	68.592 (27.649–96.869)	56.836 (15.073–87.372)	−0.171 (−0.520– −0.042)
	Female	64.949 (23.103–94.802)	50.112 (11.598–79.793)	−0.228 (−0.563– −0.065)
	Both	66.802 (25.641–95.586)	53.474 (13.665–82.957)	−0.200 (−0.529– −0.062)
Diet low in fruits	Male	73.895 (65.310–83.149)	46.175 (35.627–58.284)	−0.375 (−0.492– −0.267)
	Female	74.088 (66.107–82.950)	44.341 (33.928–56.542)	−0.402 (−0.517– −0.293)
	Both	74.004 (66.377–82.688)	45.261 (34.847–57.180)	−0.388 (−0.496– −0.282)
Diet low in vegetables	Male	40.503 (23.951–59.575)	3.467 (1.790–9.987)	−0.914 (−0.954– −0.759)
	Female	39.486 (22.936–58.669)	3.226 (1.666–9.468)	−0.918 (−0.957– −0.757)
	Both	39.993 (23.508–58.867)	3.343 (1.759–9.544)	−0.916 (−0.955– −0.751)
Diet low in whole grains	Male	82.563 (75.203–90.092)	84.068 (77.218–91.031)	0.018 (0.005–0.036)
	Female	80.516 (72.192–88.364)	82.163 (74.147–89.815)	0.020 (0.005–0.044)
	Both	81.552 (73.652–89.237)	83.111 (75.692–90.380)	0.019 (0.008–0.035)
Diet low in nuts and seeds	Male	64.907 (32.562–81.146)	43.074 (18.872–65.409)	−0.336 (−0.560– −0.160)
	Female	67.234 (33.953–82.902)	45.690 (20.034–67.532)	−0.320 (−0.548– −0.159)
	Both	66.048 (33.217–81.898)	44.382 (18.625–66.423)	−0.328 (−0.543– −0.165)
Diet low in milk	Male	94.508 (88.302–99.043)	96.002 (88.915–100.000)	0.016 (−0.012–0.048)
	Female	94.639 (88.337–99.270)	95.651 (88.066–100.000)	0.011 (−0.015–0.039)
	Both	94.569 (88.259–99.154)	95.827 (88.545–100.000)	0.013 (−0.013–0.044)
Diet low in fiber	Male	37.193 (24.425–50.594)	19.658 (10.693–29.732)	−0.471 (−0.620– −0.311)
	Female	40.044 (25.811–53.939)	22.406 (12.763–33.065)	−0.440 (−0.596– −0.276)
	Both	38.611 (25.529–51.752)	21.021 (12.611–30.549)	−0.456 (−0.580– −0.332)
Diet low in seafood omega-3 fatty acids	Male	99.745 (99.314–99.996)	96.338 (91.803–99.959)	−0.034 (−0.078– −0.000)
	Female	99.813 (99.510–99.998)	97.162 (93.146–99.990)	−0.027 (−0.065–0.000)
	Both	99.778 (99.468–99.996)	96.747 (92.791–99.974)	−0.030 (−0.068– −0.000)
Diet low in polyunsaturated fatty acids	Male	87.430 (69.042–95.867)	67.899 (36.442–91.612)	−0.223 (−0.483–0.024)
	Female	88.299 (71.746–95.898)	69.446 (38.411–91.784)	−0.214 (−0.464–0.018)
	Both	87.859 (70.390–95.926)	68.683 (37.169–91.776)	−0.218 (−0.467–0.019)

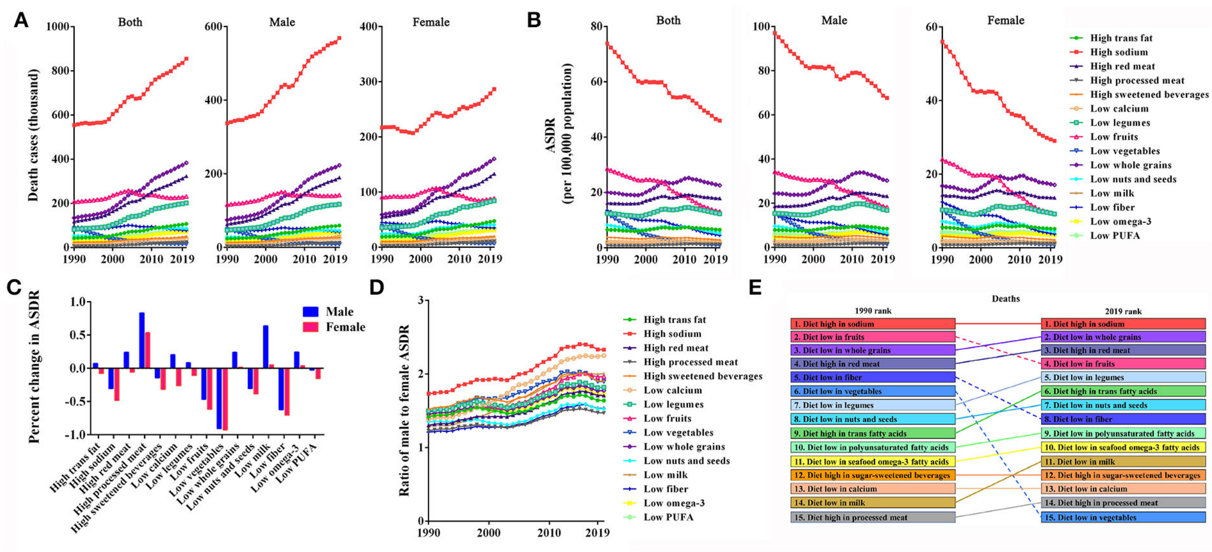

FIGURE 2
Impact of individual factors of dietary risk on death burden in China from 1990 to 2019. **(A,B)** Deaths and ASDRs in individual factors of dietary risk by sex. **(C)** Percent changes in ASDRs in men and women. **(D)** Male-to-female ratios of ASDRs in individual factors of dietary risk. **(E)** Ranking of deaths due to individual dietary risk factors.

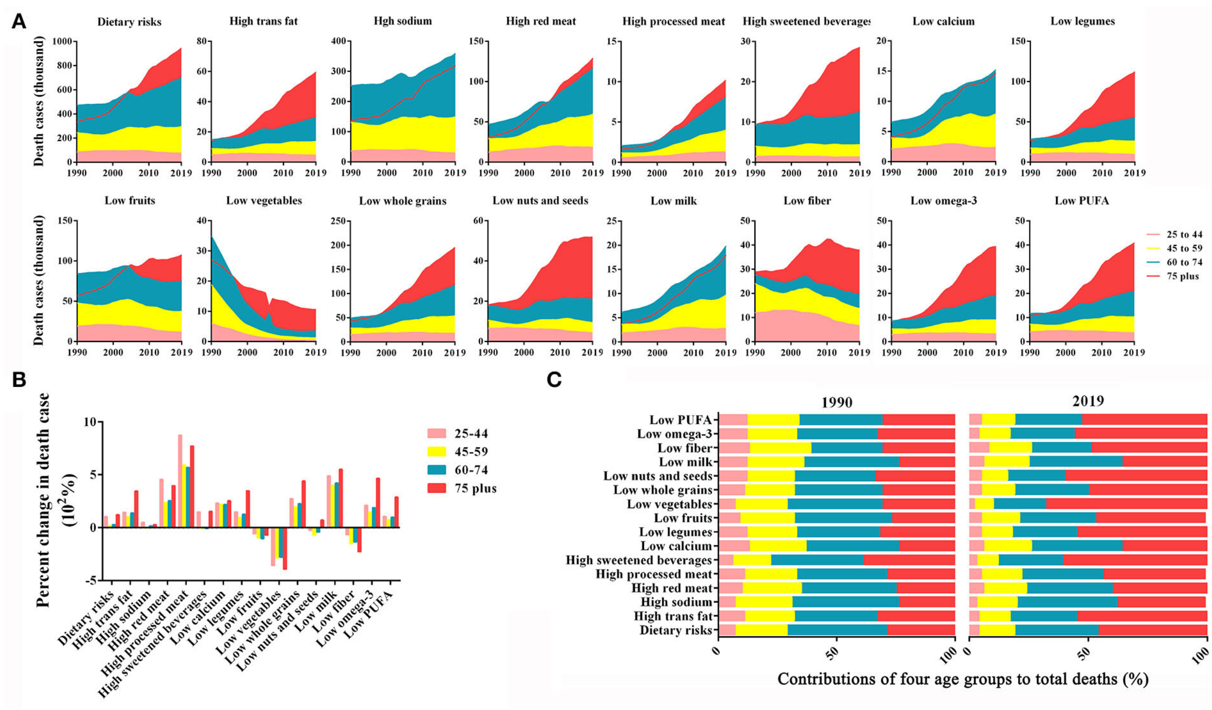

FIGURE 3
Burden of dietary risk-related deaths in various age groups of China in individual dietary risk factors from 1990 to 2019. **(A)** The contribution of each age group to total deaths. **(B)** The percent changes in deaths in the four age groups. **(C)** The four age groups as percentages of total deaths.

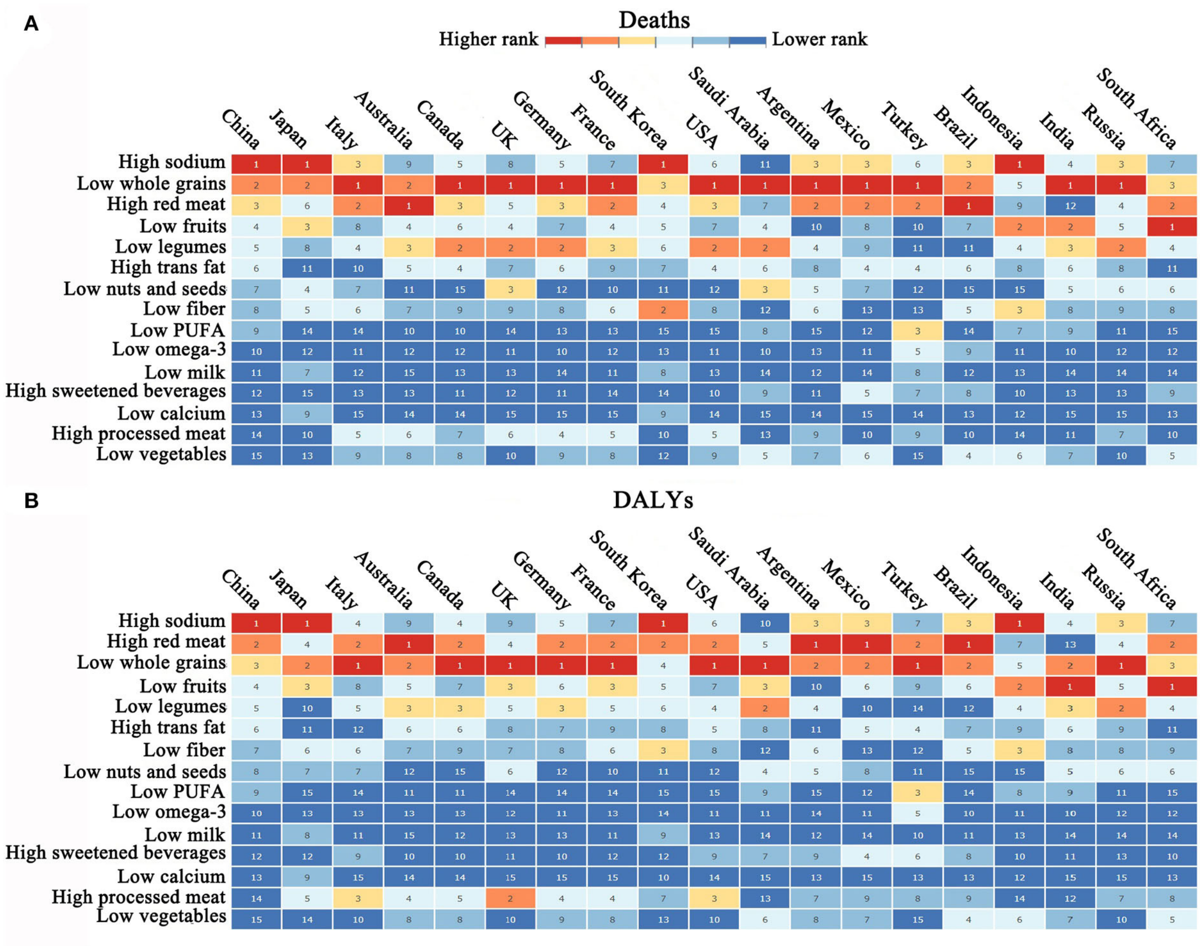

FIGURE 4
Comparative view of dietary risk-related death burden across the G20 states [This figure was sourced from GBD 2019 study (https://vizhub.healthdata.org/gbd-compare/)]. **(A,B)** Ranking of dietary risk-related death and DALYs in the G20 states.

Discussion

Diet-related disease burden has been widely documented, but not well-understood in China. Data on dietary risk factors related to health burden in China were comprehensively reviewed in this study, and the trend of the health impacts of dietary risk was presented annually by the numbers and ASRs of death and DALYs. From 1990 to 2019, dietary risk factors had become major challenges that seriously threaten the health of Chinese residents. The number of death and DALYs due to dietary risk increased significantly in China, but the ASDR and ASR-DALYs showed overall downward trends with the proportion growth of the elderly population. It is vigilant that dietary intakes differ by gender contributing to differences in death burden between men and women, and the gap is widening year by year. Compared with Chinese women, men have a heavier dietary risk-related burden as a result of unhealthy eating. Women have been reported a better diet quality than men, with better eating behavior and healthier weight management, which can be reflected in lower energy density, higher carbohydrate energy ratio, and higher frequency of cooking in women's diet. Conversely, the established impression is that men consume more lipids and fewer carbohydrates than women (17, 18). Moreover, compared with women, men reported less favorable attitudes and a weaker sense of behavioral control regarding fruit and vegetable intake, let alone perception of the importance of health (19). It is likely that the gap between the sexes will continue to widen in the future if this trend continues. Thus, the significant gender difference in dietary risk-related death should be taken into account in national prevention programs.

In the past 3 decades, the influence of traditional Chinese food culture on Chinese dietary structure is still strong. It is encouraging to see the age-standardized SEV rate for diets high in sodium gradually decreasing, but the sodium intake is still twice the World Health Organization's (WHO) tolerable upper intake (<2.0 g/d), and home food preparation accounted for more than 67% of sodium intake (20). Sodium-rich diet was also responsible for the majority of diet-related deaths, which is similar to that of Japan and Korea which are members of the G20 along with China. According to data from the WHO, the consumption of high sodium levels has been linked to a number of NCDs in adults and children, such as cardiovascular disease, hypertension, and stroke, and the reduction of sodium intake is a cost-effective public health intervention for preventing NCDs (21). In China, ischemic heart disease was the chief cause of diet-related death, followed by stroke. According to a meta-analysis of 616,905 participants, dietary sodium intake and cardiovascular disease risk are significantly correlated, and an increase in sodium intake of 1 g was associated with an increase in cardiovascular disease risk of up to 6% (22). Health outcomes and healthcare costs can be significantly improved by reducing dietary salt by 3 g per day, according to the Coronary Heart Disease Policy Model (23). Therefore, a low-sodium diet should be a public health goal of the Chinese Health Sector, and education on sodium-reduced intake should be promoted. In addition, the dietary structure of Chinese residents is facing the challenges of western eating habits, mainly manifested in the rising number of deaths from high red meat and processed meat consumption but low whole grains intake during 1990–2019. In prospective studies, consumption of red and processed meat is associated with an increased risk of ischemic heart disease, and such effects could be mediated by the association between red and processed meat and plasma non-high-density lipoprotein cholesterol and systolic blood pressure. Every 100 g of red or processed meat consumed each day would increase the risk of colorectal cancer by 12%, and the carcinogenic potential of these foods can be summarized as the presence of carcinogens or their precursors produced by food processing. However, the risk of colorectal cancer decreases by 17% with each 90 g/day increase in whole grains (24–26). Western diet represented by highly red meat and processed foods may promote diverse forms of NCDS through gut microbiome-mediated inflammatory responses; on the contrary, diets rich in whole grains without altering the gut microbiome significantly reduce systemic low-grade inflammation (27, 28). Thus, Chinese residents should pay attention to choosing healthy dietary habits and avoid excessive intake of unhealthy foods when they are enjoying the fresh experience brought by the fusion of China and the West. Although the challenges are still severe, the Chinese government's great efforts and achievements in improving the livelihood and health awareness of residents in the past 30 years are still worthy of recognition. The most significant improvement is reflected by the significantly decreased burden of death linked to low fruit and vegetable intake.

Here, the burden of dietary risk-related deaths in various age groups was also fully evaluated. Seniors (60–74 years and 75+ years) had the highest absolute numbers of deaths across all dietary risk factors at the end of the study period, and the greatest increase in deaths occurred in 75+ years within the study period. This is an inevitable result of the accelerated aging of China's population and the sharp rise in the proportion of old age. Therefore, policymakers should place dietary interventions at the top of their priority list for the foreseeable future. A diet low in fruits and vegetables demonstrated a full-scale decline; however, the problem of low vegetable intake in people over 75 years was still significant, which is because the poor chewing ability of the elderly destroys the desire for vegetable intake. Caregivers can help to reduce this death burden by learning to make more soft, chewy, and low-nutrient-dense vegetable foods for the senior population. It is vigilant that young people like to pursue sensory pleasures, pay less and less attention to diet matching, and avoid dietary risks, resulting in a significant upgrade in the percentage of deaths caused by dietary risks in the 25–44 years.

In conclusion, dietary risk continues to pose a major public health threat in China. The health effects of dietary risk caused by gender differences are serious, and the dietary risk-related death burden was much higher in men than in women, contrary to global survey data. The gap between the sexes will likely widen further if this trend continues. Sodium-rich diets are also the leading causes of diet-related deaths at the end of the study period. Furthermore, the Chinese diet is excessively influenced by western dietary culture, represented by high red and processed meat intake, which is widely reported to be associated with a variety of NCDS. Age is also an important reference for assessing the burden of diet-related deaths. The elderly were the key population for dietary interventions, followed by young adults. GBD provides comprehensive and objective data that can guide the designation of policies and measures to effectively ameliorate the negative effects of dietary risk. Considering that eating habits are very complex personal behaviors, analyzing the health effects of a certain dietary risk alone may lead to ignoring the superposition of certain factors. In the future, it is necessary to establish an evaluation model for joint analysis of multiple dietary risk factors.

Limitations of the study

There are some limitations in this study although the GBD database provides a relatively detailed estimate of China's dietary burden. Similar to previous reports (1, 15), the data came from various regions and countries may have huge differences in the accuracy, quality, comparability, and the extent of data loss, which inevitably caused the value deviations, even though several statistical methods are used to adjust the data as much as possible. In addition, our analysis of the dietary burden in China is implemented at the national level without further analyzing local features, such as the differences between urban and rural areas.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HX and XT conceived, analyzed, drew, and drafted the manuscript. XG contributed to data analysis. TY and JL consistently contributed to references as well as drew the figures. DD edited the manuscript for submission. DS reviewed and approved the submitted manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.997773/full#supplementary-material

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EDITED BY
Mainul Haque,
National Defense University of Malaysia, Malaysia

REVIEWED BY
Maria Morales Suare-Varela,
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Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh
Susmita Sinha,
Khulna City Medical College and Hospital, Bangladesh
Kona Chowdhury,
Gonoshathaya Samaj Vittik Medical College, Bangladesh

*CORRESPONDENCE
Zhihui Li
zhihuili@mail.tsinghua.edu.cn
Ai Zhao
aizhao18@tsinghua.edu.cn

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Association between dairy consumption and the risk of diabetes: A prospective cohort study from the China Health and Nutrition Survey

Yucheng Yang[1,2], Xiaona Na[1,2], Yuandi Xi[3], Menglu Xi[1,2], Haibing Yang[1,2], Zhihui Li[1,2]* and Ai Zhao[1,2]*

[1]Vanke School of Public Health, Tsinghua University, Beijing, China, [2]Institute for Healthy China, Tsinghua University, Beijing, China, [3]School of Public Health, Capital Medical University, Beijing, China

Diet is closely related to the risk of diabetes; yet the relationship between dairy consumption and the risk of diabetes is unclear with conflicting evidence from previous studies. This study used data from the Chinese Health and Nutrition Survey to investigate the association between dairy consumption and diabetes. A total of 15,512 adults were included; dairy consumption at each survey was assessed by the 3-day 24-h recall and weighed food record methods, and diabetes occurrence was derived from self-reported information. The association between dairy consumption and diabetes was explored using Cox regression and further stratified with BMI and energy intake. Results indicated that 12,368 (79.7%) participants had no dairy consumption, while 2,179 (14.0%) and 947 (6.1%) consumed dairy at 0.1–100 and >100 g/day, respectively. After adjusting for potential confounders, dairy consumption of 0.1–100 g/day was associated with lower risk of diabetes in all participants (HR 0.53, 95% CI:0.38 –0.74; $P < 0.001$) and males (HR 0.50, 95% CI: 0.31–0.80; $P = 0.004$). According to the restricted cubic splines (RCS), the protective effect on diabetes was significant in the total population with dairy consumption ranging from 25 to 65 g/day (HR < 1, $P = 0.025$). In the stratified analysis, consuming 30–80 g/day was associated with reduced diabetes risk among the ≤2,000 kcal/day energy intake group (HR < 1, $P = 0.023$). In conclusion, dairy consumption was inversely associated with a reduced diabetes risk in Chinese population. Further studies are required to examine the optimal level of dairy consumption for preventing diabetes in the Chinese population.

KEYWORDS

dairy consumption, milk, BMI, energy intake, diabetes

Introduction

Diabetes affected the health of approximately 425 million people worldwide in 2015, and it is estimated that this number will increase to 629 million by 2040 (1). In China, the total number of diabetic patients was about 109.6 million, accounting for 10.6% of China's total population (2). The risk factors for diabetes are complex, including obesity, family genetics, lifestyle, and diet (3, 4). Growing evidence has suggested that dietary and nutritional factors, including dairy consumption, may play an important role in the development of diabetes (5, 6).

Dairy is a source of human nutrition and plays an important role in a balanced diet (7, 8). Several epidemiological studies have shown that high consumption of dairy may have protective effects against cancer, coronary heart disease, and all-cause mortality (9–12). Previous studies revealed that dairy can promote weight loss and improve body composition in adults, and it likely contributes to reducing the risk of diabetes (13, 14). However, recent epidemiologic studies on the association between dairy consumption and diabetes have shown conflicting results. A systematic review and meta-analysis showed that higher consumption of dairy was positively associated with diabetes, but this association was found only in Asian and Australian populations, not American and European populations (6). Nevertheless, a study that followed 3,454 middle-aged and elderly Spanish populations found that high consumption of dairy products, especially yogurt, was beneficial in preventing diabetes (15). A study of three large prospective cohort studies in the US evaluated the relationship between dairy consumption and diabetes found that yogurt was associated with a lower risk of diabetes, whereas cheese had the opposite effect (16). Another study on Dutch adults showed that dairy consumption was not associated with diabetes (17).

Different from western countries, dairy products are rarely included in traditional Chinese diets. With the rapid advancement of urbanization, the consumption of dairy products by Chinese residents has been increasing. We hypothesized there is a benefit of dairy consumption on diabetes prevention in the Chinese population. To test this hypothesis, data from a nationwide, prospective cohort study with long-term follow-up was used to explore the associations between dairy consumption and diabetes in the Chinese population. In addition, whether BMI and energy intake affect the relationship between dairy consumption and diabetes or not was further examined.

Materials and methods

Study design and participants

This study was a secondary analysis of data collected from an ongoing prospective cohort study named China Health and Nutrition Survey (CHNS) (18), which completed ten rounds from 1989 to 2015. All data for this study are publicly available on the website http://www.cpc.unc.edu/projects/china. All participants signed informed consent before enrolling in the study. This study was approved by the National Institute of Nutrition and Food Safety (China) and the institutional review committees of the University of North Carolina (USA).

Since the dietary data codes for 1989 and 1993 were not identifiable from the CHNS database, in this study, we used the data collected from this longitudinal open cohort study in 1997, 2000, 2004, 2006, 2009, 2011, and 2015. Because the year of participants entering the cohort was varied, the time each participant entered the cohort was the individual's baseline. By the end of 2015, there were 26,896 available participants in the CHNS, who had not been diagnosed with diabetes at baseline. We excluded participants younger than 18 years old at baseline ($n = 7,165$), participants with missing complete dietary data ($n = 33$), participants who had a total energy intake <500 or >4,500 kcal/day ($n = 30$), participants with a body mass index (BMI) > 40kg/m^2 ($n = 459$), and participants with fewer than two visits in this study ($n = 3,697$). Finally, we included 15,512 adults in our study from 1997 to 2015 (Figure 1).

Definition of diabetes

In our study, the outcome variable was primarily defined as self-reported diabetes. Diabetes was identified by one question in the questionnaire: 'Has your doctor ever told you that you have diabetes?' If the participant answered: 'Yes', then proceeded to ask: 'How old were you when you were diagnosed with diabetes?'

Covariates at baseline

The baseline questionnaire included questions on socio-demographic, lifestyle factors, and health-related information. Socio-demographic characteristics were specifically included as follows: age, gender, income, education level, and living area; lifestyle factors including smoking status and physical activity; health-related information including BMI and disease history. BMI was calculated as weight divided by height squared (kg/m^2). Physical activity included occupational physical activity, transportation physical activity, leisure time physical activity, and housework physical activity (19). Each participant's metabolic equivalent time of physical activity (MET hours/week) was calculated in weeks based on the allocation of metabolic equivalents (MET). Disease history was defined as having at least one of the following diseases: hypertension, myocardial infarction, stroke, and cancer.

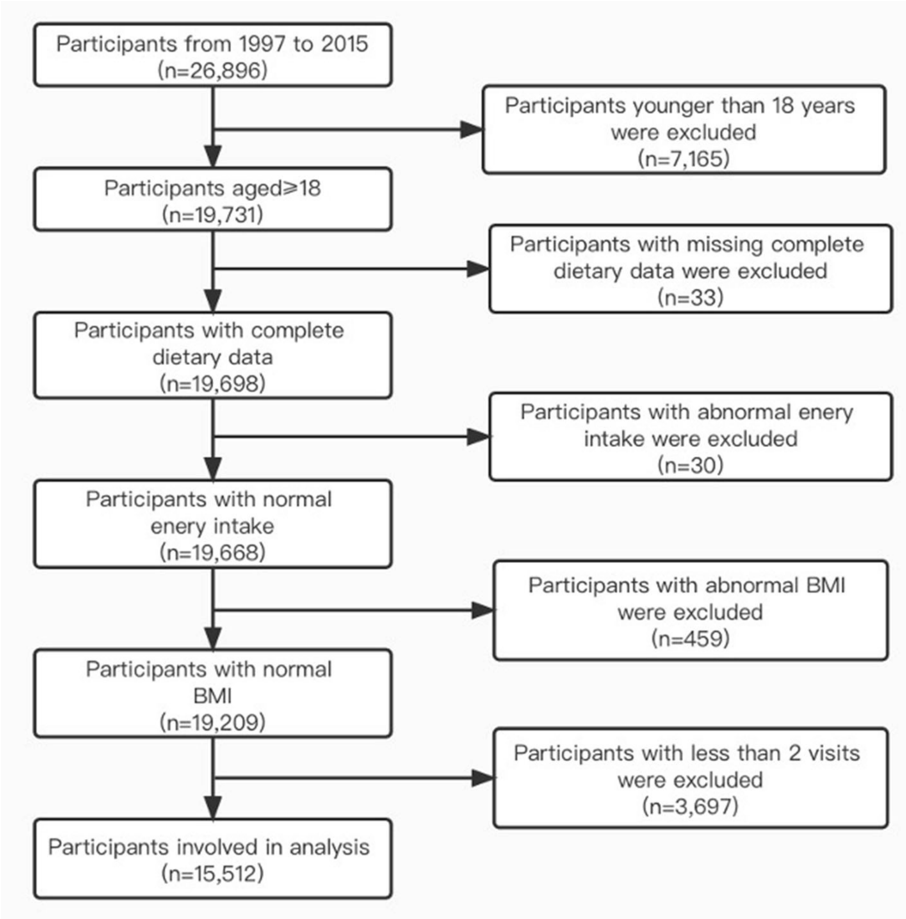

FIGURE 1
Flow chart of participant selection.

Dietary consumption information

The three-day (including two working days and one weekend day) 24-h recall was used to collect dietary data at the individual level. Participants were required to recall food intake except for oil, salt, and condiments within 24 h before the survey. The consumption of oil, salt, and condiments were investigated at the household level by weighing accounting method and further divided into individuals according to the person to family energy consumption ratio (20). The Chinese Food Composition Table (1991 (21), 2004 (22), and 2009 (23) editions) was referenced to calculate the energy and nutrient intake of individuals. Dairy consumption was defined as the total consumption of liquid milk, powdered milk, yogurt, and other dairy products such as cream and cheese. In this study, the average consumption of dairy from 1997 to 2015 was calculated based on a 3-day 24-h recall. Dairy consumption was divided into three groups: no consumption, 0.1–100 g/day, and >100 g/day.

Statistical analysis

Statistical analyses were performed using R version 4.1.1, a two side P-value < 0.05 considered to be statistically significant. The median and 25th and 75th quartiles were used to describe the non-normally distributed numerical variables, and frequency and percentage were used to describe the categorical variables. Chi-squares (χ^2) tests and one-way analysis of variance (ANOVA) were used to compare baseline characteristics of the total study population according to the dairy consumption level. The association between dairy consumption and diabetes was explored using Cox proportion hazard regression and further stratified by gender. The Cox proportion hazard regression included three models: Model 1 didn't adjust for any confounder; Model 2 adjusted for age, gender, education level, living area, income, smoking status, BMI, disease history, and physical activity; Model 3 further adjusted for intake of vegetables, fruit, meat, alcohol, carbohydrate, and energy based on Model 2. The non-linear association between dairy consumption and diabetes was also evaluated using Cox models with restricted cubic splines (RCS). We further examined the stratified analysis to identify the potential effects among participants with different BMI and energy intake levels. To verify the robustness of our research data, we did a sensitivity analysis to exclude participants who died within 2 years of the baseline survey.

Result

Baseline characteristics of the participants

Table 1 shows the baseline characteristics of the participants. Among the 15,512 participants included in this study, the mean age of participants was 43.4 years; 7,376 (47.6%) were males. In total, 12,368 (79.7%) of the participants had no dairy consumption in eight rounds of the survey from 1997 to 2015. Of participants with dairy consumption, 2,179 (14.0%) and 947 (6.1%) consumed 0.1–100 g/day and >100 g/day dairy, respectively. Participants with higher consumption were older, had smoked, and had lower levels of education and income; meanwhile, BMI and physical activity levels tended to increase with dairy consumption. In addition, statistical differences in age, gender, living area, and disease history were also significant.

Dietary intake characteristics of the participants

Table 2 shows the dietary intake characteristics of the participants. Foods and nutrients consumption among the three groups were statistically significant. Compared with the no consumption group, participants with the highest dairy consumption had a higher intake of meat, eggs, protein, and calcium, but lower consumption of cereals, carbohydrates, and energy. Furthermore, participants with higher dairy consumption generally had a lower intake of fruits, fats, and dairy calcium, but a higher intake of vegetables.

Association between dairy consumption and risk of diabetes

Table 3 shows the associations between dairy consumption and diabetes. During a median follow-up of 9.0 years, a total of 390 (2.5%) diabetes cases were newly diagnosed. No association was found between dairy consumption and diabetes in the crude model. After multivariable adjustment (Model 2), an inverse association was observed between consuming 0.1–100 g/day of dairy and diabetes (HR 0.53, 95% CI: 0.38–0.74; $P < 0.001$); a similar relationship was observed in Model 3 (HR 0.60, 95% CI: 0.43–0.86; $P = 0.005$) in which food and nutrient consumption was further adjusted. However, among those who consumed >100 g/day of dairy, dairy consumption was not associated with the risk of diabetes.

In the gender stratified analysis, there were no associations between dairy consumption and diabetes in females. However, after multivariable adjustment (Model 2), consuming 0.1–100 g/day of dairy was related to a lower risk of diabetes in comparison to no dairy consumption in males (HR 0.50, 95% CI: 0.31–0.80; $P = 0.004$), and the similar relationship was observed in Model 3 (HR 0.61, 95% CI: 0.37–0.98; $P = 0.044$).

Non-linear association between dairy consumption and risk of diabetes

The non-linear relationships between dairy consumption and diabetes among the overall population and certain populations are shown in Figure 2. Among the total participants, dairy consumption of about 25–65 g/day was associated with a decreased risk of diabetes (HR < 1, $P = 0.025$), then the risk of diabetes increased with increasing consumption. In the subgroup analysis, there was no association between dairy consumption and the incidence of type 2 diabetes at different BMI levels. Among those with an energy intake of ≤2,000 kcal/day, dairy consumption of about 30–80 g/day was associated with a decreased risk of diabetes (HR < 1, $P = 0.023$), but no association was observed in the higher energy intake groups.

Sensitivity analysis

In the sensitivity analysis (Supplementary Table 1), we excluded participants who died within 2 years of the baseline survey. Among all participants and male participants, the associations between dairy consumption on average and diabetes were similar to the results shown in Table 3. However, for female participants, compared with the no consumption group, there was an additional positive association between consuming 0.1–100 g/day of dairy and diabetes (HR 0.55, 95% CI: 0.34–0.88; $P = 0.013$) in Model 2.

Discussion

In the current study, we investigated the association between dairy consumption and diabetes among Chinese adults. We found that, in 15,512 individuals, there was a non-linear association between dairy consumption and diabetes. Those who consumed 0.1–100 g/day of dairy were positively associated with diabetes compared to the no dairy consumption group.

TABLE 1 Baseline characteristics of the participants by levels of dairy consumption.

	Dairy consumption			*P*
	No consumption *N* = **12,386**	**0.1–100g/day** *N* = **2,179**	**>100g/day** *N* = **947**	
Age, M (P25, P75)	41.0 [31.0,53.0]	43.0 [33.0,54.0]	50.0 [37.0,61.0]	<0.001
Gender, *n* (%)				<0.001
Male	6,008 (81.5%)	976(13.2%)	392 (5.31%)	
Female	6,378 (78.4%)	1203 (14.8%)	555 (6.82%)	
Education level, *n* (%)				<0.001
Junior high school or below	9,820 (86.7%)	1,134 (10.0%)	372 (3.28%)	
Senior high school or vocational school	2,071 (65.9%)	747 (23.8%)	325 (10.3%)	
University or above	484 (46.9%)	298 (28.9%)	250 (24.2%)	
Living area, *n* (%)				<0.001
East	4,022 (68.2%)	1,152 (19.5%)	725 (12.3%)	
Central	4,937 (85.6%)	746 (12.9%)	85 (1.47%)	
West	3,427 (89.1%)	281 (7.31%)	137 (3.56%)	
Income, yuan, *n* (%)				<0.001
<30,000	10,834 (81.2%)	1,871 (14.0%)	631 (4.73%)	
≥30,000	706 (61.3%)	216 (17.4%)	264 (21.3%)	
Smoking status, *n* (%)				<0.001
Never	8,305 (78.5%)	1,538 (14.5%)	736 (6.96%)	
Yes	4,079 (82.8%)	640 (13.0%)	2,110(4.26%)	
BMI, kg/m2, M (P25, P75)	22.3 [20.4,24.7]	23.0 [21.0,25.3]	23.4 [21.2,25.6]	<0.001
Physical activity, MET-hour/week, M (P25, P75)	130 [0.00,613]	180 [11.6,577]	501 [120,1,293]	<0.001
Disease history a, *n* (%)				<0.001
No	9,530 (81.0%)	12,569 (13.3%)	672 (5.71%)	
Yes	2,856 (76.3%)	610 (16.3%)	275 (7.35%)	

[a]Disease history included hypertension, myocardial infarction, stroke, and cancer.

The protective effect on diabetes was most significant in the population with dairy consumption ranging from 25 to 65 g/day.

Our finding on the positive association between dairy consumption and risk of diabetes was supported by previous studies in Western populations, such as European Prospective Investigation into Cancer and Nutrition (EPIC) and Mediterranean populations (24–26). However, several studies have reported that higher dairy consumption can reduce the risk of diabetes (27, 28), this is contrary to our findings. This inconsistency may be attributed to differences in Chinese and Western dietary habits. Among the Chinese population, dairy consumption is generally low, and limited types of dairy are consumed. In this study, dairy products mainly included liquid milk, milk powder, yogurt, and other dairy products. But in the above studies, the definitions of dairy products were different: some included milk beverages or cream and ice cream (24, 26). On the other hand, the inconsistent results may be because of the potential confounders considered in different studies. In the current study, after further adjusting the baseline and dietary variables (model 3), the protective associations we expected were not observed, which may support the notion that the nutrients in dairy are the key protective factor regarding diabetes. In addition, it is generally believed that dairy consumption is associated with a healthier diet and a better lifestyle (29); the disappearance of the protective effect of dairy consumption on diabetes after adjusting for dietary factors may also be related.

The protective mechanism of dairy consumption on diabetes can be explained from the following aspects (Figure 3) (30–42). Firstly, dairy contains high amounts of essential micronutrients for our body, such as vitamin D, calcium, and magnesium, which can affect insulin sensitivity. Vitamin D may benefit pancreatic β cell function, and calcium and magnesium could both improve insulin sensitivity, thereby helping to improve insulin secretion, which is conducive to the control of blood glucose levels (30, 31). Secondly, whey protein and casein are the two most abundant proteins in dairy, of which whey protein can increase the concentration of amino acids after digestion and promote insulin secretion (32). Whey protein can also improve energy intake balance and promote weight loss, thereby affecting the development of diabetes (33, 34). Furthermore, leucine is an essential amino acid in protein, recent evidence points to the possibility that mitochondrial dysfunction may lead

TABLE 2 Dietary intake characteristics of the participants by levels of dairy consumption. Median (P25, P75).

	No consumption *N* = 12,368	0.1–100g/day *N* = 2,179	>100g/day *N* = 947	*P*
Food consumption				
Vegetables intake, g/day	215 [138,300]	205 [144,279]	240 [171,327]	<0.001
Fruit intake, g/day	0.00 [0.00,37.2]	46.7 [4.44,100]	100 [33.3,180]	<0.001
Meat intake, g/day	38.3 [10.0,74.4]	56.7 [31.5,91.6]	70.0 [36.7,110]	<0.001
Cereal intake, g/day	275 [192,367]	245 [185,314]	250 [193,327]	<0.001
Egg intake, g/day	13.3 [0.67,26.7]	25.7 [12.8,40.7]	36.8 [20.0,60.0]	<0.001
Alcohol intake, g/week	0.00 [0.00,579]	0.00 [0.00,600]	0.00 [0.00,181]	<0.001
Energy and nutrient consumption				
Carbohydrate intake, g/day	300 [242,361]	258 [216,300]	223 [174,275]	<0.001
Fat intake, g/day	65.5 [49.6,83.9]	77.1 [61.8,94.7]	75.2 [57.8,95.4]	<0.001
Protein intake, g/day	63.4 [53.2,74.6]	67.8 [57.9,79.5]	71.6 [58.5,85.2]	<0.001
Energy intake, kcal/day	2,098 [1,772, 2,444]	2,037 [1,751, 2,337]	1,904 [1,577, 2,216]	<0.001
Total calcium intake, g/day	343 [273,435]	414 [338,505]	579 [470,731]	<0.001
Dairy calcium intake, g/day	0.00 [0.00,0.00]	39.3 [16.3,68.8]	173 [136,236]	<0.001

TABLE 3 HRs (95% CIs) of diabetes risk according to dairy consumption.

	No consumption	0.1–100g/day	*P*	>100g/day	*P*
All participants					
Case/*n*	327/12,386	44/2,179		19/947	
Model 1	1.00 (Reference)	0.76 [0.56, 1.05]	0.095	1.52 [0.96, 2.43]	0.076
Model 2	1.00 (Reference)	0.53 [0.38, 0.74]	<0.001	0.96 [0.57, 1.57]	0.865
Model 3	1.00 (Reference)	0.62 [0.44, 0.88]	0.008	1.516 [0.88, 2.61]	0.132
Male					
Case/*n*	164/6,008	22/976		8/392	
Model 1	1.00 (Reference)	0.82 [0.52, 1.28]	0.376	1.47 [0.72, 3.01]	0.289
Model 2	1.00 (Reference)	0.50 [0.31, 0.80]	0.004	0.82 [0.39, 1.75]	0.610
Model 3	1.00 (Reference)	0.61 [0.37, 0.98]	0.044	1.32 [0.60, 2.93]	0.488
Female					
Case/*n*	163/6,378	22/1,203		11/555	
Model 1	1.00 (Reference)	0.72 [0.46, 1.12]	0.149	1.58 [0.85, 2.93]	0.146
Model 2	1.00 (Reference)	0.55 [0.34, 0.89]	0.146	1.10 [0.55, 2.18]	0.791
Model 3	1.00 (Reference)	0.66 [0.11, 1.09]	0.109	1.57 [0.74, 3.37]	0.290

Model 1 had no adjustment for confounders; Model 2 adjusted for age, gender, education level, living area, income, smoking status, BMI, disease history, and physical activity; Model 3 was based on Model 2 and further adjusted for intake of vegetables, fruit, meat, alcohol, carbohydrate, and energy.

to insulin resistance, and the leucine of dairy could promote mitochondrial production and increase the body's antioxidant capacity, which provides a possible way to relieve insulin resistance (35–38). Thirdly, the oligosaccharides contained in dairy can promote the growth of bifidobacterium growth in the gut, and bifidobacterium has the effect of inhibiting obesity (39), which is an important cause of diabetes. Additionally, in a rodent study, mice fed a high-dairy diet reduced the number of obesity-causing bacteria such as Desulfovibrio and Bacteroidetes (40), which can affect the development of diabetes. Consumption of dairy products can also increase the number of butyrate-producing bacteria in the Firmicutes phylum. Butyrate is an anti-inflammatory short-chain fatty acid that regulates gut health and improves beta cell function, thereby reducing insulin resistance (41, 42).

A dose-response meta-analysis suggested a linear inverse association between low-fat dairy and diabetes (43). However, in our study, we found a non-linear relationship between dairy consumption and diabetes. The protective effect was only observed in those who consumed 0.1–100 g/day of dairy

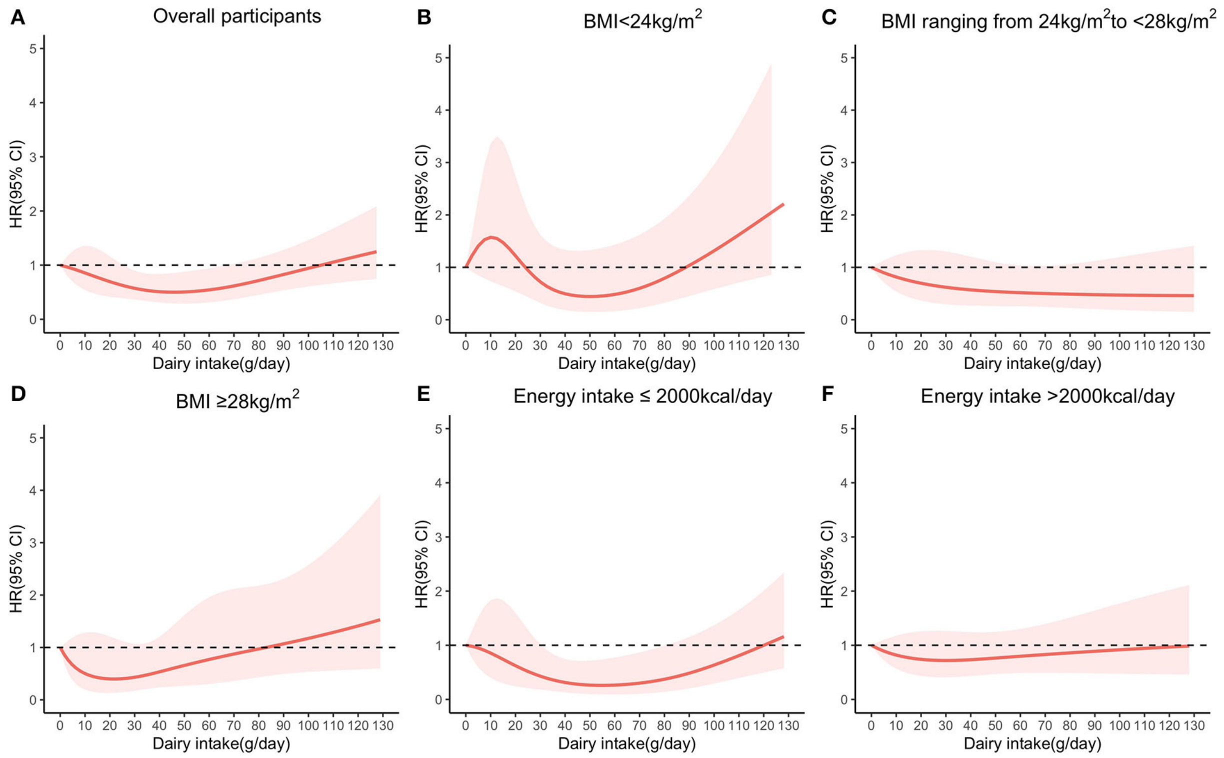

FIGURE 2
Restricted cubic spline plots to evaluate relationships between dairy consumption and diabetes among **(A)** overall participants; **(B)** participants with BMI < 24 kg/m^2; **(C)** participants with BMI ranging from 24 to <28 kg/m^2; **(D)** participants with BMI ≥28 kg/m^2. According to the median energy intake of 2,094.4 kcal/day, we stratified energy intake as **(E)** participants with energy intake of ≤2,000 kcal/day and **(F)** participants with energy intake of >2,000 kcal/day. HR and 95% CI were adjusted for age, gender, education level, living area, income, smoking status, BMI, disease history, physical activity, vegetable intake, fruit intake, meat intake, carbohydrate intake, and energy intake. BMI and energy intake were not adjusted in the corresponding stratified model.

in adjusted Model 2; when participants' dairy consumption exceeded 100 g/day, no association was observed. More particularly, the RCS Cox regression in the current study further revealed that the consumption of 25–65 g/day of dairy might be associated with reduced diabetes risk. Previous research has pointed out that dairy may have adverse health effects when consumed in excess (12, 44, 45). This association may be due to the increased risk of hormone-dependent diseases caused by animal oestrogens in dairy (45, 46). A previous study in India also demonstrated that ingestion of excessive dairy could reduce the insulin sensitivity of individuals, thereby affecting the risk of diabetes (47). Moreover, higher dairy consumption is accompanied by greater energy intake, which increases body weight and therefore may increase the risk of developing diabetes (48). In the stratified analysis, we also found a significant inverse association between dairy consumption and diabetes risk in the ≤2,000 kcal/day energy intake group, which supports the previous view that there is a close relationship among dairy consumption, energy intake, and the risk of diabetes (49).

It should be noted that the recommended amounts for dairy consumption in the dietary guidelines of the US and Australia are 710 ml and 500 g, respectively (50, 51). According to the Chinese Dietary Guidelines (2016) (52), the recommended consumption of dairy products is 300 g/day, while the latest Chinese Dietary Guidelines (2022) revised the recommended consumption of dairy products to 300–500 g (53). According to the RCS analysis, the risk of diabetes was reduced only with 25–65 g/day of dairy consumption in the total population. Similar to the results of a previous study conducted in a Chinese population, higher dairy consumption was not necessarily better (12). Although according to the current Chinese study, there is still a great gap between dairy consumption (average consumption is 12 g/d) and recommendation (53), it is time to seriously consider the most optimal consumption level of dairy for varied populations. The recommended consumption of dairy for the Chinese population may require further verification.

In the stratified analyses, we found that the association between dairy consumption and diabetes also differed by gender. Among males, those who consumed 0.1–100 g/day of dairy had a significantly lower risk of diabetes in adjusted Models, which was

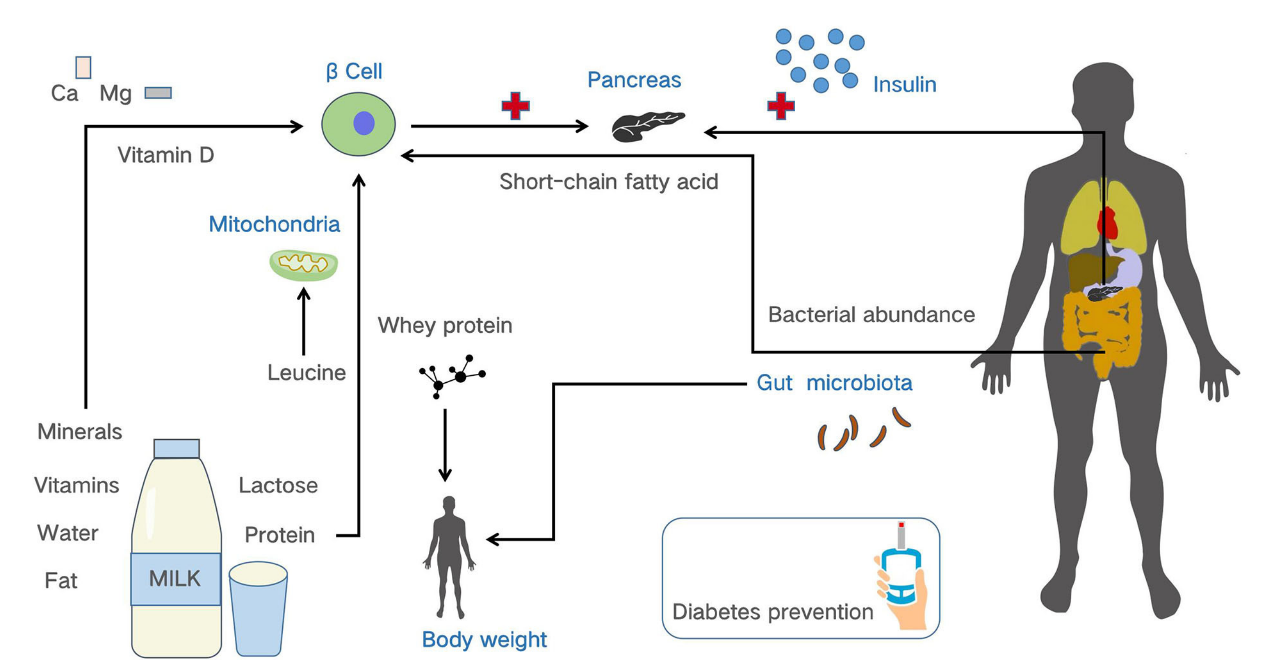

FIGURE 3
The possible mechanisms of dairy components in preventing diabetes (30–42).

similar results to the Health Examinees (HEXA) study among Korean adults (54). However, a study of 2,375 males aged 45–59 years found no association between the consumption of dairy and the risk of diabetes (55). Interestingly, a cross-sectional study in Qingdao, China found that an inverse relationship between diabetes prevalence and dairy consumption in females (56), but not in males, which is the exact opposite of our findings. Prolactin is involved in regulating glucose homeostasis and insulin sensitivity (57). For females under the action of body hormones, the hormonal effects of dairy may not be significant; however, this active substance may affect the risk of diabetes in males. The gender differences due to different socio-cultural characteristics and dietary structures also differ between males and females. A prospective study among black women in the U.S. found no link between yogurt and diabetes because the association was attenuated after controlling for healthy eating behaviors associated with yogurt consumption (58). However, our study did not measure hormone levels in each participant and dairy, and there is insufficient evidence to determine whether dairy consumption changed insulin levels. In conclusion, further research is needed to clarify the distinctive effect of dairy consumption on the risk of diabetes in different genders.

Obesity is closely related to chronic non-communicable diseases, including diabetes (48, 59). Several studies have revealed the certain role of obesity in the chain of association between dairy consumption and obesity. Recent studies has found that neither whole milk nor low-fat milk was associated with weight change, and cheese consumption may be beneficial for lowering BMI (60). A prospective cohort study of postmenopausal women found an inverse relationship between low dairy consumption and diabetes; this relationship was more pronounced in the high BMI group (61). One animal study revealed the possible mechanism that dairy products can modulate the gut microbiota and circulate metabolites, resulting in weight loss (40). However, there is no evidence in our study that dairy consumption was associated with the risk of diabetes in different BMI categories (<24, from 24 to <28, ≥ 28 kg/m^2), which could necessitate further investigation to verify.

Limitation

To our knowledge, this is the first report that there is a non-linear association between dairy consumption and diabetes in the Chinese population. However, several limitations of the current study should be noted. First, the determination of the outcome variable was based on self-reported diabetes rather than biochemical indicators. In CHNS, the blood samples of the participants were only collected in 2009 and limited biomarkers were measured, which does not allow us to diagnose diabetes, hence the incidence of diabetes among the overall population may be underestimated. Moreover, we did not distinguish between types of diabetes, and the incidence of specific types of diabetes and its association with dairy consumption could not be observed. Second, due to the low consumption of dairy in the

Chinese population, we did not distinguish between dairy types when analyzing the relationship between dairy consumption and diabetes, which may lead to inconsistencies between our findings and those of previous studies. Previous research pointed out that the relationship between dairy and diabetes appears to be related to dairy type (60). Besides, the proportions of micronutrients in different processed dairy products are varied (8, 62), therefore the mis-classification bias may not be ruled out in the current study. Third, dietary intake in this study was estimated from three dietary recall questionnaires, which may not represent long-term intake well and may suffer from recall bias. Furthermore, with the development of the economy, the consumption of dairy increases, and the dynamic changes of dairy consumption with age may also contribute to the development of diabetes. Finally, although our models adjusted for many covariates and the sensitivity analysis showed that the results were stable, the relationship between dairy consumption and diabetes might be ascribed to other potential residual confounding bias, such as genetic backgrounds of diabetes and other environmental factors.

Conclusion

In conclusion, we found that moderate consumption of dairy can help reduce the risk of diabetes in the Chinese population. As the effects of dairy consumption on the health of different populations are not uniform, our study provides new insights that require careful consideration of the optimal consumption amount of dairy for diabetes prevention.

Recommendation

In view of the findings of this current study and the dietary habits of the Chinese population, we suggest that moderate consumption of dairy in daily life in the Chinese population may be an effective lifestyle intervention for the prevention of diabetes. In addition, the energy from dairy should be taken into consideration, and balanced energy in the daily diet should be achieved.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving human participants were reviewed and approved by the National Institute of Nutrition and Food Safety (China) and the institutional review committees of the University of North Carolina (USA). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YY: conceived the idea. YY and XN: performed the statistical analyses and designed the study. YY, ZL, and AZ: wrote the manuscript. YX, MX, and HY: participated in the discussion and revised the manuscript. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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EDITED BY
Farhana Akter,
Chittagong Medical College, Bangladesh

REVIEWED BY
Kona Chowdhury,
Gonoshathaya Samaj Vittik Medical College, Bangladesh
Subhasish Das,
International Centre for Diarrhoeal Disease Research (ICDDR), Bangladesh

*CORRESPONDENCE
Getachew Tilahun Gessese
getas125@yahoo.com

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Breastfeeding performance index and associated factors among children aged 0–6 months in Ethiopia: Analysis of the 2019 Ethiopia Mini Demographic and Health Survey

Getachew Tilahun Gessese[1]*, Berhanu Teshome Woldeamanuel[2], Takele Gezahegn Demie[3], Tolesa Diriba Biratu[2] and Simegnew Handebo[3]

[1]Department of Nutrition, School of Public Health, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, [2]Department of Epidemiology and Biostatistics, School of Public Health, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, [3]Department of Health Education and Health Promotion, School of Public Health, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

Background: Infants under the age of 6 months are commonly affected by malnutrition globally. The higher the breastfeeding performance index (BPI), the greater the advantage of breastfeeding will be. However, there is a lack of literature in the context of Ethiopia. Therefore, this study is aimed at investigating the magnitude and determinants of the breastfeeding performance index score among mothers of children under the age of 6 months in Ethiopia.

Methods: This study was conducted using the 2019 Ethiopia Mini Demographic and Health Survey (EMDHS) dataset. A stratified, two-stage cluster sampling technique was used in the study. The survey data were weighted using the "svy" function in STATA version 16. Descriptive statistics, bivariable and multivariable logistic regression were employed in the analysis. An adjusted odds ratio (*AOR*) with a 95% confidence interval (*CI*) was reported. The results were considered statistically significant if the p-value was < 0.05. The goodness of fit of the model was checked using the Hosmer–Lemeshow test.

Results: A total of 4,273 mothers with children under the age of 6 months were included in the analysis. Our analysis revealed that the prevalence of low breastfeeding performance index was 79.05% (95% *CI*: 78.01, 81.59). A unit increase in child age (*AOR* = 11.56; 95% *CI*: 6.97, 19.17), the richest wealth quintile (*AOR* = 2.76; 95% *CI*: 1.18, 6.5), a higher level of education (*AOR* = 5.41; 95% *CI*: 2.08, 14.05), being married or living with partner (*AOR* = 2.73; 95% *CI*: 1.18, 6.27), being women from Somali (*AOR* = 5.11; 95% *CI*: 2.08, 12.56), Afar (*AOR* = 3.03; 95% *CI*: 1.16, 7.91), Oromia (*AOR* = 1.88; 95% *CI*: 1.03, 3.41), Diredawa city administration (*AOR* = 2.89; 95% *CI*: 1.04, 8.07), and antenatal care (ANC) visit (*AOR* = 2.05; 95% *CI*: 1.31, 3.19) were positively associated with the low breastfeeding performance index.

Conclusion: The prevalence of the low breastfeeding performance index was found to be high. Hence, the findings of the study suggest the need to target interventions aimed at improving breastfeeding performance toward mothers with higher socioeconomic and demographic status and educational status. Antenatal care clients are among the targets of the intervention.

KEYWORDS

breastfeeding, breastfeeding performance index, infant feeding, breast milk, Ethiopia

Introduction

Many developing countries are affected by malnutrition, which has serious ramifications for individual health and national development in terms of lost human capital and economic output (1–4). Infants under the age of 6 months are commonly affected by malnutrition globally (4). The third Copenhagen Consensus in 2012 highlighted nutrition as the best investment for poor countries, with every dollar invested yielding a US$ 30 return (5). As optimal breastfeeding is one of the recommended nutrition interventions among infants and young children and contains various subcomponents (6, 7), the breastfeeding performance index (BPI) therefore attempts to synthesize key elements of optimal breastfeeding habits into a single summary variable by combining the many characteristics of breastfeeding practices (8).

The World Health Organization (WHO) defines optimal breastfeeding as the initiation of breastfeeding within 1 h of birth, exclusive breastfeeding for the first 6 months of life, and continuous breastfeeding for up to 2 years or beyond, with appropriate complementary feeding starting at 6 months (5, 9).

Adhering to all three WHO recommendations is crucial to lowering both newborn and child mortality as breastfeeding protects against illness and aids the recovery of sick children (10, 11). This is because for newborns, breast milk is the best food. It is safe, hygienic, and includes antibodies that help protect children against a variety of ailments. Breastmilk provides all of the energy and nutrients that an infant requires during the first few months of life, and it continues to provide up to half or more of a child's nutritional needs during the second half of the 1st year and up to one-third of a child's nutritional needs during the 2nd year (12). Therefore, optimal breastfeeding reduces the risk of child mortality (10, 13–17). In addition, children who are breastfed score higher on intelligence quotient (IQ) tests, are less likely to be overweight or obese, and are less likely to develop diabetes later in life (9, 12, 18).

Except for a few rare medical conditions specified by the WHO and UNICEF, exclusive breastfeeding from birth is possible, and virtually every mother can breastfeed (19). Compared with exclusively breastfed newborns, infants who were predominantly, partially, or not breastfed had a significantly higher risk of all-cause and infection-related mortality (10). Therefore, to promote the best growth, development, and health, infants should be breastfed exclusively for the first 6 months of life (20).

However, breastfeeding duration is shorter in high-income countries than in low and middle-income ones. Even in low- and middle-income nations, only 37% of infants younger than 6 months are breastfed exclusively (21). Nearly two out of every three infants are not exclusively breastfed for the recommended 6 months, a rate that has remained unchanged for the past two decades (12), though it is known that mothers should practice exclusive breastfeeding (22).

The national Infant and Young Child Feeding (IYCF) Strategy of Ethiopia recommends exclusive breastfeeding as one of the components in its guide to infant and young child feeding practice (23), and has been implemented over decades. However, in 2019, only 59% of children under the age of 6 months are exclusively breastfed. In a similar year, 72% of newborns were breastfed within 1 h of birth, declining from 73% in 2016; and 12% of children received a prelacteal food, increasing from 8% in 2016. Furthermore, contrary to the recommendation that children under 6 months be exclusively breastfed, 14% of infants also received water, 1% received non-milk liquids, such as juices and clear broth, and another 8% received other milks before reaching the age of 6 months (24).

Mixed feeding is one of the global challenges, having its own risks to health and child survival. According to Monge-Montero C. et al.'s systematic review and meta-analysis, the overall prevalence of mixed milk feeding varied between 23 and 32 across different age intervals and geographies around the world; the highest rate was identified for the age group of 4–6 months (25). In addition, a study revealed its impact on child health, indicating the number of episodes of bronchiolitis in infants with exclusive breastfeeding and mixed feeding was reduced by 41 and 37%, respectively, compared with infants who did not breastfeed. This indicates that though mixed feeding is better than not breastfeeding at all, switching from exclusive breastfeeding to mixed feeding increased the incidence of bronchiolitis (26).

As a result, the higher the breastfeeding performance index, the greater the advantage of breastfeeding will be. Senarath U et al. found that assessing breastfeeding practice using the breastfeeding performance index was both feasible and beneficial for intervention (27).

According to the scant literature on the subject available in Ethiopia, the prevalence of low, medium, and high BPI was 18.41, 57.96, and 23.63%, respectively (8). Another recent study by Hailu WS et al. indicated that the prevalence of low breastfeeding performance index was 40.7% in the north-west part of Ethiopia (28).

Various factors were found to have an effect on the low breastfeeding performance index. According to Hailu WS et al., occupation of the mother, marital status, antenatal visits, postnatal care follow-up, attitudes of mother toward breastfeeding, and breast-feeding knowledge of the mother, were among the determinates of the BPI score (28).

Given the scarcity of recent evidence on the breastfeeding performance index in the country in general and with regard to what factors contribute to the determinants of the breastfeeding performance index in particular. Therefore, the objectives of this analysis were to determine the prevalence of the breastfeeding performance index and identify factors affecting it to guide evidence-based interventions and policy directives.

Methods

Study design

With permission of the Demographic and Health Survey (DHS) program, a secondary data analysis was performed using the 2019 EMDHS extracted from http://www.DHSprogram.com. The Ethiopian Demographic and Health Survey (EDHS) was undertaken in nine Ethiopian regions (Tigray, Afar, Amhara, Oromia, Somali, Benishangul Gumuz, the Southern Nations Nationalities and Peoples (SNNP), which currently includes Sidama and Southwestern Ethiopia regions, Gambella, and Harari) and two chartered city administrations (Addis Ababa and Dire Dawa) from 21 March 2019 to 28 June 2019. The study design was cross-sectional and is described in detail in the Ethiopia Mini Demographic and Health Survey (EMDHS) 2019 (29).

Sampling technique and study population

The sample of the 2019 Demographic and Health Survey (EDHS) was designed to provide data at the national (urban and rural) and regional levels. A stratified, two-stage cluster sampling technique was used in the study. Enumeration areas (EAs) were the sampling units for the first stage of the 2019 EDHS sample, where 305 of them were randomly chosen. In the second stage, a representative sample of 8,794 households with 9,012 reproductive-age women who gave birth in the last 5 years was chosen. However, this study's analysis was limited to 4,273 women with infants aged 0–6 months (29).

Data extraction

The Ethiopian DHS 2019 data were downloaded in STATA format from the Measure DHS website. We explored and coded the data after having a better knowledge of the details. The final analysis used data with information on a wide range of prospective variables, such as socio-demographic traits, economic variables, and breastfeeding patterns.

Study variables

The outcome variable was the breastfeeding performance index (BPI) among 0–6-month old children. The BPI was calculated by assigning one point to each of seven infant feeding practices: first suckling within an hour of birth; absence of pre-lacteals; non-use of feeding bottles; current breastfeeding; not receiving liquids, formula, or other milk; and not receiving solids in the previous 24 h (Table 2). A low breastfeeding performance index score was declared for women who did not practice one or more of the breastfeeding performance index scoring variables according to the recommended standard, leading to partial breastfeeding practice. Therefore, women with ≤6 breastfeeding performance scores were categorized as having a low BPI, whereas women with a breastfeeding performance score of 7 were considered as having a high BPI. The independent variables in the study were: child characteristics, such as sex and age; mother's characteristics, such as age, level of education, marital status, religion, region, place of residence, use of ANC, place of delivery, cesarean section delivery, post-natal care, and the household wealth index were used to estimate the household's economic status.

Statistical analysis

STATA version 12 was used to analyze the data. The survey data were weighted using the "svy" function in STATA version 16. Descriptive statistics in the form of frequencies and percentages with confidence intervals (*CIs*) were used to describe the study population in relation to independent variables. The association between the breastfeeding performance index and independent variables was analyzed using binary and multivariable logistic regression models. Variables with a statistically significant association with BPI in bivariable logistic regression (*p*-value 0.2) were considered for inclusion in the final multivariable model. In the final multivariable logistic regression model, the relationship of BPI with independent variables was considered significant at a *p*-value of$<$ 0.05. Both crude odds ratios (*CORs*) and adjusted odds ratios (*AORs*) were reported with 95% confidence intervals. The goodness of fit of the model was checked using the Hosmer–Lemeshow test ($F = 0.25$). Tables and graphs were used to summarize the findings.

Results

Socio-demographic and reproductive health characteristics of the respondents

A nearly equal proportion (one in every five) of respondents came from one of the five wealth index categories. Almost half (51.6%) of women did not have any exposure to education, while more than one-third (36%) had only a primary level of education. The vast majority (93.2%) of women were married or living with their partners, and nearly 90% of them were from any of the three bigger regions; Oromia, Amhara, and SNNP regions. About 43.5% of women attended antenatal care (ANC) four or more times and nearly a quarter of them, 24.1 and 23.3%, respectively, had infants aged 0– and 1–month old (Table 1).

TABLE 1 Socio-demographic and reproductive health characteristics of women and children enrolled in the analysis of the breastfeeding performance index (BPI), the 2019 Ethiopia Mini Demographic and Health Survey (EMDHS) ($n = 4,273$).

Variables		Weighted frequency	Weighted percentage
Wealth index	Poorest	880	20.60
	Poor	883	20.68
	Middle	838	19.61
	Richer	800	18.71
	Richest	872	20.40
Region	Tigray	313	7.40
	Afar	53	1.25
	Amhara	892	21.08
	Oromia	1623	38.39
	Somali	218	5.16
	Benishangul Gumuz	49	1.17
	SNNPR*	886	20.95
	Gambella	21	0.5
	Harari	12	0.29
	Addis Ababa	138	3.27
	Diredawa	23	0.55
Place of residence	Urban	1120	26.23
	Rural	3152	73.77
Educational status of the mother	No education	2203	51.57
	Primary	1538	36.0
	Secondary	360	8.42
	Higher	171	4.01
Sex of the child	Male	2257	52.84
	Female	2015	47.16
Age of the child in months	0 month	1029	24.08
	1 month	996	23.32
	2 months	800	18.72
	3 months	564	13.21
	4 months	382	8.94
	5 months	245	5.72
	6 months	257	6.02
Age category of the mother	<20	209	4.89
	20-34	2964	69.37
	≥35	1099	25.73
Religion	Orthodox	1573	36.82
	Protestant	1234	28.90
	Muslim	1392	32.59
	Others**	72	1.70
Marital status	Married or living with partner	3983	93.23

(Continued)

Breastfeeding performance index

The breastfeeding performance index (BPI) scoring system for infants 0–6 months included seven components (Table 2). The minimum BPI score was 0 while the maximum was 7. The mean score and standard deviation (SD) for the breastfeeding performance index were 5.15 (1.39).

About a quarter (14.17%) of the respondents had no timely initiation of breastfeeding, and nearly one in ten respondents (10.38%) practiced prelacteal feeding. Nearly two-thirds (64.95) of the respondents were breastfed in the last 24 h (Table 2).

The prevalence of the low breastfeeding performance index was 79.05% (95% *CI*: 78.01, 81.59). This implies that only one out of five breastfeeding mothers with children under the age of 6 months correctly performs the recommended breastfeeding practice (Figure 1).

Factors associated with low breastfeeding performance index

In the final multivariable model adjusted for the potential confounders, the BPI was significantly associated with age of the child, wealth index, educational status, marital status, region of residence, and number of antenatal care visits.

A 1-month increase in child age increases the odds of low breastfeeding performance by eleven times ($AOR = 11.56$; 95% $CI = 6.97, 19.17$). The odds of having a low breastfeeding performance index were more than two and a half times higher in the richest wealth quintile than in the poorest ($AOR = 2.76$; 95% *CI*: 1.18, 6.5). In addition, the low breastfeeding performance index was more than five times higher among

TABLE 1 (Continued)

Variables		Weighted frequency	Weighted percentage
	Single or living alone	289	6.77
Antenatal care visits	Not attended	944	25.03
	1–3 times visits	1185	31.43
	Four and more visits	1642	43.54
Place of delivery	Home	1788	47.91
	Health facility	1944	52.09
Cesarean section delivery	No	3544	93.99
	Yes	227	6.01
Postnatal visit	No	3248	86.15
	Yes	522	13.85

*South Nations Nationalities and People's Region.
**includes Catholic, Traditional, and others.

TABLE 2 The breastfeeding performance index components and the scoring system among infants aged 0–6 months, Ethiopia, 2019.

Feeding practices		Weighted frequency	Weighted percentage	score
Timely initiation of breastfeeding	≤1 hr	2740	75.83	1
	>1 hr	873	24.17	0
Pre-lacteal feeding	Yes	375	10.38	0
	No	3239	89.62	1
Current breastfeeding	Yes	1305	64.95	1
	No	704	35.05	0
Liquids given	Yes	541	26.92	0
	No	1469	73.08	1
Bottle feeding	Yes	639	16.94	0
	No	3132	83.06	1
Solid food given	Yes	1305	64.95	0
	No	704	35.05	1
Formula milk given	Yes	78	3.88	0
	No	1932	96.12	1

women with a higher level of education than among women with no education (*AOR* = 5.41; 95% *CI*: 2.08, 14.05). Being married or living with a partner increases the odds of low breastfeeding performance (*AOR* = 2.73; 95% *CI*: 1.18, 6.27) as compared with singles or living alone due to divorce, widowed, or any other reason. Compared with women from the Tigray region, women from Somali (*AOR* = 5.11; 95 % *CI*: 2.08, 12.56), Afar (*AOR* = 3.03; 95% *CI*: 1.16, 7.91), Oromia (*AOR* = 1.88; 95% *CI*: 1.03, 3.41) regions, and Diredawa city administration (*AOR* = 2.89; 95% *CI*: 1.04, 8.07) had higher odds of having a low breastfeeding performance index. Having 1–3 antenatal care visits during their index child's pregnancy was associated with two times higher odds of low breastfeeding performance index (*AOR* = 2.05; 95% *CI*: 1.31, 3.19) than women with no antenatal care visits (Table 3).

Discussion

Breastfeeding, more than any other preventive measure, has the greatest potential influence on child health and mortality (30). Our analysis determined the breastfeeding performance of mothers having infants < 6 months of age by using the breastfeeding performance index, which comprises seven components, and identified factors contributing to low breastfeeding performance in Ethiopia from the 2019 Mini Demographic and Health Survey data of Ethiopia.

About four women out of five had a low breastfeeding performance index (79.05%). This indicates that the proportion of mothers with a high BPI was slightly lower in this study than the finding reported by Haile D. and Biadgilign S., where 23.6% of mothers had a high BPI (8). The difference may be related to the relatively higher cut-off point used to determine the low BPI category in our study that resulted in a low proportion of mothers with a high breastfeeding performance index.

Various maternal, child, and healthcare service-related factors were found to have affected the breastfeeding performance index. Our investigation revealed that child age, region of residence, household wealth quintile, antenatal care (ANC) contacts, educational status, and marital status as factors significantly associated with the breastfeeding performance index.

Child age is found to affect the breastfeeding performance index of mothers. For every 1-month increase in the child's age, mothers had an eleven times higher odds of low breastfeeding performance. Evidence indicates that as the age of the child increases, the probability of suboptimal breastfeeding increases (31–33). This could be related to mothers' tendency to substitute breastfeeding with other child feeding practices as the child's age advances. Substituting breastfeeding with other child feeding practices may be related to increased mothers' probability of getting back to work as the age of the child increases and maternity leave ends, leading mothers to cease breastfeeding early (32). Moreover, it may be related to shorter birth intervals and shorter duration of traditional postpartum care in Ethiopia by letting the mother stay in the home, which is for a maximum of 80 days (34).

In addition, economic status was among the factors impacting breastfeeding. Compared with women from the poorest wealth quintile category, the low breastfeeding performance index was more than two and half times higher

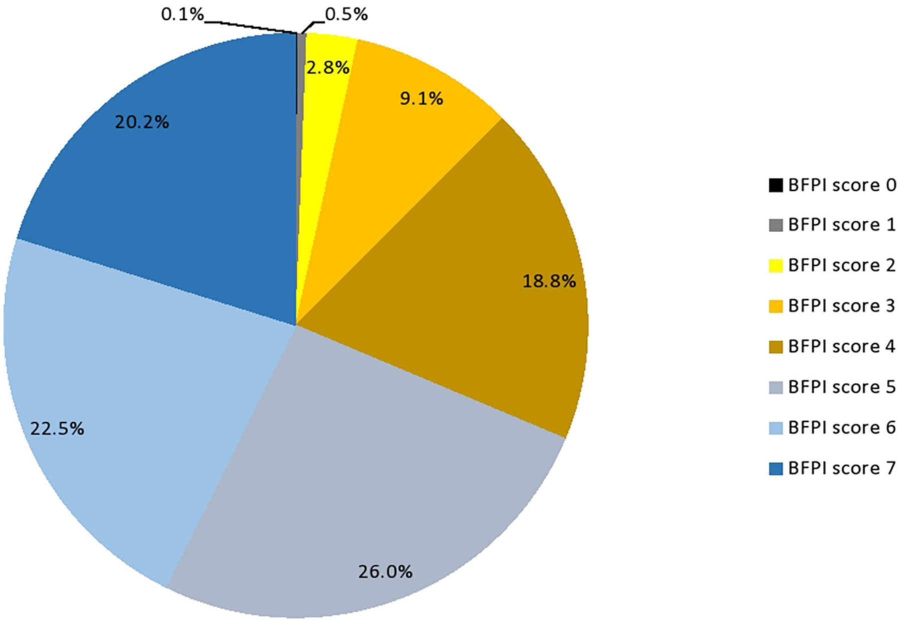

FIGURE 1
Breastfeeding performance score of reproductive age mothers in Ethiopia.

among women from the richest wealth quintile category. Even though some findings indicate that mothers with a higher income status breastfeed better (33, 35), in contrast, there are findings indicating that mothers with a higher income category breastfeed less than those from low income categories (36, 37) and this supports the finding in our study. This could occur because mothers with higher income levels can afford infant formula and thus easily substitute breastfeeding with it while focusing on other life activities. In addition, another study claimed that a lack of workplace breastfeeding laws, support, and arrangements may interfere with the breastfeeding practice of employed mothers (38) with a better income status.

Furthermore, having a higher educational status increased the odds of low breastfeeding performance among mothers. It was more than five times higher than those women with no education. Despite studies indicating a positive association between breastfeeding and education (39, 40), a study by Tang K. et al. supports our finding that mothers with higher educational status breastfeed less, particularly with regard to exclusive breastfeeding practice, as opposed to early initiation of breastfeeding (37). This may happen because their educational status enables mothers to understand the benefits of breastfeeding. On the other hand, women with a better educational status may be engaged in income-generating employment. Therefore, it may result in a lack of time to focus on breastfeeding practice as opposed to women with low educational status who tend to be housewives.

Unexpectedly, women who are married or have a partner living with them had an increased low breastfeeding performance index as compared with singles or those living alone due to divorce, widowed, or any other reason. However, similar findings were reported by studies in some parts of Ethiopia where single mothers breastfeed better than married mothers (33, 41). This might be related to both the income status and work situation of mothers. Married mothers and those who live with their partners may afford breast milk substitutes more than single mothers or those who live alone.

Our analysis revealed that having antenatal visits increased the odds of having a low breastfeeding performance index. Unlike the positive association between antenatal care services and breastfeeding practice reported elsewhere (42–44), findings in this nationally representative large-scale study may possibly indicate improper breastfeeding counseling to ANC attendant mothers. It may also be due to the selective accessibility of the antenatal service in the healthcare system of the country to those mothers who are wealthier, highly educated, and employed mothers with the capacity to afford breastfeeding substitutes and have less time freedom to breastfeed their children in line with the recommendation regardless of their breastfeeding literacy.

Regional differences were observed in the breastfeeding performance index. Compared with women from the Tigray region, women from Somali, Afar, and Oromia regions, and Diredawa city administration had Higher odds of having a low breastfeeding performance index. Similar inter-regional discrepancies were reported in Ethiopia (45),

TABLE 3 Factors associated with the BPI in children aged 0–6 months in Ethiopia, the bivariate and multivariate multilevel logistic regression analysis (n = 1,985).

Variables		Low BPI	
		COR (95% CI)	AOR (95% CI)
Age of the child		10.85 (6.52, 18.08)	11.56 (6.97, 19.17)
Wealth index	Poorest	1	1
	Poor	1.19 (.71, 1.99)	1.46 (.79, 2.70)
	Middle	1.31 (.81, 2.12)	1.79 (.99, 3.24)
	Richer	1.32 (.79, 2.21)	1.73 (.91, 3.29)
	Richest	2.87 (1.62, 5.08)	2.76 (1.18, 6.50
Educational status of the mother	No education	1	1
	Primary	1.28 (.88, 1.86)	1.27 (.91, 1.79)
	Secondary	1.15 (.65, 2.02)	.99 (.49, 2.02)
	Higher	6.21 (2.59, 14.86)	5.41 (2.08, 14.05)
Antenatal care visits	Not attended	1	1
	1–3 times visits	1.94 (1.27, 2.97)	2.05 (1.31, 3.19)
	Four and more visits	1.72 (1.18, 2.51)	1.40 (.88, 2.23)
Marital status	Married or living with partner	2.15 (.99, 4.64)	2.73 (1.18, 6.27)
	Single or living alone	1	1
Region	Tigray	1	1
	Afar	1.35 (.64, 2.89)	3.03 (1.16, 7.91)
	Amhara	1.42 (.76, 2.67)	1.74 (.82, 3.68)
	Oromia	1.28 (.68, 2.41)	1.88 (1.03, 3.41)
	Somali	1.69 (.83, 3.41)	5.11 (2.08, 12.56)
	Benishangul Gumuz	.82 (.48, 1.41)	1.20 (.60, 2.42)
	SNNPR	.79 (.40, 1.55)	.98 (.49, 1.95)
	Gambella	.82 (.45, 1.50)	.78 (.31, 1.93)
	Harari	1.46 (.71, 3.01)	1.51 (.68, 3.36)
	Addis Ababa	1.83 (.90, 3.69)	1.03 (.42, 2.55)
	Diredawa	2.67 (1.18, 6.03)	2.89 (1.04, 8.07)

which can be explained by variations in socio-economics, culture, and healthcare service availability and accessibility across regions.

Strength and limitations

One of the strengths of the study was that the analysis depends on a nationally representative survey with a large sample size that ensures high precision in the findings. In addition, the study dealt with a composite index, which enables us to determine the broader picture of breastfeeding practice, which otherwise could remain obscured within the individual practices that constitute the index and thus may mask the existence of important relationships between BPI and its determinants.

However, the limitation of this study is that we were unable to check the association between the low breastfeeding performance index and childhood illnesses due to lack of data on such variables. Though it is not possible to determine the cause-effect relationship in this regard due to the chicken egg dilemma in the nature of the study design, had the data been obtained and analyzed, it would have the benefit of exposing the possible link between the BPI and childhood illness.

Conclusion

We found that four out of five mothers do not fulfill the optimal exclusive breast breastfeeding practice. Child age, antenatal care service, and maternal socio-economic and demographic factors affect the breastfeeding performance of women. However, the analysis revealed the rarely reported relationships between breastfeeding practice and its determinants. The direction of the relationship between factors with the breastfeeding performance index was found to be mostly inversed and against commonly supported scientific insights that are reported when the breastfeeding performance index score subcomponent practices are analyzed separately. Our findings suggest that factors determining breastfeeding might have shifted toward an unusual direction of relationship with the breastfeeding performance of mothers. Therefore, in addition to redirecting the usual focus of intervention targets by eliminating the usual perception that better socio-economic, demographic, and service factors result in better breastfeeding practices, it also implies the need to validate findings with further longitudinal investigations in the local context to strengthen evidence and re-orient the policy interventions.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: http://www.DHSprogram.com.

Ethics statement

The study used data from the 2019 EMDHS obtained from Measure DHS data archive http://www.DHSprogram.com, with the appropriate request and permission. The DHS program owns data that are collected following all the necessary ethical procedures in accordance with the relevant guidelines and regulations. Therefore, for the data used in this analysis, all methods were carried out in accordance with relevant guidelines and regulations. The DHS Program is authorized to distribute, at no cost, unrestricted survey data files for legitimate academic research. Registration is required for access to data. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GTG conceived the study design. GTG, BTW, TGD, SH, and TDB carried out the statistical analysis and conducted the literature review. GTG, BTW, and TGD wrote the draft manuscript, while SH and TDB reviewed and commented on the draft manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Mainul Haque,
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Ras Al Khaimah Medical and Health Sciences University,
United Arab Emirates

*CORRESPONDENCE
Khadijeh Mirzaei
mirzaei_kh@tums.ac.ir;
mina_mirzaei101@yahoo.com

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Is there any putative mediatory role of inflammatory markers on the association between ultra-processed foods and resting metabolic rate?

Niki Bahrampour[1], Farideh Shiraseb[2], Sahar Noori[1], Cain C. T. Clark[3] and Khadijeh Mirzaei[2]*

[1]Department of Nutrition, Science and Research Branch, Islamic Azad University (SRBIAU), Tehran, Iran, [2]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran, [3]Centre for Intelligent Healthcare, Coventry University, Coventry, United Kingdom

The resting metabolic rate (RMR) represents the largest component of total daily energy expenditure. The sale of ultra-processed foods (UPF) is increasing globally; however, UPF can have many adverse effects, including increasing inflammatory markers and altering RMRs. This cross-sectional study included 285 healthy overweight and obese women. Anthropometric measurements were evaluated using a bioelectrical impedance analyzer InBody 770 scanner. High-sensitivity C-reactive protein (hs-CRP), plasminogen activator-1 (PAI-1), monocyte chemoattractant protein (MCP-1), and interleukin-1 beta (IL-1β) blood levels were measured after a 12-h fasting. Indirect calorimetry was used to evaluate the RMR by using the Weir equation, and RMR deviation (RMR estimated - RMR actual), RMR per body mass index (BMI), and free fat mass (FFM) were estimated. A validated food frequency questionnaire (FFQ) was used, and seven groups of UPFs were extracted based on the NOVA method. A negative association between the RMR [β = −0.159, 95% confidence interval (CI): −0.471, −0.052, *P* = 0.044], RMR per BMI (β = −0.014, 95% CI: −0.025, −0.006, *P* = 0.036), and RMR per FFM (β = −0.241, 95% CI: −0.006, −0.000, *P* = 0.041) using the NOVA score was observed after adjusting for confounders. This association disappeared after inclusion of each inflammatory marker. All the markers may inversely mediate the relationship between the mentioned variables and the NOVA score. hs-CRP and MCP-1 also had a negative effect on the relationship between the NOVA score and RMR deviation. Finally, UPF intake is likely related with the RMR, mediated through changes in the production of hs-CRP, PAI-1, MCP-1, and IL-1β.

KEYWORDS

resting metabolic rate, ultra-processed foods (UPFs), inflammation, high-sensitivity C-reactive protein (hs-CRP), monocyte chemoattractant protein (MCP-1)

Introduction

Knowledge of the resting metabolic rate (RMR) is necessary because it represents the largest component of total daily energy expenditure and has ramifications for nutrition support. Obesity and alterations in the RMR have a close link (1); indeed, obesity is one of the most important reasons for decreases in metabolism, and given that the prevalence of obesity and overweight has doubled in more than 70 countries since 1980 (50% of women are overweight and obese), an important consideration is the concomitant change in the RMR (1–3). The RMR is defined as the energy requirement of humans when they are awake in a normal temperature room, after food absorption, and not engaging in any activity for 12 h (4). Many previous studies have reported that the RMR is usually impacted by sex disparities, obesity, age, and racial/ethnic differences (4). For example, the RMR has been shown to be higher in men than in women due to their muscle mass (5), while aging has also been shown to affect the RMR (6). Dietary intake represents another factor that can affect the RMR; for instance, a recent study suggested that consuming protein in obese persons could contribute to an increase in resting energy expenditure (REE) (7). Lichtenbelt et al. found that consumption of polyunsaturated fatty acids to a greater extent than saturated fatty acids can result in an increasing RMR due to a higher oxidation rate (8). Other studies have reported that low-carbohydrate (<45% energy from carbohydrate) and low glycemic foods facilitate a RMR reduction in weight loss plans, largely due to more availability and the presence of endocrine mediators in anabolic and catabolic pathways (9). In order to identify processed foods, the NOVA classification system represents a novel tool for gaining insights into the epidemic (10). Foods are separated into unprocessed foods, processed culinary ingredients, processed foods, and ultra-processed foods (UPFs). UPFs refer to foods that are produced through industrial processes like hydrogenation, hydrolysis, extruding, molding, reshaping, and frying, and adding flavors, colors, emulsifiers, humectants, non-sugar sweeteners, and other additives (11); sodas, breakfast cereals, packaged cakes, and pre-prepared frozen foods are examples of this group.

There are serious concerns about ultra-processed food (UPF) intake and obesity (11). The sale of UPFs is increasing all over the world (to 43.7% until 2013) and has replaced fresh foods in low- and middle-income countries (12, 13). The 2015–2020 dietary guidelines for Americans suggest people increase high-quality dietary patterns for preventing chronic diseases (10). UPFs are made with various additives (salt, sugar, fat, etc.) and are low in dietary fiber and micronutrients (14), and the extant literature suggests a positive relationship between obesity, inflammation, and consumption of UPFs (14). In addition, recent studies have shown that a higher intake of UPFs is associated with lowering RMRs, slowing satiation, and weight gain, through lower protein, antioxidants, fiber, and higher energy density, and refined grain content present in them (15). Furthermore, unhealthy UPFs can interrupt gut–brain signaling, change vascular stiffness, and increase inflammatory markers (16, 17). Plasminogen activator-1 (PAI-1) is secreted by adiposity tissues in the blood and may have a negative effect on RMRs (18, 19). Moreover, UPF intake can increase the serum level of monocyte chemoattractant protein (MCP)-1 (20), while another inflammatory marker, interleukin-6 (IL-6), is decreased in a diets abundant in ω-3 polyunsaturated fatty acids (PUFAs) (21). Anti-inflammatory diets, such as the Mediterranean diet, which has a high amount of vegetables and fruit, fiber, and vitamins C and E, are related to decreased serum levels of pro-inflammatory biomarkers, like high-sensitivity C-reactive protein (hs-CRP) (22). Indeed, nutrients in these diets are low in UPF and may be important in regulating the immune system and changes in RMR (18).

To the best of our knowledge, no study has evaluated the impact of inflammatory markers on the relationship between RMR and UPF intake, using the NOVA classification, in Iran. Therefore, this study was designed to assess the possible mediatory role of inflammatory markers in the association between ultra-processed foods and the resting metabolic rate.

Materials and methods

Study population

This cross-sectional study was performed with 285 overweight and obese women, who were referred to healthcare centers in Tehran, Iran. Participants were selected using multistage random sampling. The inclusion criteria were given as follows: aged between 18 and 48 years, body mass index (BMI) scores 25–29.9 kg/m^2 for overweight and 30 kg/m^2 for obesity, and without any chronic diseases, like hypertension, kidney or liver disorders, and cardiovascular diseases, which was ascertained by a face-to-face anamnesis interview. Women who were smokers; were alcohol consumers; had prescribed medication; and were pregnant, breastfeeding, or in menopausal stage; or had a history of weight loss in the

Abbreviations: RMR, resting metabolic rate; LED, low energy density; HED, high energy density; UPFs, ultra-processed foods; PA, physical activity; WC, waist circumference; WHR, waist-to-hip ratio; BMI, body mass index; PAI-1, plasminogen activator-1; IL-6, interleukin-6; PUFA, polyunsaturated fatty acids; MCP-1, monocyte chemoattractant protein; hs-CRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; IC, indirect calorimetry; BSA, body surface area; FFM, free fat mass; FFQ, food frequency questionnaire; IPAQ, the International Physical Activity Questionnaire; METs, metabolic equivalents; ANOVA, one-way analysis of variance; ANCOVA, analysis of covariance.

last 6 months were excluded. In addition, only participants with a total energy intake between 800 and 4,200 kcal/d were included (23).

Experimental methods

This study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the ethics committee of Tehran University of Medical Sciences (TUMS) with the following identification: IR.TUMS.VCR.REC.1398.463. Written informed consent was obtained from all patients prior to participation.

Anthropometric measurements

Weight, BMI, and body fat mass (BFM) were measured using a multi-frequency bioelectrical impedance analyzer (BIA) InBody 770 scanner (Inbody Co., Seoul, Korea), where the women wore light clothes, without any metal subjects, and in accordance with manufacturer's protocols. Anthropometric measurements were conducted between 8 and 9 a.m., after 12 h of fasting. The participants were asked to refrain from any non-habitual physical activity for the preceding 72 h. The test–re-test reliability of BIA in our laboratory was r = 0.98. BFM (kg), free fat mass (FFM) (kg), and fat mass index (FMI) (kg/m^2) were extracted. The height of the participants was measured with a Seca 216 stadiometer, to the nearest 0.1 cm, with the participants in a standing position and unshod. The arm muscle circumference (cm) of the participants were also measured according to standard kinanthropometrist guidelines.

Serum biochemical measuring

After fasting for 12 h, blood samples were drawn from the participants. The samples of blood were collected in parent tubes containing 0.1 EDTA, and tests were analyzed utilizing the Auto-Analyzer BT 1500 (Selectra 2; Vital Scientific, Spankeren, Netherlands). hs-CRP, PAI-1, MCP-1, and interleukin-1 beta (IL-1β) levels were measured by an immunoturbidimetric test using the Pars Azmoon kit (Pars Azmoon Inc., Tehran, Iran). Serum levels of high-density lipoprotein cholesterol (HDL-C), fasting blood sugar (FBS), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), insulin, and triglyceride (TG) were also measured. Insulin resistance was assessed as HOMA-IR (homeostasis model assessment-estimated insulin resistance) = [glucose] (mmol/l) × [insulin] (μU/ml)/22.5 (24).

Energy expenditure measurements

Indirect calorimetry (IC) is considered an accurate method of determining the RMR and was used to evaluate the RMR after an overnight fast. Respiratory gases were gathered using the MetaLyzer 3B-R3 (Cortex Biophysik GmbH, Leipzig, Germany) spirometer. The participants were asked to refrain from the consumption of caffeine and vigorous activity for a day prior to RMR measurements. The participants were asked to sleep in a silent place in a temperature between 24 and 26°C the night before the test and be free from emotional stress. Gaseous exchange was analyzed in the last 20 min of the resting time and during a minimum of 5 consecutive minutes in a steady-state condition. The RMR was measured using the Weir equation: RMR = [O_2 consumed (liter) × 3.941 + produced Co_2 (liter) × 1.11] × 1,440 min/d by assessing the amount of CO_2 produced and O_2 consumed through a one-way valve between the participants and the machine (25). RMR deviation was computed as RMR estimated - RMR actual (26). The RMR was also calculated per body surface area (BSA) using the Du Bois formula, BMI, and FFM (which were derived from BIA results) (27–29).

Dietary intake and NOVA score assessment

A validated food frequency questionnaire (FFQ), with 147 items, was used to assess the average food consumption of the participants over the past year (30). All dietary intakes, including foods and beverages, were converted to grams (31) and entered into Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR). In order to classify processed foods, the NOVA method was used (32). A total of 37 UPF items were categorized into seven food groups, and then the mean daily intake of each of seven UPF groups was divided by the total daily intake of UPF and multiplied by 100. These groups included non-dairy beverages (Cola, nectar drink, and instant coffee), cookies–cakes [cookies, biscuit, pastries (creamy and non-creamy), cake, pancake, doughnut, industrial bread, toasted bread, noodles, and pasta), dairy beverages [ice cream (non-pasteurized), ice cream (pasteurized), chocolate milk, and cocoa milk], potato chips—salty snacks [chips (crisps), crackers, and cheese puff], processed meat fast foods [burger, sausage, bologna, and pizza], oil sauces (margarine, ketchup, and mayonnaise), and sweets (jam, rock candy, candies, chocolates, sweets, nogal, sohan, Gaz, and sesame halva) (32).

Other variables

The physical activity (PA) of the participants was also evaluated *via* the short form of the International Physical

Activity Questionnaire (IPAQ) (33). The metabolic equivalent (MET) and MET-minutes per week (MET-min/wk) were ascertained by summing the activity hours per week.

Statistical analysis

The normality of data was evaluated using a Kolmogorov–Smirnov test. General characteristics of the participants within different tertiles of the NOVA score were described as mean ± standard deviation (SD) for quantitative variables and frequency (%) for categorical variables. Chi-square tests and one-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used for categorical variables and dietary intake in order to compare the differences among tertiles of NOVA scores. The NOVA score was divided into three groups (T1 < 383.681, 383.681 < T2 < 467.713, and T3 > 467.713). Bonferroni *post hoc* tests were used to investigate differences between tertiles. Linear regression was also used to investigate the relationship between outcomes and exposure in crude and two adjusted models and the role of inflammatory markers. Model 1 was adjusted for age, energy intake, BMI, physical activity, job status, and supplement intake. In model 2, additional controlling for legumes and vegetables was conducted. The results are shown as a beta (β) with 95% confidence intervals (95% CI). Pearson correlation was utilized to discern the association between inflammatory markers, RMR, and NOVA score. All analyses were conducted using Statistical Package for Social Sciences) SPSS) version 25 software (SPSS Inc., Chicago, Illinois), where $P < 0.05$ was considered statistically significant.

TABLE 1 Distribution of general variables of the participants among tertiles of UPF intake.

Quantitative variables	**T1 (<383.681)**	**T2 (383.681–467.713)**	**T3 (>467.713)**	***P*-value**	***P**-value**
Age (year)	36.48 ± 9.13	38.75 ± 8.77 [b]	34.86 ± 9.35 [c]	**0.003**	**0.004**
Weight (kg)	81.95 ± 12.38	79.88 ± 10.97	81.66 ± 13.32	0.33	0.22[a]
Height (cm)	161.57 ± 5.88	160.11 ± 5.88	161.76 ± 5.79	**0.04**	0.91[a]
WC (cm)	97.28 ± 17.05	97.13 ± 12.69	97.95 ± 16.05	0.93	0.24[a]
BFM (kg)	34.93 ± 8.39	33.83 ± 7.80	35.42 ± 9.88	0.32	0.25[a]
FFM (kg)	47.01 ± 5.93	46.21 ± 5.44	46.26 ± 5.61	0.32	0.41[a]
BMI (kg/m^2)	31.36 ± 4.11	31.19 ± 3.98	31.25 ± 4.79	0.94	0.31[a]
Arm muscle circumference (cm)	28.64 ± 4.56	28.22 ± 1.98	28.11 ± 2.83	0.40	0.21[a]
FMI (kg/m^2)	13.42 ± 3.16	13.31 ± 3.23	13.61 ± 3.79	0.78	0.45[a]
PA (METs-hour-week)	1454.73 ± 2424.86	825.17 ± 901.18	1365.72 ± 2653.36	0.09	0.15
Hs-CRP (mg/dl)	4.30 ± 4.62	4.21 ± 4.64 [b]	4.48 ± 4.77 [c]	0.94	<**0.001**
IL-1 (mg/dl)	2.58 ± 0.89	2.74 ± 1.02	2.84 ± 0.92	0.64	0.95
MCP-1 (mg/dl)	57.51 ± 94.78	54.33 ± 109.98	36.96 ± 54.65	0.38	0.27
PAI-1 (mg/dl)	20.26 ± 39.58	14.20 ± 24.73	13.31 ± 20.37	0.40	0.33
Insulin	1.20 ± 0.24	1.24 ± 0.23	1.19 ± 0.19	0.41	0.41
HOMA_IR index	3.24 ± 1.34	3.58 ± 1.38	3.14 ± 1.00	0.07	0.05
Qualitative variables					
Supplementation intake n (%)				0.31	0.05
Yes	58 (36.7)	47 (29.7)	53 (33.5)		
No	51 (29)	61 (34.7)	64 (36.4)		
Income status n (%)				0.58	0.18
Weak	33 (37.5)	31 (35.2)	24 (27.3)		
Moderate	60 (33.0)	61 (33.5)	61 (33.5)		
High	35 (32.7)	31 (29.0)	41 (38.3)		
Marital status n (%)				0.27	0.88
Single	35 (32.1)	31 (28.4)	43 (39.4)		
Married	92 (33.6)	96 (35.0)	86 (31.4)		

SD, Standard deviation; METs, Metabolic Equivalents; PA, physical activity; BMI, body mass index; WC, waist circumference; BFM, body fat mass; FFM, fat free mass; FMI, fat mass index; hs-CRP, high sensitive- C reactive protein; IL-1, interleukin-1; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor- 1, HOMA-IR index, insulin resistant.
Quantitative variables were showed by means ± SD and qualitative variables were showed by number (percentage).
P-values resulted from one-way ANOVA analysis and chi-square test. *P*-value < 0.05 was considered significant with bold font.
**P*-values resulted from ANCOVA analysis and were adjusted for age, BMI, PA, and energy intake.
[a]Variables just adjusted for age, energy intake, and PA and BMI was considered as collinear.
Bonferroni *Post hoc* test was used to investigate differences between tertiles. [b,c]Between two means is significant difference at 0.05.

Results

Study population characteristics

As shown in **Supplementary Table 1**, according to NOVA screening, most of the UPF intakes were *via* non-dairy beverages (39.12), and the smallest contribution was from oils and sauces (4.33%). General characteristics of the participants across NOVA score tertiles are shown in **Table 1**. The mean (SD) of weight, FFM, and BMI was 80.92 (12.39) kg, 46.76 (5.59) kg, and 31.02 (4.29) kg/m^2, respectively. In addition, the total mean (SD) of serum levels of hs-CRP, IL-1β, MCP-1, and PAI-1 was 4.31 (4.65), 2.73 (0.94), 50.69 (92.46), and 16.10 (29.92) mg/dl, respectively. A total of 142 women had a moderate income, and 148 were taking dietary supplements. Age and height were significantly different among NOVA tertiles ($P < 0.05$) in the crude model. After adjusting for confounding variables, such as age, BMI, PA, and energy intake, hs-CRP, and age were all significant ($P < 0.05$) (**Table 1**).

Dietary intake across NOVA score tertiles

The dietary intake of subjects between NOVA tertiles is shown in **Table 2**. All of the food groups and components were statistically different among NOVA tertiles, except whole grain, vitamin D, and trans fat ($P < 0.05$). After adjusting for energy, vegetables ($P = 0.003$), legumes ($P = 0.04$), linolenic acid ($P = 0.02$), total fiber ($P < 0.001$), beta-carotene ($P = 0.01$), vitamin B1 ($P = 0.002$), B6 ($P < 0.001$), B9 ($P < 0.001$), biotin ($P = 0.01$), magnesium ($P = 0.002$), copper ($P = 0.008$), and chromium ($P = 0.009$) remained significantly different.

Distribution of resting metabolic rate measurements among NOVA score tertiles

According to **Table 3**, the mean RMR was not significantly different between the tertiles of NOVA in the crude model. Deviation from the estimated normal RMR was significantly different in model 2 ($P = 0.04$).

Association between the resting metabolic rate and related variables and NOVA score

The relationship between the RMR and NOVA score is shown in **Table 4**. No significant relationship of RMR variables were observed among NOVA groups in crude models. In model 1, a negative association between the RMR per BMI (β = −0.012, 95% CI: −0.022 to −0.002, $P = 0.038$) with the NOVA score was observed. This negative relationship remained after adjusting for all confounders in model 2. In addition, a negative association was appeared between the NOVA score and RMR (β = −0.15, 95% CI: −0.471 to -0.052, $P = 0.04$), and the RMR per FFM (β = −0.24, 95% CI: −0.006 to -0.000, $P = 0.04$) in model 2.

The correlation between inflammatory markers and the resting metabolic rate variables

The correlation between inflammatory markers and the RMR variables is shown in **Supplementary Table 2**. hs-CRP had a weak positive linear relationship with the RMR ($r = 0.146$, $P = 0.024$) and RMR per FFM ($r = 0.128$, $P = 0.048$), respectively.

Assessing the mediating role of inflammatory markers between ultra-processed foods intake and resting metabolic rate

The mediatory role of inflammatory markers on the relationship between UPF intakes and RMR is shown in **Supplementary Figure 1**. The association between the NOVA score and RMR (P-value $_{primary}$ = 0.04), RMR per BMI (P-value $_{primary}$ = 0.03), and RMR per FFM (P-value $_{primary}$ = 0.04) is shown in **Table 4**. After adjusting for all confounders (**Table 5**), it was evident that all of the markers may inversely mediate the relationship between the mentioned variables and NOVA scores. Furthermore, by entering hs-CRP (P-value $_{after}$ = 0.54), IL-1β (P-value $_{after}$ = 0.42), MCP-1(P-value $_{after}$ = 0.93), and PAI-1(P-value $_{after}$ = 0.43) as confounding variables, along with the other confounders in model 2, a potential negative relationship between the NOVA score and RMR per BSA was evident. In addition, hs-CRP ($P = 0.564$) and MCP-1 ($P = 0.911$) also had a possible negative mediatory role in the relationship between NOVA score groups and RMR deviation from normal.

Discussion

To the author's knowledge, this is the first study to have investigated the possible mediatory role of inflammatory markers on the relationship between UPF and RMR in obese and overweight women. In this study, we found that with increasing NOVA scores, RMR deviation from the calculated normal RMR was increased, which indicates that with increasing UPF consumption, RMR decreased. In addition, a significant negative association between the RMR, RMR per BMI, and RMR per FFM, with NOVA score was observed after adjusting all confounders. This suggests that all the included markers

TABLE 2 Intake of UPF, food groups, and nutrients according to the UPF tertiles in overweight and obese women.

Variables	Total mean ± SD	T1 (<383.681)	T2 (383.681–467.713)	T3 (>467.713)	*P*-value	*P**-value
Energy (kcal)	2633.28 ± 809.43	2916.67 ± 654.47	2267.60 ± 712.43	2713.37 ± 904.86	**<0.001**	–
NOVA food groups						
Non-dairy beverages (g/d)	177.35 ± 93.22	124.06 ± 25.54	157.15 ± 27.64	251.24 ± 126.71	**<0.001**	**<0.001**
Cookies-cakes (g/d)	98.91 ± 44.20	75.57 ± 25.62	97.28 ± 28.00	124.06 ± 57.16	**<0.001**	**<0.001**
Dairy beverages (g/d)	47.83 ± 27.95	37.47 ± 18.48	46.62 ± 22.11	59.47 ± 35.79	**<0.001**	**<0.001**
Potato chips- salty snack (g/d)	22.10 ± 13.89	17.35 ± 9.09	22.65 ± 10.16	26.34 ± 18.85	**<0.001**	**<0.001**
Processed meat- fast food (g/d)	41.13 ± 25.42	28.40 ± 12.60	40.23 ± 14.20	54.88 ± 35.16	**<0.001**	**<0.001**
Oil-sauce (g/d)	18.26 ± 8.72	16.76 ± 8.54	17.86 ± 7.41	20.19 ± 9.76	**0.005**	**0.005**
Sweet (g/d)	36.86 ± 24.06	30.67 ± 15.11	36.91 ± 17.18	43.03 ± 33.87	**<0.001**	**<0.001**
Food groups						
Fruits (g/d)	528.90 ± 338.16	605.77 ± 317.15	466.28 ± 317.37	513.25 ± 370.04	**0.01**	0.34
Vegetables (g/d)	433.57 ± 263.25	526.61 ± 264.20	382.92 ± 226.81	385.49 ± 275.07	**<0.001**	**0.003**
Nuts (g/d)	14.37 ± 16.18	17.82 ± 17.78	11.44 ± 14.35	13.79 ± 15.69	**0.01**	0.51
Meat (g/d)	64.57 ± 50.17	67.37 ± 40.97	54.08 ± 41.67	73.51 ± 65.01	**0.02**	0.25
Whole grains (g/d)	7.58 ± 10.41	9.14 ± 11.23	6.76 ± 9.01	6.74 ± 10.83	0.17	0.36
Legumes (g/d)	52.69 ± 41.27	63.43 ± 49.57	45.83 ± 35.76	48.31 ± 34.08	**0.005**	**0.04**
Nutrients						
Protein (g/d)	91.31 ± 31.45	101.24 ± 25.30	78.89 ± 28.96	93.71 ± 35.30	**<0.001**	0.11
Total fat (g/d)	95.13 ± 35.17	103.81 ± 34.89	82.52 ± 29.36	99.01 ± 37.40	**<0.001**	0.43
Carbohydrate (g/d)	372.45 ± 124.59	417.51 ± 104.94	318.88 ± 113.02	380.60 ± 134.31	**<0.001**	0.10
SFA (g/d)	28.40 ± 11.54	30.86 ± 11.41	24.76 ± 10.29	29.58 ± 12.03	**<0.001**	0.62
Cholesterol (mg/d)	264.06 ± 113.12	276.57 ± 105.30	242.75 ± 104.47	272.77 ± 126.13	**0.03**	0.37
PUFA (g/d)	20.08 ± 9.56	22.58 ± 10.51	17.40 ± 8.31	20.23 ± 9.08	**<0.001**	0.71
Linolenic acid (g/d)	1.21 ± 0.66	1.43 ± 0.74	1.04 ± 0.58	1.16 ± 0.60	**<0.001**	**0.02**
Trans fat (g/d)	0.0007 ± 0.002	0.001 ± 0.003	0.0006 ± 0.001	0.0005 ± 0.001	0.09	0.12
Total fiber (g/d)	47.34 ± 21.36	57.26 ± 21.37	40.35 ± 19.20	44.33 ± 19.79	**<0.001**	**<0.001**
Beta-carotene (mg/d)	5123.54 ± 3403.75	5983.44 ± 3233.19	4811.75 ± 3878.53	4568.82 ± 2879.15	**0.001**	**0.01**
C (mg/d)	188.40 ± 116.76	215.84 ± 103.63	164.99 ± 104.12	184.18 ± 134.97	**0.002**	0.33
D (μg)	1.95 ± 1.55	2.09 ± 1.84	1.82 ± 1.51	1.96 ± 1.25	0.377	
E (mg/L)	17.01 ± 9.05	18.75 ± 9.46	15.49 ± 8.54	16.78 ± 8.89	**0.01**	0.60
B1 (mg/d)	2.13 ± 0.73	2.44 ± 0.67	1.84 ± 0.66	2.12 ± 0.74	**<0.001**	**0.002**
B2 (mg/d)	2.27 ± 0.87	2.47 ± 0.77	2.01 ± 0.82	2.33 ± 0.95	**<0.001**	0.72
B6 (mg/d)	2.19 ± 0.75	2.51 ± 0.63	1.93 ± 0.70	2.14 ± 0.81	**<0.001**	**<0.001**
Folate (μg/d)	620.27 ± 192.93	706.78 ± 171.92	542.35 ± 173.64	611.01 ± 196.96	**<0.001**	**<0.001**
Biotin (mg/d)	38.25 ± 16.81	43.60 ± 14.44	34.89 ± 14.78	36.24 ± 19.54	**<0.001**	**0.01**
Sodium (mg/d)	4482.75 ± 1757.72	4853.93 ± 1702.71	4032.31 ± 1367.83	4559.15 ± 2048.83	**0.001**	0.77
Potassium (mg/d)	4509.82 ± 1727.13	5089.18 ± 1580.68	3934.96 ± 1545.09	4500.85 ± 1854.49	**<0.001**	0.16
Magnesium (mg/d)	475.67 ± 171.57	546.11 ± 159.40	410.33 ± 149.70	470.04 ± 177.79	**<0.001**	**0.002**
Copper (mg/d)	2.02 ± 0.75	2.32 ± 0.64	1.72 ± 0.65	2.00 ± 0.82	**<0.001**	**0.008**
Chromium (mg/d)	0.12 ± 0.10	0.15 ± 0.12	0.10 ± 0.07	0.10 ± 0.08	**<0.001**	**0.009**

SD, Standard deviation; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids.
P-values are resulted from ANOVA analysis. *P*-value < 0.05 was significant with bold font.
**P*-values presented resulted from ANCOVA analysis and were adjusted for energy except energy intake.

may inversely mediate the relationship between the mentioned variables and NOVA score. In addition, hs-CRP and MCP-1 also had a possible negative mediatory role in the relationship between NOVA score groups and RMR deviation from normal.

High levels of CRP indicate low-grade inflammation that is, often, associated with several non-communicable diseases, including obesity, cardiovascular disease (CVD), and diabetes (34–37). In a study of 670 adolescent girls in Iran, it was found that there is a positive and significant relationship between adherence to a Western diet and higher serum levels of CRP (38). Western diets contain high amounts of refined grains, snacks, red meats and organ meat, pizza, fruit

TABLE 3 The distribution of RMR subcategories between UPF intake tertiles.

Variables	T1 (<383.681)	T2 (383.681–467.713)	T3 (>467.713)	*P*-value	*P**-value
RMR (kcal)					
Crude	1576.69 ± 280.39	1564.44 ± 238.68	1592.00 ± 259.98	0.772	
Model 1[b]	1602.81 ± 30.98	1542.07 ± 31.25	1530.21 ± 32.54		0.315
Model 2[c]	1560.92 ± 31.46	1598.37 ± 30.93	1525.47 ± 32.72		0.290
RMR deviation (kcal)					
Crude	-9.53 ± 12.58	-7.23 ± 13.49	-7.97 ± 11.82	0.429	
Model 1	-5.49 ± 1.62	-10.88 ± 1.64	-9.75 ± 1.71		0.066
Model 2	-9.77 ± 1.64	-5.75 ± 1.61	-10.68 ± 1.71		**0.045**
RMR per BSA (kcal)					
Crude	844.85 ± 115.94	855.77 ± 120.64	857.10 ± 105.98	0.720	
Model 1	827.22 ± 14.55	875.55 ± 14.68	836.33 ± 15.29		0.062
Model 2	837.45 ± 14.69	873.18 ± 14.44	827.73 ± 15.27		0.086
RMR per BMI (kcal)					
Crude	50.65 ± 8.75	51.01 ± 8.54	52.64 ± 9.24	0.275	
Model 1	52.46 ± 1.01	50.15 ± 1.02	50.59 ± 1.06		0.267
Model 2	52.31 ± 1.02	50.74 ± 1.01	50.10 ± 1.06		0.320
RMR per FFM (kcal)					
Crude	33.33 ± 4.35	33.99 ± 4.93	34.28 ± 4.10	0.335	
Model 1	34.42 ± 0.54	32.58 ± 0.55	33.55 ± 0.57		0.065
Model 2	33.01 ± 0.54	34.33 ± 0.53	33.18 ± 0.57		0.204

One way ANCOVA.
[a]Mean ± SD was presented.
**p* for [b]Mean ± SE was presented and adjusted for energy intake, age, job status, supplement intake, physical activity, BMI.
P-value < 0.05 was significant with bold font.
**p* [c]Mean ± SE was presented and adjusted for model 1 + legumes and vegetables.

juices, industrial compote, mayonnaise, sugar, soft drinks, sweets, and desserts. On the other hand, the consumption of fruits and vegetables is inversely correlated with CRP levels, which is comparable to the findings in our study, where fruit and vegetable intake decreased with increasing NOVA scores, and the amount of hs-CRP increased (38). Findings of Lopes et al. suggest that a positive association between excess intake of UPFs and CRP levels in women may be mediated by adipocytes (39). The positive association between the consumption of UPFs and the CRP seen in women may be partly explained by the greater accumulation of body fat in women as BMI is strongly associated with CRP levels in women (40, 41). The consumption of UPFs is known to lead to the overproduction of reactive oxygen species and thereby enhances inflammation by increasing hs-CRP levels and decreasing adiponectin (42–44); indeed, the mechanism that may justify the mediatory role of hs-CRP on the relationship between UPFs and RMR may be related to insulin. In the presence of obesity, CRP levels increase (45, 46), and elevated levels are associated with inflammation and insulin resistance (46). However, insulin sensitivity is inversely related to the RMR (47), which indicates that with consumption of UPFs, hs-CRP levels, inflammation, and insulin resistance increase, which has a decreasing effect on the RMR.

In a group of healthy individuals with normal weight and overweight, the association between RMR and hs-CRP levels, indicative of inflammation, was investigated, and the authors reported that sex significantly affects the age-related changes in body composition, in addition to changes in body composition–REE relationship (48). From a biological perspective, IL-6, which is expressed in adipose tissue, stimulates the production of CRP in the liver and leads to higher levels of circulating hs-CRP. In addition, adipocytes produce and secrete fewer pro-inflammatory and anti-inflammatory cytokines, especially enlarged adipocytes, which may be associated with impaired glucose–insulin homeostasis and impaired energy metabolism (49–52). The products secreted by adipose tissue affect systemic metabolism by inflammatory cytokines, leptin, and PAI-1 (53). In fact, some of the nutritional properties of UPFs, such as high energy density, high glycemic load, and high content of saturated and trans fats, may stimulate inflammation by increasing oxidative stress (39). The results of Yunsheng et al. show that dietary fiber may have protective effects against hs-CRP (54), while in a recent review article (55), King et al. suggested that dietary fiber reduced lipid oxidation, which, in turn, was associated with reduced inflammation. Dietary fiber also helps maintain a healthy gut environment and natural flora, which help prevent inflammation (55); indeed, in our

TABLE 4 Association between resting metabolic rate and related variables and UPF intakes.

Variables	β*	95% CI	*P*-value
RMR (kcal)			
Crude	0.156	−0.100–0.411	0.231
model 1	−0.184	−0. 000 to −0. 000	0.054
model 2	−0.159	−0.471 to −0.052	**0.044**
RMR deviation (kcal)			
Crude	0.004	−0.009 to 0.017	0.529
Model 1	−0.002	−0.018 to 0.015	0.842
Model 2	−0.006	−0.023 to 0.010	0.454
RMR per BSA (kcal)			
Crude	0.036	−0.077–0.149	0.531
Model 1	−0.019	−0.166–0.128	0.799
Model 2	−0.061	−0.208–0.085	0.412
RMR per BMI (kcal)			
Crude	0.003	−0.005–0.012	0.462
Model 1	−0.012	−0.022 to −0.002	**0.038**
Model 2	−0.014	−0.025 to −0.006	**0.036**
RMR per FFM (kcal)			
Crude	0.003	−0.002–0.007	0.265
Model 1	−0.121	0.000–0.000	0.059
Model 2	−0.241	−0.006 to −0.000	**0.041**

All values were presented as 95% Confidence intervals (95% CI).
P-value < 0.05 was significant with bold font. UPF, ultra-processed foods; RMR, resting metabolic rate; BSA, body surface area; BMI, body fat mass; FFM, free fat mass.
β* regression coefficients refer to the UPF tertiles relationship.
Model 1: Adjusted for age, energy intake, BMI, physical activity, job status, and supplement intake.
Model 2: Adjusted for model 1 + legumes and vegetables intake.

study, with the increasing NOVA score and increasing CRP, the amount of dietary fiber intake decreased.

The study by Bibiloni et al. showed an association between omega-3 and PIA-1 PUFAs in healthy women (56). PUFA intake in the Western diet mainly includes n-6 PUFA (mainly linoleic acid and arachidonic acid), with a ratio of n6:n-3 ranging from 10 to 20:1 (57). Arachidonic acid (AA) is released from the membrane through the lipoxygenase pathway to pro-inflammatory eicosanoids, which are involved in inflammatory activation (58). When n-3 PUFA intake is higher, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) partially replace AA in the cell membrane; thus, fewer biologically active substances are formed, and the balance of n-6 and n-3 eicosanoids changes to compounds with less inflammatory activity (59). Another study, by Miller and colleagues, showed that total fiber intake was inversely related to PAI-1, while insoluble fiber was inversely associated with PAI-1 and MCP-1 in overweight women (60). In our study, with the increasing NOVA score, the intake of linolenic acid and dietary fiber decreased, and the amount of hs-CRP increased, although no significant difference was seen in MCP-1 and PIA-1. The mechanism of the mediatory role of MCP-1, like hs-CRP,

TABLE 5 The association of the mediating effect of inflammatory markers on RMR subcategories between UPF tertiles in overweight and obese women.

		NOVA screener		
RMR variables	**Inflammatory markers**	**β***	**95% CI**	***P*-value**
RMR (kcal)	PAI-1	−0.190	−0.643 to 0.264	0.409
	IL-1	−0.363	−1.070 to 0.344	0.305
	hs-CRP	−0.110	−0.433 to 0.212	0.500
	MCP-1	−0.029	−0.369 to 0.311	0.866
RMR deviation (kcal)	PAI-1	−0.011	−0.035 to 0.014	0.384
	IL-1	−0.019	−0.061 to 0.023	0.369
	hs-CRP	−0.005	−0.023 to 0.013	0.564
	MCP-1	−0.001	−0.020 to 0.018	0.911
RMR per BSA (kcal)	PAI-1	−0.088	−0.310 to 0.134	0.435
	IL-1	−0.147	−0.517 to 0.223	0.426
	hs-CRP	−0.049	−0.211 to 0.112	0.547
	MCP-1	−0.006	−0.172 to 0.159	0.939
RMR per BMI (kcal)	PAI-1	−0.006	−0.022 to 0.009	0.434
	IL-1	−0.012	−0.036 to 0.013	0.331
	hs-CRP	−0.004	−0.014 to 0.007	0.516
	MCP-1	−0.001	−0.012 to 0.011	0.910
RMR per FFM (kcal)	PAI-1	−0.004	−0.013 to 0.005	0.399
	IL-1	−0.002	−0.014 to 0.011	0.790
	hs-CRP	−0.001	−0.007 to 0.005	0.719
	MCP-1	−2.326	−0.006 to 0.006	0.994

UPF, ultra-processed foods; RMR, resting metabolic rate; BSA, body surface area; FFM, fat free mass; BMI, body mass index; hs-CRP, high-sensitive C-reactive protein; IL-1, interleukin 1; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemoattractant protein-1.
Variables were adjusted for age, energy, BMI, physical activity, job status and supplement intake, legumes and vegetables intake.
Logistic regression was used; β* regression coefficients refer to UPF groups.
All values were presented as 95% Confidence intervals (95% CI).

may also be related to insulin secretion and resistance. MCP-1 secretion is stimulated by tumor necrosis factor α (TNFα), IL-6, and IL-1β, which are secreted from adipose tissue (61, 62).

Elevated MCP-1 levels are associated with insulin resistance and type 2 diabetes (T2DM) (63, 64), and as noted earlier, insulin resistance is inversely related to RMR (47). However, MCP-1 and hs-CRP had mediating effects on the association between RMR and UPF, which could be due to differences in the rate of inflammation and fiber intake (total, soluble, and insoluble), as compared with previous studies.

In a randomized controlled trial performed by Hall et al., it was reported that energy intake was higher during adherence to a UPF diet (16). Participants consumed more carbohydrates and fats and gained weight and body fat. The authors also showed that eating UPFs reduced the secretion of the hunger hormone ghrelin and also increased the level of the satiety hormone PYY (YY peptide) (11). Thus, UPFs may more efficiently regulate and stimulate biological mechanisms of hunger and satiety control than processed foods. The authors also asserted that with the unprocessed diet, a decrease in the inflammatory biomarker of hs-CRP was observed and that inflammation may be associated with satiety signals in animal studies (65).

Evidence is emerging regarding the mechanisms that strengthen the link between UPFs and adverse health outcomes. The mechanisms proposed are as follows: poor nutritional profile, UPFs are rich in sodium, added sugars, trans fats, and replace unprocessed foods in the diet (66–70), decrease in intestinal and brain satiety signal due to changes in physical properties caused by food processing and higher glycemic load (71–74), carcinogens formed during high-temperature cooking (acrylamide) (75, 76), and inflammatory responses associated with cellular nutrients and industrial food additives, increased intestinal permeability, and dysbiosis of the intestinal microflora (65, 77, 78).

Carbohydrate metabolism is more energy-intensive than fat metabolism, while protein metabolism requires the most energy (79–81). Processed foods have lower nutrient densities (less content and variety of nutrients per calorie) than whole foods, where extra simple carbohydrates (82–84) and less dietary fiber that make them chemically and structurally simple and digestible (82, 83, 85). All these reduce the volume of meals and reduce satiety, which consequently lead to increased daily caloric intake (31–39), which is associated with obesity and systemic inflammation (86–88).

The strengths of this study are the use of an FFQ questionnaire, which has been specifically validated in the Iranian population. Nevertheless, residual confounding related to recall bias must be acknowledged. Examining this association in one gender and only in Tehran represent limitations of this study because these results cannot be extrapolated to the entire Iranian population and all individuals. The cross-sectional design of this study precludes causal inferences being made. In addition, using BIA may overestimate lean body mass.

Conclusion

Ultra-processed foods may be related with changes in the production and secretion of cytokines and inflammatory factors and, ultimately, cause inflammation and reduced RMRs. A negative association between the RMR, RMR per BMI, and RMR per FFM with the NOVA score was observed in the present study. UPF intake is likely related with the RMR, RMR per BMI, and RMR per FFM, mediated by the production of hs-CRP, PAI-1, MCP-1, and IL-1β. hs-CRP and MCP-1 levels also had a possible negative mediatory role in the relationship between NOVA score groups and RMR deviation from normal. Given the novel evidence provided, further work, in the form of interventional studies, is needed in this area.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Tehran University of Medical Sciences and Health Services. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NB and FS designed the project. FS collected the samples and analyzed the data. NB and SN wrote the manuscript. FS, CC, and NB reviewed and edited the manuscript. KM conducted the research and had primary responsibility for the final content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.932225/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The mediatory role of inflammatory markers on the relationship between UPF intakes and RMR.

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EDITED BY
Farhana Akter,
Chittagong Medical College, Bangladesh

REVIEWED BY
Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh
Suhad Maatoug Bahijri,
King Abdulaziz University, Saudi Arabia

*CORRESPONDENCE
Yan-bin Ye
yanbinye72@163.com
Fang-fang Zeng
zengffjnu@126.com

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The association between dietary branched-chain amino acids and the risk of cardiovascular diseases in Chinese patients with type 2 diabetes: A hospital-based case–control study

Lu Zheng[1], Jun Cai[1], Yong-hui Feng[1], Xin Su[1], Shi-yun Chen[1], Jia-zi Liu[1], Wan-lin Li[1], Rui-qing Ouyang[1], Jun-rong Ma[1], Chen Cheng[1], Ying-jun Mu[1], Shi-wen Zhang[1], Kai-yin He[2], Fang-fang Zeng[1]* and Yan-bin Ye[2,3]*

[1]Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou, China, [2]Department of Clinical Nutrition, The First Affiliated Hospital, Jinan University, Guangzhou, China, [3]Department of Clinical Nutrition, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Previous studies showed conflicting evidence on the association between the intake of dietary branched-chain amino acid (BCAA) and the risk of cardiovascular disease (CVD). However, this relationship has not been studied in patients with type 2 diabetes. Therefore, we evaluated the effects of total and individual dietary BCAA (leucine, isoleucine, and valine) intake on CVD risk among individuals with type 2 diabetes in China.

Materials and methods: A total of 419 patients with type 2 diabetes who have been diagnosed with CVD (within 2 weeks) were recruited between March 2013 and September 2015 in China. Cases with CVD were 1:1 matched to controls with type 2 diabetes but without CVD by age (±5 years) and sex. A validated 79-item semiquantitative food frequency questionnaire (FFQ) was administered to assess the participants' dietary data. Total dietary BCAA per individual was the summation of the daily intake of isoleucine, leucine, and valine. OR and corresponding CIs were computed by conditional logistic regression models adjusted for potential confounders.

Results: Median values of the daily intake of total BCAA were 11.87 g, with an interquartile range of 10.46–13.15 g for cases, and 12.47 g, with an interquartile range of 11.08–13.79 g for controls ($P = 0.001$). Dietary BCAA was inversely related to CVD risk after multivariable adjustment ($OR_{Q4-Q1} = 0.23$, 95%CI = 0.10, 0.51, P trend <0.001 for total BCAA; $OR_{Q4-Q1} = 0.20$, 95%CI = 0.07, 0.53, P trend = 0.001 for leucine). For each 1-S.D. increase in total dietary BCAA, leucine or valine intake was associated with 54% (95%CI = 29%, 70%, $P = 0.001$), 64% (95%CI = 29%, 82%, $P = 0.003$), or 54% (95%CI = 1%, 79%, $P = 0.049$) decrease in the risk of CVD, respectively. Whole grains, starchy vegetables, mushrooms, fruit, eggs, and dairy and dairy product-derived BCAA were found to attenuate CVD risk (*P* ranged: = 0.002–0.027).

Conclusion: Higher BCAA intake, in particular leucine and valine, might be associated with a lower risk of CVD.

KEYWORDS

branched-chain amino acids, BCAA, isoleucine, leucine, valine, cardiovascular diseases, type 2 diabetes

Introduction

Type 2 diabetes is one of the risk factors for cardiovascular diseases (CVD) (1). The prevalence of diabetes among Chinese adults increased from 10.9% in 2013 to 12.4% in 2018 (2). Participants who shifted from impaired fasting glucose to diabetes had 61% increased risk for CVD and a 75% increased risk for congenital heart disease (CHD) (3). Similarly, the hazard ratio among the participants with insulin resistance, which later becomes type 2 diabetes, and the risk of CVD and CHD were 3.68 and 2.76, respectively (3). Thus, good management of type 2 diabetes in terms of lifestyle factor is necessary for preventing CVD in patients with type 2 diabetes.

Diets are considered as one of several fundamental factors in preventing or developing many chronic non-communicable diseases, including type 2 diabetes and CVD. Protein intake may play important role in the development of type 2 diabetes and possibly cardiovascular diseases (4). Previous studies from systematic reviews and meta-analyses indicated that the consumption of total protein and animal protein, including red meat and processed meat, was positively associated, while the consumption of plant protein, such as soy, was negatively associated with the risk of type 2 diabetes and CVD mortality (5, 6).

Branched-chain amino acids (BCAAs) such as leucine (Leu), isoleucine (Ile), and valine (Val) are exogenous essential amino acids derived from animal and/or plant protein-containing foods rather than endogenously synthesized (7). It was found that the BCAA diet had significant mediating effects on protein synthesis, glucose homeostasis, and obesity prevention (8). A systematic review and meta-analysis reported that while adherence to dietary BCAA, the risk of type 2 diabetes and obesity was increased by 1.32 and 0.62, respectively (9). Increased ingestion of dietary BCAA promotes thrombosis formation (10). In addition, adverse metabolic effects mediated by isoleucine and valine were reported in rodents (11). The actual benefit to metabolic health from dietary BCAA was observed during the restriction of dietary BCAA in mice (11). Circulating BCAA was positively associated with incident cardiovascular disease (12). The relationships between diets and the pathogenesis of diabetes coinciding with CVD might be caused by the metabolism of BCAA, which could be observed as an increase in circulating BCAA levels (13). The higher chance of being CVD in patients with type 2 diabetes could possibly be attributed to the increase in plasma BCAA that activate the mammalian target of rapamycin (MTOR) signaling pathway (14, 15). Higher intake of BCAA and the corresponding components have been suggested to be associated with lower triglyceride levels, blood pressure, obesity risk, and CVD risk or mortality; however, null associations were observed by other studies (Supplementary Tables 1, 2).

To our knowledge, no study has evaluated the effects of BCAA on CVD risk among type 2 diabetes subjects. Therefore, to better understand the association between dietary BCAA intake and CVD risk in type 2 diabetes subjects, we aimed to investigate the association between dietary BCAA intake and CVD risk in Chinese patients with type 2 diabetes.

Abbreviations: S.D, standard deviation; IQR, interquartile range; BCAA, branched-chain amino acids; CVD, cardiovascular diseases; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist–hip ratio; FPG, fasting plasma glucose; 2hPG, 2-h postprandial blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; TC, total cholesterol; MET, metabolic equivalent; FFQ, food frequency questionnaire.

Materials and methods

Study design

We performed a 1:1 matched hospital-based case–control study [one case with type 2 diabetes and a CVD diagnosis within 2 weeks was matched for age (±5 years) and sex with 1 control with type 2 diabetes only] at the Endocrinology Department, the Neurology Department, and the Cardiology Department of the First Affiliated Hospital of Sun Yat-sen University, Guangdong, China, between 2013 and 2015.

The study protocol, including other study-related documents, adhered to the Declaration of Helsinki guidelines and was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [No. (2017)019]. All participants were asked to sign informed consent forms before any epidemiological data, and biological specimens were collected. We followed the reporting guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (16).

Study population

All patients aged between 30 and 85 years admitted to the Endocrinology Department, the Neurology Department, and the Cardiology Department of the First Affiliated Hospital of Sun Yat-sen University, between 2013 and 2015 were considered for inclusion in the study.

Inclusion criteria

Patients who were either natives of Guangdong or had resided in Guangdong for at least 5 years and had a history of at least 2 years of type 2 diabetes were enrolled. Only those who were diagnosed with CVD within 2 weeks after the date of the type 2 diabetes diagnosis were considered cases. The controls recruited corresponded to the cases who were patients with type 2 diabetes, had never been self-reported or diagnosed with CVD, exhibited no symptoms of cardiac involvement, had normal EKG levels, and had negative exercise tests.

Exclusion criteria

Patients who had confirmed type 1 diabetes or gestational diabetes mellitus (GDM) and a history of cancer, hepatic disease, renal disease, autoimmune disorders, diabetic retinopathy, and congenital heart disease were first excluded. Then, patients who were physically disabled, had a disturbance of consciousness, had significant changes in their dietary habits or routine activities over the previous year, had an incomplete dietary assessment (≥10% missing values), had an implausible intake of total daily energy (<700 or >4,200 kcal per day for males, <500 or >3,500 kcal per day for females), or refused to participate in the study were also excluded.

Ascertainment of diseases

We ascertained individuals as having type 2 diabetes according to the American Diabetes Association. Type 2 diabetes is defined as a fasting plasma glucose level ≥7.0 mmol L^{-1}, a 2-h plasma glucose level ≥11.1 mmol L^{-1}, or an A1C level ≥6.5% (17). The assessments of CVD were described in a previous study (18). Briefly, CVD referred to non-fatal acute myocardial infarction, hospitalization for unstable angina, and non-fatal stroke. The China Society of Cardiology of the Chinese Medical Association has provided diagnostic criteria for non-fatal myocardial infarction and (19) and unstable angina (20), comprising typical symptoms, elevated cardiac enzyme levels, and electrocardiographic findings.

Data collection

Dietary assessment

A validated and reproducible 79-item semiquantitative food questionnaire (FFQ) was used to collect dietary information from each case and control (21). All cases completed dietary questionnaires during the 12 months prior to the diagnosis of a CVD. Both cases and controls were assessed for dietary intake *via* a face-to-face interview by a well-trained dietitian. For each food item, participants were asked to report on a frequency range of never, per day, per week, per month, and per year and to report the quantity of the average consumption of each food item. A photobook with different food portion sizes was provided to more precisely estimate the quantity of food intake.

All frequencies were converted to daily intake by dividing each possible frequency by 7 (per week), 30 (per month), and 365 (per year), and the portion sizes of each food item were calculated into grams per day. Energy, isoleucine, leucine, valine, and protein intake were calculated according to the China Food Composition Tables 2009, which includes the nutrient portion and energy of each food item (22). Total BCAA intake was obtained by the summation of isoleucine, leucine, and valine values in 100 g of a food item for each participant. Due to the non-normality of nutrients, the nutrient density method was used to normalize all nutrient data. The nutrient density model is a traditional approach used in nutritional epidemiological studies to adjust for the effect of total caloric intake (23). The nutrient residual (energy-adjusted) model was applied in this study by conducting a regression analysis of the nutrient intakes of individuals based on their total caloric intakes as previously described (24). The residual model was expressed as energy-adjusted intake = a + b, where a = residual of subjects in the regression model with nutrient intake as the dependent variable and total energy intake as the independent variable, and b = the expected nutrient intake for a person with a mean energy intake. To further analyze whether dietary BCAA obtained from different sources would interfere with the risk of CVD, we further categorized different food items into 16 food groups (e.g., whole grains, refined grains, tubers, starchy vegetables, non-starchy vegetables, legumes, beans, soy and soy products, fruit, unprocessed meat, processed meat, poultry, fish and seafood, dairy and dairy products, and eggs) based on their common nutritional values (Table 1).

TABLE 1 Example of food items constituting the 16 food groups.

Foods or food groups	Food items
Whole grains	Whole grain breakfast cereal, cooked oatmeal, wholewheat bread, purple rice, brown rice, other grains, bran
Refined grains	Refined grain breakfast cereal, white rice, white bread or bun, biscuits, waffle, crackers, pasta
Tubers	French fried, baked or mashed potatoes, potatoes, sweet potatoes, cassava, arrowroot, yam, taro, tapioca,
Mushrooms	Shiitake and relatives, oyster mushroom, wood ear mushroom, button mushroom, needle mushroom
Starchy vegetables	Carrot, pumpkin, broccoli, lotus root, wax gourd, towel gourd, other gourds
Non-starchy vegetables	Tomatoes, lettuce and mixed salad greens, lettuce salad, kale, spinach, other dark green leafy vegetables, green or red pepper or chili
Legumes	String beans, beans or lentils, peas or lima beans
Beans	Green beans, black beans, kidney beans, pinto beans
Soy and soy products	Soybean, tofu, soymilk
Fruit	Apple or juice, guava, orange or juice, grapefruit or juice, other non-sterile fruit juice, berries, mangoes, papaya, melons, kiwi, banana, water melon
Unprocessed meat	All red meat or offal such as pork, beef, lamb, liver, heart, kidney, spleen, tripe
Processed meat	Hot dog, sausage, bacon, ham, or smoked meat
Poultry	Chicken with skin, chicken without skin, goose, duck
Fish and seafood	Canned meat fish, sardine or salmon or anchovies or bluefish or trout or other fish, shrimp or prawn or lobster, scallops or oysters or mussels or clams, squid, octopus, sea crab
Dairy and dairy products	Whole milk or whole milk powder, skim low fat milk or skim low fat milk powder, sour cream, sherbet, ice cream, cheese, cottage, yogurt
Eggs	Eggs

Other covariates

Demographic information such as sex, education level (primary school or less, secondary/high school, college/university, or above), lifestyle habits (e.g., tobacco smoking, alcohol drinking status, tea drinking, and physical activity), history of chronic diseases, and medicine use (e.g., hypertension, dyslipidemia, insulin use, and oral hypoglycemic use) were collected for both cases and controls using a structured questionnaire *via* a face-to-face interview by a well-trained dietitian. Physical activity was evaluated by the Chinese version of the IPAQ (25), in which the metabolic equivalents-hour per week (MET-h/week) was computed to determine the activity level for each individual.

Anthropometric data, including weight (kg) and height (m), were ascertained using standard procedures and measuring equipment by trained personnel. We calculated BMI for each individual by dividing each individual weight in kilograms by their height in meters squared. We defined smokers or alcohol drinkers as smoking at least one cigarette per day or drinking alcohol once a week continuously for at least 6 months. Tea drinkers were people who drank tea at least twice a week. Individuals with a mean systolic pressure (SBP) $\geq$140 mmHg and/or a diastolic blood pressure (DBP) $\geq$90 mmHg and/or self-reported antihypertensive therapy were classified as hypertensive.

Dyslipidemia was determined according to the China Atherosclerosis Society guidelines and was defined as a cholesterol level of $\geq$200 mg/dl, a low-density lipoprotein cholesterol (LDL-c) level of $\geq$130 mg/dl, a high-density lipoprotein cholesterol (HDL-c) level of <40 mg/dl, triglyceride (TG) level of $\geq$160 mg/dl, or lipid-lowering drug use (26).

Statistical analyses

The normality of continuous variables was checked by the Kolmogorov–Smirnov test before running any statistical analysis. Demographic data among participants were summarized by descriptive statistics. Continuous normally distributed variables are expressed as the mean ± S.D., and skewed distributions are expressed as medians and interquartile ranges. Categorical variables are expressed as frequencies or percentages. For group comparisons, a paired *t*-test was applied for continuous variables with a normal distribution, whereas the Wilcoxon signed-rank test was used for non-normally distributed variables. The Pearson chi-square or Fisher's exact test was used for the categorical variables. The correlation coefficients between the intake levels of each BCAA and CVD risk factors, as well as protein intake adherence to food groups, were determined by Spearman's correlation coefficient. The total energy intake was adjusted for each food item using the residual method (23).

To determine the risk of CVD, total and individual BCAA intake were analyzed as both categorical and per S.D. increments. We grouped energy-adjusted intakes of total or individual BCAA into quartiles (Q_1-Q_4) based on control subjects by sex, and the sex-specific cutoffs were then applied to the cases. The lowest quartile (Q_1) served as the reference group. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression with different models. The first model was adjusted for age and sex. The second model was performed based on Model 1 and further adjusted for BMI (kg/m^2), hypertension (SBP $\geq$ 190 mmHg and/or DBP $\geq$ 90 mmHg), physical activity (MET-h/day),

TABLE 2 Characteristics included cases and controls.

Characteristics	Cases ($n = 419$)		Controls ($n = 419$)		*P*
	Mean/n	S.D./%	Mean/n	S.D./%	
Age (years)	62.08	9.67	62.06	9.55	0.926
BMI (kg/m^2)	24.36	3.23	23.80	3.46	0.011
WHR (male ≥ 0.9, female ≥ 0.85), *n* (%)	358	85.4	341	81.4	0.114
Blood pressure (mmHg)					
Systolic	136.77	21.38	130.20	17.46	<0.001
Diastolic	79.05	11.89	77.33	10.87	0.157
Education level, *n* (%)					0.001
<Middle school	163	39.0	148	35.4	
Middle/High school	131	31.3	101	24.2	
≥College	119	28.5	168	40.2	
Current smokers†, *n* (%)	131	31.4	115	27.4	0.208
Alcohol drinkers‡, *n* (%)	53	12.7	56	13.4	0.758
Tea drinkers§, *n* (%)	188	45.0	220	52.5	0.029
Antidiabetic medication therapy, *n* (%)	379	91.3	408	97.8	<0.001
Antihypertension drug use, *n* (%)	283	68.7	162	39.1	<0.001
Family history of diabetes, *n* (%)	48	11.5	135	32.2	<0.001
Family history of hypertension, *n* (%)	63	15.0	101	24.1	<0.001
Physical activity (MET-h/d)	25.64	3.86	26.07	3.93	0.009
Plasma glucose (mmol/L)‖					
FPG	7.30	2.73	7.80	3.83	0.711
2hPG	11.35	5.53	11.20	6.43	0.789
HbA1C (%)	7.50	2.43	9.10	3.43	<0.001
Plasma lipids (mmol/L)‖					
HDL	0.90	0.30	1.10	0.40	0.086
LDL	2.80	1.00	3.05	1.20	0.252
TG	1.60	1.30	1.40	1.00	0.005
TC	4.30	1.40	4.70	1.63	0.037

Test for differences of cases and controls using a paired t-test for normally distributed continuous variables; Wilcoxon signed-ranks test for skewed distributed continuous variables; Pearson's chi-square test or Fisher's exact test for categorical variables; $P < 0.05$ indicates significant difference.
‖Values are presented as median (IQR).
†Current smokers refer to participants who had been smoking at least one cigarette per day.
‡Alcohol drinkers refer to participants who had been smoking drinking alcohol once a week continuously for at least 6 months.
§Tea drinkers refer to participants who had been drinking tea at least twice a week.

antihypertensive drug use (yes/no), smoking status (yes/no), drinking status (yes/no), tea drinking (yes/no), and total energy intake (kcal/d). Last, a multivariable model was adopted to fully adjust for the second model and daily nutrient intake (g/d), including saturated fatty acids, total dietary fibers, and total dietary aromatic amino acids (AAAs). $P < 0.05$ were considered significant. All statistical tests were two-sided using SPSS version 26.0 (IBM Corp, Armonk, NY).

Results

The mean ± standard deviation for age was 62.08 ± 9.67 years for cases and 62.06 ± 9.55 years for controls. This study presented a mean BMI of 24.08 kg/m^2, in which the BMI of cases was substantially higher than that of controls ($P = 0.011$). Our cases had higher systolic blood pressure, but were less likely to drink tea and had less daily physical activity (MET-h/d). Importantly, with respect to the controls, the cases had higher TG levels ($P = 0.005$) but lower total cholesterol (TC) levels ($P = 0.037$) (Table 2).

Daily dietary nutrients and food group intake among cases and controls are shown in Tables 3, 4, respectively. Cases had lower total dietary BCAA intake than controls (median = 11.87, IQR = 2.68 g/d vs. median = 12.47, IQR = 2.71 g/d, $P = 0.001$), of which the consumption levels of dietary isoleucine, leucine, and valine were found to be significantly lower in cases (all $P < 0.05$). The level of total protein intake was lower for cases.

TABLE 3 Daily dietary nutrients and food group intake after energy-adjusted among 419 pairs of cases and controls.

Characteristics	Cases ($n = 419$)		Controls ($n = 419$)		P
	Median	IQR	Median	IQR	
Total energy (kcal/d)	1,469.67	615.43	1,554.27	629.45	0.031
Total dietary fibers (g/d)	10.82	5.23	13.46	7.98	<0.001
Total carbohydrate (g/d)	212.11	37.20	215.23	36.35	0.625
Total fat (g/d)	131.10	109.41	153.63	151.65	0.003
Saturated fatty acids (g/d)	13.96	5.35	14.74	4.50	0.040
Total protein (g/d)	82.27	27.18	96.44	56.68	<0.001
Plant-based protein (g/d)	31.63	16.11	45.56	48.83	<0.001
Animal-based protein (g/d)	34.93	14.79	35.94	14.92	0.282
Total dietary BCAA (g/d)	11.87	2.68	12.47	2.71	0.001
Plant-based BCAA (g/d)	3.98	2.37	4.35	2.65	0.001
Animal-based BCAA (g/d)	6.10	2.48	6.31	2.68	0.171
Dietary isoleucine (g/d)	2.84	0.64	2.92	0.63	0.009
Dietary leucine (g/d)	5.63	1.13	5.87	1.17	<0.001
Dietary valine (g/d)	3.45	0.71	3.52	0.65	0.012

Plant-based protein included protein from vegetables (starchy vegetables and non-starchy vegetables), legumes, soy, grains (whole grains and refined grains), mushrooms, beans, tubers, and fruits.
Animal-based protein included protein from unprocessed meat, poultry, fish and seafood, eggs, dairy and dairy products, and processed meat.
Test for differences of cases and controls using the Wilcoxon signed-ranks test; $P < 0.05$ indicates significant difference.

TABLE 4 Distribution of food group intake after energy-adjusted among 419 cases and 419 controls.

Characteristics	Cases ($n = 419$)		Controls ($n = 419$)		P
(g per day)	Median	IQR	Median	IQR	
Whole grains	0.13	3.70	1.95	12.00	<0.001
Refined grains	521.87	194.72	493.03	157.77	0.004
Tubers	19.62	22.71	24.07	26.67	0.129
Mushrooms	26.53	38.37	33.19	56.78	0.003
Starchy vegetables	144.38	72.66	163.49	77.59	<0.001
Non-starchy vegetables	69.75	43.92	75.02	44.23	0.008
Legumes	11.18	18.49	13.57	18.76	0.040
Beans	23.24	30.07	24.88	30.84	0.329
Soy and soy products	14.57	30.64	21.38	44.92	<0.001
Fruit	24.66	40.48	40.79	52.63	<0.001
Unprocessed meat	99.56	49.51	92.82	54.47	0.143
Processed meat	1.07	2.29	0.74	1.53	0.001
Poultry	20.18	22.91	21.74	22.93	0.434
Fish and seafood	48.26	39.71	48.46	37.95	0.171
Dairy and dairy products	0.12	19.03	4.45	104.24	<0.001
Egg	22.96	17.12	26.11	26.29	<0.001

Test for differences of cases and controls using the Wilcoxon signed-rank test; $P < 0.05$ indicates significant difference.

For cases, the total BCAA from animal-based foods was higher than those from plant-based foods ($P = 0.001$). In addition, the daily intake of refined grain and processed meat was significantly higher in cases, while the daily intake of total energy, whole grains, mushrooms, vegetables, legumes, soy and soy products, fruit, dairy and dairy products, and eggs was obviously decreased (all $P < 0.05$).

The results revealed that the consumption levels of dietary isoleucine, leucine, and valine, as well as total dietary BCAA, were positively correlated with the intake amount of soy and soy products, vegetables, mushrooms, eggs, dairy and dairy products, poultry, red meat, and fish and seafood (all $P < 0.05$) (Table 5). Among all food groups, the intake level of total dietary BCAA was more strongly positively correlated with the intake of mushrooms ($r_s = 0.464$, $P < 0.001$), followed by the intake of fish and seafood, eggs, and soy and soy products. In contrast, the intake of starchy vegetables, poultry, red meat, dairy and dairy products, legumes, non-starchy vegetables, and whole grains had weaker positive relationships. We found that consuming more refined grains would lower amount of total BCAA ($r_s = -0.291$, $P < 0.001$) (Table 5).

The ORs, 95% Cis, and P-values for CVD risk according to levels of dietary BCAA intake are given in Table 6. Participants whose total dietary BCAA was in the highest quartile were 0.46 times less likely to have CVD than those in the lowest quartile after adjustment for age and sex (Model 1). When further adjustment was conducted for all possible covariances, there was a 0.23-fold risk of CVD for patients with type 2 diabetes in the highest quartile of total dietary BCAA (OR = 0.23, 95% CI = 0.10, 0.51, P trend $\leq$ 0.001, Model 3). When each specific BCAA was considered, the fully adjusted model (Model 3) revealed that the highest quartile of dietary isoleucine and leucine intake decreased the risk of CVD was 0.20 (95% CI = 0.07, 0.53, $P = 0.001$), while the consumption of isoleucine and valine showed no significant association, compared to the reference quartile. Similarly, significant negative associations between dietary leucine, valine, and total BCAA intake per S.D. and CVD risk in the fully adjusted model were simultaneously observed.

We further identified the relationship between the risk of CVD in patients with type 2 diabetes and food-derived BCAA intake per S.D. categorized by nutrients (Table 7). A higher consumption of mushrooms would reduce the risk of developing CVD for patients with type 2 diabetes by 25% for each 1–S.D. increase (95% CI = 7%, 39%, $P = 0.009$), followed by 24% per 1–S.D. increase in fruit consumption (95% CI = 3%, 41%, $P = 0.027$) and 24% per 1–S.D. increase in dairy and dairy product consumption (95% CI = 9%, 36%, $P = 0.002$), as well as per 1–S.D. increase in fruit, dairy and dairy product, whole grains, starchy vegetables and eggs consumption, respectively.

TABLE 5 Spearman's correlation coefficients between dietary BCAA and protein intake adherence to food groups among 838 participants.

Food groups (g/d)	Isoleucine (g/d)	*P*	Leucine (g/d)	*P*	Valine (g/d)	*P*	Overall BCAA (g/d)	*P*
Whole grains	0.776	0.435	−0.003	0.930	−0.038	0.283	0.115	0.001
Refined grains	−0.261	<0.001	−0.215	<0.001	−0.137	<0.001	−0.291	<0.001
Soy and soy products	0.180	<0.001	0.159	<0.001	0.149	<0.001	0.231	<0.001
Non-starchy vegetables	0.111	0.002	0.092	0.008	0.111	0.002	0.127	<0.001
Starchy vegetables	0.138	<0.001	0.111	0.001	0.110	0.002	0.185	<0.001
Legumes	0.101	0.004	0.065	0.064	0.990	0.089	0.165	<0.001
Beans	0.087	0.013	0.056	0.108	0.010	0.772	0.088	0.012
Tubers	0.035	0.314	0.023	0.521	0.020	0.564	0.093	0.008
Mushrooms	0.184	<0.001	0.139	<0.001	0.147	<0.001	0.464	<0.001
Fruit	0.025	0.471	0.022	0.535	0.014	0.680	0.081	0.021
Eggs	0.217	<0.001	0.192	<0.001	0.214	<0.001	0.242	<0.001
Dairy and dairy products	0.118	0.001	0.134	<0.001	0.114	0.001	0.172	<0.001
Poultry	0.210	<0.001	0.223	<0.001	0.226	<0.001	0.180	<0.001
Processed meat	0.028	0.419	0.040	0.256	0.042	0.229	−0.015	0.676
Red meat	0.331	<0.001	0.369	<0.001	0.356	<0.001	0.177	<0.001
Fish and seafood	0.430	<0.001	0.397	<0.001	0.434	<0.001	0.367	<0.001

All values were adjusted for age, sex, BMI (kg/m^2), hypertension (SBP ≥190 mmHg and/or DBP ≥90 mmHg), physical activity (MET-h/day), antihypertension drug use (yes/no), smoking status (yes/no), drinking status (yes/no), tea drinking (yes/no), total energy intake (kcal/d), and daily nutrients intake (g/d), including saturated fatty acids, total dietary fibers, and total dietary aromatic amino acids (AAAs).
$P < 0.05$ indicates significant difference.

Discussion

Our case–control study showed inverse associations between total dietary BCAA intake and CVD risk among patients with type 2 diabetes. Similarly, the highest quartiles of dietary isoleucine, leucine, and valine intake might provide beneficial effects against CVD among patients with type 2 diabetes when compared to the reference quartile. When the sources of food-derived dietary BCAA were taken into account, the levels of dietary BCAA among cases mainly came from animal-based foods rather than plant-based foods. Moreover, subjects with type 2 diabetes who regularly consumed whole grains, starchy vegetables, mushrooms, fruit, eggs, and dairy and dairy products had significantly lower risks of developing CVD.

Although the association between dietary BCAA and CVD risk among individuals with type 2 diabetes has not been reported, several studies have demonstrated the effect of dietary BCAA on metabolic biomarkers (e.g., TG, SBP, insulin, and HOMA-IR), obesity, type 2 diabetes, and CVD risk or mortality (Supplementary Tables 1, 2). A cross-sectional study of female twins in 1997 found that dietary BCAA was significantly associated with lower blood pressure (27). Likewise, US adults who consumed high amounts of essential amino acids were found to have lower all-cause and CVD mortality (28). This inverse relationship may be attributed to the protective effects of some specific amino acids of BCCA because total dietary BCCA is composed of amino acids that have some common features in their chemical structures and catabolism (29). In particular, a lower risk of CVD was associated with a higher intake of leucine (30), which was consistent with our study. A similar finding was found regarding the risk of obesity, and obesity risk was found to be reduced by 41.6, 37.4, and 44.1% as dietary isoleucine, leucine, and valine intake increased, respectively (31). Dietary isoleucine was positively associated with levels of fasting plasma glucose, triglycerides, and blood pressure, while dietary leucine was found to substantially decrease triglyceride levels (32). In addition, the negative association between CVD risk and dietary BCAA may likely be related to a low risk of atherosclerosis. The association between dietary BCCA, particularly leucine, and improvements in dyslipidemia and atherosclerosis-related factor development was recently found in subjects with higher serum triglyceride concentration (33). Dietary leucine and other amino acids prevented atherosclerosis by downregulating triglyceride-rich VLDL and inhibiting triglyceride biosynthesis in macrophages (29). Furthermore, each 1–S.D. increment of log 10-transformed dietary isoleucine, leucine, or valine intake was associated with a decrease in the risk of CVD mortality (33). This was also in line with our study, in which isoleucine was found to have no significant association with the risk of CVD. In contrast, the incidence of type 2 diabetes, CVD, and hypertension increased with dietary BCCA (34–36). Moreover, an increase in thrombosis formation occurs with increased ingestion of dietary BCAA (10). A similar finding from a meta-analysis showed that the restriction of dietary BCAA intake, which generally occurs with a simultaneous decrease in total protein intake, was inversely associated with impaired

TABLE 6 Odd ratios and corresponding 95% confidence intervals according to dietary BCAA intake and the risk of CVD in type 2 diabetes individuals.

	Quartile of BCAA intake (OR, 95%CI)				*P* trend	BCAA intake per 1-S.D. (OR, 95%CI)	*P*
	Q1	Q2	Q3	Q4			
Isoleucine							
N (case/control)	116/93	115/95	95/115	93/116			
Median (g/d)	2.34	2.74	3.02	3.42			
Model 1	1	0.99 (0.67, 1.46)	0.67 (0.45, 0.99)	0.64 (0.44, 0.95)	0.008	0.86 (0.75, 0.99)	0.031
Model 2	1	1.03 (0.66, 1.62)	0.71 (0.45, 1.12)	0.77 (0.49, 1.20)	0.125	0.90 (0.77, 1.07)	0.230
Model 3	1	0.79 (0.45, 1.39)	0.46 (0.22, 0.96)	0.45 (0.17, 1.19)	0.062	0.58 (0.26, 1.27)	0.174
Leucine							
N (case/control)	118/91	117/93	98/112	86/123			
Median (g/d)	4.74	5.48	6.00	6.71			
Model 1	1	0.96 (0.66, 1.40)	0.67 (0.45, 1.00)	0.54 (0.37, 0.81)	0.001	0.82 (0.72, 0.95)	0.006
Model 2	1	1.03 (0.66, 1.61)	0.75 (0.47, 1.20)	0.65 (0.41, 1.02)	0.026	0.88 (0.75, 1.04)	0.123
Model 3	1	0.62 (0.35, 1.10)	0.34 (0.16, 0.71)	0.20 (0.07, 0.53)	0.001	0.36 (0.18, 0.71)	0.003
Valine							
N (case/control)	117/92	106/104	101/109	95/114			
Median (g/d)	2.90	3.32	3.63	4.05			
Model 1	1	0.81 (0.55, 1.20)	0.75 (0.51, 1.10)	0.67 (0.45, 0.98)	0.037	0.88 (0.76, 1.01)	0.065
Model 2	1	0.79 (0.50, 1.26)	0.70 (0.44, 1.10)	0.74 (0.48, 1.16)	0.170	0.91 (0.78, 1.08)	0.275
Model 3	1	0.59 (0.33, 1.05)	0.44 (0.22, 1.00)	0.38 (0.14, 1.02)	0.113	0.46 (0.21, 0.99)	0.049
Total BCAA							
N (case/control)	123/86	112/98	102/108	82/127			
Median (g/d)	9.61	11.53	12.74	14.65			
Model 1	1	0.81 (0.55, 1.21)	0.66 (0.44, 0.98)	0.46 (0.31, 0.69)	<0.001	0.77 (0.66, 0.89)	<0.001
Model 2	1	0.90 (0.56, 1.45)	0.69 (0.44, 1.10)	0.50 (0.32, 0.80)	0.002	0.77 (0.65, 0.91)	0.003
Model 3	1	0.66 (0.38, 1.13)	0.39 (0.20, 0.77)	0.23 (0.10, 0.51)	<0.001	0.46 (0.30, 0.71)	0.001

Model 1 = adjusted for age and sex.
Model 2 = adjusted for age, sex, BMI (kg/m^2), hypertension (SBP $\geq$ 190 mmHg and/or DBP $\geq$ 90 mmHg), physical activity (MET-h/day), antihypertension drug use (yes/no), smoking status (yes/no), drinking status (yes/no), tea drinking (yes/no), and total energy intake (kcal/d).
Model 3 = fully adjusted for age, sex, BMI (kg/m^2), hypertension (SBP $\geq$ 190 mmHg and/or DBP $\geq$ 90 mmHg), physical activity (MET-h/day), antihypertension drug use (yes/no), smoking status (yes/no), drinking status (yes/no), tea drinking (yes/no), total energy intake (kcal/d), and daily nutrients intake (g/d), including saturated fatty acids, total dietary fibers, and total dietary aromatic amino acids (AAAs).
$P < 0.05$ indicates significant difference.

glucose in rodents (37). By reducing either dietary isoleucine or valine, hepatic insulin sensitivity was promoted, resulting in an improvement in glucose tolerance in rodents (11). In addition, a 2.46 unit increase in BMI was observed with the increased consumption of dietary isoleucine (11).

Dietary sources have been linked to the incidence of many chronic diseases (38–41). We hypothesized that plant-based BCAA was responsible for lowering CVD risk in our study. A higher incidence of CVD cases or CVD mortality was found in individuals who had a higher animal-to-plant protein ratio intake (40, 42). In addition, a higher risk of type 2 diabetes corresponds to greater levels of animal protein intake (41). While some studies found a null association between CVD risk and the consumption of fish, eggs, dairy, or plant protein (42), we found a reduction in risk with the increased intake of plant-based diets, eggs, and dairy and dairy products. An umbrella review of observational studies recently proposed convincing evidence of total dairy consumption in reducing the risk of hypertension, CVD, and diabetes (43). The elevation of HDL-c and PON-1, an enzyme that protects LDL from lipid peroxidation, was found after egg ingestions; therefore, individuals with metabolic syndrome who had consumed eggs presented a decrease in C-reactive protein levels, insulin levels, and insulin resistance, compared to baseline (44).

Dietary BCAA may drive the pathogenesis of cardio-metabolic diseases through the alteration of plasma BCAA concentrations since 80% of dietary BCAA consumption enters circulation (13). Studies have stated that increasing dietary BCCA may induce mTORC1 activity (14, 15) which is responsible for metabolic changes (45). Some believed that the elevation of serum BCAA levels is probably a consequence of disease rather than a cause (46) since endogenous factors, such as insulin, are able to regulate BCAA metabolism and degradation (47). In addition, the increase in amino acid oxidation was

TABLE 7 Odd ratios and corresponding 95% confidence intervals with the fully adjustment model according to BCAA intake categorized by food groups and the risk of CVD in patients with type 2 diabetes.

Food groups (g BCAA/per S.D.)	*β*	SE	(OR, 95%CI)	*P*
Whole grains	−0.248	0.108	0.78 (0.63, 0.97)	0.022
Refined grains	0.074	0.090	1.08 (0.90, 1.29)	0.408
Soy and soy products	−0.266	0.217	0.77 (0.50, 1.17)	0.220
Non-starchy vegetables	−0.178	0.093	0.84 (0.70, 1.00)	0.055
Starchy vegetables	−0.240	0.094	0.79 (0.66, 0.95)	0.011
Legumes	−0.065	0.094	0.94 (0.78, 1.13)	0.490
Beans	0.186	0.150	1.20 (0.90, 1.62)	0.214
Tubers	0.116	0.091	1.12 (0.94, 1.34)	0.201
Mushrooms	−0.283	0.109	0.75 (0.61, 0.93)	0.009
Fruit	−0.277	0.126	0.76 (0.59, 0.97)	0.027
Eggs	−0.193	0.087	0.82 (0.69, 0.98)	0.027
Dairy and dairy products	−0.276	0.091	0.76 (0.64, 0.91)	0.002
Poultry	−0.075	0.082	0.93 (0.79, 1.09)	0.362
Processed meat	−0.010	0.086	0.99 (0.84, 1.17)	0.908
Red meat	0.017	0.103	1.02 (0.83, 1.24)	0.871
Fish and seafood	0.139	0.094	1.15 (0.96, 1.38)	0.137

Fully adjusted for age, sex, BMI (kg/m^2), hypertension (SBP ≥190 mmHg and/or DBP ≥90 mmHg), physical activity (MET-h/day), antihypertension drug use (yes/no), smoking status (yes/no), drinking status (yes/no), tea drinking (yes/no), total energy intake (kcal/d), and daily nutrients intake (g/d) including saturated fatty acids, total dietary fibers, and total dietary aromatic amino acids (AAAs).
$P < 0.05$ indicates significant difference.

likely to be a consequence of impaired protein synthesis, which was caused by a limitation of diet-derived amino acid intake (48). Therefore, higher BCAA intake could decrease protein degradation and oxidative stress (49), while adequate BCAA consumption is essential for maintaining glucose homeostasis and body weight (9).

Our findings were in contrast with some other studies possibly due to the different amounts of dietary protein intake despite the sources of protein (e.g., egg and dairy). The associations of dietary BCAA or specific sourced proteins and the risk of diabetes or hypertension were found to have a non-linear relationship, indicating that the risk of diseases may increase as certain thresholds of some nutrients are surpassed (50, 51). Additional evidence for these dissimilarities of the risk of diseases might be related to genetic variations among individuals. Studies have demonstrated that a variety of individual genes are responsible for the difference in BCAA metabolic pathways and may affect the level of plasma BCAA together with dietary BCAA (52, 53).

Limitations

There are some limitations that need to be taken into consideration when interpreting our results. First, we conducted a case–control study, so a causal relationship between exposures and diseases cannot be determined. Second, dietary information among participants was assessed by a food frequency questionnaire (FFQ); therefore, recall bias is inevitable. Third, selection bias still exists; however, we have tried to solve this bias by recruiting both groups from the same referral hospital. Fourth, although we considered some potential confounders in this study, we could not completely exclude other confounding factors that could interfere with these associations. Finally, we did not measure the levels of circulating BCAA which may also affect the reliability of the study.

Recommendations

The results from this study have certain clinical and public health implications for the primary prevention of CVD, especially in individuals with type 2 diabetes. However, further prospective studies, including clinical trials, may be warranted to better understand the associations between dietary BCAAs and CVD risk among subjects with type 2 diabetes. Additional information on circulating BCAA should be collected, and if possible, genetic expression that is involved in the BCAA metabolic pathway may also be addressed to identify more details about the relationship between dietary BCAA and the risk of diseases.

Conclusion

This case–control study indicated that the increased dietary intake of total BCAA and leucine might have some protective effect on the risk of CVDs in patients with type 2 diabetes. Plant-derived BCAA such as whole grains, mushrooms, and fruit, as well as eggs and dairy and dairy products, was associated with a lower incidence of CVD in individuals with type 2 diabetes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [no. (2017)019]. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Y-bY and F-fZ contributed to the conception and design of the study and manuscript revision. LZ had responsibility for the data analyses and wrote the manuscript. JC, Y-hF, XS, S-yC, J-zL, W-lL, R-qO, J-rM, Y-jM, S-wZ, and K-yH collected the data and made a great contribution to the revised work. All authors have reviewed and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.999189/full#supplementary-material

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EDITED BY
Mainul Haque,
National Defence University of Malaysia, Malaysia

REVIEWED BY
Susmita Sinha,
Khulna City Medical College and Hospital, Bangladesh
Kona Chowdhury,
Gonoshathaya Samaj Vittik Medical College, Bangladesh
Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh

*CORRESPONDENCE
Aihua Gu
aihuagu@njmu.edu.cn
Haibing Yang
yhbing111@163.com

†These authors have contributed equally to this work and share first authorship

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Comparisons of tri-ponderal mass index and body mass index in discriminating hypertension at three separate visits in adolescents: A retrospective cohort study

Jia Hu[1,2,3†], Yi Zhong[4†], WenXin Ge[4], Huiling Lv[1], Ziyao Ding[3,5], Di Han[3], Bo Hai[3], Hui Shen[2,3], Jieyun Yin[4], Aihua Gu[1*] and Haibing Yang[1,2,3*]

[1]State Key Laboratory of Reproductive Medicine, School of Public Health, Nanjing Medical University, Nanjing, China, [2]Suzhou Institute of Advanced Study in Public Health, Gusu School, Nanjing Medical University, Suzhou, China, [3]Suzhou Center for Disease Prevention and Control, Suzhou, China, [4]Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, School of Public Health, Medical College of Soochow University, Suzhou, China, [5]Institute of Child and Adolescent Health, School of Public Health, Peking University, Beijing, China

Objective: To estimate whether the new obesity indicator tri-ponderal mass index (TMI) has a better capacity to predict adolescent hypertension (HTN) and HTN subtypes at three separate blood pressure (BP) visits than the conventionally used body mass index (BMI).

Methods: A total of 36,950 adolescents who had initial normal BP from 2012 to 2019 were included in Suzhou, China. HTN was defined as having three separate visits of elevated BP in 2020. The area under the receiver-operating characteristic curve (AUC), false-positive rate, false-negative rate, total misclassification rates, net reclassification improvement (NRI), and integrated discrimination improvement were calculated to compare the discriminative ability of HTN between BMI and TMI.

Results: TMI had better predictive abilities than BMI among all of the participants when predicting HTN (difference in AUC = 0.019, 95% CI = 0.007–0.031; NRI = 0.067, 95% CI = 0.008–0.127) and isolated systolic hypertension (difference in AUC = 0.021, 95% CI = 0.005–0.036; NRI = 0.106, 95% CI = 0.029–0.183). The difference in prediction abilities between BMI and TMI was more obvious in the subgroup of age ≥16. Also, TMI outperformed BMI in predicting adolescent HTN in girls but not in boys.

Conclusion: Compared with BMI, TMI may have a better predictive capacity for HTN, particularly in girls and older adolescents. TMI has the potential to be used as an effective predictor for HTN in clinic practice. Further studies are needed to verify the utility of TMI.

KEYWORDS

adolescents, body mass index, hypertension, pediatric, tri-ponderal mass index

Introduction

Hypertension (HTN) is a widespread chronic disease that receives increased global health attention, especially in pediatric populations (1, 2). The prevalence of HTN among children aged 6–19 has increased by 75–79% in the past 15 years (2). Nevertheless, the diagnosis rate of adolescent HTN needs to be improved. In Europe and the US, only 13–26% of children with HTN were properly identified (3). Additionally, adolescent HTN has been identified as an established risk factor for cardiovascular disease (4–6), organ damage (7), and premature death (8), and may turn into adulthood HTN (9–11). Therefore, to reduce the potential burden of disability and premature death, early and precise detection of HTN in children and adolescents is in need.

The measurement of HTN in children and adolescents is more unstable and complicated than in adults (2) due to regression to the mean (12), the "white-coat" effect (13), and anxiety (14). However, numerous studies suggested that the prevalence of HTN validated by multiple BP measurements is considerably lower than that of elevated BP defined by a single visit in children and adolescents (15–17). A systematic review indicated that the overall prevalence of elevated BP in participants aged 3–20 decreased from 12.1% at the first visit to 5.6 and 2.7% at the second and third visits, respectively (18). Therefore, HTN assessment based on three separate BP visits is required for an accurate understanding of BP levels in children and adolescents, which have been recommended by the latest standards in many countries (19–21).

In general, adolescents with overweight and obesity were more susceptible to HTN than normal weight individuals, regardless of sex (22). It is well acknowledged that the increased prevalence of pediatric HTN couples with the obesity epidemic (23). Body mass index (BMI), a measurement based on a person's height and weight, is the current screening standard for obesity. However, it has been revealed that BMI does not distinguish between fat mass and lean mass (24). Generally, weight is not proportional to height squared in children and adolescents, resulting in BMI instability (25, 26). To compensate for the significant changes in BMI during childhood, age-in-month cutoffs have been widely used (27). Nevertheless, the cutoffs are multiple and complex, with many age- and sex-specific thresholds.

Recently, Peterson et al. (28) found that tri-ponderal mass index (TMI, measured in kg/m^3), an emerging indicator of obesity, may perform as a more valid obesity indicator to measure body fat in adolescents. Unlike BMI, TMI is relatively stable during adolescence, and its centile cutoffs fluctuate within a narrow range. Wang et al. have suggested a threshold with only four cutoffs to screen for overweight and obesity in children aged 7–18 years (29). Additionally, TMI has a lower overall misclassification rate than BMI in discriminating central obesity and HTN in overweight adolescents (30). Hence, TMI was considered a more reliable index for overweight and obesity (28–30). However, a systematic review (31) concluded that evidence of whether TMI outperforms BMI in identifying BP remains limited and inconsistent, while prospective reports are insufficient. In addition, whether TMI outperforms BMI in predicting HTN measured by three separate times is far from the conclusion.

Therefore, we used data through three separate BP visits from the Health Promotion Program for Children and Adolescents (HPPCA) in Suzhou of China to verify whether TMI has better accuracy than BMI in discriminating adolescent HTN and HTN subtypes.

Materials and methods

Study design and participants

This study was a retrospective cohort analysis based on HPPCA data for nine consecutive years (from 2012 to 2020). HPPCA is a large-scale ongoing school-based monitoring program conducted in Suzhou, China. Detailed information about HPPCA was published in the previous studies (32, 33). In brief, HPPCA provided free annual health check-ups for all school-based students aged 6–17 years in Suzhou to assess the growth and development of children and adolescents. Students are examined in general hospitals, centers for disease prevention and control, or community medical institutions. Students in the third year of junior high school or senior high school who would take other special physical examinations for school entrance were excluded from the study because their data are not currently accessible.

To figure out the epidemic status of HTN among adolescents in Suzhou, we selected 66 junior or senior high schools attending HPPCA to conduct specific BP surveillance in 2020. All participants who had elevated BP in the first BP measurement were included in the second visit at least 2 weeks later; only those with elevated BP at the second visit were included in the third visit. To eliminate the "white-coat" effect, the second and third BP measurements were conducted by a familiar school nurse of the particular student, following the same criteria as the HPPCA. Almost all students with elevated BP at their first (follow-up rate: 97.16%) or second (follow-up rate: 98.01%) visit participated in the follow-up BP measurement, except for children who transferred to another school or took extended sick leave. The initial sample consisted of 46,788 school-based adolescents aged 12–17 years. To accurately portray the morbidity of HTN in adolescents, we used the 2020 surveillance data as an endpoint and excluded 9,838 children with elevated BP at their initial HPPCA visit from 2012 to 2019. **Figure 1** shows the flowchart of the detailed study design, which was coherent with other large-scale surveillance studies in China (17, 34).

This study was approved by the Ethics Committee of the Suzhou Center for Disease Prevention and Control (No. SZJK2020-XW001). Written informed consent was obtained from all the participants or their guardians.

Anthropometric measurements and weight status classification

All physical examinations were performed by well-trained health professionals using the same type of age-appropriate equipment and following the same procedures. Participants were requested to remove their shoes and wear light clothing before being measured to an accuracy of 0.1 cm (height) and 0.1 kg (weight). BMI is calculated as weight (kg) divided by the square of height (m), whereas TMI is calculated as weight (kg) divided by the cube of height (m).

Participants were classified as underweight, normal weight, overweight, and obesity according to the latest Chinese pediatric standards of age- and sex-specific BMI cutoffs (21) and the TMI criteria proposed by Wang et al. (29) on a Chinese population, respectively. Noteworthy, the TMI cutoffs to define adolescent overweight and obesity were 13.1 and 14.1 kg/m^3 for participants under 16, respectively (29). The corresponding TMI cutoffs for those aged 16 or over were 14.0 and 15.8 kg/m3, respectively (29).

Blood pressure measurements and definitions

The BP of children and adolescents was measured each visit on the right arm using a clinically validated Electronic Blood Pressure Monitor (i.e., Omron HBP1300, HBP1320) of appropriate size after a 15 min sit-down rest period in a quiet environment. The BP device was placed at the same level as the participant's heart and right arm cuff. Three consecutive BP values were measured at 2-min intervals for each visit, and the average of the two closest BP readings was recorded for diagnosis and statistical analysis.

BP status was also categorized according to the Chinese standard "Reference of screening for elevated BP among children and adolescents aged 7∼18 years" (WS/T 610-2018) (21). Elevated BP was defined as systolic blood pressure (SBP), diastolic blood pressure (DBP), or both equal to or above the age-, sex-, and height-specific 95th percentile. Notably, HTN is diagnosed only when elevated BP is present at all three separate visits (21). Based on 3 separate visits, isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and systolic and diastolic hypertension (SDH) was defined as SBP $\geq$ P95 and DBP $<$ P95, DBP $\geq$ P95 and SBP $<$ P95, and SBP $\geq$ P95 and DBP $\geq$ P95, respectively.

Statistical analysis

The basic information about the participants was described in the total sample and by age and sex. Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables were described as n (%). Student's *t*-test and Chi-square test were used to compare differences between groups, respectively.

The AUC, the false-positive rate (FPR), the false-negative rate (FNR), and total misclassification rates were used to directly measure the discrimination ability between youth BMI and TMI. The net reclassification improvement (NRI) measures the correct movement in categories—upwards for events and downwards for non-events—using reclassification tables constructed separately for participants with and without events (35). We only obtained continuous NRI because no established NRI categories guide clinical decisions for HTN risk in Chinese children were found. The integrated discrimination improvement (IDI) essentially measures how the R^2 (explained variance) improves when a new risk factor is introduced (36). Analyses were conducted using SAS statistical software (version 9.4, SAS Institute) and R (version 4.2.0, R Foundation for Statistical Computing). All reported *P*-values were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the participants

The overall population consists of 36,950 adolescents aged 12–17 years from HPPCA in 2020. **Table 1** demonstrates the primary characteristic of the overall participants. A total of

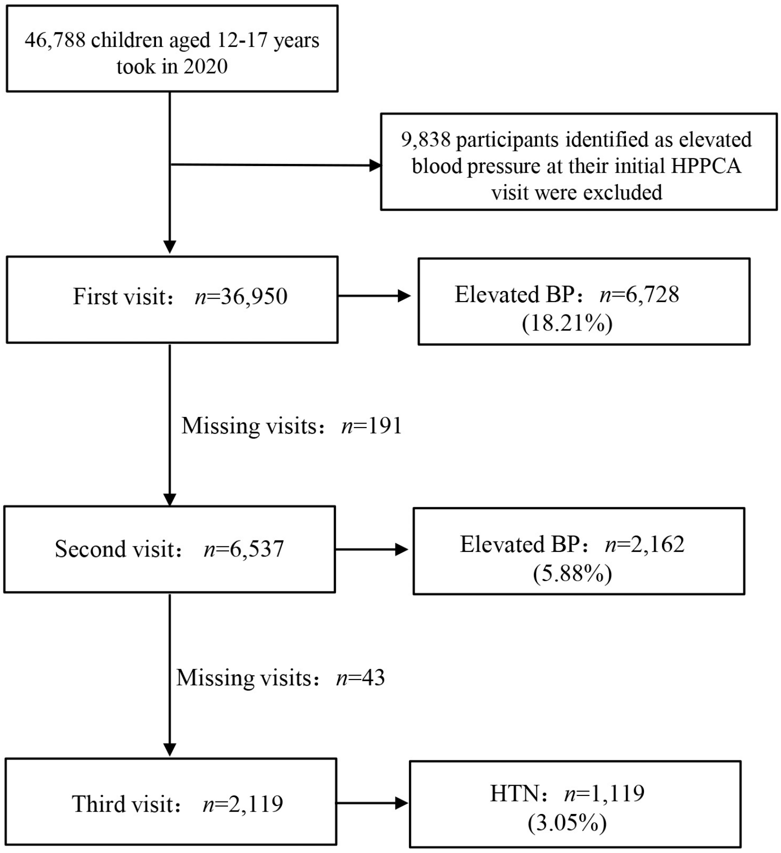

FIGURE 1
Details of the study population selection. HPPCA, health promotion program for children and adolescents; BP, blood pressure; HTN, hypertension.

18,797 boys account for 50.87% of the overall population. The average age of the overall population was 14.39 (SD = 1.68) in 2020. Compared with girls, boys had higher BMI (21.42 vs. 20.45 kg/m^2, $P < 0.001$). According to BMI cutoffs, the prevalence of overweight and obesity among adolescents in 2020 was 17.20 and 10.28%, respectively. According to TMI cutoffs, the corresponding prevalence was 13.27 and 18.97%. Comparisons between included and excluded populations from the first visit to the second visit (97.16% of cooperation rate) and the second visit to the third (98.01% of cooperation rate) are shown in **Supplementary Tables 1**, **2**, respectively. The vast majority of the variable characteristics yielded no significant difference between included and excluded populations from the first visit to the second visit. A slight difference was found between included and excluded populations from the second visit to the third visit.

After the three visits, the incidence of HTN, ISH, IDH, and SDH decreased to 3.05, 1.79, 0.42, and 0.83%, respectively. During the three visits, boys had higher SBP and prevalence of ISH than girls, while girls had a higher prevalence of IDH than boys (all $P < 0.05$).

Analysis of the anthropometric indicators for predicting hypertension and hypertension subtypes

The comparison predictors (95% CI) of the discriminative ability between TMI and BMI for HTN and HTN subtypes are shown in **Tables 2–5**. **Supplementary Tables 3–6** show detailed results performed by gender. Generally speaking, TMI had higher AUCs than BMI, and its NRIs significantly increased both in HTN (difference in AUC = 0.019, 95% CI = 0.007-0.031; NRI = 0.067, 95% CI = 0.008-0.127) and in ISH (difference in AUC = 0.021, 95% CI = 0.005–0.036; NRI = 0.106, 95% CI = 0.029–0.183).

When predicting ISH (difference in AUC = 0.039, 95% CI = 0.011–0.066; NRI = 0.366, 95% CI = 0.223–0.508; IDI = 0.002, 95% CI = 0.004–0.005) and SDH (difference in AUC = 0.035, 95% CI = 0.006–0.064; NRI = 0.002, 95% CI = 0.001–0.004; IDI = 0.002, 95% CI = 0.001–0.004), the difference between TMI and BMI were more notable in those with age ≥ 16. For girls, there was a statistically significant difference in the AUCs of TMI vs. BMI for discriminating HTN

TABLE 1 Basic characteristics of Chinese adolescents.

Variables	Overall	Boys	Girls	*P*-value
	n = 36,950	*n* = 18,797	*n* = 18,153	
Initial HPPCA visit				
Age (year)	10.23 ± 2.77	10.21 ± 2.77	10.25 ± 2.77	0.169
Height (cm)	143.50 ± 17.21	144.50 ± 18.08	142.50 ± 16.19	<0.001
Weight (kg)	38.52 ± 14.20	40.04 ± 15.32	36.96 ± 12.74	<0.001
BMI (kg/m^2)	18.06 ± 3.26	18.47 ± 3.44	17.62 ± 3.01	<0.001
TMI (kg/m^3)	12.61 ± 1.94	12.82 ± 2.04	12.40 ± 1.80	<0.001
SBP (mmHg)	102.92 ± 11.65	104.10 ± 12.31	101.80 ± 10.80	<0.001
DBP (mmHg)	64.42 ± 7.10	64.29 ± 7.22	64.56 ± 6.97	<0.001
In 2020				
Age (year)	14.39 ± 1.68	14.36 ± 1.68	14.42 ± 1.69	0.001
Height (cm)	165.35 ± 8.65	169.30 ± 9.05	161.20 ± 5.84	<0.001
Weight (kg)	57.62 ± 12.71	61.83 ± 14.01	53.27 ± 9.40	<0.001
BMI (kg/m^2)	20.94 ± 3.61	21.42 ± 3.92	20.45 ± 3.19	<0.001
TMI (kg/m^3)	12.68 ± 2.15	12.66 ± 2.28	12.70 ± 2.01	0.091
District				
Urban	22,398 (60.62%)	11,403 (60.66%)	10,996 (60.57%)	0.863
Rural	14,552 (39.38%)	7,394 (39.34%)	7,157 (39.43%)	
BMI status				
Underweight	2,089 (5.65%)	1,255 (6.68%)	834 (4.59%)	<0.001
Normal weight	24,706 (66.86%)	10,858 (57.76%)	13,848 (76.28%)	
Overweight	6,357 (17.20%)	4,086 (21.74%)	2,271 (12.51%)	
Obesity	3,798 (10.28%)	2,598 (13.82%)	1,200 (6.61%)	
TMI status				
Underweight and normal	25,047 (67.79%)	12,518 (66.60%)	12,529 (69.02%)	<0.001
Overweight	4,893 (13.24%)	2,316 (12.32%)	2,577 (14.20%)	
Obesity	7,010 (18.97%)	3,963 (21.08%)	3,047 (16.79%)	
SBP (mmHg)				
First visit	114.32 ± 12.46	118.20 ± 12.24	110.30 ± 11.36	<0.001
Second visit	120.47 ± 13.16	123.90 ± 13.32	116.50 ± 11.77	<0.001
Third visit	126.13 ± 11.91	129.90 ± 11.51	121.70 ± 10.82	<0.001
P for trend	<0.001	<0.001	<0.001	
DBP (mmHg)				
First visit	68.55 ± 8.41	68.56 ± 8.66	68.53 ± 8.14	0.708
Second visit	72.91 ± 8.69	72.74 ± 8.88	73.10 ± 8.45	0.101
Third visit	75.32 ± 8.27	75.22 ± 8.44	75.43 ± 8.06	0.569
P for trend	<0.001	<0.001	<0.001	
ISH (*n*, %)				
First visit	4,103 (11.10%)	2,460 (13.09%)	1,643 (9.05%)	<0.001
Second visit	1,161 (3.16%)	729 (3.90%)	432 (2.39%)	<0.001
Third visit	658 (1.79%)	402 (2.15%)	256 (1.42%)	<0.001
P for trend	<0.001	<0.001	<0.001	
IDH (*n*, %)				
First visit	1,526 (4.13%)	690 (3.67%)	836 (4.61%)	<0.001
Second visit	408 (1.11%)	153 (0.82%)	255 (1.41%)	<0.001
Third visit	156 (0.42%)	53 (0.28%)	103 (0.57%)	<0.001
P for trend	<0.001	<0.001	<0.001	

(Continued)

TABLE 1 (Continued)

Variables	Overall	Boys	Girls	*P*-value
	n **= 36,950**	***n*** **= 18,797**	***n*** **= 18,153**	
SDH (*n*, %)				
First visit	1,099 (2.97%)	476 (2.53%)	623 (3.43%)	<0.001
Second visit	593 (1.61%)	280 (1.50%)	313 (1.73%)	0.073
Third visit	305 (0.83%)	139 (0.74%)	166 (0.92%)	0.063
P for trend	<0.001	<0.001	<0.001	
Elevated BP (*n*, %)				
First visit	6,728 (18.21%)	3,626 (19.29%)	3,102 (17.09%)	<0.001
Second visit	2,162 (5.88%)	1,162 (6.22%)	1,000 (5.53%)	0.909
Third visit (HTN)	1,119 (3.05%)	594 (3.18%)	525 (2.91%)	0.133
P for trend	<0.001	<0.001	<0.001	

HPPCA, Health Promotion Program for Children and Adolescents; BMI, body mass index; TMI, tri-ponderal mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ISH, isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic and diastolic hypertension; BP, blood pressure; HTN, hypertension.

TABLE 2 Comparison of anthropometric indices in predicting hypertension in Chinese adolescents.

	AUC (95%CI)				NRI (95%CI)		IDI (95%CI)	
	TMI	**BMI**	**Difference**	***P*-value**	**Difference**	***P*-value**	**Difference**	***P*-value**
Total	0.645 (0.628, 0.662)	0.626 (0.608, 0.643)	0.019 (0.007, 0.031)	0.002	0.067 (0.008, 0.127)	0.027	0.000 (−0.000, 0.001)	0.424
Sex								
Boys	0.646 (0.623, 0.669)	0.645 (0.622, 0.669)	0.000 (−0.016, 0.017)	0.951	−0.023 (−0.105, 0.059)	0.579	−0.001 (−0.003, 0.000)	0.076
Girls	0.642 (0.617, 0.667)	0.602 (0.577, 0.628)	0.040 (0.021, 0.059)	<0.001	0.209 (0.123, 0.296)	<0.001	0.002 (0.001, 0.003)	<0.001
Age								
<16	0.634 (0.614, 0.655)	0.619 (0.598, 0.640)	0.015 (0.001, 0.029)	0.037	0.009 (−0.080, 0.063)	0.815	0.000 (−0.001, 0.000)	0.542
=16	0.673 (0.644, 0.703)	0.638 (0.607, 0.668)	0.036 (0.017, 0.055)	<0.001	0.352 (0.246, 0.458)	<0.001	0.006 (0.004, 0.008)	<0.001
BMI								
Underweight	0.507 (0.295, 0.720)	0.623 (0.485, 0.760)	−0.115 (−0.345, 0.114)	0.325	−0.173 (−0.763, 0.418)	0.566	0.000 (−0.002, 0.000)	0.165
Normal weight	0.530 (0.503, 0.556)	0.518 (0.491, 0.544)	0.012 (−0.013, 0.037)	0.357	0.084 (−0.006, 0.173)	0.067	0.000 (0.000, 0.000)	0.059
Overweight	0.537 (0.504, 0.570)	0.527 (0.494, 0.560)	0.010 (−0.020, 0.039)	0.518	0.039 (−0.078, 0.155)	0.518	0.000 (−0.000, 0.001)	0.112
Obesity	0.534 (0.500, 0.567)	0.557 (0.524, 0.590)	−0.023 (−0.047, 0.001)	0.060	−0.148 (−0.262, −0.034)	0.011	−0.003 (−0.004, −0.001)	<0.001
TMI								
Underweight and Normal	0.533 (0.505, 0.561)	0.532 (0.503, 0.560)	0.001 (−0.025, 0.027)	0.938	0.034 (−0.062, 0.130)	0.490	0.000 (−0.000, 0.000)	0.756
Overweight	0.507 (0.467, 0.547)	0.531 (0.491, 0.572)	−0.025 (−0.056, 0.007)	0.129	0.008 (−0.128, 0.144)	0.908	−0.000 (−0.001, 0.000)	0.072
Obesity	0.561 (0.533, 0.588)	0.565 (0.538, 0.592)	−0.004 (−0.023, 0.015)	0.670	−0.107 (−0.200, −0.014)	0.024	−0.001 (−0.002, 0.000)	0.048

AUC, area under the curve; CI, confidential interval; NRI, net reclassification index; IDI, integrated discrimination improvement; BMI, body mass index; TMI, tri-ponderal mass index.

(difference in AUC = 0.040; 95% CI = 0.021–0.059; NRI = 0.209, 95% CI = 0.123–0.296; IDI = 0.002, 95% CI = 0.001–0.003), ISH (difference in AUC = 0.044; 95% CI, 0.017–0.072; NRI = 0.318, 95% CI = 0.197–0.440; IDI = 0.002, 95% CI = 0.000–0.002), and IDH (difference in AUC = 0.044; 95% CI, 0.001–0.087; IDI = 0.002, 95% CI = 0.000–0.003). No difference was found in the AUCs of TMI vs. BMI for HTN and its subtypes in boys.

As shown in Figure 2, TMI had lower FNR ($P < 0.05$) but higher FPR ($P < 0.001$) and total misclassification rates ($P < 0.001$) in predicting HTN for children compared with BMI. TMI had significantly lower FPR ($P < 0.001$) and total misclassification rates ($P < 0.001$) in girls as well as significantly higher FPR ($P < 0.05$) and total misclassification rates ($P < 0.001$) in boys. For boys, the FPR, FNR, and total misclassification rates for TMI were 35.0% (95% CI = 34.3–35.7%), 41.4% (95% CI = 37.5–45.4%) and 35.2% (95% CI = 35.2–35.2%), respectively; the corresponding rates for BMI were 33.4% (95% CI = 32.7–34.1%), 43.1% (95% CI = 39.1–47.1%) and 33.7% (95% CI = 33.7–33.7%), respectively. For girls, the FPR, FNR, and total misclassification rates for TMI were 37.0% (95% CI = 36.3–37.7%), 40.0%

TABLE 3 Comparison of anthropometric indices in predicting isolated systolic hypertension in Chinese adolescents.

	AUC (95%CI)				NRI (95%CI)		IDI (95%CI)	
	TMI	**BMI**	**Difference**	***P*-value**	**Difference**	***P*-value**	**Difference**	***P*-value**
Total	0.649 (0.627, 0.671)	0.628 (0.606, 0.650)	0.021 (0.005, 0.036)	0.009	0.106 (0.029, 0.183)	0.007	0.000 (−0.000, 0.001)	0.071
Sex								
Boys	0.650 (0.623, 0.678)	0.645 (0.617, 0.673)	0.005 (−0.013, 0.024)	0.581	0.020 (−0.079, 0.119)	0.693	0.000 (−0.001, 0.001)	0.943
Girls	0.633 (0.598, 0.668)	0.589 (0.553, 0.624)	0.044 (0.017, 0.072)	0.001	0.318 (0.197, 0.440)	< 0.001	0.002 (0.000, 0.002)	<0.001
Age								
<16	0.643 (0.617, 0.668)	0.630 (0.604, 0.657)	0.012 (−0.005, 0.030)	0.163	0.013 (−0.078, 0.104)	0.781	−0.000 (−0.000, 0.000)	0.846
=16	0.666 (0.626, 0.706)	0.628 (0.587, 0.668)	0.039 (0.011, 0.066)	0.005	0.366 (0.223, 0.508)	<0.001	0.002 (0.004, 0.005)	<0.001
BMI								
Underweight	0.497 (0.020, 0.975)	0.525 (0.201, 0.850)	−0.028 (−0.693, 0.637)	0.934	0.378 (−0.689, 1.446)	0.487	0.000 (−0.000, 0.000)	0.856
Normal weight	0.528 (0.494, 0.563)	0.518 (0.483, 0.553)	0.011 (−0.023, 0.044)	0.537	0.082 (−0.036, 0.200)	0.171	0.000 (−0.000, 0.000)	0.490
Overweight	0.513 (0.471, 0.556)	0.499 (0.458, 0.539)	0.015 (−0.060, 0.090)	0.696	0.030 (−0.119, 0.180)	0.690	0.000 (−0.000, 0.000)	0.481
Obesity	0.543 (0.500, 0.585)	0.548 (0.507, 0.588)	−0.005 (−0.036, 0.026)	0.751	−0.038 (−0.181, 0.104)	0.597	−0.000 (−0.001, 0.000)	0.409
TMI								
Underweight and Normal	0.545 (0.508, 0.581)	0.542 (0.504, 0.579)	0.003 (−0.033, 0.039)	0.860	0.058 (−0.069, 0.184)	0.372	0.000 (−0.000, 0.000)	0.544
Overweight	0.496 (0.445, 0.546)	0.512 (0.462, 0.562)	−0.016 (−0.054, 0.022)	0.403	0.027 (−0.150, 0.204)	0.763	0.000 (−0.000, 0.000)	0.620
Obesity	0.562 (0.527, 0.598)	0.557 (0.523, 0.591)	0.005 (−0.019, 0.029)	0.679	−0.005 (−0.122, 0.123)	0.935	0.000 (−0.000, 0.001)	0.443

AUC, area under the curve; CI, confidential interval; BMI, body mass index; NRI, net reclassification index; IDI, integrated discrimination improvement; TMI, tri-ponderal mass index.

TABLE 4 Comparison of anthropometric indices in predicting isolated diastolic hypertension in Chinese adolescents.

	AUC (95%CI)				NRI (95%CI)*		IDI (95%CI)	
	TMI	**BMI**	**Difference**	***P*-value**	**Difference**	***P*-value**	**Difference**	***P*-value**
Total	0.581 (0.535, 0.626)	0.554 (0.505, 0.603)	0.027 (−0.007, 0.060)	0.119	NA	NA	0.002 (0.000, 0.004)	0.006
Sex								
Boys	0.572 (0.493, 0.651)	0.584 (0.497, 0.670)	−0.012 (−0.066, 0.043)	0.675	NA	NA	0.002 (−0.000, 0.005)	0.178
Girls	0.601 (0.545, 0.658)	0.557 (0.499, 0.615)	0.044 (0.001, 0.087)	0.043	NA	NA	0.002 (0.000, 0.003)	0.004
Age								
<16	0.543 (0.490, 0.595)	0.533 (0.479, 0.587)	0.010 (−0.029, 0.048)	0.628	NA	NA	0.000 (−0.000, 0.002)	0.306
=16	0.687 (0.598, 0.776)	0.671 (0.576, 0.766)	0.016 (−0.031, 0.064)	0.496	NA	NA	0.008 (0.003, 0.014)	0.004
BMI								
Underweight	0.526 (0.133, 0.919)	0.655 (0.421, 0.889)	−0.129 (−0.610, 0.352)	0.599	−0.799 (−0.841, −0.757)	<0.001	−0.000 (−0.002, 0.000)	0.350
Normal weight	0.539 (0.479, 0.601)	0.498 (0.438, 0.558)	0.041 (−0.014, 0.095)	0.142	NA	NA	0.000 (0.000, 0.000)	0.067
Overweight	0.503 (0.408, 0.598)	0.549 (0.441, 0.658)	−0.047 (−0.136, 0.042)	0.302	NA	NA	−0.000 (−0.000, 0.000)	0.667
Obesity	0.523 (0.414, 0.632)	0.588 (0.479, 0.697)	−0.066 (−0.154, 0.023)	0.145	NA	NA	−0.000 (−0.002, 0.002)	0.682
TMI								
Underweight and Normal	0.522 (0.457, 0.586)	0.502 (0.438, 0.567)	0.020 (−0.035, 0.075)	0.484	NA	NA	0.000 (−0.000, 0.000)	0.228
Overweight	0.501 (0.403, 0.599)	0.490 (0.372, 0.608)	0.011 (−0.072, 0.094)	0.795	NA	NA	0.000 (−0.001, 0.000)	0.672
Obesity	0.534 (0.452, 0.617)	0.570 (0.481, 0.659)	−0.036 (−0.097, 0.025)	0.249	NA	NA	0.000 (−0.002, 0.002)	0.781

AUC, area under the curve; CI, confidential interval; NRI, net reclassification index; IDI, integrated discrimination improvement; BMI, body mass index; TMI, tri-ponderal mass index.
*NA, Not recognized because the model construction conditions are not met.

(95% CI = 35.8–44.2%) and 37.1% (95% CI = 37.1–37.1%), respectively; the corresponding rates for BMI were 41.5% (95% CI = 40.8–42.5%), 42.5% (95% CI = 38.2–46.7%) and 41.6% (95% CI = 41.6–41.6%), respectively. In total, the FPR, FNR, and total misclassification rates for TMI were 31.0% (95% CI = 30.6–31.5%), 46.7% (95% CI = 43.8–49.7%) and 31.5% (95% CI = 31.5–31.5%), respectively; the corresponding rates for BMI were 29.7% (95% CI = 29.2–30.1%), 51.0% (95% CI = 48.1–54.0%) and 30.3% (95% CI = 30.3–30.3%), respectively.

TABLE 5 Comparison of anthropometric indices in predicting systolic and diastolic hypertension in Chinese adolescents.

	AUC (95%CI)				NRI (95%CI)		IDI (95%CI)	
	TMI	BMI	Difference	*P*-value	Difference	*P*-value	Difference	*P*-value
Total	0.659 (0.627, 0.692)	0.648 (0.615, 0.682)	0.011 (−0.012, 0.035)	0.353	−0.067 (−0.180, 0.046)	0.244	−0.000 (−0.001, −0.000)	0.003
Sex								
Boys	0.652 (0.604, 0.701)	0.661 (0.614, 0.708)	−0.008 (−0.044, 0.027)	0.640	−0.074 (−0.241, 0.093)	0.386	−0.000 (−0.002, −0.000)	0.017
Girls	0.674 (0.630, 0.718)	0.645 (0.599, 0.692)	0.028 (−0.003, 0.059)	0.076	−0.042 (−0.195, 0.110)	0.586	−0.001 (−0.002, −0.000)	0.013
Age								
<16	0.666 (0.624, 0.708)	0.641 (0.597, 0.684)	0.025 (−0.006, 0.056)	0.109	−0.067 (−0.214, 0.079)	0.369	−0.000 (−0.000, −0.000)	0.095
ł16	0.671 (0.621, 0.720)	0.635 (0.581, 0.690)	0.035 (0.006, 0.064)	0.016	0.002 (0.001, 0.004)	<0.001	0.002 (0.001, 0.004)	<0.001
BMI								
Underweight	0.547 (0.172, 0.922)	0.662 (0.432, 0.891)	−0.114 (−0.362, 0.133)	0.365	−0.105 (-1.086, 0.876)	0.834	−0.000 (−0.001, 0.000)	0.375
Normal weight	0.523 (0.470, 0.576)	0.532 (0.478, 0.586)	−0.009 (−0.060, 0.043)	0.741	−0.033 (−0.214, 0.148)	0.723	0.000 (−0.000, 0.000)	0.964
Overweight	0.593 (0.532, 0.654)	0.567 (0.507, 0.628)	0.026 (−0.033, 0.084)	0.394	0.134 (−0.075, 0.344)	0.210	0.000 (−0.000, 0.001)	0.532
Obesity	0.487 (0.426, 0.548)	0.557 (0.498, 0.617)	−0.070 (−0.184, 0.044)	0.227	−0.174 (−0.376, 0.027)	0.090	−0.000 (−0.002, 0.000)	0.090
TMI								
Underweight and normal	0.512 (0.455, 0.570)	0.532 (0.472, 0.591)	−0.020 (−0.070, −0.031)	0.453	0.015 (−0.182, 0.211)	0.885	0.000 (−0.000, 0.000)	0.890
Overweight	0.531 (0.451, 0.612)	0.587 (0.511, 0.663)	−0.056 (−0.122, 0.011)	0.101	−0.167 (−0.418, 0.083)	0.189	−0.001 (−0.002, 0.000)	0.013
Obesity	0.558 (0.511, 0.606)	0.570 (0.521, 0.620)	0.012 (−0.047, 0.022)	0.492	−0.220 (−0.385, −0.000)	0.009	−0.000 (−0.001, −0.000)	0.015

AUC, area under the curve; CI, confidential interval; NRI, net reclassification index; IDI, integrated discrimination improvement; BMI, body mass index; TMI, tri-ponderal mass index.

Discussion

In this study, we assess the capacity of TMI and BMI to predict adolescent HTN and HTN subtypes. Our study found that TMI slightly outperformed BMI in predicting adolescent HTN and ISH. Additionally, TMI may have a stronger predictive power for HTN in girls, while no difference was observed in boys. Considering age, it showed higher discrimination power in predicting HTN for the subgroup of age $\geq$ 16 than its counterparts.

Several studies have reported a positive correlation between weight gain and BP levels in children and adolescents (17, 34, 37, 38). However, there were limited studies that compared the correlation of TMI and BMI with BP, as summarized in a systematic review (31). According to Wang et al. (39), TMI outperformed BMI in detecting children and adolescents with HTN in the Chinese population. A similar finding was obtained in Italian research (30), in which the total misclassification rate of TMI in predicting HTN in adolescents was around one-third of the BMI percentile. In a longitudinal analysis, the current study's findings support that TMI had a better ability to predict teenage HTN than BMI. We hypothesized that this might be related to the fact that TMI in children and adolescents correlates with body fat percent equal to or better than BMI (28, 40, 41) and has a superior ability to predict central obesity (30).

When it comes to subtypes of adolescent HTN, we found that TMI outperformed BMI in predicting adolescent ISH. However, TMI and BMI did not differ in predicting IDH or SDH. This disparity can be explained because obesity primarily impacts central pulsatile hemodynamic alterations, which are directly related to increased SBP, but has little effect on DBP (42). Previous finding revealed that SBP increases more stable yearly from childhood to adulthood compared with DBP (43). Furthermore, adolescents with a higher BMI were reported to have higher left ventricular weight, aortic wave amplitude, and SBP than their normal-weight counterparts (44).

Interestingly, we discovered that TMI outperformed BMI when diagnosing adolescent HTN in girls but not in boys. In detail, TMI had lower rates of false positives and total misclassification than BMI in girls but had the opposite results in boys. The disparity could be attributed to hormonal and puberty differences between boys and girls (45, 46). A previous study found that TMI performed better in predicting obesity in girls (29). Therefore, TMI may also have better prediction performance on girls' HTN. Additionally, we discovered that the difference between BMI and TMI for predicting ISH and SDH was more obvious in the subgroup of age $\geq$ 16, while such a difference was not found in the subgroup of age $<$ 16. Wang et al. revealed that the accuracy of TMI classification of overweight and obesity increased along with age, especially after the age of 16 (29). As a result, this disparity could be that TMI's predictive power increases with age and does not significantly outperform BMI until late adolescence.

According to a systematic review by Sun et al. (31), TMI can better discriminate central obesity and reflect body fat storage. Earlier studies (47) have also reported that an index based on cubic powers of height predicts obesity equal to or better

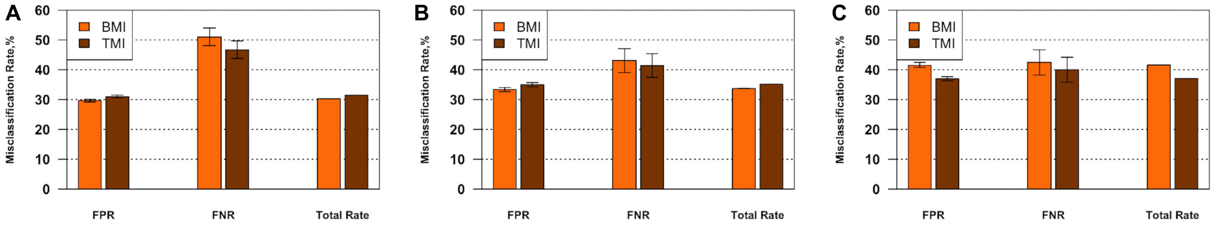

FIGURE 2
FPR, FNR, and total misclassification rates with 95% confidential intervals for TMI vs. BMI in predicting HTN in overall participants **(A)**, boys **(B)**, and girls **(C)** aged 12–17 years, respectively. BMI, body mass index; TMI, tri-ponderal mass index; FPR, false-positive rate; FNR, false-negative rate; HTN, hypertension.

than BMI. Thus, an increasing number of researchers (28–30) recommend the use of TMI to detect body fat in adolescents. Based on previous researches (30, 39), we assume that TMI has a better predictive power for adolescent BP than BMI. TMI cut-off values can be considered a satisfactory alternative indicator to screening for obesity risk in children and adolescents due to the low fluctuations in TMI with age. As proposed previously by Wang et al. (29), TMI cut-off values can significantly reduce the amount of computation and complexity required for overweight and obesity screening compared to previous BMI-based screening. These could assist more primary health care workers in effectively identifying and better preventing and controlling obesity.

The current study has many significant advantages. First, this study was a retrospective investigation employing a longitudinal methodology. Compared to previous cross-sectional studies (30, 39), the fluctuations in height, body fat percentage, and BP during adolescence were fully considered. To the best of our knowledge, among the studies comparing TMI with BMI on teenage HTN, the current study is the first to include all subtypes and employ BP effects at three visits, which significantly reduced the misdiagnosis rate of HTN. The second and third BP measures in this study were taken by known school nurses on the campus of the specific students, which could be advantageous in eliminating the "white-coat" effect. Moreover, the 2020 specific BP surveillance showed a good collaboration level, with 97.16% for the second and 98.01% for the third visit. Additionally, the large sample size and standard measurement data obtained from this study's general population improve the conclusions' robustness.

Study limitations

First, this study recruited adolescents from Suzhou, a developed location in eastern China that is geographically restricted and not representative of other regional or ethnic groups. Second, the second or third BP visit was only for children with elevated BP diagnosed at the previous visit, as recommended by other large-scale surveillance studies (21). Children with BP $< P_{95}$ at the first or second visit were not followed at the subsequent visit, which may underestimate the prevalence of HTN. Besides, not every child with BP $\geq P_{95}$ at the first or second visit was enrolled at the subsequent visit. However, the cooperation rates were around 98%, and the included group was generally representative of the overall population. And the subtle difference in characteristics in population from the second visit to the third visit could be attributed to increased variability from a smaller sample size during the third visit. Additionally, we were unable to compare the validity of all obesity indicators for predicting HTN because information such as waist circumference and the waist-to-height ratio was not collected.

Conclusion

TMI was a more reliable index of adolescent HTN and ISH than BMI, although differences exist between age and sex stratums. However, there was a comparable performance in the prediction of IDH and SDH. In contrast to the complex BMI-for-age charts, the cutoffs for TMI are greatly simplified. Therefore, the application of TMI may promote the primary prevention of adolescent HTN and health management of children. In the future, results of our studies should be replicated in large cross-sectional and longitudinal studies in other racial and ethnic population. In addition, longer follow-up studies that continue into adulthood should be conducted to assess the relative merits of TMI and BMI in the prediction of HTN. Besides, future studies would verify TMI's utility in clinical practice and eventually contribute to establishing an optimum standard of TMI.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Suzhou Center for Disease Prevention and Control. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

HY and AG contributed to the design and concept of the manuscript. JH and YZ were responsible for the analysis, interpretation of data, and manuscript drafting. DH, ZD, and BH organized the database. WG and HL performed the statistical analysis. HS and JY were responsible for the critical revision of the manuscript for intellectual content. All authors wrote the manuscript and had final approval of the submitted and published versions.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1028861/full#supplementary-material

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Prediction of cardiovascular diseases mortality- and disability-adjusted life-years attributed to modifiable dietary risk factors from 1990 to 2030 among East Asian countries and the world

Nawsherwan[1]*, Wang Bin[1], Zhang Le[1], Sumaira Mubarik[2]*, Guo Fu[3] and Yan Wang[1]*

[1]Xiamen Cardiovascular Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China, [2]Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University, Wuhan, China, [3]State Key Laboratory of Cellular Stress Biology, Innovation Center for Cell Signaling Network, School of Medicine, Xiamen University, Xiamen, China

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EDITED BY
Farhana Akter,
Chittagong Medical College, Bangladesh

REVIEWED BY
Nosheen Masood,
Fatima Jinnah Women University, Pakistan
Ijaz Haq,
The University of Haripur, Pakistan
Saima Shakil Malik,
Augusta University, United States

*CORRESPONDENCE
Nawsherwan
nawshermkd177@gmail.com
Sumaira Mubarik
sumairaawan86@gmail.com
Yan Wang
wy@medmail.com.cn

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Background: Unhealthy eating habits are a significant modifiable risk factor for cardiovascular diseases (CVDs); nevertheless, no evidence of their impact on the CVD burden has been reported in East Asian countries. We aimed to determine the trend and predict the future CVDs burden attributed to modifiable dietary risk factors in the East Asian countries (China, Japan, South Korea, and North Korea) and the world.

Methods: The Global Burden of Disease (GBD) 2019 data were used to find the trend of CVDs [ischemic heart disease (IHD) and ischemic stroke (IS)] mortality- and disability-adjusted life-years (DALYs) attributed to dietary risk factors in the East Asian countries and the world (1990–2019) and its prediction from 2020 to 2030. We used the joinpoint regression model and the autoregressive integrated moving average (ARIMA) model for trend and future forecast, respectively.

Results: From 1990 to 2019, regardless of sex, the age-standardized mortality rate (ASMR) and DALYs of IHD attributed to dietary risk factors significantly decreased in Japan, South Korea, and the world. However, the ASMR of IHD significantly increased in Chinese males and for both sexes in North Korea. The ASMR and DALYs of IHD and IS due to dietary risk factors were higher in males than in females in the world. From 2020 to 2030, the ASMR of IHD is predicted to increase in South Korean females and Japanese males. Globally, a diet low in whole grains was the top risk factor for the highest IHD mortality and DALYs in 2019, followed by a diet low in legumes and a diet high in sodium. A diet low in whole grains, a diet high in sodium, and a diet low in legumes were the leading risk factors for high IHD mortality in East Asian countries.

Conclusion: The trend of IHD and IS burden due to dietary risk factors varies substantially across the East Asian countries compared to the trend of CVDs burden in the world. The study findings may help the public health policymakers to design proper strategies for improvement of the quality of life to combat the CVDs burden in the future for the East Asian countries.

KEYWORDS

dietary risk factors, IHD trend, IS trend, prediction, ARIMA model

Introduction

Cardiovascular diseases (CVDs) are the leading cause of premature mortality and morbidity among non-communicable diseases (NCDs) worldwide (1). CVDs refer to a class of diseases that involves the heart and blood vessels, including IHD, IS, heart failure, hypertensive heart disease, and several other vascular and cardiac problems. CVDs are a significant public health problem and are an important contributor to the cost of medical care (2). In 2017, 17.8 million people died of CVDs, representing one-third of all death across the globe (1). Moreover, 330 million years of life were lost and 35.6 million years lived with disability in 2017 worldwide (3, 4). In 2030, the projected CVDs mortality would be more than 23 million deaths around the world (5). Both developing and developed countries have experienced higher rates of CVDs mortality in the past decades. However, CVDs were more incident in developed countries (6). Based on the World Health Organization (WHO) report, low- and middle-income countries had over three-quarters of CVDs mortality, which is considered a growing epidemic problem in recent years (7).

The huge burden of CVDs could be attributed to several factors including a sedentary lifestyle, obesity, hypertension, diabetes, excessive alcohol consumption, and unhealthy diet or dietary risk factors (8). Based on GBD 2019 study, the dietary risk factors that can cause CVDs are either an over-consumed diet (sodium, trans-fatty acids, sugar-sweetened beverages, red meat, and processed meat) or an under-consumed diet (whole grains, legumes, vegetables, fruits, nuts and seeds, milk, fiber, calcium, omega-3 fatty acids from seafood, and polyunsaturated fatty acids) (2). Several studies observed the trend of CVDs associated with various risk factors in different regions of the world. For example, Wang et al. (9) reported the trend of IHD attributed to several risk factors (i.e., smoking, low physical activity, air pollution, and dietary risk factors) in the high socio-demographic index (SDI) and low SDI countries from 1990 to 2017. Amini et al. (10) determined the trend of CVDs mortality, incidence, and mortality-to-incidence ratio in different countries based on the Human Development Index (HDI) from 1990 to 2017.

Roth et al. (2) observed the trend of CVDs mortality and DALYs associated with various risk factors ranging from low physical activity, tobacco use, and air pollution, to dietary risk factors at the global, regional, and national levels from 1990 to 2019. Moreover, Wu et al. (11) determined the trend of CVDs mortality (i.e., IHD and stroke) attributed to tobacco exposure in China, Japan, the USA, and the world from 1990 to 2017. However, no or limited studies (2, 9, 12) observed the trend of CVDs (i.e., IHD and IS) mortality and DALYs attributed to modifiable dietary risk factors in the East Asian countries and the world. To advise health policymakers and set standards for decision-makers, accurate, consistent, and comparable analysis of long-term trends and patterns at a country and global level is required. Therefore, we aimed to determine the trend of CVDs mortality and DALYs attributed to modifiable dietary risk factors in East Asian countries and the world (1990–2019) and its prediction from 2020 to 2030.

Materials and methods

Data source

In this study, the data were extracted according to sex (male, female, and both sex combined) on ASMR of CVDs and DALYs rates (per 100,000 persons) from the GBD free online database (GBD (13) http://ghdx.healthdata.org/gbd-results-tool) from 1990 to 2019. In addition, according to sex (male and female), age-specific data on CVD mortality and DALYs rates were extracted for different age groups (i.e., 50–54, 55–59, 60–64, 65–69, 70–74, and 75–79 years). GBD is an international cooperative project that estimates the disease burden at regional, national, and global levels. The GBD data is managed by the Institute for Health Metrics and Evaluation (IHME) and analyzed by a group of more than 1,800 researchers in more than 100 countries. GDB estimates the burden of disease indices, including prevalence, incidence, mortality rate, years of life lost (YLL), years lived with disability (YLD), and DALYs for several diseases and injuries. Moreover, the GBD data are provided by different organizations like World Bank Open Data, WHO, and Global Health Observatory for different political and social research (3, 4).

Variables under study

In the present study, the considered risk factor was a dietary risk factor, and the outcomes were ASMR of IHD and IS and DALYs rates for the East Asian countries and the world from 1990 to 2019. The dietary risk factor was a composite of an over-consumed diet (sodium, trans-fatty acids, sugar-sweetened beverages, red meat, and processed meat) and an under-consumed diet (whole grains, legumes, vegetables, fruits, nuts and seeds, milk, fiber, calcium, omega-3 fatty acids from seafood, and polyunsaturated fatty acids) (2). DALYs are defined as the sum of years lived with disability (YLDs) and years of life lost (YLLs) (4).

Statistical analysis

Joinpoint regression for trend analysis (1990–2019)

To assess the temporal trends of IHD and IS burden, we estimated the average annual percentage change (AAPC) for IHD and IS mortality and DALYs with the joinpoint regression analysis. AAPC represents the trend of IHD and IS burden in the whole period from 1990 to 2019. Additionally, AAPC is a weighted average of the yearly percentage change determined by the joinpoint model, with weights corresponding to the duration of the annual percentage change (APC) interval. The APC shows the IHD and IS burden trend in each segment determined by using the joinpoint regression software. From 1990 to 2019, we produced AAPCs and their 95% confidence intervals (CIs) for each trend segment identified by the model. Furthermore, we estimated AAPCs for each decade (i.e., 1990–1999, 2000–2009, and 2010–2019). Based on age groups (i.e., 50–54, 55–59, 60–64, 65–69, 70–74, and 75–79 years), AAPC for IHD and IS burden was obtained for both males and females from 1990 to 2019. AAPC is considered significant when it is different from 0 at the alpha of 0.05. This analysis was conducted using the joinpoint regression program version 4.8.0.1 (April 2020) from the Surveillance Research Program of the U.S. National Cancer Institute (NCI).

ARIMA model for forecasting (2020–2030)

To forecast future CVD mortality and DALY rates, the autoregressive integrated moving average (ARIMA) (p, d, q) model was utilized. It generates forecasts utilizing the shift and lag of historical data, based on past values in the time series (an autoregressive: AR term) and the error caused by previous predictions (a moving average: MA term). In the ARIMA model, integrated (I term) denotes the differencing of raw observed data to keep the time series stationary, i.e., data values are replaced by the difference from prior values. The letters p, d, and q in the ARIMA model stand for the order of autoregression, degree of difference, and order of moving average, respectively. The zero value of any letter (p, d, q) indicates that a particular component is not involved in the model. For instance, ARIMA (2, 1, 0) indicates two AR terms, one degree of difference, and no MA term in the model. To confirm the AR and MA parameters, we constructed the model and determined the autocorrelation function (ACF) and partial autocorrelation function (PACF) of model residuals. To evaluate the best fitting model for data, different goodness-of-fit indices including the lowest value in Bayesian information criterion (BIC) and highest R^2 (the coefficient of determination), ACF, and PACF of residuals were determined (14, 15). We applied the model to predict the CVDs mortality and DALYs rate from 2020 to 2030. Finally, we used the predicted rates and conducted the joinpoint point regression analysis to determine the trend from 2020 to 2030. The analysis was conducted using the SPSS Amos for Windows version 22 (IBM Corporation, Chicago, USA) and the joinpoint regression program version 4.8.0.1 (April 2020) from the Surveillance Research Program of the U.S. National Cancer Institute (NCI).

Results

The temporal trend in the ASMR of IHD and IS attributed to dietary risk factors

For both sexes (1990–2019), the ASMR of IHD attributed to modifiable dietary risk factors in Japan, South Korea, and the world significantly decreased by 3.4% (95% CI: −3.6, −3.3), 4.9% (95% CI: −5.2, −4.7) and 1.4% (95% CI: −1.6, −1.3) per year, respectively. However, the ASMR of IHD in North Korea significantly increased by 0.6% (95% CI: 0.5, 0.8). Moreover, the ASMR of IS in China, Japan, South Korea, North Korea, and the world significantly decreased by 0.6% (95% CI: −0.9, −0.2), 5.0% (95% CI: −5.4, −4.7), 4.5% (95% CI: −4.7, −4.3), 0.2% (95% CI: −0.3, −0.2), and 1.7% (95% CI: −1.8, −1.5) per year, respectively. From 2020 to 2030, the ASMR of IHD and IS attributed to modifiable dietary risk continued to significantly decline in China, North Korea, and the world (Table 1 and Figure 1).

For male subjects (1990–2019), the ASMR of IHD significantly decreased by 3.2% (95% CI: −3.4, −3.0) in Japan, 5.3% (95% CI: −5.7, −4.9) in South Korea, and 1.4% (95% CI: −1.5, −1.3) per year in the world. On the other hand, the ASMR of IHD significantly increased by 0.4% (95% CI: 0.2, 0.6) and 0.5% (95% CI: 0.3, 0.6) per year in China and North Korea, respectively. From 2020 to 2030, the ASMR of IHD and IS significantly decreased in China, North Korea, and the world (Table 1 and Figure 2).

For female subjects (1990–2019), the ASMR of IHD in Japan, South Korea, and the world significantly decreased by 4.1% (95% CI: −4.2, −3.9), 5.0% (95% CI: −5.3, −4.6) and 1.6% (95% CI: −1.7, −1.5) per year, respectively, but

TABLE 1 The temporal trend in the ASMR of IHD and IS attributed to modifiable dietary risk factors in China, Japan, South Korea, North Korea, and the world (1990–2019) and its prediction (2020–2030).

Trend		World		China		Japan		South Korea		North Korea	
1990–2019	Mortality	AAPC	95%CI	AAPC	95%CI	AAPC	95%CI	AAPC	95%CI	AAPC	95%CI
IHD	Both sexes	−1.4*	−1.6, −1.3	0.1	−0.2, 0.4	−3.4*	−3.6, −3.3	−4.9*	−5.2, −4.7	0.6*	0.5, 0.8
	Male	−1.4*	−1.5, −1.3	0.4*	0.2, 0.6	−3.2*	−3.4, −3.0	−5.3*	−5.7, −4.9	0.5*	0.3, 0.6
	Female	−1.6*	−1.7, −1.5	−0.2	−0.5, 0.2	−4.1*	−4.2, −3.9	−5.0*	−5.3, −4.6	0.6*	0.5, 0.8
IS	Both sexes	−1.7*	−1.8, −1.5	−0.6*	−0.9, −0.2	−5.0*	−5.4, −4.7	−4.5*	−4.7, −4.3	−0.2*	−0.3, −0.2
	Male	−1.4*	−1.7, −1.1	−0.1	−0.5, 0.3	−4.8*	−5.1, −4.5	−4.8*	−5.0, −4.5	−0.2*	−0.2, −0.1
	Female	−2.0*	−2.2, −1.8	−1.2*	−1.6, −0.8	−5.5*	−6.0, −5.0	−4.4*	−4.7, −4.2	−0.4*	−0.4, −0.3
Prediction											
2020–2030											
IHD	Both sexes	−1.9*	−2.2, −1.6	−2.0*	−2.5, −1.5	−1.3*	−1.6, −1.1	4.7*	3.4, 6.1	−1.0*	−1.0, −0.9
	Male	−1.8*	−2.0, −1.6	−2.3*	−2.8, −1.8	0.8*	0.2, 1.4	−1.9*	−2.2, −1.6	−0.8*	−0.9, −0.8
	Female	−2.1*	−2.5, −1.7	−2.1*	−2.6, −1.6	0.2	−0.2, 0.7	0.8*	0.1, 1.5	−1.3*	−1.4, −1.3
IS	Both sexes	−0.4*	−0.7, −0.1	−0.9*	−0.1, −0.7	−0.3	−0.7, 0.1	1.0	−0.3, 2.3	−1.1*	−1.1, −0.9
	Male	−1.5*	−1.6, −1.5	−0.5*	−0.7, −0.3	2.1*	1.5, 2.7	−0.1	−0.9, 0.7	−1.1*	−1.1, -1, 0
	Female	−0.2	−0.6, 0.2	−1.3*	−1.5, −1.1	0.1	−0.3, 0.5	1.1	−0.5, 2.7	−1.4*	−1.4, −1.3

IHD, Ischemic heart disease; IS, ischemic stroke; AAPC, average annual percent change, *statistically significant ($p < 0.05$).

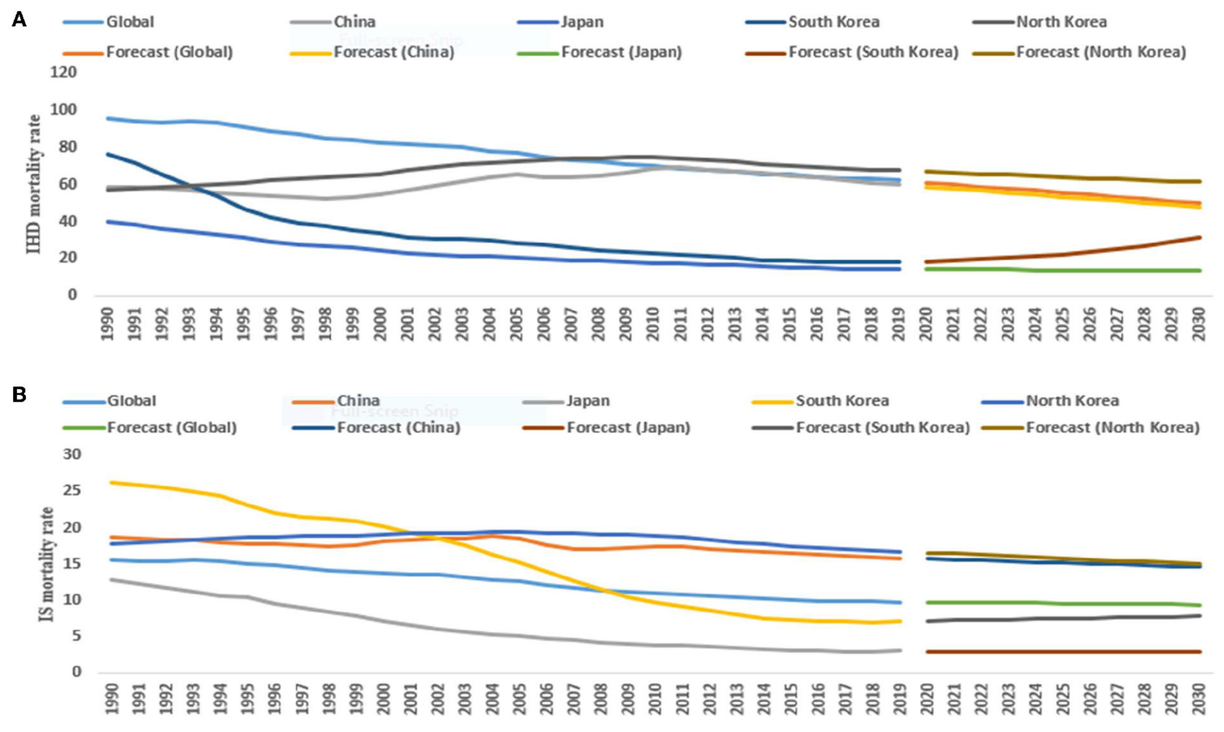

FIGURE 1
The temporal trends in the ASMR (per 100,000 persons) of IHD (ischemic heart diseases) **(A)** and IS (ischemic stroke) **(B)** (1990–2019) and its prediction (2020–2030) for both sexes in the East Asian countries and world.

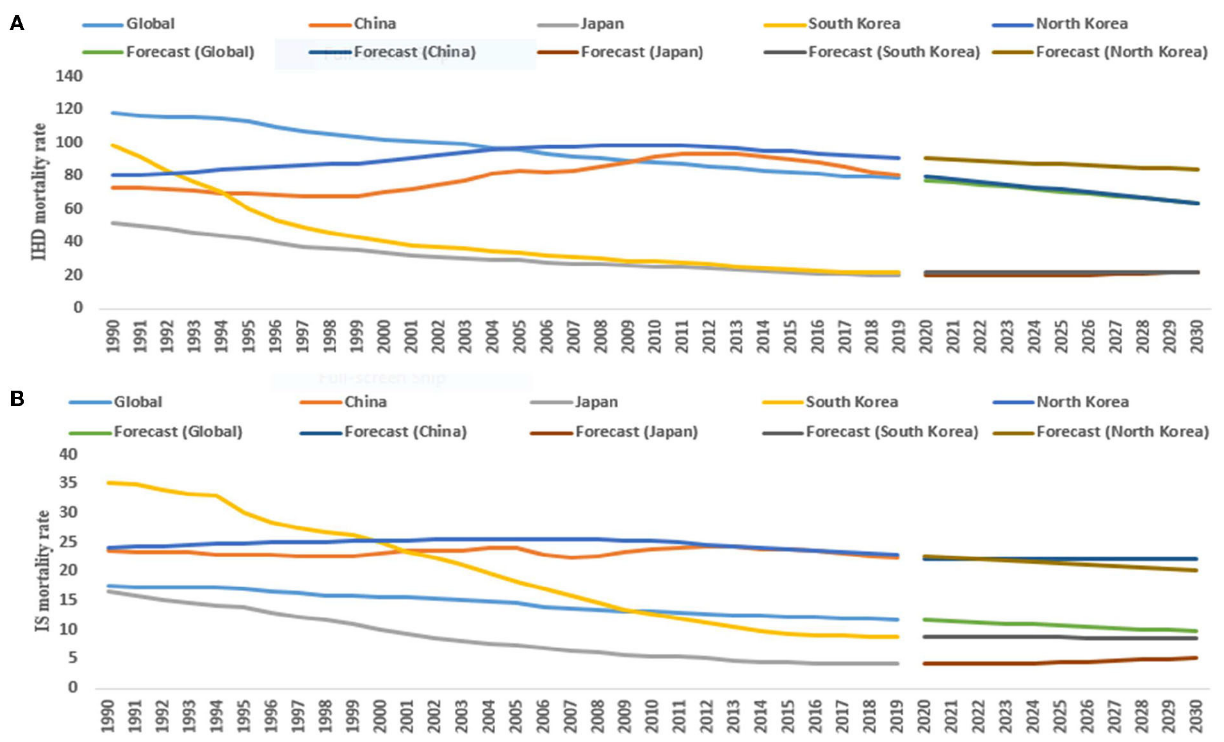

FIGURE 2
The temporal trends in the ASMR (per 100,000 persons) of IHD (ischemic heart diseases) **(A)** and IS (ischemic stroke) **(B)** (1990–2019) and its prediction (2020–2030) for males in the East Asian countries and world.

significantly increased in North Korea by 0.6% (95% CI: 0.5, 0.8). From 2020 to 2030, the ASMR of IHD and IS significantly decreased in China and North Korea (Table 1 and Figure 3).

The temporal trend in the age-standardized DALYs rate of IHD and IS attributed to dietary risk factors

For both sexes (1990–2019), the age-standardized DALYs rate of IHD attributed to modifiable dietary risk factor significantly decreased by 0.4% (95% CI: −0.6, −0.1), 3.0% (95% CI: −3.2, −2.8), 5.3% (95% CI: −5.5, −5.2), and 1.3% (95% CI: −1.4, −1.2) per year in China, Japan, South Korea, and the world, respectively. However, the age-standardized DALYs rate of IHD significantly increased by 0.5% (95% CI: 0.4, 0.6) per year in North Korea. Furthermore, the age-standardized DALYs rate of IS in China, Japan, South Korea, North Korea, and the world significantly decreased by 0.5% (95% CI: −1.0, −0.1), 3.7% (95% CI: −3.9, −3.5), 4.3% (95% CI: −4.5, −4.1), 0.2% (95% CI: −0.3, −0.2), and 1.4% (95% CI: −1.5, −1.2) per year, respectively. From 2020 to 2030, the age-standardized DALYs rate of IHD and IS attributed to dietary risk significantly declined in China, North Korea, and the world but significantly increased in Japan and South Korea (Table 2 and Supplementary Figure S1).

The age-standardized DALYs rate of IHD in the male population (1990–2019) significantly decreased by 2.8% (95% CI: −3.0, −2.7) in Japan, 5.5% (95% CI: −5.9, −5.1) in South Korea, and 1.3% (95% CI: −1.5, −1.0) per year in the world. However, the age-standardized DALYs rate of IHD significantly increased by 0.4% (95% CI: 0.3, 0.5) per year in North Korea. From 2020 to 2030, the age-standardized DALYs rate of IHD and IS significantly decreased in China, North Korea, and the world (Table 2 and Supplementary Figure S2).

In female population (1990–2019), the age-standardized DALYs rate of IHD in China, Japan, South Korea and the world significantly decreased by 0.8% (95% CI: −1.0, −0.6), 4.0% (95% CI: −4.1, −3.8), 5.7% (95% CI: −5.9, −5.5), and 1.5% (95% CI: −1.6, −1.3) per year, respectively, but significantly increased by 0.5% (95% CI: 0.4, 0.6) in North Korea. From 2020 to 2030, the age-standardized DALYs rate of IHD and IS significantly declined in North Korea but significantly increased in South Korea (Table 2 and Supplementary Figure S3).

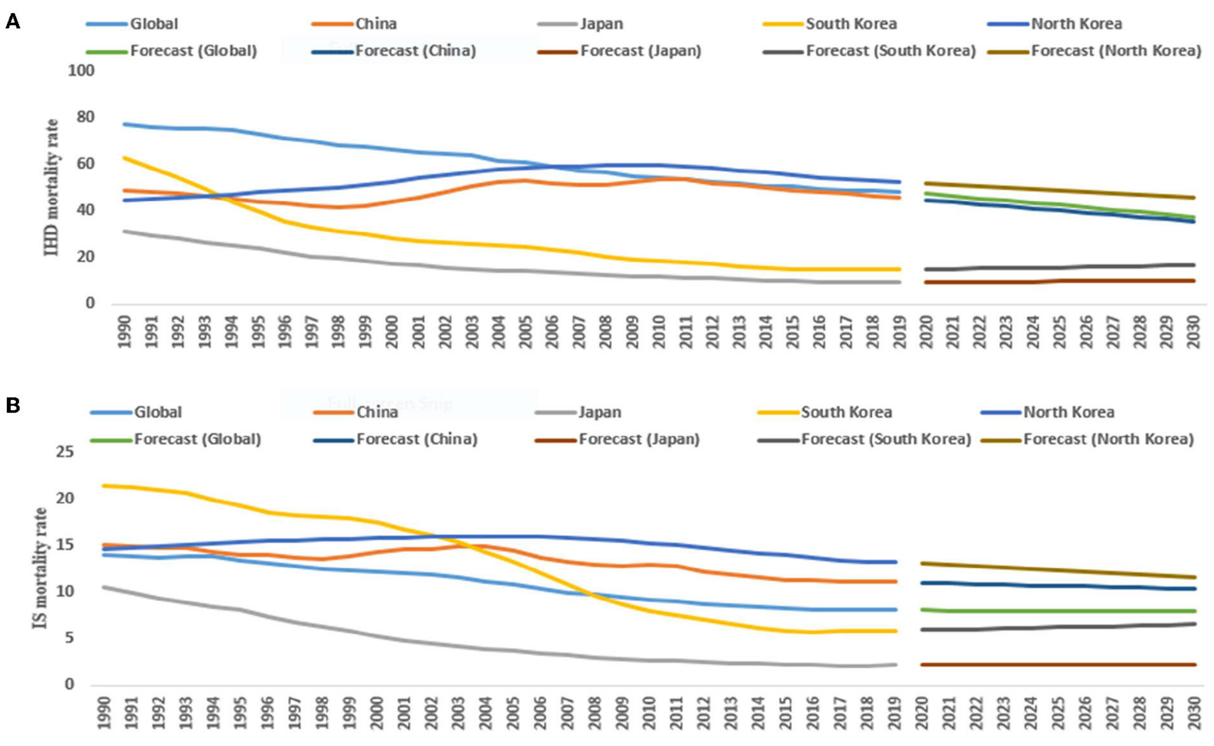

FIGURE 3
The temporal trends in the ASMR (per 100,000 persons) of IHD (ischemic heart diseases) **(A)** and IS (ischemic stroke) **(B)** (1990–2019) and its prediction (2020–2030) for females in the East Asian countries and world.

The ASMR and DALYs rate of IHD and IS in the East Asian countries and the world in different decades

Regardless of the sex (male, female, and both sex combined), a significant downward trend in the ASMR and DALYs rate of IHD and IS was observed in all three decades (i.e., 1990–1999, 2000–2009, and 2010–2019) in Japan, South Korea, and the world. However, the ASMR and DALYs rate of IHD significantly increased in China (2000–2009) and North Korea (1990–1999 and 2000–2009) (Supplementary Tables S1–S6).

The ASMR and DALYs rate of IHD and IS by age groups

Both in males and females, the mortality and DALYs rate of IHD and IS significantly declined in all age groups in Japan, South Korea, and the world from 1990 to 2019. Moreover, the declining trend of IHD and IS mortality and DALYs rates was higher in females than those in males regardless of the age groups. However, the mortality and DALYs rate of IHD showed a significant upward trend in the male aged group (75–79 years) in China. In North Korea, the mortality and DALYs rate of IHD significantly increased in all age groups regardless of sex (Supplementary Tables S7–S12).

Ranking of dietary risk factors attributed to IHD and IS

Figure 4 shows the ranking of dietary risk factors attributed to the mortality and DALYs of IHD and IS in the East Asian countries and the world in 2019. Globally, a diet low in whole grains was the most significant factor in IHD mortality (18.6 per 100,000 persons) and DALYs (393.5 per 100,000 persons) in 2019, followed by a diet low in legumes and a diet high in sodium (Supplementary Tables S13, S14). Dietary risk factors including a diet low in whole grains (China and Japan), a diet high in sodium (North Korea), and a diet low in legumes (South Korea) were the leading risk factors of IHD mortality in the East Asian countries (Supplementary Table S13). Moreover, a diet high in sodium, a diet high in red meat, and a diet low in whole grains were the leading risk factors for higher IS mortality and DALY the East Asia countries and the world (Supplementary Table S15).

TABLE 2 The temporal trend in the age-standardized DALYs rate of IHD and IS attributed to modifiable dietary risk factors in China, Japan, South Korea, North Korea, and the world (1990–2019) and its prediction (2020–2030).

Trend		**World**		**China**		**Japan**		**South Korea**		**North Korea**	
1990-2019	**DALYs**	**AAPC**	**95%CI**	**AAPC**	**95%CI**	**AAPC**	**95%CI**	**AAPC**	**95%CI**	**AAPC**	**95%CI**
IHD	Both sexes	−1.3*	−1.4, −1.2	−0.4*	−0.6, −0.1	−3.0*	−3.2, −2.8	−5.3*	−5.5, −5.2	0.5*	0.4, 0.6
	Male	−1.3*	−1.5, −1.0	−0.0	−0.2, 0.2	−2.8*	−3.0, −2.7	−5.5*	−5.9, −5.1	0.4*	0.3, 0.5
	Female	−1.5*	−1.6, −1.3	−0.8*	−1.0, −0.6	−4.0*	−4.1, −3.8	−5.7*	−5.9, −5.5	0.5*	0.4, 0.6
IS	Both sexes	−1.4*	−1.5, −1.2	−0.5*	−1.0, −0.1	−3.7*	−3.9, −3.5	−4.3*	−4.5, −4.1	−0.2*	−0.3, −0.2
	Male	−1.2*	−1.5, −0.9	−0.2	−0.5, 0.1	−3.8*	−4.0, −3.6	−4.5*	−4.8, −4.3	−0.2*	−0.3, −0.2
	Female	−1.6*	−1.7, −1.4	−1.0*	−1.4, −0.6	−3.8*	−4.1, −3.6	−4.1*	−4.4, −3.9	−0.3*	−0.4, −0.3
Prediction											
2020–2030											
IHD	Both sexes	−1.5*	−1.6, −1.5	−2.0*	−2.5, −1.6	0.8*	0.3, 1.4	6.0*	4.5, 7.4	−0.8*	−0.8.−0.7
	Male	−1.4*	−1.5, −1.4	−2.0*	−2.5, −1.5	−0.2	−0.7, 0.3	−2.0*	−2.3, −1.6	−0.8*	−0.8.−0.7
	Female	−1.7*	−1.7, −1.6	−2.0*	−2.3, −1.6	−0.2	−0.6, 0.2	6.8*	5.5, 8.0	−1.2*	−1.2, −1.1
IS	Both sexes	−0.8*	−1.0, −0.6	−0.5*	−0.6, −0.4	1.4*	1.0, 1.9	1.2*	0.2, 2.2	−0.9*	−0.9, −0.8
	Male	−0.6*	−0.8, −0.4	−0.1*	−0.1, −0.0	−0.7*	−1.1, −0.4	−0.3	−1.0, 0.4	−1.0*	−1.0, −0.9
	Female	−0.1	−0.4, 0.1	−0.4	−0.9, 0.1	2.0*	1.6, 2.4	1.8*	0.6, 3.1	−1.0*	−1.0, −0.9

DALYs, Disability-adjusted life years, IHD, Ischemic heart disease; IS, ischemic stroke; AAPC, average annual percent change, *statistically significant ($p < 0.05$).

Discussion

The study of the GBD 2019 data revealed the trend of ASMR of IHD and IS and DALYs rate attributed to modifiable dietary risk factors in the East Asian countries and the world (1990–2019), and its prediction from 2020 to 2030. We observed that regardless of the sex (male, female, and both sex combined), the ASMR and DALYs rate of IHD attributed to modifiable dietary risk factors significantly decreased in Japan, South Korea, and the world. However, the ASMR of IHD significantly increased in China (male) and North Korea (male, female, and both sex combined) from 1990 to 2019. Moreover, the ASMR and DALYs rate of IHD and IS significantly decreased in China, North Korea, and the world (male and both sex combined) from 2020 to 2030. Globally, a diet low in whole grains was the most significant factor in IHD mortality and DALYs in 2019, followed by a diet low in legumes and a diet high in sodium. A diet low in whole grains (China and Japan), a diet high in sodium (North Korea), and a diet low in legumes (South Korea) were the leading risk factors of IHD mortalin the East Asian countries.

The temporal trend in IHD and IS burden in the East Asian countries and the world

IHD and IS are the primary consequences of dietary risk factors. These dietary risk factors are the sum of either an over-consumed diet (sodium, trans-fatty acids, sugar-sweetened beverages, red meat, and processed meat) or an under-consumed diet (whole grains, legumes, vegetables, fruits, nuts and seeds, milk, fiber, calcium, omega-3 fatty acids from seafood, and polyunsaturated fatty acids). Globally, 7.94 million CVD annual deaths and 188 million annual DALYs are attributed to dietary risk factors (2). Based on 2017 data, 10 million CVD mortality and 207 million DALYs were due to dietary risk factors (16).

Our study found that for both sexes, the ASMR of IHD due to dietary risk factors significantly decreased (AAPC; −1.4%) from 95.6 to 62.4 per 100,000 persons from 1990 to 2019. The age-standardized DALYs rate of IHD significantly decreased (AAPC; −1.3%) from 1876.6 in 1990 to 1271.3 per 100,000 persons in 2019 in the world. Similarly, Dong et al. (12) reported a significant decrease in the age-standardized diet-related overall CVDs mortality (138.5–87.4 per 100,000 persons) and DALYs rate (2880.6–1870.1 per 100,000 persons) with an overall estimated annual percentage change (EAPC) of −1.3% from 1990 to 2019.

Our study also observed that the ASMR and DALYs rate of IHD and IS due to dietary risk factors were higher in male subjects than in female subjects. Moreover, the negative AAPC in the ASMR and DALYs rate of IHD and IS are comparatively lower in males than in the female population in the world, suggesting a milder declining trend in the mortality and DALYs rate of IHD and IS in males. Dong et al. (12) also observed that due to dietary risk factors, men suffered higher CVDs deaths and DALYs burden than women worldwide. These differences reflect the distribution of different risk factors between genders. Furthermore, several pathophysiological factors, the protective role of estrogen, and differences in vascular hemodynamics may also play some significant roles in gender differences (17–19).

Among the East Asian countries (for both sexes), Japan and South Korea experienced a significantly decreasing trend

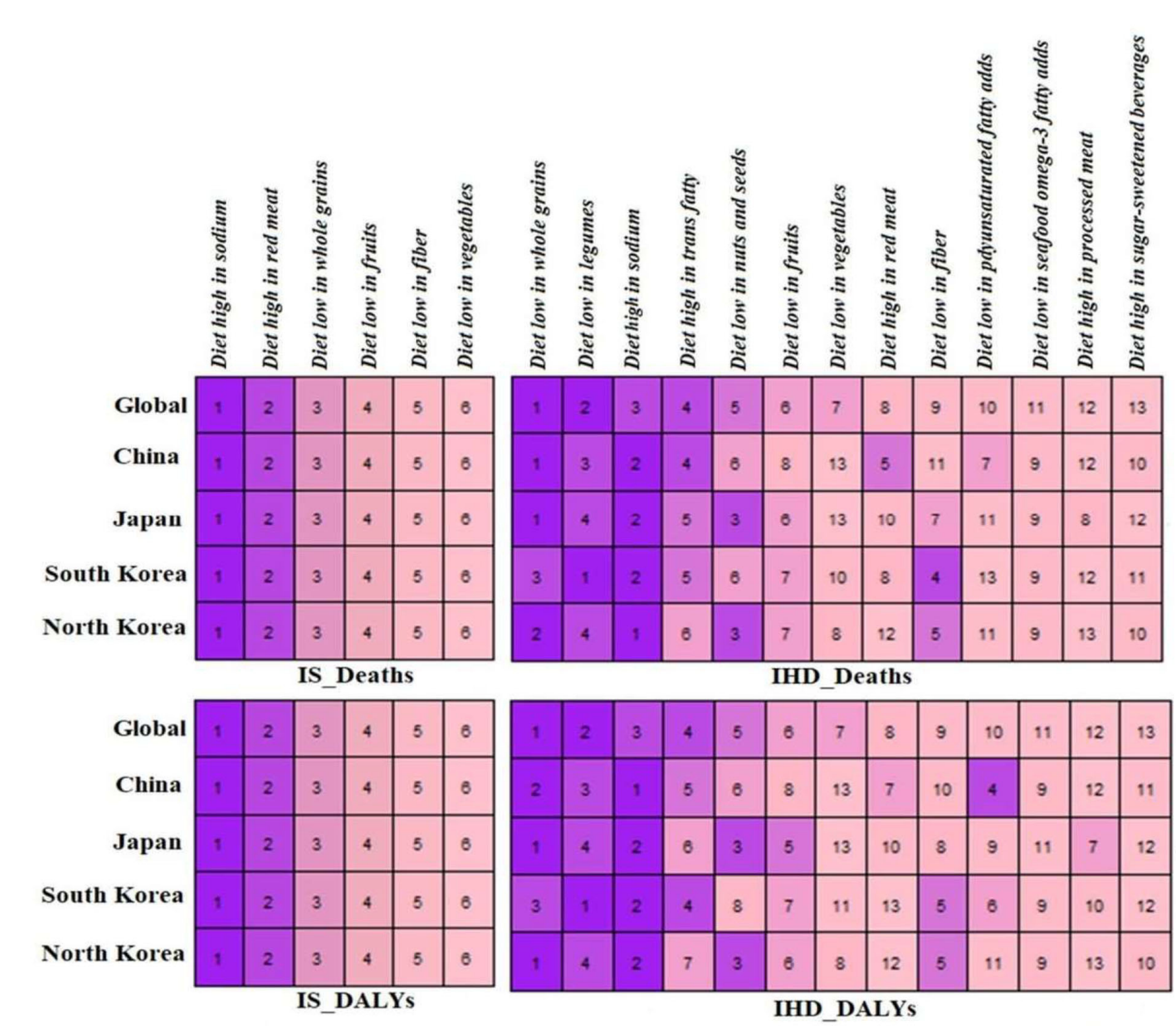

FIGURE 4
Ranking the dietary risk factors for mortality and DALYs due to ischemic heart disease (IHD), ischemic stroke (IS) for world, China, Japan, South Korea and North Korea, 2019.

in the ASMR and DALYs rate of IHD and IS, which could be linked to their healthy food patterns. The Japanese diet primarily consists of seafood, fruits, and vegetables (20). According to a Japanese cohort study, adults who followed the Japanese dietary guidelines at baseline had lower rates of CVD deaths than those who did not (21). In a GBD study of cardiovascular diseases and risk factors (1990–2019), Roth et al. (2) reported a decreasing trend of age-standardized DALYs rate due to IHD in Japan and South Korea. Healthy diet habits improved living standards, and diagnosis of CVDs at an earlier stage could be attributed to the decreases in the ASMR and DALYs rate of IHD and IS (22, 23). However, in a national-level cross-sectional survey (1998–2016), the IHD deaths due to dietary risk factors substantially increased in South Korea during the study period (24).

Due to the dietary risk factors, the trend of ASMR and DALYs rate of IHD significantly increased in North Korea (male, female, and both sex combined). North Korea had about four-fold higher ASMR and DALYs rate of IHD compared with South Korea. In a GBD study in 2004, WHO estimated that North Korea had three times higher CVD than South Korea (25). In the South-East Asian Region (SEAR), North Korea had the highest death rate from CVD (26). The higher rates of CVD mortality in the North Korean population could be attributed to their exposure to malnutrition in their infancy and developmental phase during the time of economic hardship (mid-to-late-1990s) (27).

In China, males experienced two times higher ASMR of IHD compared with females and had a significantly increased trend of IHD mortality from 1990 to 2019, which is comparable with the GBD study (28). Based on previous reports, the incidence of coronary heart disease occurs later (10–15 years) in women than in men. Moreover, due to the protective effect of estrogen on the cardiovascular system, women had a lower incidence of CVD than men (29, 30). China observed an increasing trend of diet-related CVD death and DALYs rates (12). The "Healthy China Action Plan (2019–2030)", the most recent health and nutrition-related policy has been launched including the popularization of health knowledge, promotion of a balanced diet, and physical activities to reduce CVD mortality and morbidity (31). Moreover, the differences in the ASMR and DALYs rate of IHD and IS among the East Asian countries could be due to variations in diet quality, lack of knowledge related to a healthy diet, and levels of exposure to different dietary risk factors (2).

The ASMR of IHD and IS due to dietary risk factors tended to decline until 2030 in China, North Korea (male, female, and both sex combined), and the world (male and both sex combined). However, a significant upward trend was observed in Japanese male subjects. In addition, the age-standardized DALYs rate of IHD and IS continued to decline until 2030 in China, North Korea, and the world (male and both sex combined) but significantly increased in Japan (both sexes) and South Korea (female and both sexes). In Japan, high salt intake is considered a national epidemic (32, 33), and the predicted increasing trend of IHD and ischemic burden could be attributed to high salt consumption. In our findings, a diet high in sodium is the leading risk factor for high IS mortality and DALYs and the second risk factor for high IHD mortality and DALYs in Japan. The latest National Health and Nutrition Survey (NHNS) in 2016 reported that the average daily salt consumption in the Japanese population was 9.9 g (10.8 g for men and 9.1 g for women) (34) which is much larger than the WHO's recommended level (<5.0 g per day) (35).

The IHD and IS burden in different decades

We observed a significant downward trend in the ASMR and DALYs rate of IHD and IS attributed to dietary risk factors in all three decades in Japan, South Korea, and the world. However, the ASMR and DALYs rate of IHD significantly increased in China from 2000to 2009 and in North Korea from 1990 to 1999 and 2000 to 2009. Tian et al. (28) reported an increased trend of IHD DALYs attributed to dietary risk factors in the Chinese population from 1999 to 2010, which is in accordance with our findings. Diet is one of the key risk factors among the many established risk factors associated with the CVD burden (3). Several complex factors influence diet quality and food choices such as the economy, culture, and the nutrition environment (36).

In China, the rapid economic development and cultural exchanges have shifted people's food consumption choices from a traditional diet to a westernized diet which may contribute to observed increases in chronic diseases. A westernized diet such as the fast-food (FF) industry has increased rapidly in China in the last two decades (37, 38). The number of people who eat FF has increased by 40.20% from 14.70% in 2000 to 20.61% in 2008 in China (39). Moreover, the total revenue (in million US$) of FF increased from 10,464 to 94,218 from 1999to 2013, indicating an increased trend in FF consumption in China (40). Fast-food consumption (FFC) can increase the risk of CVD (41) and the rapid FFC could be one of the attributable risk factors for the high burden of IHD deaths and DALYs from 1999 to 2010 in China.

The IHD and IS burden in different age groups

Regardless of sex, the IHD and IS burden attributed to dietary risk factors significantly declined in all age groups in Japan, South Korea, and the world. However, the mortality and DALYs rate of IHD significantly increased in all age groups in North Korea. The transition in diet from traditional Asian diets to westernized diets has been observed in several Asian countries and is attributable to the high CVDs burden in the region (42). A review article reported increasing consumption of animal source food, oil, sugar, and sugar-sweetened beverages, and low consumption of whole grains and legumes in low- to middle-income countries (43). In China, the mortality and DALYs rate of IHD showed a significant upward trend in the male aged group (75–79 years). Tian et al. (28) also reported that the DALYs rate of IHD due to dietary risk factors was higher in Chinese people over 80 years old. The risk CVDs mortality and morbidity increases with increasing age (44) and could be attributed to an alteration in the arteries, atherosclerosis, decreased elasticity, and fibrosis (45).

Ranking of dietary risk factors

In 2019, a diet low in whole grains was the most significant risk factor for IHD mortality and DALYs, followed by a diet low in legumes, and a diet high in sodium in the world. Diet groups including a diet low in whole grains (China and Japan), a diet high in sodium (North Korea), and a diet low in legumes (South Korea) were the leading risk factors of IHD mortality in the East Asian countries. Moreover, a diet high in sodium, a diet high in red meat, and a diet low in whole grains were the leading risk factors for higher IS mortality and DALYs rate in East Asia countries and the world. It has been observed that two-thirds of CHD and two-fifth of acute ischemic stroke events could be avoided by adopting a healthy lifestyle (46, 47). A balanced diet is one of the significant parts of a healthy lifestyle (48). An unhealthy diet is associated with a high burden of CVD in Asian countries and the world (16, 42).

In a GBD study in 2017, CVD was the leading cause of deaths (10 million) and DALYs (207 million) attributed to dietary risk factors. A diet low in whole grains (3 million deaths and 82 million DALYs), a diet high in sodium (3 million deaths and 70 million DALYs), and a diet low in fruits (2 million deaths and 65 million DALYs) were the leading dietary risk factors for overall deaths and DALYs globally and in many counties (16). In a recent GBD study in 2019, around 6.9 million CVD deaths and 153.2 million DALYs are attributed to dietary risk factors. A diet low in whole grains significantly contributed to higher CVD deaths DALYs followed by a high intake of sodium, a diet low in fruits, a diet low in vegetables, and a diet low in seafood omega-3 fatty acids which are comparable with our findings (12). High intake of sodium is the leading dietary risk factor for IHD DALYs, IS deaths, and DALYs, and the second risk factor for IHD deaths in the Chinese population. In China, the salt intake is higher (12 g/person/day) than the WHO recommended level (5 g/person/day), which is associated with a higher prevalence of hypertension (49).

Limitations

Although IHME provides standard and improved high-quality estimates of the global burden of diseases still we had certain limitations in this study. First, our analysis relies on the GBD secondary data and all GBD limitations are also applicable to our findings as described previously (16, 50). Second, GBD does not provide sub-types of IHD such as non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina (UA), or ST-segment elevation myocardial infarction (STEMI). Third, our analyses are limited to people aged ≥50 years. Finally, out of fifteen dietary risk factors (16), 13 dietary risk factors for IHD deaths and DALYs and only six dietary risk factors were available for IS deaths and DALYs estimates in the East Asian countries and the world. Moreover, we have described trends of IHD and IS burden attributed to overall dietary risk factors and could not find trends for the individual dietary risk factor.

Conclusion

This study found that regardless of the sex, ASMR, and DALYs rate of IHD attributed to modifiable dietary risk factors significantly decreased in Japan, South Korea, and the world. Globally, the ASMR and DALYs rate of IHD and IS due to dietary risk factors were higher in male subjects than in female subjects. Among East Asian countries, the decreasing trend of IHD and IS burden in South Korea is remarkable compared with the world. However, the ASMR of IHD significantly increased in China (male) and North Korea (male, female, and both sex combined) from 1990 to 2019. From 2020 to 2030, the ASMR of IHD is predicted to increase in South Korea (female) and Japan (male). Globally, a diet low in whole grains was the top risk factor for highest IHD mortality and DALYs in 2019, followed by a diet low in legumes and a diet high in sodium. Diet low in whole grains, a diet high in sodium, and a diet low in legumes were the leading risk factors of high IHD mortality in East Asian countries. These estimates may facilitate the public health policymakers across these countries to take appropriate measures and design proper strategies to further overcome the CVDs burden attributed to dietary risk factors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

N: conceptualization, data curation, formal analysis, methodology, software, validation, visualization, writing—original draft, and writing—review and editing. WB: validation, visualization, and writing—review and editing. ZL: data curation, software, validation, visualization, and investigation. SM: data curation, validation, visualization, investigation, and writing—review. GF and YW: investigation, resources, validation, funding acquisition, project administration, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.898978/full#supplementary-material

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Associations of body mass index and sarcopenia with screen-detected mild cognitive impairment in older adults in Colombia

Gary O'Donovan[1,2]*, Olga L. Sarmiento[2], Philipp Hessel[2,3], Graciela Muniz-Terrera[1,4], Claudia Duran-Aniotz[1,5] and Agustín Ibáñez[1,6,7,8,9]

[1]Latin American Brain Health Institute (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile, [2]Facultad de Medicina, Universidad de los Andes, Bogotá, Colombia, [3]Swiss Tropical and Public Health Institute, Basel, Switzerland, [4]Heritage College of Osteopathic Medicine, Ohio University, Athens, OH, United States, [5]Centre for Social and Cognitive Neuroscience, School of Psychology, Universidad Adolfo Ibáñez, Santiago, Chile, [6]Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, United States, [7]Trinity College Dublin, Dublin, Ireland, [8]Centro de Neurociencias Cognitivas, Universidad de San Andrés, Buenos Aires, Argentina, [9]Trinity College Institute of Neuroscience (TCIN), Trinity College Dublin, Dublin, Ireland

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EDITED BY
Mainul Haque,
National Defence University of Malaysia, Malaysia

REVIEWED BY
Shuen Yee Lee,
Singapore Institute of Technology, Singapore
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Gonoshathaya Samaj Vittik Medical College, Bangladesh
Zakirul Islam,
Eastern Medical College and Hospital, Bangladesh

*CORRESPONDENCE
Gary O'Donovan
james.odonovan@uai.cl

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Background and objective: More research is required to understand associations of body mass index (BMI) and sarcopenia with cognition, especially in Latin America. The objective of this study was to investigate associations of BMI and sarcopenia with mild cognitive impairment in Colombia.

Design, setting, and participants: Data were from the National Survey of Health, Wellbeing and Aging in Colombia (SABE Colombia, in Spanish). Community-dwelling adults aged 60 years or older were invited to participate.

Methods: Trained interviewers administered a shorter version of the mini-mental state examination and mild cognitive impairment was defined as a score of 12 or less out of 19. Body mass index was defined using standard cut-offs. Sarcopenia was defined as low grip strength or slow chair stands. Logistic regression models were adjusted for age, sex, height, education, income, civil status, smoking, and alcohol drinking.

Results: The prevalence of mild cognitive impairment was 20% in 23,694 participants in SABE Colombia and 17% in 5,760 participants in the sub-sample in which sarcopenia was assessed. Overweight and obesity were associated with decreased risk of mild cognitive impairment and sarcopenia was associated with increased risk. Sarcopenia was a risk factor for mild cognitive impairment in those with normal BMI (adjusted model included 4,911 men and women). Compared with those with normal BMI and without sarcopenia, the odds ratio for mild cognitive impairment was 1.84 in those with normal BMI and sarcopenia (95% confidence interval: 1.25, 2.71). Sarcopenia was also a risk factor in those with obesity but did not present a greater risk than sarcopenia alone. Compared with those with normal BMI and without sarcopenia, the odds ratio was 1.62 in those with obesity and sarcopenia (95% confidence interval: 1.07, 2.48). Sarcopenia was not a risk factor for mild cognitive impairment in those with overweight. Similar results were observed when reference values from Colombia were used to set cut-offs for grip strength. Similar results were also observed in cross-validation models, which suggests the results are robust.

Conclusion: This is the first study of the combined associations of sarcopenia and obesity with cognition in Colombia. The results suggest that sarcopenia is the major predictor of screen-detected mild cognitive impairment in older adults, not overweight or obesity.

KEYWORDS

cognition, overweight, obesity, sarcopenia, South America

Introduction

The proportion of people living with dementia is predicted to increase by around 75% by 2050 in the UK and other countries in western Europe and by around 200% in Colombia and other countries in Latin America (1). It is important to identify modifiable risk factors because a 5-year delay in onset might halve the prevalence of dementia (2). Nearly all the evidence about potentially modifiable risk factors for cognitive impairment comes from studies in high-income countries and there is an urgent need for more evidence from low-income and middle-income countries, particularly from Latin America (3). A risk factor is an exposure or a behavior that is causally related to a health problem and the existence of causal evidence in high-income countries does not negate the need for causal evidence elsewhere (4, 5). Indeed, consistency of association is one of the fundamental considerations when inferring causality (4, 5). Sarcopenia is a muscle disease characterized by low muscle strength (6) and evidence from high-income countries suggests that sarcopenia is a risk factor for cognitive impairment (7). Obesity is a risk factor for cognitive impairment (3) and evidence from high-income countries also suggests that sarcopenic obesity presents a greater risk for cognitive impairment than sarcopenia alone or obesity alone (8, 9). We are not aware of any studies of the combined associations of sarcopenia and obesity with cognitive impairment in Colombia. There are several mechanisms that may explain why sarcopenic obesity presents a greater risk for cognitive impairment (10). For example, sarcopenia may cause an imbalance in the secretion of myokines and memory impairment (11) and sarcopenic obesity may exacerbate the secretion of pro-inflammatory myokines (10).

In modern epidemiology, it is understood that cross-sectional studies can provide important information about etiology (12). For example, the difference in prevalence between two exposure groups can be viewed as a causal effect itself (12). It is also understood that it is important to gather evidence from each country in Latin America because the region is so difficult to comprehend (13). There is great cultural and ethnic diversity in Latin America (13). There are also varying levels of income and healthcare in the region (13, 14). Colombia may be particularly difficult to understand because the country has suffered 50 years of civil war (15). The National Survey of Health, Wellbeing and Aging in Colombia (SABE Colombia, according to its initials in Spanish) is the largest nationally representative survey of older adults in Colombia (16). The aim of the present analysis was to investigate associations of obesity and sarcopenia with mild cognitive impairment in SABE Colombia.

Materials and methods

Participants

The National Survey of Health, Wellbeing and Aging in Colombia is described in detail elsewhere (16). Briefly, the target population was community-dwelling adults aged 60 years or older living in urban and rural areas of Colombia. Participants were selected using a multistage area probability sampling design and there were four selection stages: municipalities, blocks, housing units, and households. The response rate was around 62% in urban areas, around 77% in rural areas, and around 70% overall (16). Data were collected across all departments (that is, states) and the final sample was deemed to be representative of the population of older adults living in households in Colombia (16). Sarcopenia was assessed in a sub-sample that was also designed to be nationally representative (17). People living in 86 of 244 municipalities in Colombia were invited to participate, including people living in the four large cities of Bogotá, Medellín, Cali, and Barranquilla (17). The sample size in the sub-sample was 6,161, assuming that the proportion of older adults was 6%, that the maximum error was 6%, and that the non-response rate was 20% (17). The final sub-sample included 5,760 people, which is equivalent to 93% of the target sample size. Trained interviewers conducted face-to-face interviews in the participant's home between April and September 2015 (16). Volunteers completed the shorter version of the Folstein Mini-Mental State Examination (MMSE) described below and were invited to complete the survey if they had a score of 13 or more (16). Otherwise, a friend or family member was invited to complete the survey on behalf of the participant. A friend or family member completed the interview in 17.5% of cases (16). Institutional review boards of Universidad de Caldas (CBCS-021-14) and Universidad del Valle (09–014 and 011–015) approved the study and all participants gave written informed consent.

Outcome variable

The outcome variable was mild cognitive impairment. The versions of the MMSE used in Latin America and the Caribbean are shorter than the original version in an attempt to reduce the low literacy bias (18). The shorter version of the MMSE used in SABE Colombia has six questions and participants were asked: to state the date and the day of week (4 points); to repeat and remember three words (3 points); to state in reverse order the numbers 1, 3, 5, 7, 9 (5 points); to take a piece of paper in their right hand, fold it in half using both hands, and put it on their lap (3 points); to reiterate the three words given earlier (3 points); and, to copy a drawing of two overlapping circles (1 point). A score of 12 or less out of 19 was used to screen for mild cognitive impairment in SABE Colombia (16). The shorter version of the MMSE used in SABE Colombia has been validated in a study of 1,301 adults aged 60 years or older living in households in Chile (19). The prevalence of mild cognitive impairment was 10.7% using the threshold of 12 or less out of 19 in the shorter version of the MMSE and 8.1% using the threshold of 6 or more out of 33 in the criterion measure (19), which was the Short Portable Mental Status Questionnaire (20).

Exposure variables

The main exposure variables were BMI and sarcopenia. Participants were asked to take off their shoes and to remove any heavy objects, such as coins, keys, and coats. Trained interviewers measured weight and height, and body mass index was expressed as weight in kilograms divided by height in meters squared. Body mass index values greater than 75 were deemed to be dubious and were not included in the present analysis. Body mass index cut-offs were defined using World Health Organization guidelines: normal was 18.5–24.9 kg/m^2; underweight was $<$ 18.5 kg/m^2; overweight was 25.0–29.9 kg/m^2; and, obesity was $\geq$ 30 kg/m^2 (21). Analyses were adjusted for height because of the inverse association between BMI and height in older adults (22).

Sarcopenia, or muscle failure, is a muscle disease and the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) uses low muscle strength as the primary parameter of sarcopenia because muscle strength is presently the most reliable measure of muscle function (6). The EWGSOP2 guidelines recommend that grip strength and chair stands be used to assess muscle strength (6). Grip strength was assessed using the Smedley III dynamometer (Takei Scientific Instruments, Tokyo, Japan). The interviewer adjusted the dynamometer so that it fitted the participant's hand. The interviewer also explained how to use the dynamometer and gave a demonstration. The participant was instructed to stand with their feet hip-width apart, to hold their arm to the side without touching their body, and to squeeze the device as hard as possible. Grip strength was assessed twice in each hand with 30 s of rest between tests. The highest value was used in the present analysis. Low grip strength was defined using the EWGSOP2 cut-offs of $<$ 27 kg in men and $<$ 16 kg in women (6). Participants who could not complete the assessment were included in the low grip strength group. Chair stands were assessed using a sit-to-stand test. The interviewer explained how to perform the test and gave a demonstration. The participant was instructed to stand up as quickly as possible five times without stopping. The participant was asked to keep their arms crossed against the chest and was told that they would be timed. A slow sit-to-stand test was defined using the EWGSOP2 cut-off of $>$ 15 s in men and women (6). Participants who could not complete the assessment were included in the slow chair stands group. The EWGSOP2 recommends that muscle strength be assessed to screen for sarcopenia and that muscle quality be assessed to confirm sarcopenia (grip strength and chair stands can be used to asses muscle strength and magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, and bioelectrical impedance can be used to assess muscle quality) (6). The present study was designed to screen for "probable sarcopenia" and was not designed to confirm the diagnosis (16, 17).

Covariates

The analyses were adjusted for a range of covariates that may be associated with cognition, including age, sex, education, income, civil status, cigarette smoking, and alcohol drinking (23, 24). Participants were asked about the highest level of education they had achieved, and three groups were created: no education; some primary education; and, some secondary education or more. Participants were also asked about their current individual income according to multiples of the minimum wage. Participants were asked about their current civil status, and two groups were created: not married or with partner; and, married or with partner. Participants were asked about cigarette smoking, and three groups were created: never, former smoker, and current smoker. Participants were also asked about alcohol drinking in the last month, and two groups were created: non-drinker; and, drinker. The trained interviewers also measured height.

Sensitivity analyses

The cut-offs used in the main analysis were based on European populations and may not be applicable to Colombia (6). Grip strength was assessed in 672 men and 487 women aged 18–64 years who took part in a nationally representative survey in Colombia between 2015 and 2016 (25, 26). Peak grip strength values were 38.9 ± 10.2 in men and 23.6 ± 5.3 in women (mean ± standard deviation) (25). In sensitivity analyses, cut-offs were set two standard deviations below these reference values for grip strength for adults in Colombia: < 18.5 kg in men and < 13 kg in women. We are not aware of any reference values for chair speed for adults in Colombia.

Statistical analysis

Analyses were performed using Stata SE version 17.0 for Mac (StataCorp, Texas, USA). Logistic regression was used to investigate associations of BMI and sarcopenia with mild cognitive impairment. Logistic regression models were adjusted for age and sex and further adjusted for height, education, current individual income, civil status, cigarette smoking, and alcohol drinking. Age and height were modeled as continuous variables. All other covariates were modeled as categorical variables. Odds ratios and 95% confidence intervals were calculated for all participants. Cross-fit, partialing-out lasso logistic regression was used to test the robustness of the models. In lasso regression, the dataset can be split and cross-validated. The coefficients are obtained from one sample and used in another, which is independent, and that adds robustness. Here, the dataset was split ten times and the "controls" were automatically selected from the covariates chosen *a priori* (i.e., age, sex, height, education, current individual income, civil status, cigarette smoking, and alcohol drinking). The output includes odds ratios

TABLE 1 Characteristics of participants in the National Survey of Health, Wellbeing and Aging in Colombia and the sub-sample in which sarcopenia was assessed.

	SABE Colombia	
	Survey	**Sub-sample**
Age in years, mean ± SD (n)	71 ± 8 (23,694)	71 ± 8 (5,760)
Sex		
Male, *n* (%)	10,112 (42.68)	2,325 (40.36)
Female, *n* (%)	13,582 (57.32)	3,435 (59.64)
Missing, *n* (%)	0 (0)	0 (0)
Total, *n* (%)	23,694 (100)	5,760 (100)
Mild cognitive impairment		
No, *n* (%)	19,004 (80.21)	4,789 (83.14)
Yes, *n* (%)	4,690 (19.79)	971 (16.86)
Missing, *n* (%)	0 (0)	0 (0)
Total, *n* (%)	23,694 (100)	5,760 (100)
MMSE score, mean ± SD (*n*)	14.94 ± 3.91 (23,694)	15.24 ± 3.77 (5,760)
Body mass index		
Normal, *n* (%)	7,347 (31.01)	1,710 (29.69)
Underweight, *n* (%)	771 (3.25)	160 (2.78)
Overweight, *n* (%)	7,678 (32.40)	1,991 (34.57)
Obesity, *n* (%)	4,452 (18.79)	1,161 (20.16)
Missing, *n* (%)	3,446 (14.54)	738 (12.81)
Total, *n* (%)	23,694 (100.00)	5,760 (100)
Grip strength		
Normal, *n* (%)	–	3,212 (55.76)
Low, *n* (%)	–	2,548 (44.24)
Missing, *n* (%)	–	0 (0)
Total, *n* (%)	–	5,760 (100)
Chair stands		
Normal, *n* (%)	–	2,401 (41.68)
Slow, *n* (%)	–	3,359 (58.32)
Missing, *n* (%)	–	0 (0)
Total, *n* (%)	–	5,760 (100)
Height in cm, mean ± SD (*n*)	156 ± 9 (20,585)	156 ± 9 (5,114)
Education		
None, *n* (%)	5,229 (22.07)	1,035 (17.97)
Some primary, *n* (%)	13,462 (56.82)	3,399 (59.01)
Some secondary or more, *n* (%)	4,910 (20.72)	1,299 (22.55)
Missing, *n* (%)	93 (0.39)	27 (0.47)
Total, *n* (%)	23,694 (100.00)	5,760 (100)
Civil status		
Not married or with partner, *n* (%)	11,127 (46.96)	2,699 (46.86)
Married or with partner, *n* (%)	12,557 (53.00)	3,061 (53.14)
Missing or did not answer, *n* (%)	10 (0.04)	0 (0)

(Continued)

TABLE 1 (continued)

	SABE Colombia	
	Survey	**Sub-sample**
Total, *n* (%)	23,694 (100.00)	5,760 (100)
Current income		
None, *n* (%)	3,736 (15.77)	823 (14.29)
Less than minimum wage, *n* (%)	13,468 (56.84)	3,129 (54.32)
Minimum wage, *n* (%)	3,168 (13.37)	882 (15.31)
1–2 Times minimum, *n* (%)	1,906 (8.04)	547 (9.50)
2–3 Times minimum, *n* (%)	570 (2.41)	162 (2.81)
3–4 Times minimum, *n* (%)	262 (1.11)	58 (1.01)
More than 4 times minimum, *n* (%)	229 (0.97)	54 (0.94)
Missing or did not answer, *n* (%)	355 (1.50)	105 (1.82)
Total, *n* (%)	23,694 (100.00)	5,760 (100)
Cigarette smoking		
Never smoked, *n* (%)	11,400 (48.11)	2,885 (50.09)
Former smoker, *n* (%)	9,763 (41.20)	2,291 (39.77)
Current smoker, *n* (%)	2,523 (10.65)	580 (10.07)
Missing or did not answer, *n* (%)	8 (0.03)	4 (0.07)
Total, *n* (%)	23,694 (100.00)	5,760 (100)
Alcohol drinking		
Non-drinker, *n* (%)	20,881 (88.13)	5,076 (88.12)
Drinker, *n* (%)	2,796 (11.80)	681 (11.82)
Missing or did not answer, *n* (%)	17 (0.07)	3 (0.05)
Total, *n* (%)	23,694 (100.00)	5,760 (100.00)

Data are from the National Survey of Health, Wellbeing and Aging in Colombia (SABE Colombia). Participants were community-dwelling adults aged 60 years or older. Mild cognitive impairment was defined as a score of 12 or less out of 19 on the shorter version of the mini-mental state examination (MMSE) used in SABE Colombia, which is a valid screening tool. Body mass index was defined using World Health Organization categories, where normal is 18.5–24.9 kg/m^2, underweight is $<$ 18.5 kg/m^2, overweight is 25.0–29.9 kg/m^2, and obesity is $\geq$ 30 kg/m^2. The cut-off for low grip strength was $<$ 27 kg in men and $<$ 16 kg in women. The cut-off for slow chair stands was $>$ 15 s in men and women. N is number and SD is standard deviation.

and the Wald statistic. Odds ratios are interpreted in the same way as in ordinary logistic regression models. The Wald statistic indicates whether the exposure is statistically significant.

Results

Table 1 shows the characteristics of the 23,694 participants in SABE Colombia and the 5,760 participants in the sub-sample in which sarcopenia was assessed. The sample and the sub-sample were similar. For example, age was 71 ± 8 years in the sample and 71 ± 8 years the sub-sample. The proportion of males was 43% in the sample and 40% in the sub-sample. The prevalence of mild cognitive impairment was 20% in the sample and 17% in the sub-sample. The proportion of normal weight was 31% in the sample and 30% in the sub-sample. The proportion of obesity was 19% in the sample and 20% in the sub-sample. The prevalence of sarcopenia was 44% when defined as low grip strength and 58% when defined as slow chair stands. Supplementary Figure 1 shows the flow of data in the present analysis.

Body mass index was assessed in 20,248 participants. Table 2 shows associations between BMI and mild cognitive impairment. Compared with those with normal BMI, the odds ratio for mild cognitive impairment was 1.63 in those with underweight after adjusting for age and sex (95% confidence interval: 1.37, 1.95). Compared with those with normal BMI, the odds ratio for mild cognitive impairment was 0.68 in those with overweight (95% confidence interval: 0.62, 0.75) and 0.63 in those with obesity (95% confidence interval: 0.56, 0.71). Similar associations were observed after further adjustment for height, education, income, civil status, smoking, and alcohol drinking.

Grip strength and chair stands were assessed in 5,760 participants. Table 3 shows associations between grip strength and mild cognitive impairment. Compared with those with normal grip strength, the odds ratio for mild cognitive impairment was 2.00 in those with low grip strength after adjusting for age and sex (95% confidence interval: 1.70, 2.35). Similar associations were observed after further adjustment for height, education, income, civil status, smoking, and alcohol drinking. Table 3 also shows associations between chair stands and mild cognitive impairment. Compared with those with normal chair stands, the odds ratio for mild cognitive impairment was 1.66 in those with slow chair stands after adjusting for age and sex (95% confidence interval: 1.39, 1.97). Similar associations were observed after further adjustment for height, education, income, civil status, smoking, and alcohol drinking.

Table 4 shows combined associations of BMI and sarcopenia with mild cognitive impairment when sarcopenia is defined as either low grip strength or slow stair stands. The results suggest that sarcopenia is a risk factor for mild cognitive impairment in those with normal BMI. For example, compared with those with normal BMI and without sarcopenia, the odds ratio for mild cognitive impairment was 1.84 in those with normal BMI and sarcopenia after adjusting for age, sex, height, education, income, civil status, smoking, and alcohol drinking (95% confidence interval: 1.25, 2.71). The results also suggest

TABLE 2 Associations of body mass index with mild cognitive impairment.

	Body mass index			
	Normal	**Underweight**	**Overweight**	**Obesity**
Model 1	1.00 (reference) $n = 7,347$ (21% with MCI)	1.64 (1.37, 1.95) $n = 771$ (33% with MCI)	0.68 (0.62, 0.75) $n = 7,678$ (13% with MCI)	0.63 (0.56, 0.71) $n = 4,452$ (12% with MCI)
Model 2	1.00 (reference) $n = 7,191$ (20% with MCI)	1.61 (1.34, 1.95) $n = 752$ (33% with MCI)	0.76 (0.69, 0.84) $n = 7,532$ (13% with MCI)	0.74 (0.65, 0.83) $n = 4,385$ (12% with MCI)

Values are odds ratios (95% confidence intervals). Mild cognitive impairment (MCI) was defined as a score of 12 or less out of 19 on the shorter version of the mini-mental state examination used in SABE Colombia, which is a valid screening tool. Model 1 was adjusted for age and sex ($n = 20,248$). Model 2 was adjusted for age, sex, height, education, income, civil status, smoking, and alcohol drinking ($n = 19,860$).

that sarcopenia is a risk factor in those with obesity. For example, compared with those with normal BMI and without sarcopenia, the odds ratio was 1.62 in those with obesity and sarcopenia after adjusting for all the covariates (95% confidence interval: 1.07, 2.48). Conversely, the results suggest that sarcopenia is not a risk factor for mild cognitive impairment in those with overweight. For example, compared with those with normal BMI and without sarcopenia, the odds ratio was 1.23 in those with overweight and sarcopenia after adjusting for all the covariates (95% confidence interval: 0.83, 1.83). The effect of underweight was unclear because of the low number of participants with the condition. Combined associations of body mass index and sarcopenia with mild cognitive impairment were similar when sarcopenia was defined as low grip strength alone (**Supplementary Table 1**) and when sarcopenia was defined as slow chair stands alone (**Supplementary Table 2**). However, the association of sarcopenic obesity with mild cognitive impairment was not statistically significant when sarcopenia was defined as slow chair stands (odds ratio: 1.33; 95% confidence interval: 0.93, 1.91).

The reference values for adults aged 18–64 years in Colombia were used to set the cut-offs for grip strength in the sensitivity analyses. The prevalence of low grip strength was 67% when the country-specific cut-offs were used. Not only was the prevalence of low grip strength higher, but the association between low grip strength and mild cognitive impairment was stronger when the country-specific cut-offs were used. Compared with those with normal grip strength, the odds ratio for mild cognitive impairment was 2.13 in those with low grip strength after adjusting for age, sex, height, education, income, civil status, smoking, and alcohol drinking (95% confidence interval: 1.53, 2.98). **Table 5** shows combined associations of BMI and sarcopenia with mild cognitive impairment using the country-specific cut-offs for grip strength. Sarcopenia was a risk factor for mild cognitive impairment in those with normal weight and in those with obesity in the main analysis and in the sensitivity analysis. Sarcopenia was not a risk factor in those with overweight in the main analysis or the sensitivity analysis.

Supplementary Table 3 shows associations of BMI with mild cognitive impairment in the original model and the cross-validation model. **Supplementary Table 4** shows associations of grip strength and chair stands with mild cognitive impairment in the original models and the cross-validation models. **Supplementary Figure 2** shows combined associations of BMI and sarcopenia with mild cognitive impairment in the original model and the cross-validation model. The odds ratios and the 95% confidence intervals were similar in the original models and the cross-validation models and the exposures were highly significant, which suggests that the models are robust and that sound inferences can be made.

Discussion

The aim of the present analysis was to investigate associations of BMI and sarcopenia with mild cognitive impairment in older adults in Colombia. We found that overweight and obesity were associated with decreased risk of

TABLE 3 Associations of grip strength and chair stands with mild cognitive impairment.

	Normal	**Low or slow**
Grip strength		
Model 1	1.00 (reference)	2.00 (1.70, 2.35)
Model 2	1.00 (reference)	1.90 (1.56, 2.31)
Chair stands		
Model 1	1.00 (reference)	1.66 (1.39, 1.97)
Model 2	1.00 (reference)	1.61 (1.31, 1.98)

Values are odds ratios (95% confidence intervals). Mild cognitive impairment was defined as a score of 12 or less out of 19 on the shorter version of the mini-mental state examination used in SABE Colombia, which is a valid screening tool. The cut-off for low grip strength was < 27 kg in men and < 16 kg in women. The cut-off for slow chair stands was > 15 s in men and women. Model 1 was adjusted for age and sex ($n = 5,760$ for grip strength and chair stands, including 17% with mild cognitive impairment). Model 2 was adjusted for age, sex, height, education, income, civil status, smoking, and alcohol drinking ($n = 5,000$ for grip strength and chair stands, including 14% with mild cognitive impairment).

TABLE 4 Combined associations of body mass index and sarcopenia with mild cognitive impairment, where sarcopenia is defined as low grip strength or slow chair stands.

	Body mass index			
	Normal	Underweight	Overweight	Obesity
Model 1				
No sarcopenia	1.00 (reference) n = 547 (8% with MCI)	2.02 (0.66, 6.22) n = 30 (17% with MCI)	0.51 (0.31, 0.84) n = 671 (4% with MCI)	0.86 (0.51, 1.45) n = 400 (6% with MCI)
Sarcopenia	1.82 (1.27, 2.60) n = 1,163 (22% with MCI)	1.62 (0.94, 2.81) n = 130 (25% with MCI)	1.21 (0.84, 1.73) n = 1,320 (15% with MCI)	1.42 (0.96, 2.09) n = 761 (15% with MCI)
Model 2				
No sarcopenia	1.00 (reference) n = 537 (8% with MCI)	1.81 (0.57, 5.80) n = 28 (28% with MCI)	0.58 (0.34, 0.99) n = 660 (4% with MCI)	1.01 (0.58, 1.74) n = 399 (6% with MCI)
Sarcopenia	1.84 (1.25, 2.71) n = 1,134 (22% with MCI)	1.50 (0.82, 2.74) n = 125 (24% with MCI)	1.23 (0.83, 1.83) n = 1,283 (14% with MCI)	1.62 (1.07, 2.48) n = 745 (15% with MCI)

Values are odds ratios (95% confidence intervals). Mild cognitive impairment (MCI) was defined as a score of 12 or less out of 19 on the shorter version of the mini-mental state examination used in SABE Colombia, which is a valid screening tool. Sarcopenia was defined as low grip strength (< 27 kg in men and < 16 kg in women) or slow chair stands (> 15 s in men and women). Model 1 was adjusted for age and sex (n = 5,022). Model 2 was adjusted for age, sex, height, education, income, civil status, smoking, and alcohol drinking (n = 4,911). N is number.

TABLE 5 Combined associations of body mass index and sarcopenia with mild cognitive impairment, where sarcopenia is defined using low grip strength reference values from Colombia.

	Body mass index			
	Normal	Underweight	Overweight	Obesity
Model 1				
No sarcopenia	1.00 (reference) n = 723 (12% with MCI)	1.96 (0.85, 4.53) n = 46 (20% with MCI)	0.62 (0.43, 0.90) n = 722 (7% with MCI)	0.82 (0.48, 1.40) n = 249 (8% with MCI)
Sarcopenia	2.15 (1.48, 3.11) n = 987 (22% with MCI)	1.76 (0.98, 3.12) n = 114 (25% with MCI)	1.39 (0.95, 2.05) n = 1,269 (13% with MCI)	1.69 (1.12, 2.56) n = 912 (13% with MCI)
Model 2				
No sarcopenia	1.00 (reference) n = 708 (12% with MCI)	1.64 (0.67, 4.02) n = 46 (20% with MCI)	0.72 (0.48, 1.09) n = 708 (7% with MCI)	1.04 (0.58, 1.85) n = 247 (7% with MCI)
Sarcopenia	2.25 (1.51, 3.35) n = 963 (22% with MCI)	1.70 (0.90, 3.22) n = 107 (24% with MCI)	1.45 (0.95, 2.21) n = 1,235 (13% with MCI)	1.96 (1.25, 3.08) n = 897 (13% with MCI)

Values are odds ratios (95% confidence intervals). Mild cognitive impairment (MCI) was defined as a score of 12 or less out of 19 on the shorter version of the mini-mental state examination used in SABE Colombia, which is a valid screening tool. Sarcopenia was defined using grip strength reference values from a nationally representative survey of 1,159 adults aged 18–64 years in Colombia: < 18.5 kg in men and < 13 kg in women. Model 1 was adjusted for age and sex (n = 5,022). Model 2 was adjusted for age, sex, height, education, income, civil status, smoking, and alcohol drinking (n = 4,911). N is number.

mild cognitive impairment. We also found that sarcopenia was associated with increased risk of mild cognitive impairment, whether defined as low grip strength or slow chair stands. Sarcopenic obesity did not present a greater risk for mild cognitive impairment than sarcopenia alone. Similar results were observed when reference values from Colombia were used to set the cut-offs for grip strength. Similar results were also observed in the cross-validation models, which suggests that the results are robust. Cross-sectional studies are an important first step in epidemiology and this study could pave the way for longitudinal studies in Colombia.

It is plausible that sarcopenia is associated with increased risk of cognitive impairment. Physical exercise increases the production of brain-derived neurotrophic factor and other myokines associated with brain metabolism and memory (27). Physical exercise also improves brain vascular function and cognition (28). Conversely, sarcopenia is associated with an imbalance in the secretion of myokines and memory impairment (11). Sarcopenia is also associated with vascular dysfunction and cognitive impairment (11). It is also plausible that sarcopenic obesity presents a greater risk for cognitive impairment (10). In sarcopenic obesity, lipids accumulate in skeletal muscle and induce mitochondrial dysfunction and enhanced secretion of pro-inflammatory myokines (10). There is no consensus on the definition of sarcopenic obesity (6) and it is not clear whether sarcopenia or obesity drives the pathology of the condition (10).

Relatively small cross-sectional studies of some 350 older adults in New York in the US (9) and some 1,600 older adults in Tokyo in Japan (8) suggest that sarcopenic obesity presents a greater risk for cognitive impairment. Our relatively large cross-sectional study is in agreement with a recent longitudinal study in showing that sarcopenia is the major predictor of cognitive function in older adults, not obesity (29). Batsis et al. followed 5,822 older adults in the US for 8 years (29). Compared with those without sarcopenia or obesity, the risk of impaired cognitive function was no different in obesity alone (hazard ratio: 0.98; 95% confidence interval: 0.82, 1.16), but was significantly higher in sarcopenia (hazard ratio: 1.60; 95% confidence interval: 1.42, 1.80) and sarcopenic obesity (hazard ratio: 1.20; 95% confidence interval: 1.03, 1.40) (29). Longitudinal studies in Europe and North America also suggest that overweight and obesity are risk factors for dementia in midlife, but not in later life (30, 31). These longitudinal studies in Europe and North America suggest that it is the trajectory of change rather than the current BMI that is most useful in identifying those who are more likely to develop mild cognitive impairment or dementia (31). Indeed, BMI may fall around 6–10 years before diagnosis (31). We are not aware of any such longitudinal studies in Colombia or elsewhere in Latin America.

Debates about cut-off points have hampered research in the field of sarcopenia because of a lack of study consistency (6). The EWGSOP2 uses low muscle strength as the primary parameter of sarcopenia and recommends cut-offs for grip strength and chair stands to increase the harmonization of sarcopenia studies (6). The EWGSOP2 acknowledges that its recommendations focus on European populations and suggests that local reference values be used to set cut-offs when available (6). The EWGSOP2 cut-offs and local reference values were used in the present study. The prevalence of sarcopenia was higher when reference values for Colombian adults were used to define low grip strength; however, any reclassification did not affect associations of BMI and sarcopenia with mild cognitive impairment. The Colombian Ministry of Sport provides free exercise classes to older adults in various towns and cities throughout the country (32) and it would have important implications for policymakers and members of the public if sarcopenia were a stronger predictor of cognitive impairment than obesity. Weight loss is difficult to achieve (33), but physical exercise and a healthy diet may slow or reverse sarcopenia in older adults (34, 35).

This study has some strengths and limitations. There is an urgent need for more evidence from Latin America about modifiable risk factors for cognitive impairment (3). The main strength of the present analysis is that we used data from the largest nationally representative study of older adults in Colombia to investigate associations of BMI and sarcopenia with mild cognitive impairment. It is noteworthy that we used EWGSOP2 cut-offs and local reference values to define sarcopenia. It is also noteworthy that we used cross-validation to test the robustness of the models. The main limitation is the cross-sectional design. Being underweight was associated with increased risk of mild cognitive impairment in the present study; however, there were few too participants with underweight to allow us to fully understand associations of underweight and sarcopenia with mild cognitive impairment. Any association between underweight and cognitive impairment might be explained by reverse causality, where brain pathology causes weight loss prior to the diagnosis of cognitive impairment or dementia (23). Cohort studies with long follow-up times are needed to clarify associations of BMI and sarcopenia with cognitive impairment. Some variables were self-reported and are subject to biases. The shorter version of the MMSE used in SABE Colombia is a valid screening tool (19), but it is not a clinical diagnosis of cognitive impairment. The assessment of muscle strength is a valid screening tool, but it is not a clinical diagnosis of sarcopenia (6). The prevalence of sarcopenia was higher when defined as slow chair stands than when defined as low grip strength in the present study and more research is required to determine which test of muscle strength is more strongly associated with mild cognitive impairment. The sample may have been healthier than the sub-sample and associations of BMI and sarcopenia with mild cognitive impairment may have been underestimated. Participants in the present study lived through more than 50 years of civil war and future generations may have different risk factor profiles with the implementation of the peace deal. For example, future generations may benefit from higher levels of education and may suffer from higher levels of obesity.

Conclusion

Nearly all the evidence about potentially modifiable risk factors for cognitive impairment has come from high-income countries and more evidence from low-income and middle-income countries has been called for (3). The National Survey of Health, Wellbeing and Aging in Colombia is the largest nationally representative study of older adults in Colombia. The present analysis suggests that sarcopenia is the major predictor of mild cognitive impairment in older adults in Colombia, not overweight or obesity. Sarcopenia is avoidable and more should be done to encourage physically active lifestyles and healthy diets in Colombia because the proportion of people living with dementia is predicted to increase dramatically by 2050 (1).

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The user agreement does not permit sharing the data directly. Requests to access these datasets should be directed to the Colombian Ministry of Health (repositorio@minsalud.gov.co). The original name of the study is in Spanish: Salud, Bienestar, and Envejecimiento (SABE Colombia).

Ethics statement

The studies involving human participants were reviewed and approved by the Universidad de Caldas, Colombia and Universidad del Valle, Colombia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GO'D: conceptualization, methodology, validation, formal analysis, and writing—original draft preparation. OS, PH, GM-T, CD-A, and AI: writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1011967/full#supplementary-material

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EDITED BY
Mainul Haque,
National Defence University of Malaysia, Malaysia

REVIEWED BY
Fatemeh Haidari,
Ahvaz Jundishapur University of Medical Sciences, Iran
Rahnuma Ahmad,
Medical College for Women and Hospital, Bangladesh
Kona Chowdhury,
Gonoshathaya Samaj Vittik Medical College, Bangladesh

*CORRESPONDENCE
Khadijeh Mirzaei
mirzaei_kh@tums.ac.ir

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Red, white, and processed meat consumption related to inflammatory and metabolic biomarkers among overweight and obese women

Farideh Shiraseb[1], Dorsa Hosseininasab[2], Atieh Mirzababaei[1], Reza Bagheri[3], Alexei Wong[4], Katsuhiko Suzuki[5] and Khadijeh Mirzaei[1]*

[1]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran, [2]Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran, Iran, [3]Department of Exercise Physiology, University of Isfahan, Isfahan, Iran, [4]Department of Health and Human Performance, Marymount University, Arlington, VA, United States, [5]Faculty of Sports Sciences, Waseda University, Tokorozawa, Japan

Background: Considering that a high meat intake is directly associated with obesity, it is critical to address the relationship between consuming different types of meat with inflammation and metabolism in overweight and obese cohorts. Thus, we evaluated the association between red, white, and processed meat consumption with inflammatory and metabolic biomarkers in overweight and obese women.

Methods: The current cross-sectional study was conducted on 391 overweight and obese Iranian women. Dietary intake was obtained from a food frequency questionnaire (FFQ) with 147 items. The anthropometric measurements, serum lipid profile, and inflammatory markers were measured by standard protocols. All associations were assessed utilizing one-way analysis of variance (ANOVA), analysis of covariance (ANCOVA), and linear regression models.

Results: In the adjusted model, it was established that higher intake of processed meat had a significant positive association with leptin levels (β: 0.900, 95% CI: 0.031;1.233, p = 0.015). Moreover, after considering the confounders, a significant positive association between processed meat and macrophage inflammatory protein (MCP-1) levels was observed (β: 0.304, 95% CI:0.100;1.596, p = 0.025). Positive significant associations between high-sensitivity C-reactive protein (hs-CRP) (β:0.020, 95% CI:0.000;0.050, P = 0.014) and plasminogen activator inhibitor 1 (PAI-1) (β:0.263, 95% CI:0.112;0.345, p = 0.053) and MCP-1 (β:0.490, 95% CI: 0.175;1.464, p = 0.071) levels with red meat were also shown; while there was a significant negative association between red meat and the homeostasis model assessment of insulin resistance (HOMA-IR) (β: −0.016, 95% CI: −0.022, −0.001, p = 0.033). Furthermore, a significant negative association were established following confounding adjustment between Galectin-3 (Gal-3) (β: −0.110, 95% CI: −0.271;0.000, p = 0.044), MCP-1 (β: −1.933, 95% CI: −3.721;0.192, p = 0.022) and Homeostatic

Model Assessment for Insulin Resistance (HOMA-IR) (β: −0.011, 95% CI: −0.020,0.000, $p = 0.070$) levels with high adherence of white meat intake. In contrast, a significant marginally positive association between PAI-1 levels and high adherence to white meat intake (β: −0.340, 95% CI: −0.751;0.050, $p = 0.070$) has been shown.

Conclusions: Higher red and processed meat consumption were positively associated with inflammatory and metabolic markers in overweight and obese women. In contrast, negative relationships between high adherence to white meat and various inflammatory and metabolic parameters were established. Further studies are needed to confirm the causality of these associations and potential mediating pathways.

KEYWORDS

red meat, white meat, inflammatory markers, processed meat, obesity, women

Introduction

Global obesity rates are rising (1). Currently, more than 26% of Iranian adults are obese, however, Iranian women are more affected than males (57 vs. 22%) (2). Obesity is defined as a genetically based chronic multifactorial condition that is brought on by the buildup of extra fat tissue (3). Numerous serious comorbidities are caused by it, including insulin resistance, hypertension, diabetes mellitus, and low-grade inflammation (1, 4–6). Excess adipose tissue produces and secretes an increasing number of inflammatory mediators into the systemic circulation, enhancing the inflammatory profile (7, 8). Among these are acute-phase proteins, including plasminogen activator inhibitor 1 (PAI-1), and classic peptide mediators of inflammation such as interleukin 1 (IL-1) (9, 10), macrophage inflammatory protein (MCP-1) (11), transforming growth factor (TGF-b) (12), and high-sensitivity C-reactive protein (hs-CRP) (13). Moreover, increasing abdominal fat mass is associated with insulin resistance as one inflammation indicator (14) and ablation of Galectin-3 (Gal-3), which hastens lipid-induced atherogenesis and plays an essential role in cell-cell adhesion, cell-matrix interactions, macrophage activation, metastasis, and apoptosis (15, 16).

Various factors are directly related to causing obesity and as a result, causing inflammation or changes in inflammatory levels, but undoubtedly one of the most important factors is food intake, which is, directly and indirectly, effective in changing inflammatory levels (17, 18). The food sources received from the main food groups, especially protein intake from different sources, are effective in causing obesity and consequently inflammation, or directly in the occurrence of inflammation (19–21). One of the food items that have conflicting and challenging results in studies on inflammation and metabolic diseases is getting protein from different food sources, especially red and processed meat (22–24). Research to date indicates that a high meat intake is directly associated with obesity. Indeed, inflammation and insulin resistance related to excess adipose tissue have been proposed to explain the documented link between red meat consumption and metabolic disorders in obese cohorts (22–24). This relationship may be explained by the negative effects of saturated fat, animal protein, and red meat's high iron content, mainly heme iron, saturated fatty acid (SFA) that has been linked to increased adiposity,

Abbreviations: FFQ, food frequency questionnaire; ANOVA, one-way analysis of variance; ANCOVA, analysis of covariance; MCP-1, macrophage inflammatory protein; hs-CRP, high-sensitivity C-reactive protein; PAI-1, plasminogen activator inhibitor 1; HOMA-IR, homeostasis model assessment of insulin resistance; Gal-3, Galectin-3; TGF-b, transforming growth factor; IL-1, interleukin 1; SFA, saturated fatty acid; IL-6, interleukin 6; BMI, body mass index; TUMS, Tehran University of Medical Sciences; FFQ, food frequency questionnaire; WC, waist circumference; TG, triglyceride; HC, hip circumference; NC, neck circumference; WHR, waist-to-hip ratio; WHtR, weight-to-height ratio; SMM, skeletal muscle mass; FFM, fat-free mass; BFM, body fat mass; BMC, bone mass content; SLM, soft lean mass; FMI, fat mass index; FFMI, fat-free mass index; FBS, fasting blood sugar; Chole, total cholesterol; LDL-c, Low-density lipoprotein cholesterol; HDL-c, High-density lipoprotein cholesterol; SGPT, Serum glutamic pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase; SBP, Systolic blood pressure; DBP, diastolic blood pressure; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalents; β, beta; CI, Confidence Interval; CVD, cardiovascular disease; PAH, polycyclic aromatic hydrocarbons; TNF-a, necrosis factor-alpha; GOF, goodness of fit; R2, R squared; AGEs, advanced glycation end products; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; DHN-MA, Mercapturic acid of dihydroxynonane; HNE, hydroxynonenal; MUFA, monounsaturated fatty acids; SFA, saturated fatty acid; EPA, eicosapentaenoic acid; DHA, Docosahexaenoic acid.

inflammation, and insulin resistance (IR) (25–27). On the other hand, several studies have shown that fish and its components favor inflammatory markers (28–30). For instance, eating white meat improves interleukin 6 (IL-6) synthesis, affecting hs-CRP development in the liver (21). Despite these findings, investigations evaluating the relationship between consuming different types of meat and inflammatory and metabolic markers in overweight and obese cohorts are scarce. Addressing these relationships in overweight and obese women is particularly important, as they are more likely to develop inflammatory and metabolic abnormalities than their male counterparts (31, 32).

According to an explanation and despite the existing controversies regarding the relationship between the consumption of red and processed meat with inflammatory factors needed. In addition, this issue has not been investigated sufficiently in Iran, especially in obese and overweight women, so with a view more comprehensively, the intake of red, processed, and white meat was examined in the present study. Therefore, we evaluated the relationship between red, white, and processed meat consumption with inflammatory and metabolic biomarkers in overweight and obese women.

Materials and methods

Participants

In this cross-sectional study recruited, a total of 391 healthy overweight (BMI = 25–29.9), and obese (BMI $\geq$ 30) women, aged 18–56 years old that had been referred to health centers in Tehran. The exclusion criteria were as follows: smoking; chronic disease histories such as the history of hypertension, cardiovascular diseases, diabetes mellitus, impaired renal and liver function inflammatory diseases, cancer, thyroid disease, regular use of medicine (including oral contraceptive pill), alcohol use, supplement consumption (vitamins and minerals and both) pregnancy, lactation period, and menopause, people who had been on an arbitrary special diet plan and anyone whose body weight had changed noticeably during the previous year, participated in sports, if their total calorie consumption did not fall between 800 and 4,200 (17,556–3,344 kJ) (33), and individuals with weight fluctuations in the past year were also excluded from the study. Before participating in the study, each participant signed a written informed consent form. The study was approved by the Ethical Committee of the Tehran University of Medical Sciences (TUMS) and performed according to the ethical standards of the Declaration of Helsinki (IR.TUMS.VCR.REC.1395.1597).

Study design

In this descriptive cross-sectional study, sampling and data collection were completed in 2018. Multi-stage random cluster sampling was performed among health centers affiliated with the TUMS to select certain regions from among all the regions of the city; 20 clusters were selected. Two visits were conducted: in the first visit, a demographic questionnaire, food frequency questionnaire (FFQ), blood pressure as well as anthropometric and body composition measurements were performed. In the second visit, blood samples were taken from individuals. All measurements were performed in the Nutrition and Biochemistry Laboratory of the School of Nutritional and Dietetics at TUMS.

Dietary assessments

Dietitians assessed dietary intake using a validated 147-item semi-quantitative food frequency questionnaire (FFQ) by face-to-face interview (34, 35). Individuals reported the frequency of each food item consumed in the past year, which was consequently converted to grams per day using household measures (36). Energy and dietary nutrients were calculated using the Iranian Food Composition Table and NUTRITIONIST IV (version 7.0; N-Squared Computing, Salem, OR). The current study is based on the consumption of three different types of meat extracted from the FFQ as gram/day: (1) the red meat category was defined as the sum of red (beef, lamb, sheep) and organ meats (beef liver, kidney, tongue, and heart); (2) white meat consisted of fish and poultry, such as chicken and turkey; and (3) processed meats included sausages, hamburger, Kalbas, Mortadella, and canned fish. All kinds of meat intake were adjusted by energy intake by residual method.

Anthropometric and body composition assessment

The anthropometrics and body composition examination were conducted between 8 and 9 a.m., following a 12-h overnight fast. Participants also abstained from unusual physical activity for 72 h prior to the assessments. Weight was measured using a digital scale (Seca, Hamburg, Germany) in light clothing and without shoes with a precision near 0.1 kg, and stature was measured *via* a stadiometer with an accuracy close to 0.1 cm. Hip circumference (HC) and waist circumference (WC) were measured separately in the smallest and largest girth, respectively, with accuracy nearest to 0.1 cm. A multi-frequency bioelectrical impedance analyzer (BIA) called the InBody 770 Scanner was used to measure body composition (Inbody Co., Seoul, Korea). Using electrical impulses from the hands and feet, this device measures the resistance of bodily tissues. Participants were instructed to thoroughly urinate (void) and refrain from drinking water 30 min before the test. Participants were instructed to remove any metal objects, including tools, jewelry, coats, jackets, and shoes, following the manufacturer's instructions (25). They were also requested to remove their socks before the device was placed on them, to boost accuracy. Our BIA in our lab has a test-retest reliability of r = 0.98.

BMI, skeletal muscle mass (SMM), fat-free mass (FFM), body fat mass (BFM), bone mass content (BMC), soft lean mass (SLM), visceral fat level (cm), trunk fat, waist to hip ratio (WHR), fat mass index (FMI), fat-free mass index (FFMI) as body composition components were established with a BIA.

Biochemical assessment

Blood samples were taken after a 10–12 h fast, and serum was stored at −80 °C. All tests were analyzed according to the manufacturer's guidelines. The glucose oxidase method was utilized for fasting blood sugar (FBS) appraisal, and the affront level was measured by an enzyme-linked immunosorbent measure (ELISA) unit (Human affront ELISA unit, DRG Pharmaceuticals, GmbH, Germany). Triglyceride (TG), total cholesterol (Chole), Low-density lipoprotein cholesterol (LDL-c), and High-density lipoprotein cholesterol (HDL-c) were measured by related packs (Pars Azemun, Iran). Serum glutamic pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) were evaluated utilizing the Universal League of Clinical Chemistry and Research facility Medication standardization. The HOMA-IR was assessed as the item of fasting glucose and affront level isolated by 22.5 with a molar unit (mmol/L) (37). The Enzyme-Linked Immunosorbent Assays (ELISA) technique was used to evaluate the levels of inflammatory biomarkers (such as hs-CRP and IL-1b), Gal-3. (R&D Systems, Minneapolis, MN), MCP-1 (Zell Bio GmbH, ULM, Germany), TGF-β (HUMAN TGF-BETA 1 Quantikine ELIZA kit R&D System-USA), PA-I (Human PAI-1*96 T ELIZA kit Crystal Company) and serum leptin concentrations (Mediagnost, Reutlingen, Germany). The inter-assay and intra-assay variability for all tests were <12 and 10%, respectively.

Blood pressure

Systolic and diastolic blood pressure (SBP, DBP) were assessed after 15 min of rest using an automatic sphygmomanometer (OMRON, Germany). Three measurements at 1-min intervals were taken and averaged.

Demographic variables and physical activity

A demographic questionnaire was utilized to assess quality characteristics such as education, employment, marital status, economic levels, and family history of obesity. The validated International Physical Activity Questionnaire (IPAQ) was converted to Minutes per week using Metabolic Equivalents (MET-min/week) to determine physical activity criteria (38).

Statistical analysis

The sample size was computed according to the following formula: $n = [(Z\ 1\text{-}\alpha + Z1\text{-}\beta) \times (\sqrt{1\text{-}\ r^2})/r)^2]$ which $r = 0.21$, $\beta = 0.90$ and $\alpha = 0.05$. The evaluation of the histogram curve and the Kolmogorov-Smirnov test was used to ensure that the data were distributed normally ($p > 0.05$). In addition according to the central limit theorem, all dependent variables are taken into account using the normal distribution (39, 40). The mean and standard deviation were used to describe quantitative variables, whereas number and percent (%) were used to represent categorical variables. One-way analysis of variance (ANOVA) was validated for assessing the mean difference of quantitative variables across red, processed, and white meat' medians. Relationships between inflammatory indicators were investigated, and analysis of covariance (ANCOVA) was employed to control the effect of confounders in 2 models. The Chi-square (χ^2) test was used to examine categorical variables. Three models used linear regression to control for confounders and covariates points and validated associations between red, processed, and white meat consumption and inflammatory markers. This analysis was present by beta (β) and 95% Confidence Interval (CI) and goodness of fit (GOF) of r squared (R^2). All linear regression analysis's assumptions and concerns, including normality, the normality of residual error, linearity, homoscedasticity, and collinearity, were evaluated. IBM SPSS version 26.0 was used to conduct statistical analyses (SPSS, Chicago, IL, USA). The significance level was set at 2-sided $P < 0.05$ and $P = 0.05$–0.07, considered marginally significant.

Results

Study population characteristics

The present study was conducted on 391 obese and overweight Iranian women, of which 27% were single, 46.8% had a college education, and 27.3% had good economic status. The means and standard deviation (SD) of age, weight, BMI and WHR, FFM, and BFM of individuals were 36.681 (9.150) years, 80.320 (11.065) kg, 31.011 (3.920) kg/m^2, 1.162 (4.575), 46.523 (5.690) kg and 34.804 (8.800) kg, respectively. Moreover, the mean intake of red meat was 40.161 (19.660) gr/day, while white and processed meat had mean intakes of 59.300 (40.421) gr/day and17.896 (14.325) gr, respectively.

Population characteristics among medians of red, white, and processed meat consumption

General characteristics of participants, such as body composition, biochemical assessment, and others among lower vs. higher than the median of processed meat, red meat, and white meat intake, are presented in Table 1. *P*-values for all variables were reported before the adjustment in the crude model by ANOVA, and after adjustment with potential confounders, including age, BMI, physical activity, and energy intake (Table 1).

General characteristics of participants among processed meat intake categories

Among processed meat categories, there was a significant mean difference for SBP ($p < 0.001$). But, significance was lost after adjusting for potential confounders ($p = 0.130$). In the adjusted model, in body composition variables, there were significant mean differences for SMM ($p = 0.054$), FFM ($p = 0.030$), SLM ($p = 0.022$), and trunk fat ($p = 0.041$), FMI ($p = 0.062$) and in categorical variables; economic status ($p = 0.011$) (Table 1).

General characteristics of participants among red meat intake categories

There was a significant difference in economic status ($p = 0.0003$), education level ($p = 0.002$), and housing ownership ($p = 0.010$) before and after adjustment Table 1. Moreover, the crude model showed a marginally significant difference between groups for BFM ($p = 0.071$). High adherence to red meat was associated with lower levels of TG ($p = 0.023$) and WC ($p = 0.034$). No significant differences were noted in other variables ($p > 0.05$) (Table 1).

General characteristics of participants among white meat intake categories

After adjusting for potential confounders, there was a significant marginal difference in BMI ($p = 0.072$). There were also significant differences in economic status ($p = 0.002$), education level ($p = 0.001$), and housing ownership ($p = 0.016$). Women with a higher intake of white meat had marginally significantly higher mean HDL ($p = 0.070$), total cholesterol ($p = 0.030$), and lowered FBS ($p = 0.041$), but these associations were not present after controlling confounders (Table 1).

Dietary intake of the study population across intakes of red, white, and processed meat

The dietary intake of the participants across two groups to intakes of red meat, white meat, and processed meat is shown in Table 2. The mean energy intake in low and high-intake processed meat was 2,763.591 vs. 2,447.06 kcal/day, respectively, and was statistically significant ($p = 0.002$). Additionally, the intake of energy was high in low intake white meat, 2,695 vs. 2,495.27 gr with ($p = 0.053$). After adjustment for confounders (including age, BMI, physical activity, and total energy intake) mean of red meat, protein, vegetables, saturated fatty acid (SFA), eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), zinc, copper, potassium, vitamins of C, A, B3, B6, and B12 consumption was higher in the upper median group of red meat ($p \leq 0.05$). In contrast, intake of total fiber, linoleic acid, polyunsaturated fatty acids (PUFA), and vitamin E were low in participants with high red meat intake ($p \leq 0.05$). Our results also showed that sodium and vitamin B12 were significantly higher ($p \leq 0.05$) in subjects with increased consumption of processed meat compared to those with low intake. Protein, vegetables, EPA, DHA, zinc, calcium, potassium, and vitamins of A, B3, B6, B2, and B12 consumption was greater in those with high white meat intake ($p < 0.05$). On the other hand, fat, monounsaturated fatty acids (MUFA), linoleic acid, PUFA, Manganese, and vitamin E consumption was low in participants with high white meat intake ($p \leq 0.05$).

Inflammatory biomarkers among medians of red, white, and processed meat

There was no significant difference in PAI-1, Gal-3, hs-CRP, or MCP-1 between low and high processed meat intake categories before adjustment ($p > 0.05$), but in model 2 that adjusted for potential confounder, mean PAI-1 ($p = 0.052$), Gal-3 ($p = 0.054$), hs-CRP ($p = 0.050$), MCP-1 ($p = 0.046$) was higher in a participant with high adherence of proceeded meat, Table 3. The mean of HOMA-IR ($p = 0.045$) and IL1b ($p = 0.071$) was low in women with a high intake of red meat in models 1 and 2. However, in the crude model mean of HOMA-IR was high in subjects with a high white meat intake ($p = 0.024$), but in model 2 mean of its index was low in subjects with a high intake of white meat with no significance ($p = 0.610$). The mean of leptin was higher in those with a low intake of white meat in the crude model ($p = 0.882$); after adjustment, this association remained significant ($p = 0.024$), (Table 3).

Association between red, white as well as processed meat and inflammatory biomarkers

In the crude model, there was a significant association between HOMA-IR and processed meat (β: 0.410, 95% CI: 0.070;0.750, $p = 0.011$), but after adjusting for potential confounders, in model 3 this association disappears (β: −0.007,

TABLE 1 Study participant characteristics between medians of processed meat, red meat, and white meat (g/d) in 391 obese and overweight women.

Variables	Processed meat median		*P*-value	*P*-value†	Red meat median		*P*-value	*P*- value†	White meat median		*P*-value	*P*-value†
	Low (<19.82)	High (>19.83)			Low (<36.46)	High (>36.47)			Low (<49.56)	High (>49.57)		
Age (years)	34.401 ± 0.856	36.150 ± 0.874	0.094	0.841	36.930 ± 0.774	35.400 ± 0.781	0.102	0.181	36.400 ± 0.812	36.001 ± 0.734	0.255	0.726
Physical activity (MET-minutes/week)	1,081.961 ± 149.235	896.100 ± 153.414	0.681	0.396	1,000.751 ± 191.942	1,361.091 ± 195.476	0.212	0.200	1,060.001 ± 201.422	1,273.274 ± 181.101	0.725	0.440
Anthropometric variables												
Weight (kg)	80.337 ± 0.692	78.035 ± 0.682	0.405	**0.024**	79.321 ± 0.677	78.947 ± 0.716	0.101	0.706	78.958 ± 0.688	79.322 ± 0.685	0.752	0.706
Height (cm)	162.062 ± 0.645	160.255 ± 0.624	0.650	**0.050**	161.331 ± 0.616	160.997 ± 0.643	0.851	0.701	161.041 ± 0.624	161.307 ± 0.626	0.186	0.770
HC (cm)	105.361 ± 0.224	105.085 ± 0.215	0.355	0.397	105.120 ± 0.216	105.271 ± 0.220	0.094	0.648	104.988 ± 0.214	105.400 ± 0.210	0.730	0.160
WC (cm)	98.102 ± 0.520	97.362 ± 0.511	0.590	0.321	99.325 ± 0.374	98.182 ± 0.372	0.112	**0.034**	97.950 ± 0.504	97.504 ± 0.517	0.295	0.535
NC (cm)	38.265 ± 0.915	36.877 ± 0.908	0.651	0.297	37.200 ± 0.875	37.978 ± 0.926	0.752	0.545	36.855 ± 0.882	38.292 ± 0.881	0.282	0.252
BMI (kg/m^2)	30.50 ± 0.387	30.77 ± 0.398	0.395	0.634	30.868 ± 0.344	30.272 ± 0.355	0.286	0.242	30.100 ± 0.351	30.969 ± 0.326	0.112	**0.072**
Body composition												
WHR	0.931 ± 0.000	0.924 ± 0.000	0.161	0.542	0.934 ± 0.000	0.921 ± 0.000	0.302	0.215	0.930 ± 0.000	0.920 ± 0.000	0.314	0.264
WHtR	0.601 ± 0.000	0.601 ± 0.000	0.800	0.437	0.608 ± 0.000	0.605 ± 0.000	0.171	0.282	0.608 ± 0.000	0.605 ± 0.000	0.437	0.341
BFM (%)	40.687 ± 0.385	41.342 ± 0.377	0.530	0.611	40.824 ± 0.367	41.202 ± 0.386	**0.071**	0.487	41.278 ± 0.372	40.732 ± 0.376	0.664	0.315
FFM (kg)	47.325 ± 0.566	45.567 ± 0.555	0.154	**0.030**	46.644 ± 0.547	46.188 ± 0.572	0.294	0.567	46.214 ± 0.552	46.637 ± 0.550	0.861	0.603
SMM (kg)	25.954 ± 0.334	25.033 ± 0.324	0.151	**0.054**	25.600 ± 0.314	25.350 ± 0.331	0.620	0.590	25.314 ± 0.324	25.657 ± 0.326	0.843	0.460
SLM (kg)	44.615 ± 0.521	42.951 ± 0.511	0.152	**0.022**	43.977 ± 0.502	43.534 ± 0.532	0.336	0.550	43.584 ± 0.513	43.952 ± 0.517	0.691	0.612
FFMI	17.986 ± 0.112	17.722 ± 0.112	0.140	0.110	17.866 ± 0.101	17.821 ± 0.112	0.342	0.791	17.761 ± 0.100	17.932 ± 0.100	0.221	0.262
FMI	12.544 ± 0.110	12.834 ± 0.110	0.966	**0.062**	12.631 ± 0.100	12.734 ± 0.111	0.110	0.500	12.751 ± 0.114	12.612 ± 0.114	0.204	0.387
VFL (cm^2)	15.197 ± 0.201	15.191 ± 0.201	0.767	0.994	15.163 ± 0.191	15.223 ± 0.200	0.241	0.837	15.334 ± 0.190	15.0415 ± 0.19	0.874	0.301
Trunk fat (%)	303.765 ± 2.340	309.651 ± 2.304	0.794	**0.041**	306.467 ± 2.242	306.674 ± 2.372	0.154	0.941	308.303 ± 2.272	304.793 ± 2.272	0.160	0.281
BMC (kg)	2.641 ± 0.024	2.584 ± 0.031	0.260	0.125	2.661 ± 0.030	2.642 ± 0.041	0.241	0.781	2.633 ± 0.031	2.671 ± 0.031	0.642	0.491

(Continued)

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TABLE 1 (Continued)

Variables	Processed meat median		*P*-value	*P*-value†	Red meat median		*P*-value	*P*- value†	White meat median		*P*-value	*P*-value†
	Low (<19.82)	High (>19.83)			Low (<36.46)	High (>36.47)			Low (<49.56)	High (>49.57)		
Biochemical components												
TG (mg/dl)	112.662 ± 7.061	120.932 ± 7.502	0.560	0.441	123.361 ± 5.860	104.542 ± 5.900	0.64	**0.023**	110.231 ± 6.870	117.292 ± 5.823	0.587	0.903
TC (mg/dl)	176.521 ± 3.501	176.911 ± 3.720	0.584	0.943	182.141 ± 3.450	182.231 ± 3.472	0.971	0.980	180.872 ± 3.943	181.597 ± 3.348	**0.030**	0.701
HDL (mg/dl)	47.564 ± 1.114	45.932 ± 1.174	0.253	0.332	46.571 ± 1.092	46.955 ± 1.102	0.511	0.802	44.604 ± 1.220	48.111 ± 1.032	**0.070**	0.152
LDL (mg/dl)	96.036 ± 2.495	96.221 ± 2.652	0.481	0.962	92.981 ± 2.342	93.592 ± 2.351	0.800	0.851	91.301 ± 2.612	94.582 ± 2.211	0.4264	0.57
FBS (mg/dl)	85.682 ± 1.055	87.832 ± 1.112	0.662	0.172	87.362 ± 0.932	86.964 ± 0.930	0.222	0.761	86.864 ± 1.005	87.241 ± 0.852	**0.041**	0.272
Insulin (mIU/ ml)	1.200 ± 0.022	1.194 ± 0.022	0.500	0.804	1.236 ± 0.025	1.183 ± 0.025	0.191	0.131	1.200 ± 0.021	1.191 ± 0.022	0.145	0.731
GOT (µKat/L)	17.951 ± 0.781	16.442 ± 0.8320	0.320	0.201	18.242 ± 0.771	17.421 ± 0.783	0.602	0.4611	17.971 ± 0.672	17.134 ± 0.671	0.362	0.590
GPT (µKat/L)	18.662 ± 1.421	17.881 ± 1.510	0.752	0.722	19.970 ± 1.375	17.765 ± 1.381	0.411	0.260	18.862 ± 1.401	17.861 ± 1.190	0.562	0.922
SBP (mmHg)	112.845 ± 1.532	109.340 ± 1.090	**<0.001**	0.130	110.892 ± 1.372	111.9303 ± 1.38	0.952	0.596	111.822 ± 1.586	110.660 ± 1.341	0.531	0.213
DBP (mmHg)	78.310 ± 1.090	77.380 ± 1.150	0.150	0.574	77.431 ± 0.975	77.485 ± 0.972	0.481	0.960	78.440 ± 1.091	76.9110 ± 0.92	0.510	0.452
Categorical variables												
Economic status												
Low level	55 (77.5)	16 (22.5)	**0.043**	**0.011**	58 (65.9)	30 (34.1)	**0.001**	**0.003**	50 (56.8)	38 (43.2)	**0.012**	**0.022**
Moderate level	105 (66.5)	33.5 (53)			86 (47.3)	96 (52.7)			92 (50.5)	90 (49.5)		
High level	55 (59.13)	38 (40.9)			42 (39.3)	65 (60.7)			39 (36.4)	68 (63.6)		
Education level												
Illiterate	1 (50)	1 (50)	0.941	0.782	2 (50)	2 (50)	**0.009**	**0.002**	2 (50)	2 (50)	**0.003**	**0.001**
Under diploma	17 (48.6)	18 (51.4)			34 (69.4)	15 (30.6)			30 (61.2)	19 (38.8)		
Diploma	43 (47.8)	47 (52.2)			78 (51.7)	73 (48.3)			83 (55)	68 (45)		
Master and higher	54 (51.9)	50 (48.1)			80 (43.2)	105 (56.8)			70 (37.8)	115 (62.2)		
Marital status											**0.05**	0.08
Single	25 (50)	25 (50)	0.971	0.823	52 (48.1)	56 (51.9)	0.675	0.425	43 (39.8)	65 (60.2)		
Married	90 (49.7)	91 (50.3)			142 (50.5)	139 (49.5)			142 (50.5)	139 (49.5)		
Housing ownership												
Owner	73 (66.4)	37 (33.6)	0.952	0.725	79 (58.5)	56 (41.5)	**0.015**	**0.010**	76 (56.3)	59 (43.7)	**0.041**	**0.016**
Others	142 (66.7)	71 (33.3)			110 (44.9)	135 (55.1)			112 (45.7)	133 (54.3)		

HC, Hip circumference; FBS, Fasting blood sugar; TC, Total cholesterol; TG, Triglyceride; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; hs-CRP, High-sensitivity C-reactive protein; Il-1β, Interleukin-1β; TAC, Total antioxidant capacity; BMI, Body mass index; BFM, Body fat mass; FFM, Fat-free mass; FFMI, Fat-free mass index; FMI, Fat mass index; WC, Waist circumference; NC, neck circumference; WHR, Waist hip ratio; VFL, Visceral fat level.

Values are mean ± SD for crude model and mean ± SE for adjusted model and qualitative variables are presented as n (%).

All variables adjusted with age, energy intake, physical activity, BMI. BMI consider as collinear variable for body composition and anthropometric measurements.

The crude p-value was obtained from one-way analysis of variance (ANOVA).

† Adjust p-value obtained from an analysis of covariance (ANCOVA).

$P < 0.05$ consider as significant, $P = 0.05–0.07$ consider as marginally significant.

Bold values means significant p-value $P < 0.05$.

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TABLE 2 Dietary intakes of study population between medians of processed meat, red meat, and white meat in 391 obese and overweight women.

Variables	Processed meat median		*p*-value†	Red meat median		*p*-value†	White meat median		*p*-value†
	Low (<19.82)	High (>19.83)		Low (<36.46)	High (>36.47)		Low (<31.02)	High (>31.03)	
	Mean ± SD			Mean ± SD			Mean ± SD		
Food groups									
Cereal (g/d)	448.280 ± 18.741	417.501 ± 18.744	0.330	433.401 ± 17.332	427.391 ± 18.180	0.261	435.962 ± 18.321	425.681 ± 17.310	0.272
Whole grain (g/d)	106.130 ± 5.842	91.011 ± 5.845	0.370	105.485 ± 5.264	92.812 ± 5.520	0.120	95.020 ± 5.587	483.766 ± 18.403	0.164
Refined grain (g/d)	490.500 ± 19.628	474.842 ± 19.623	0.544	481.190 ± 16.422	468.492 ± 17.435	0.602	491.751 ± 18.401	473.090 ± 17.383	0.127
Fruits (g/d)	680.850 ± 30.234	622.445 ± 30.231	0.332	659.170 ± 26.221	677.145 ± 27.504	0.376	641.784 ± 27.700	681.055 ± 26.164	0.162
Vegetables (g/d)	470.861 ± 22.652	378.493 ± 22.654	0.167	408.146 ± 20.990	473.478 ± 22.022	**0.005**	389.584 ± 21.977	483.762 ± 20.762	**0.001**
Legumes (g/d)	106.035 ± 4.361	99.832 ± 4.361	0.29	102.941 ± 3.693	100.970 ± 3.874	0.722	102.476 ± 3.900	101.585 ± 3.694	0.570
Nuts (g/d)	37.271 ± 1.240	34.864 ± 1.874	0.284	13.220 ± 1.432	15.651 ± 1.522	0.268	14.700 ± 1.505	14.103 ± 1.465	0.775
Dairy (g/d)	346.560 ± 22.191	333.133 ± 22.191	**0.04**	327.064 ± 22.330	346.383 ± 23.001	0.550	313.610 ± 24.647	360.154 ± 23.684	0.173
Eggs (g/d)	26.501 ± 1.171	25.634 ± 1.760	0.680	21.011 ± 1.352	21.306 ± 1.431	0.882	26.099 ± 1.384	26.190 ± 1.341	0.885
White Meat (g/d)	64.555 ± 4.360	74.456 ± 6.570	0.702	40.564 ± 4.789	54.003 ± 5.075	0.080	35.402 ± 4.113	87.905 ± 3.987	**<0.001**
Red meat (g/d)	23.290 ± 1.450	21.032 ± 2.182	0.397	9.261 ± 1.070	33.55 ± 1.144	**<0.001**	36.790 ± 1.695	41.933 ± 1.642	**0.050**
Processed meat (g/d)	4.351 ± 0.974	26.635 ± 1.466	**0.001**	10.987 ± 1.536	11.433 ± 1.631	0.845	17.237 ± 1.570	18.881 ± 1.523	0.430
Energy and macronutrients									
Energy (kcal/d)	2,763.590 ± 71.711	2,447.060 ± 71.714	**0.002**	2,644.850 ± 66.642	2,522.055 ± 68.653	0.201	2,695.801 ± 74.656	2,495.270 ± 71.751	**0.053**
Carbohydrates (g/d)	370.852 ± 42.570	330.475 ± 46.580	0.092	375.291 ± 4.268	367.676 ± 4.475	0.560	369.344 ± 4.985	366.442 ± 4.838	0.634
Fat (g/d)	99.930 ± 0.515	112.695 ± 0.395	0.264	94.150 ± 1.822	93.864 ± 1.910	0.535	98.29 ± 2.1443	91.471 ± 2.084	**0.030**
protein (g/d)	92.001 ± 0.212	93.284 ± 0.166	0.327	86.300 ± 1.543	92.826 ± 1.614	**0.002**	81.420 ± 1.665	97.835 ± 1.610	**<0.001**
Total fiber (g/d)	45.930 ± 1.184	42.451 ± 1.776	0.101	47.49 ± 1.432	42.18 ± 1.430	**0.008**	44.68 ± 1.435	45.02 ± 1.398	0.917
MUFA (g/d)	31.252 ± 0.814	33.020 ± 1.211	0.222	32.565 ± 0.933	30.921 ± 0.995	0.233	33.360 ± 0.942	30.372 ± 0.919	**0.032**
PUFA (g/d)	20.06 ± 0.690	21.200 ± 1.034	0.364	22.200 ± 0.774	18.400 ± 0.821	**0.001**	22.173 ± 0.791	18.715 ± 0.790	**0.004**
SFA (g/d)	27.615 ± 0.685	28.789 ± 1.037	0.340	26.961 ± 0.782	29.296 ± 0.837	**0.044**	28.195 ± 0.844	28.000 ± 0.000	0.981
TFA (g/d)	0.001 ± 0.000	0.001 ± 0.000	0.262	0.001 ± 0.000	0.001 ± 0.000	0.531	98.07 ± 2.194	91.350 ± 2.134	**0.064**
Linolenic acid (g/d)	1.22 ± 0.041	1.184 ± 0.076	0.684	1.197 ± 0.052	1.231 ± 0.064	0.650	1.243 ± 0.055	1.187 ± 0.054	**<0.001**
Linoleic acid (g/d)	17.313 ± 0.681	18.440 ± 1.032	0.366	19.633 ± 0.762	15.440 ± 0.811	**<0.001**	19.931 ± 0.794	15.510 ± 0.773	0.420
EPA (g/d)	0.035 ± 0.000	0.034 ± 0.000	0.860	0.022 ± 0.000	0.041 ± 0.000	**0.016**	0.010 ± 0.000	0.051 ± 0.000	**<0.001**
DHA (g/d)	0.110 ± 0.010	0.129 ± 0.015	0.585	0.093 ± 0.010	0.13 ± 0.011	**0.015**	0.053 ± 0.012	0.170 ± 0.015	**<0.001**
Micronutrients									
Iron (mg/d)	18.880 ± 1.521	18.14 ± 0.36	0.090	18.544 ± 0.271	18.776 ± 0.293	0.581	18.484 ± 0.291	18.844 ± 0.282	0.451
Zinc (mg/d)	12.910 ± 0.184	12.866 ± 0.274	0.891	12.286 ± 0.202	13.584 ± 0.217	**<0.001**	12.154 ± 0.2152	13.280 ± 0.210	**0.011**
Copper (mg/d)	2.00 ± 0.035	1.94 ± 0.044	0.295	1.940 ± 0.031	2.041 ± 0.034	**0.046**	1.950 ± 0.034	2.021 ± 0.035	0.204
Calcium (mg/d)	1,162.161 ± 32.742	1,172.45 ± 26.406	0.834	1,166.026 ± 30.483	1,164.521 ± 32.34	0.970	1,111.252 ± 30.720	1,224.595 ± 29.775	**0.015**
Magnesium (mg/d)	462.410 ± 6.674	446.394 ± 10.055	0.185	450.163 ± 7.712	463.011 ± 8.191	0.265	448.360 ± 8.021	465.145 ± 7.775	0.165
Potassium (mEq/d)	4,264.320 ± 84.152	4,197.241 ± 126.681	0.664	4,079.702 ± 95.605	4,428.041 ± 101.455	**0.014**	4,066.015 ± 99.734	4,412.294 ± 97.071	**0.016**
Manganese (mg/d)	7.160 ± 0.155	6.634 ± 0.231	**0.061**	7.164 ± 0.185	6.824 ± 0.195	0.205	7.335 ± 0.185	6.701 ± 0.186	**0.015**
Sodium (mg/d)	4,120.562 ± 93.875	4,560.734 ± 141.312	**0.015**	4,350.365 ± 109.855	4,149.211 ± 116.558	0.214	4,226.274 ± 115.031	4,283.491 ± 111.975	0.721

(Continued)

TABLE 2 (Continued)

Variables	Processed meat median Low (<19.82) Mean ± SD	Processed meat median High (>19.83) Mean ± SD	*p*-value†	Red meat median Low (<36.46) Mean ± SD	Red meat median High (>36.47) Mean ± SD	*p*-value†	White meat median Low (<31.02) Mean ± SD	White meat median High (>31.03) Mean ± SD	*p*-value†
Vitamin C (mg/d)	185.302 ± 7.992	180.140 ± 12.031	0.721	169.271 ± 9.092	199.950 ± 9.655	**0.020**	174.865 ± 9.705	192.964 ± 9.391	0.095
Vitamin E (mg/d)	17.732 ± 0.811	18.850 ± 1.230	0.456	20.351 ± 0.912	15.521 ± 0.974	**<0.001**	20.404 ± 0.931	15.815 ± 0.904	**0.001**
Vitamin A (mg/d)	781.430 ± 29.713	760.85 ± 44.732	0.702	707.300 ± 33.542	851.30 ± 35.60	**0.004**	698.516 ± 34.612	855.571 ± 33.544	**0.001**
Thiamin (mg/d)	2.10 ± 0.034	2.07 ± 0.045	0.634	2.134 ± 0.034	2.054 ± 0.032	0.120	2.081 ± 0.035	2.114 ± 0.031	0.654
Riboflavin (mg/d)	2.16 ± 0.043	2.19 ± 0.060	0.616	2.155 ± 0.054	2.197 ± 0.056	0.551	2.060 ± 0.052	2.275 ± 0.042	**0.003**
Niacin (mg/d)	25.25 ± 0.547	26.18 ± 0.810	0.345	24.585 ± 0.616	26.604 ± 0.651	**0.025**	22.480 ± 0.560	28.330 ± 0.541	**<0.001**
Vitamin B6 (mg/d)	2.16 ± 0.031	2.13 ± 0.021	0.654	2.041 ± 0.041	2.292 ± 0.044	**<0.001**	1.971 ± 0.042	2.341 ± 0.042	**<0.001**
Folate (mcg/d)	606.990 ± 9.032	582.53 ± 13.591	0.131	643.004 ± 8.985	603.032 ± 10.484	0.621	599.32 ± 10.881	603.501 ± 10.540	0.763
Vitamin B12 (mcg/d)	4.193 ± 0.185	4.95 ± 0.276	**0.020**	3.771 ± 0.201	5.161 ± 0.211	**<0.001**	3.87 ± 0.200	4.962 ± 0.205	**<0.001**

MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TFA, trans fatty acid; EPA, Eicosapentaenoic acid; DHA., Docosahexaenoic acid.
Values are mean ± SD obtained from one-way analysis of variance (ANOVA).
Nutrients and food groups were adjusted for age, BMI, physical activity and total energy intake. P-value for energy intake obtained from controlling age,BMI, and physical activity.
† Adjust p-value obtained from an analysis of covariance.
$P < 0.05$ consider as significant, P = 0.05–0.07 consider as marginally significant.
Bold values means significant p-value $P < 0.05$.

95% CI: −0.021;0.007, p = 0.384). Result in the crude model showed that increased intake of processed meat had a significant positive association with the level of leptin (β: 0.172, 95% CI:0.020;0.321, p = 0.021) and Gal-3 (β: 0.052, 95% CI: 0.001,0.205, p = 0.031) that after adjustment in model 3 it remained significant (β: 0.900, 95% CI: 0.031;1.233, p = 0.015). A positive association with the level of MCP-1 (β:17.287, 95% CI: −12.692;47.267, p = 0.250) was not statistically significant, but after considering the confounding factors, a significant relationship was observed (β:0.304, 95% CI:0.100;1.596, p = 0.025) Table 4. Moreover, a positive significant association between the level of hs-CRP, PAI-1 and MCP1 and high adherence to red meat (β:0.020, 95% CI:0.001;0.050, p = 0.014), (β:0.263, 95% CI:0.112;0.345, p = 0.053), (β:0.490, 95% CI: 0.175;1.464, p = 0.071) and inverse association with HOMA-IR (β: −0.016, 95% CI: −0.022, −0.001, p = 0.033) in model 3 was established. Our analysis demonstrated a significantly negative association between levels of Gal-3 and MCP-1 and high adherence to white meat (β: −0.110, 95% CI: −0.271;0.000, p = 0.044) and (β: −1.933, 95% CI: −3.721;0.192, p = 0.022) after adjustment for confounder. In contrast, a significant positive association between the level of PAI-1 and high adherence to white meat (β: 0.154, 95% CI: 0.021;0.283, p = 0.028) was observed in the crude model, but after adjustment, this association reached marginal significance (β: −0.340, 95% CI: −0.751;0.050, p = 0.070). After controlling potential confounders, there was a marginally significant inverse association between higher intake of white meat with HOMA-IR (β: −0.011, 95% CI: −0.020,0.000, p = 0.070) (Table 4).

Discussion

In this study, we evaluated the relationship between the consumption of red, white, and processed meats with inflammatory and metabolic biomarkers in overweight and obese women. We found that red meat intake was positively associated with PAL-1, hs-CRP, and MCP-1 levels. Moreover, processed meat intake was positively associated with different biomarkers such as leptin, Gal-3, and MCP-1. On the contrary, negative relationships between high adherence to white meat intake and Gal-3, MCP-1, PA1, and HOMA-IR were established.

In the current cross-sectional study, greater processed meat intakes were initially positively associated with higher HOMA-IR and leptin levels. However, HOMA-IR was no longer associated with processed meat intake after adjustment for all confounders. After controlling for all confounders in the last model of adjustment, there was a positive association between processed meat intake and levels of leptin, Gal-3, and MCP-1. In line with our study, a cohort study displayed that processed meat consumption was positively associated with leptin and CRP in both men and women after 9 years of follow-up (41). Another study expressed that higher processed meat consumption is positively associated with inflammatory markers in 403,886 British adults (42). That seems the binding capacity of iron in our body might be exceeded by consuming processed meat containing high amounts of heme iron. Oxidative stress can be increased by free iron and, as a result, act as a proinflammatory agent (43).

TABLE 3 Inflammatory biomarkers between low and high category of processed meat, red meat and white meat (g/d) in 391 obese and overweight women.

Variables		Processed meat median		*P*-value	*P*-value†	Red meat median		*P*-value	*P*-value	White meat median		*P*-value	*P*-value†
		Low (<19.82)	High (>19.83)			Low (<36.46)	High (>36.47)			low (<31.02)	High (>31.03)		
HOMA-IR	Crude	3.321 ± 1.411	3.172 ± 1.215	0.435		3.480 ± 1.400	3.201 ± 1.122	0.091		3.144 ± 1.215	3.530 ± 1.313	**0.024**	
	Model 1	3.000 ± 00.315	2.921 ± 0.412		0.884	3.489 ± 0.261	2.626 ± 0.291		**0.045**	3.303 ± 0.284	2.865 ± 0.291		0.301
	Model 2	2.937 ± 0.334	3.026 ± 0.443		0.882	3.511 ± 0.340	2.274 ± 0.392		**0.045**	3.104 ± 0.341	2.927 ± 0.374		0.610
Leptin (mg/L)	Crude	26.301 ± 12.192	29.932 ± 11.170	0.164		27.436 ± 11.970	27.952 ± 11.922	0.846		27.894 ± 11.553	12.310 ± 1.832	0.882	
	Model 1	25.923 ± 1.451	29.670 ± 1.865		0.124	27.184 ± 1.653	27.546 ± 1.616		0.884	27.640 ± 1.651	27.129 ± 1.581		0.821
	Model 2	26.532 ± 1.475	28.711 ± 1.920		0.391	27.763 ± 1.642	27.004 ± 1.606		0.754	29.156 ± 1.654	25.660 ± 1.572		**0.024**
PAI1 (mg/L)	Crude	17.081 ± 30.690	17.481 ± 30.695	0.950		12.845 ± 23.124	18.876 ± 34.841	0.201		13.580 ± 22.321	18.755 ± 36.312	0.270	
	Model 1	7.920 ± 9.134	37.592 ± 12.041		**0.07**	15.574 ± 8.116	17.651 ± 8.970		0.860	13.722 ± 8.294	19.587 ± 8.723		0.631
	Model 2	6.282 ± 9.231	40.230 ± 12.313		**0.052**	23.16 ± 11.055	14.33 ± 12.840		0.641	12.665 ± 10.310	26.690 ± 11.012		0.380
Gal-3 (mg/L)	Crude	4.946 ± 1.320	5.594 ± 2.035	0.782		23.160 ± 11.051	14.332 ± 12.842	0.660		3.865 ± 5.867	4.665 ± 9.161	0.642	
	Model 1	2.065 ± 1.532	6.961 ± 2.021		0.080	3.040 ± 1.396	3.874 ± 1.542		0.690	3.191 ± 1.421	3.66 ± 1.500		0.820
	Model 2	1.800 ± 1.532	7.381 ± 2.040		**0.054**	4.371 ± 1.832	3.396 ± 2.132		0.750	3.100 ± 1.721	4.885 ± 1.833		0.511
Hs-CRP (mg/ L)	Crude	4.622 ± 5.055	3.675 ± 3.771	0.220		4.540 ± 4.566	3.901 ± 4.575	0.284		4.211 ± 4.850	4.215 ± 4.270	0.991	
	Model 1	2.531 ± 0.600	4.341 ± 0.791		0.091	5.574 ± 0.724	3.060 ± 0.801		**0.031**	4.435 ± 0.795	4.441 ± 0.834		0.990
	Model 2	2.550 ± 0.622	5.31 ± 0.831		**0.050**	5.046 ± 0.775	3.384 ± 0.902		0.220	4.152 ± 0.754	4.494 ± 0.811		0.773
IL1b (mg/L)	Crude	0.400 ± 0.532	0.301 ± 0.565	0.280		0.422 ± 0.492	0.321 ± 0.562	0.130		0.370 ± 0.535	0.375 ± 0.522	0.941	
	Model 1	0.476 ± 0.091	0.176 ± 0.425		0.081	0.540 ± 0.080	0.172 ± 0.099		**0.005**	0.410 ± 0.094	0.333 ± 0.091		0.580
	Model 2	0.462 ± 0.91	0.18 ± 0.135		0.130	0.517 ± 0.107	0.16 ± 0.1271		**0.071**	0.394 ± 0.105	0.315 ± 0.119		0.645
MCP-1 (mg/L)	Crude	56.494 ± 96.055	56.340 ± 111.661	0.991		51.200 ± 104.101	50.901 ± 81.830	0.98		52.281 ± 95.400	49.815 ± 91.681	0.842	
	Model 1	32.654 ± 22.971	108.901 ± 30.275		**0.071**	44.100 ± 21.360	63.850 ± 23.625		0.551	54.591 ± 22.003	51.324 ± 23.131		0.921
	Model 2	29.584 ± 22.921	113.874 ± 30.565		**0.046**	64.051 ± 27.554	58.971 ± 32.001		0.910	54.743 ± 25.940	69.732 ± 27.704		0.711

Gal-3, Galectin 3; Hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; IL-1b, interleukin 1 beta; MCP-1, chemoattractant protein-1; PA-1, plasminogen activator inhibitor-1; TGF-β, transforming growth factor.
Values are mean ± SD for the crude model and mean ± SE for an adjusted model.
Model 1: Adjusted for: age, BMI, physical activity, total energy intake, economic status, education, housing ownership.
Model 2: Additionally controlled for vegetables and dairy for processed meat.
The crude p-value for all variables obtained from the one-way analysis of variance (ANOVA).
† Adjust p-value obtained from an analysis of covariance.
$P < 0.05$ consider as significant, P = 0.05–0.07 consider as marginally significant.
Bold values means significant p-value $P < 0.05$.

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TABLE 4 Association between inflammatory biomarkers with processed meat, red meat, and white meat (g/d) in 391 obese and overweight women.

Variables		Processed meat			*p*-value	*p*-value*	Red meat			*p*-value	*p*-value*	White meat			*p*-value	*p*-value*
		β	CI (95%)	R^2			β	CI (95%)	R^2			β	CI (95%)	R^2		
HOMA-IR	**Crude**	0.410	0.070, 0.750	0.003	**0.011**		−0.008	−0.011, 0.001	0.013	**0.070**		0.002	−0.002, 0.007	0.012	0.320	
	Model 1	−0.003	−0.01, 0.01	0.110		0.674	−0.008	−0.011, 0.000	0.526		**0.071**	0.000	−0.004, 0.005	0.011		0.705
	Model 2	−0.007	−0.022,0.007	0.536		0.322	−0.008	−0.014,0.0021	0.011		**0.061**	0.001	−0.003,0.005	0.120		0.601
	Model 3	−0.007	−0.021, 0.000	0.570		0.381	−0.016	−0.022, −0.001	0.120		**0.033**	−0.011	−0.020, 0.000	0.240		**0.070**
Leptin (mg/L)	**Crude**	0.172	0.020, 0.321	0.240	**0.021**		−0.070	−0.171, 0.030	0.133	0.172		−0.030	−0.100, 0.040	0.450	0.445	
	Model 1	0.145	−0.030, 0.235	0.457		0.151	−0.060	−0.15, 0.030	0.526		0.195	−0.021	−0.090, 0.041	0.520		0.485
	Model 2	0.780	0.031, 0.855	0.655		**0.040**	0.000	−0.114, 0.030	0.625		0.222	−0.010	−0.09, −0.00	0.670		**0.066**
	Model 3	0.900	0.031, 1.233	0.750		**0.015**	0.000	−0.114, 0.030	0.903		0.403	−0.010	−0.09, −0.00	0.020		**0.080**
PAI1 (mg/L)	**Crude**	3.765	−8.132, 15.650	0.010	0.535		0.274	0.014, 0.540	0.040	**0.040**		0.154	0.021, 0.283	0.107	**0.028**	
	Model 1	−0.020	−0.450,0.40	0.010		0.901	0.311	0.026,0.693	0121		**0.030**	0.102	−0.440,1.054	0.100		0.126
	Model 2	−0.071	−0.521, 0.384	0.110		0.755	0.240	−0.030, 0.555	0.124		0.080	0.100	−0.030, 0.301	0.150		0.145
	Model 3	−0.140	−0.580, 0.296	0.140		0.511	0.263	0.112, 0.345	0.144		**0.053**	−0.340	−0.751, 0.050	0.161		**0.070**
Gal-3 (mg/L)	**Crude**	2.025	−2.33, 6.370	0.010	0.352		0.012	−0.115, 0.152	0.010	0.770		0.010	−0.055, 0.071	0.020	0.720	
	Model 1	0.302	−0.121, 0.180	0.070		0.690	−0.011	−0.141, 0.110	0.140		0.781	−0.020	−0.09, 0.04	0.110		0.500
	Model 2	0.011	−0.145, 0.184	0.112		0.830	−0.009	−0.145, 0.121	0.141		0.892	−0.03	−0.10, 0.03	0.110		0.360
	Model 3	0.052	0.001, 0.205	0.178		**0.031**	−0.030	−0.210, 0.200	0.172		0.788	−0.110	−0.271, −0.000	0.170		**0.044**
Hs-CRP (mg/L)	**Crude**	−0.011	−0.072,0.031	0.004	0.485		0.015	−0.020,0.041	0.004	0.455		0.005	−0.015,0.021	0.000	0.490	
	Model 1	−0.020	−0.071, 0.025	0.160		0.300	0.021	−0.005, 0.06	0.150		0.092	0.001	−0.010, 0.015	0.157		0.360
	Model 2	0.010	−0.071, 0.020	0.190		0.321	0.030	0.000, 0.060	0.190		**0.040**	0.001	−0.010, 0.060	0.186		0.264
	Model 3	0.010	−0.065, 0.040	0.198		0.732	0.020	0.001, 0.050	0.193		**0.014**	0.056	0.000, 0.110	0.188		0.445
IL1b (mg/L)	**Crude**	−0.003	−0.147, 0.146	0.050	0.990		0.001	−0.003, 0.005	0.04	0.680		0.000	−0.001, 0.002	0.04	0.590	
	Model 1	−0.003	−0.009, 0.003	0.112		0.320	0.001	−0.004, 0.005	0.135		0.510	0.000	−0.002, 0.002	0.110		0.917
	Model 2	−0.002	−0.009, 0.004	0.175		0.442	0.002	−0.002, 0.006	0.140		0.400	0.000	−0.002, 0.002	0.155		0.854
	Model 3	−0.004	−0.010, 0.000	0.190		0.175	0.000	−0.007, 0.006	0.250		0.931	0.002	−0.005, 0.009	0.189		0.615
MCP-1 (mg/L)	**Crude**	17.287	−12.692, 47.267	0.040	0.250		0.251	−0.494, 1.001	0.040	0.501		0.135	−0.20, 0.47	0.01	0.435	
	Model 1	−0.142	−1.321, 1.024	0.010		0.800	0.382	−0.481, 1.250	0.120		0.381	0.081	−0.265, 0.432	0.114		0.611
	Model 2	−0.220	−1.442, 1.001	0.120		0.721	0.365	−0.500, 1.221	0.135		0.410	0.045	−0.861, 1.200	0.140		0.743
	Model 3	0.304	0.100, 1.596	0.139		**0.025**	0.490	0.175, 1.464	0.140		**0.071**	−1.933	−3.721, −0.192	0.141		**0.022**

Gal-3, Galectin 3; Hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; IL-1b, interleukin 1 beta; MCP-1, chemoattractant protein-1; PA-1, plasminogen activator inhibitor-1; R^2, r squared; TGF-β, transforming growth factor.
Values are: beta (β), 95% confidence interval (CI).
Model 1: Adjusted for: age, BMI, physical activity, total energy intake.
Model 2: Additionally controlled for economic status, education, housing ownership.
Model 3: Additionally controlled for vegetables intake and dairy for processed meat for red meat and white meat group.
**P*-value obtained from adjustment. All p-values were obtained from linear regression.
$P < 0.05$ consider as significant, P = 0.05–0.07 consider as marginally significant.
Bold values means significant p-value $P < 0.05$.

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In our study, consumption of white meat was negatively associated with HOMA-IR, Gal-3, MCP-1, and PAL-1. In line with these findings, several studies have reported that higher consumption of white meat such as poultry has been related to lower inflammatory markers such as CRP (44–46). The consumption of fish and seafood, considered white meat, was shown to have anti-inflammatory properties due to the high contents of omega-3 fatty acids and lesser amount of heme iron and lower cholesterol (47–49).

Our results also showed a significant positive association between red meat intake and levels of PAL-1, hs-CRP, and MCP-1; however, we observed a negative association between red meat consumption and HOMA-IR. Similar to our results, in two separate studies, including 482 Iranian women and 2,500 German individuals (both studies included healthy adults), greater red meat intake was associated with a higher plasma CRP concentration (50, 51). However, in a Dutch study, only processed meat intake was associated with higher CRP, while red meat intake was not (52). In a clinical trial, replacing energy from carbohydrates with protein from unprocessed lean red meat for 8 weeks did not augment inflammatory marker concentrations (19). In a randomized cross-over controlled trial in 36 individuals aged 39–97 years (53), 5 weeks of dietary treatment with 28, 113, or 153 g of lean red meat per day had similar advantageous effects on LDL-c and similar disadvantages effects on HDL-c. The authors include lean red meat in a diet to reduce cardiovascular disease (CVD) risk (53). This discrepancy with our study can be attributed to methodological or ethnic differences. In Iran, per capita, meat consumption is around 35.5 kg/year, comprising 30 gr of red meat and 60 gr of white meat per day (54). In our study, the average consumption of red meat is generally low compared to other countries such as 136 gr/d in 2021 in the united states (55). Indeed, that seems obese/overweight women in this study population even with a higher than the median red meat intake have just reached the ordinary intake of red meat intake like other populations (54, 55). Additionally, participants with higher red meat intake in the current study also had higher BFM levels and higher vegetable intakes; hence, all this information should be considered when interpreting our results. However, it seems that the mechanism is not completely clear and there is a need to design studies for further investigations. Monton et al. evaluated the association between the consumption of red meat and circulating hs-CRP levels in 2,198 men and women and expressed a positive association in these values (50). A diet high in red and processed meat can contribute to weight gain and body fat accumulation, which induces the obesity-related inflammatory process (41). However, decreasing body fat might be more relevant than lowering the intake of dietary red and processed meat to improve circulating levels of adipokines and inflammatory markers (31).

Iron may be another component of red meat contributing to the progression of metabolic abnormalities (56–58). Indeed, iron is a prooxidant that has been related to increased oxidative stress (59). High iron contents of red meat, especially heme iron, and meat processing particularly through high-temperature cooking, results in the formation of carcinogenic chemicals, including N-nitroso-compounds (NOC) and polycyclic aromatic hydrocarbons (PAH) (60, 61). Since inflammation is a key risk factor for metabolic diseases, our results may suggest that high red and processed meat consumption can affect metabolic disease development through the inflammatory pathway. Dietary intake of heme iron, abundant in red meat, has also been related to increased CVD risk especially inflammation (62), likely through inflammation and lipid peroxidation mechanisms.

A recent study reported that increased red meat consumption is associated with higher mortality risk in both women and men (63). Mercapturic acid of dihydroxynonane (DHN-MA), a substance that indicates the production of hydroxynonenal (HNE) in food or during digestion, is excreted in large amounts by diets that include heme iron and −6 fatty acids, such as hemoglobin or red meat and safflower oil (64, 65). Foods containing heme iron and PUFAs also contain HNE (66). The HNE, an end product of the oxidative breakdown of −6 fatty acids and a well-known bioactive marker of lipid peroxidation involved in cell growth control and signaling, is the main urinary metabolite of HNE, and it is also known as DHN-MA. As a result, DHN-MA has also been employed as an oxidative stress marker (67, 68).

It has been expressed that the red meat dietary intervention resulted in significant increments in plasma concentrations of trimethylamine-N-oxide (TMAO) (69) which has been linked to inflammation and CVD (70, 71). TMAO may cause inflammation. The inflammatory cytokines IL-1 and IL-18 were generated by the TXNIP-NLRP3 inflammasome after TMAO dramatically increased oxidative stress and activated it, but it also reduced the generation of nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) (72). In addition preservatives such as sodium, nitrates, advanced glycation end products (AGEs), and their by-products may contribute to the relationship between red meat intake and increment of inflammation (73–75). Exposure to high temperatures can generate high levels of AGEs in meat, which have been shown to augment oxidative and inflammatory processes (73). Christ et al. (76) identified a functional role for NLRP3/IL-1β in the induction of innate immune memory in monocytes as triggered by a high intake of red meat and represented how this promotes inflammatory diseases (76). Apart from the meat cooking method of meat, enhancing flavor or improving preservation through methods such as smoking, salting, curing, or even adding chemical preservatives may affect oxidative stress and inflammation status (60, 77). The iron content in red meat has been related to upregulating inflammatory mediators, such as IL-6, IL-1β, and tumor necrosis factor-alpha (TNF-α) (78). Moreover, another proposed mechanism in the relationship between meat consumption and inflammation is probably related to the

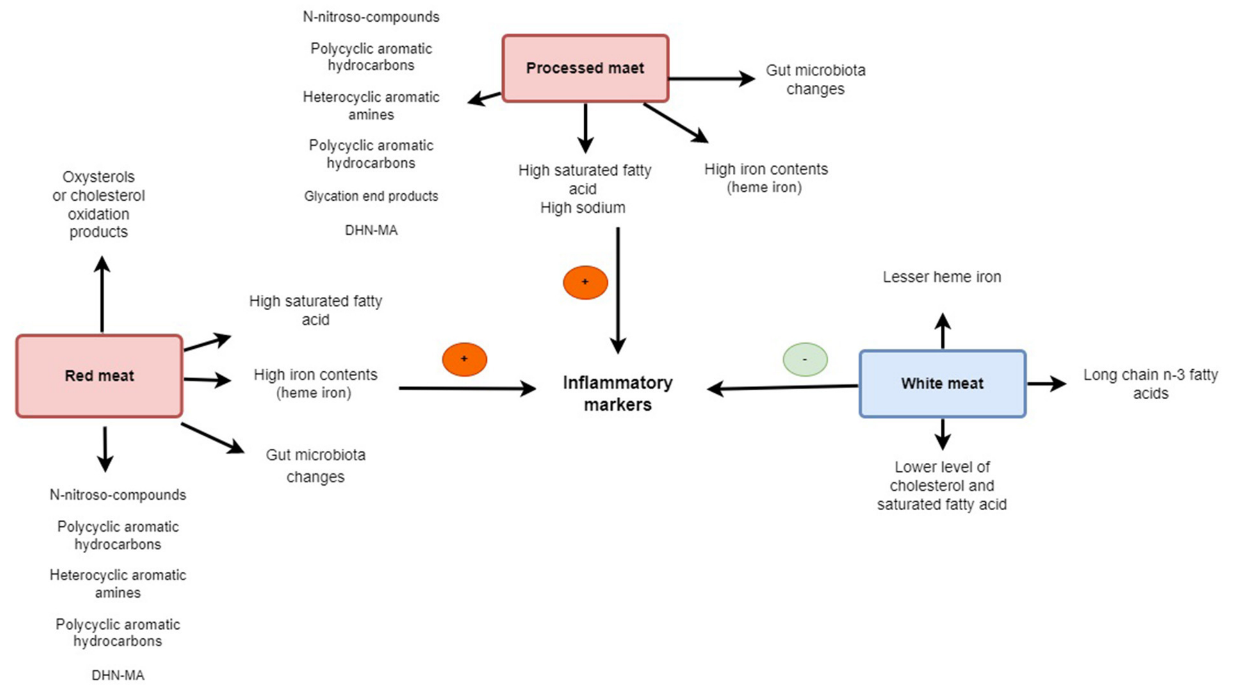

FIGURE 1
The scheme illustrates the different mechanisms of red, processed, and white meat on inflammation.

gut microbiome. It has also been displayed that red meat's gut microbiota-dependent breakdown metabolic processes can trigger inflammatory disease (70, 79). The most mechanistic relation of all kinds of meat on inflammation is present in Figure 1.

The present study has several strengths and limitations. First, this is the first study that evaluated the association between red, white, and processed meat on inflammatory and metabolic biomarkers in overweight and obese women. Second, dietary intake was assessed using a validated FFQ, which an experienced dietitian completed to decrease measurement errors. Anthropometric indices and body composition outcomes were assessed by the same person each time to improve the accuracy of the measurements (80). Nonetheless, a few limitations should be considered. First, the cross-sectional nature of the current study limited the ability to suggest a causal association between meat consumption and inflammation. Second, small errors might exist in the dietary assessment, mainly because of misremembering, overestimation, or underestimation of dietary intake and misclassification errors. Third, since our study included women only, the results are not generalizable to men and even to women with normal weight and other countries. fourth, cooking methods as important confounders didn't assess in the present study. Fifth, meat quality from the conditions of animal husbandry, especially environmental toxins, the type of food and water consumed, environmental conditions, to the stage of the cooking method and process, even genetic variation in dietary response, the culture and food habits of each society for eating of all types of meat can influence the relation of all kinds of meat with inflammation on that people. Sixth, further research must take into account other variables, such as menopause and the participant's hormonal state, which may have an impact on the accuracy of the findings. Seventh, the consumption ratio of all kinds of meats white to red meat or proceed meat, probably affects the inflammation that it is not possible to control the effect by only adjusting it in the analysis stage, and there is a need to design clinical trial studies in this field by proper diet intervention. Finally, although all the analyses were adjusted for potential confounders, residual confounding may still exist.

Conclusion

In conclusion, according to the results, it seems that the greater consumption of white meat with the mentioned mechanisms is probably negatively related to the inflammatory and metabolic factors. In contrast, the consumption of red and processed meat is positively related to the level of inflammatory factors in overweight and obese women. Of course, a higher intake of red meat had shown an association with a lower level of Gal-3 and insulin resistance, which seems that it is due to the amount of consumption that is lower than the average intake of the other population, and probably with more consumption of red meat, we might have faced different results. Perhaps the situation is clear regarding the recommendation to reduce the consumption of processed meats. However, there is a risk regarding the reduction of red meat consumption despite the reduction of inflammation, and there is concern regarding the consumption of white meat especially sea foods in Iran where some are habitual and some global concerns. Although in this suggestion, we must consider that Iran's estimated anemia prevalence ranges from 10 to 30%, with greater rates among children and teenagers, women with the prominent role of iron deficiency (81), and on the other hand, apart from poultry, seafood consumption in Iran is low due to eating habits and its consumption rate per capita is much lower (82). That change these conditions requires awareness of advantages and the provision of conditions. Other global concerns and risks are heavy metals pollution and the poisoning in sea foods (83, 84). Overall, it seems that it is very difficult to conclude the relationship of meat with inflammatory markers because limitations mentioned. It seems that to make a better judgment and suggestion for public health policy there is still a need for comprehensive studies to investigate the amount of meat consumed compared to the daily dietary protein requirement of individuals, the total energy received from that, along with taking into account controlling cooking methods, eating habits, etc. In addition, long-term controlled feeding studies are needed to confirm the causality of these associations and potential mediating pathways to determine optimal preventative dietary strategies for the progression of inflammation and inflammation-related diseases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Tehran University of Medical Sciences (Ethics Number: IR.TUMS.VCR.REC.1395.1597). The patients/participants provided their written informed consent to participate in this study.

Author contributions

FSH, DH, and AM wrote the paper. FSH performed the statistical analyses and revised the paper. KHM had full access to all of the data in the study and took responsibility for the integrity and accuracy of the data. AW, RB, and KS revised the paper. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between dietary fat intake and colorectal cancer: A multicenter case-control study in Iran

Monireh Sadat Seyyedsalehi[1,2], Giulia Collatuzzo[1], Inge Huybrechts[3], Maryam Hadji[2,4], Hamideh Rashidian[2], Roya Safari-Faramani[5], Reza Alizadeh-Navaei[6], Farin Kamangar[7], Arash Etemadi[8,9], Eero Pukkala[4,10], Marc J. Gunter[3], Veronique Chajes[3], Paolo Boffetta[1,11*†] and Kazem Zendehdel[2,12*†]

[1]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, [2]Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran, [3]International Agency for Research on Cancer, Lyon, France, [4]Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland, [5]Research Center for Environmental Determinants of Health, School of Public Health, Kermanshah Medical Sciences University, Kermanshah, Iran, [6]Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran, [7]Department of Biology, School of Computer, Mathematical, and Natural Sciences, Morgan State University, Baltimore, MD, United States, [8]Digestive Oncology Research Center, Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, [9]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, United States, [10]Finnish Cancer Registry - Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland, [11]Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, United States, [12]Cancer Biology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

The evolving trends in colorectal cancer (CRC) as one of the most common malignancies worldwide, have likely been influenced by the implementation of screening programs and changes in lifestyle habits. Changing lifestyle, including the shift in diet composition with higher fat, sugar, and animal-source foods intake, led to an increasing burden of CRC in countries undergoing rapid socioeconomic improvement. Results for the link between specific fatty acids (FAs) and CRC are generally inconclusive and more limited in developing countries than elsewhere. This study aims to investigate the association between FA intakes and CRC and its anatomical subsites in a large Iranian case-control study. A food frequency questionnaire was used to collect information on dietary intake in 865 cases and 3206 controls. We conducted multivariate logistic regression models to calculate the odds ratio (OR) and 95% confidence interval (CI). We found positive association between CRC and high intake of dietary total fat (OR highest quartile $_{Q4}$ = 1.77, 95% CI = 1.32–2.38), cholesterol (OR_{Q4} = 1.58, 95% CI = 1.22–2.05), and palmitoleic acid (OR_{Q4} = 2.16, 95% CI = 1.19, 3.91), and an inverse association with high intake of dietary heptanoic acid (OR_{Q4} = 0.33, 95% CI = 0.14, 0.79) and low intake of palmitic acid (OR lowest quartile $_{Q2}$ = 0.53, 95% CI = 0.31–0.88). None of the fat variables were

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Mainul Haque,
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Zaleha Md Isa,
National University of Malaysia, Malaysia

*CORRESPONDENCE
Paolo Boffetta
paolo.boffetta@unibo.it
Kazem Zendehdel
kzendeh@tums.ac.ir

†These authors have contributed equally to this work

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associated with rectal cancer. Our study suggests that the recommendation of limited consumption of fats may decrease the risk of CRC among the Iranian population.

KEYWORDS

gastrointestinal neoplasms, food frequency questionnaire, fat, diet, colorectal cancer

Introduction

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer death, with an estimated 1.8 million new cases and 900,000 deaths in 2020 worldwide (1). A higher incidence rate is found in men and in highly industrialized countries (2). In Iran, CRC is the fourth most common cancer, with an age-adjusted incidence rate (ASR) of 15.9 and 11.9 for men and women, respectively (1). From 2016 to 2020, previous studies identified an increasing trend in Iran and predicted a 54% increase by 2025 (3). The changing trends in CRC have likely been influenced by two factors: (i) the implementation of screening programs; (ii) changes in lifestyle habits. Colonoscopy as a gold standard for CRC screening has on the one hand the short-term effect of apparent increasing CRC incidence due to early detection; on the other, it has been proven to reduce the incidence in the long term by the removal of precancerous lesions (4). The changing lifestyle, including the shift of diet composition toward a "westernized" pattern connoted by higher fat, sugar, and animal-source foods intake, leads to an increasing burden of CRC in countries undergoing rapid socioeconomic improvement. These situations can lead to a growing concern regarding the rising number of CRC cases, in particular among those $<$50 years of age (4, 5). In particular, CRC has observed an increase in the Iranian population, especially among men and in more urbanized areas (6, 7). The investigation of dietary behaviors in Iranians have been involved different study groups, being described for example by Saneei et al. Different dietary patterns have been described by residency in Iran, with higher intake of vegetables, fruit, meat, fat, saturated fatty acids (SFA), cholesterol, vitamin C, and beta-carotene and less bread, cereal, and carbohydrates in urban compared to rural dwellers. Also, similar differences in fat, SFA, MUFA, and bread consumption was seen by race, with Turkmens having higher intakes than non-Turkmens. These findings were related to the higher incidence of esophageal cancer registered in Iranians from low socioeconomic status and living in rural areas. Indeed, nutrition deficiencies may contribute to cancer by altering metabolism of carcinogens or by impairing DNA repair (8, 9). Zamaninour et al. had recently described the prevalence of unhealthy dietary habits in Iranian population, where more than 80% of people reported suboptimal intakes of fruit, dairy products and fish, and about 60% also reported suboptimal vegetables intake (10). The identification of dietary risk factor of CRC in Iranian population has been the aim of different recent studies. A case-control study conducted in Iran showed the correlation between a pro-inflammatory diet, based on high consumption of red and processed meat and fat, was associated to CRC and colorectal adenomatous polyps (11).

At least 12% of CRC cases are directly attributable to overweight/obesity according to a recent global review (12). Diets rich in fat are also a risk factor for obesity and cancer (13). According to the literature, different roles are exerted by different types of dietary fats depending on their source such as, ω-3 polyunsaturated fatty acids (PUFAs) play a role in protecting against adipose tissue inflammation, in contrast to omega-6 (ω-6) PUFAs and some saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs), which promote inflammation (14, 15). A higher risk of CRC has been associated with high animal fat intake, but not vegetable fat (16). Although, the amount and type of different fatty acids (FAs) consumed by CRC patients resulted not to be associated either with recurrence or survival (17). To date, limited data provide the quantification of the effect exerted by FAs on CRC. Besides this, few results are available on the role played by the different types of FAs on CRC overall and by anatomical sub-sites.

Currently, screening programs in Iran are based on the identification of high-risk individuals, corresponding to first-degree relatives of CRC patients. Thus, they are based on the consultation of cancer registry. The first-degree families of CRC patients are invited to cancer screening and participate in counseling sessions, possibly leading to colonoscopy recommendation. So far, Iran does not have any screenings or plans for screening the general population at medium-risk of cancer. This makes Iran very different from most of the other countries, where non-invasive testing

Abbreviations: ASR, age-standardized incidence rate; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; EMRO, Eastern Mediterranean Region; FAs, fatty acids; FFAs, free fatty acids; FFQ, Food Frequency Questionnaire; LMIC, low and middle-income countries; MUFAs, monounsaturated fatty acids; OR, odds ratio; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acid; TFAs, trans fatty acids; WCRF, World Cancer Research Fund.

is purposed based on risk profile but also older age and are followed by the invasive endoscopic examination. This issue was addressed by Nikbakht et al. who conducted a study to investigate the use of immunochemical fecal occult blood test (IFOBT) in a mid-risk for CRC Iranian population. The study showed high responsiveness rates from the population, and high rates of positive IFOBT were found (18). Considering these evidence, better comprehension of CRC epidemiology in Iran results highly important for CRC control. In particular, the identification of risk factors of CRC may help preventing the disease and target high-risk population with secondary prevention, including colonoscopy.

This study aims to look at associations between fatty acid intakes and CRC risk considering overall and subsite-specific CRC in a large Iranian case-control study. Our analysis provides useful data to deepen the knowledge on the role of fatty acids in CRC development. Moreover, we give valuable information on the consumption of fatty products in Iran and their relationship with CRC from different anatomical sites.

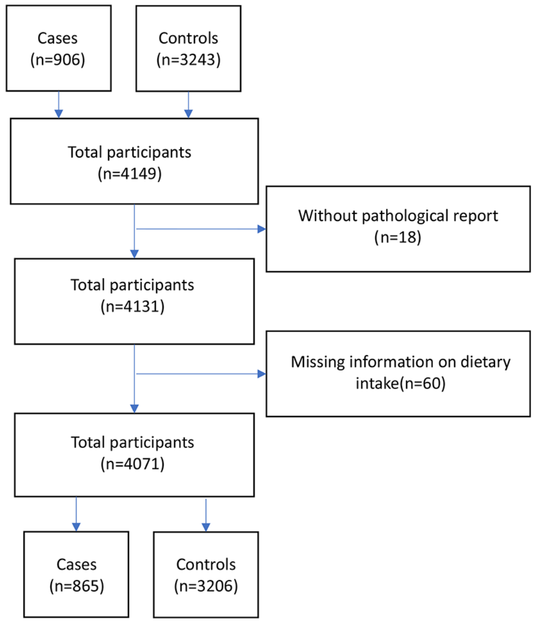

FIGURE 1
Flow diagram of the population enrollment based on the inclusion and exclusion criteria in IROPICAN study.

Materials and methods

Study design and population

A total of 4,149 participants, including 906 CRC cases with pathologic diagnosis and 3,243 controls were recruited between May 2017 and 2020 from the main cancer clinic and hosptals in 7 provinces of Iran (Tehran, Fars, Mazandaran, Kerman, Golestan, Kermanshah, and Mashhad). They were part of the IROPICAN study, a multicenter case-control study coducted in 10 Iranian provinces, which was designed to examine the link between opium use and the development of lung, colorectal, bladder, and head and neck cancers (19). For the analysis of dietary intakes of fat, we excluded participants without the pathological report diagnoses confirmation ($n = 18$); those with missing information on dietary intake and those in the highest or lowest 1% of the distribution for the ratio of energy intake to estimated energy requirement ($n = 60$). We included 865 cases and 3,206 controls in our analysis (Figure 1). Controls were enrolled concurrently with the cases among the healthy visitors of non-oncology wards. The controls had to be free of cancer at the date of recruitment. The mean age at recruitment was 58.5 years and 57.1 years for the cases and controls, respectively. In this study, we estimated around 800 colorectal cancer cases using the OR and CI95 reported by previous studies (20–22), assuming 20 and 30% exposure prevalence among controls and 80% power.

Ascertainment of CRC cases

CRC cases was defined by the International Classification of Diseases (ICD-O-3) as tumors of the colon (C18) or rectum (C19–C20). Colon cancer may be categorized as proximal (from cecum to splenic flexure, C18.0–C18.5) and distal (from descending colon to sigmoid colon, C18.6–C18.7), while rectum cancer occurs from the recto-sigmoid junction (C19) down to the rectum. Anus tumors were excluded from the study. Also, all histological types of CRC except melanoma and sarcoma were included.

Anthropometry and lifestyle collection

During a face-to-face interview, lifestyle questionnaires were used to collect information about education, tobacco use, opium use, socioeconomic status (SES), physical activity, previous illness, and use of nonsteroidal anti-inflammatory drugs (NSAIDs). At the time of enrollment, trained professionals generally measured the standing height of participants (cm). The body mass index (BMI) was calculated as weight/height squared (kg/m2). Cases were asked about their body weight before cancer diagnosis, while controls were measured their body weight at the time of the interview. Based on the Finland Job Exposure Matrix (FINJEM) (23, 24) we analyzed the estimated perceived physical activity workload (PPWL). A principal component analysis was used to calculate the socioeconomic status (SES) of the participants, and the SES was calculated based on the number of years of education the participants had and whether they owned any assets like vacuum cleaners, clothes washers, dishwashers, freezers, internet access, microwaves, laptops, mobile phones, cars, and shops (25).

Diet and fatty acids considered in the analysis

Dietary intakes were assessed with validated qualitatively Persian Cohort FFQ (26) administered by trained interviewers. The usual intake of 131 food items in separate parts including bread and cereal, meat, vegetables and fruits, dietary products, oils, sugars, species, and other group (113 items), dietary supplements (17 items), and water in the last year before cancer diagnosis were collected. For each food item, the reported frequency of consumption (daily, weekly, monthly, or yearly) was converted to frequency per day and was multiplied by the standard portion size (grams) using household measures to calculate grams per day. Using the food composition database developed for the Iranian population based on USDA food composition (27), Near-East food composition (28), and Bahrain food composition (29), macronutrients and micronutrients were calculated.

Regarding this analysis, we calculated the intake of 50 dietary fats based on our food composition table. According to previous studies (21, 22, 30) and the importance and commonplace of FAs in daily food, the gram per day of following FAs were considered in this study: (a) total fat; (b) cholesterol; (c) total SFAs, myristic acid pentadecanoic acid, palmitic acid, heptadecanoic acid, stearic acid; (d) total MUFAs, palmitoleic acid, oleic acid; (e) total PUFAs.

Statistical analyses

The means and standard deviations (±SD) for continuous variables and the frequencies for categorical variables were calculated for descriptive statistics of baseline characteristics and intake of dietary factors of cases and controls.

The normality tested by comparing a histogram of the data to a normal probability curve. After examining the distribution of the data, all nutrient intakes were log-transformed to improve normality.

For the analysis of the association between dietary fat and different type of FFAs; SFAs, PUFAs, MUFAs, and cholesterol and CRC, we conducted unconditional multivariable logistic regression models to estimate the odds ratios (ORs) and 95% CIs. Before multivariate logistic regression, correlations between different exposures were checked and ORs were adjusted by gender (male/female), age (continuous), province, BMI (continuous), tobacco (smoking and water pipe) consumption (Never /Ever), aspirin use (Yes/No), opium use (no user / irregular users / regular users'), SES (Low/ Medium/ High), work-related physical activity (sedentary/Moderate/Heavy), processed meat intake including mortadella, hamburger and sausage (continuous, g/day), calcium (continuous, mg/day), fiber intake (continuous, g/day), and energy (continuous, kcal/day). Participants with missing data for physical activity (24.93 %) were coded as distinct categories during the analysis. Quartile were calculated based on the distribution of different type of fat intake between controls of study. Besides the main analysis, continuous analyses were also run across quartiles. Furthermore, analyses were stratified by age (under and over 50), BMI, gender, SES, physical activity, and vegetable intake for comparing quartile 4 to quartile1 of different types of fat intake. Nevertheless, according to significant interaction (P-heterogeneity < 0.05) analysis we only report age category results. We repeated the analyses for all CRC patients and then after stratification for sub-sites, including colon overall, proximal colon, distal colon, and rectum. All statistical analyses were carried out using Stata 14 (Stata Statistical Software: Release 14. College Station, TX: Stata Corp LLC). We considered p values <0.05 as statistically significant.

Ethical considerations

The study was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD) (Code: IR.NIMAD.REC.1394.027). All participants signed a written informed consent to participate in the study.

Results

The current study included a total of 865 incident CRC cases, 434 cancers of the colon, 404 rectal cancer cases, 27 cases from unknown sub-site, and 3,206 controls; their socio-demographic characteristics, dietary factors intakes, and the distribution of selected CRC risk factors are shown in Table 1. One-third ($N = 145$) of the colon cancers were in the proximal colon, 42% ($N = 185$) in the distal colon, and 23% ($N = 104$) to the overlapping region between proximal and distal colon. In our study, the male to female ratio was 2, and around 76% of all participants were older than 50 years of age. Fars and Tehran provinces had the largest share of the study population. Significant differences between cases and controls were observed for tobacco use, family history, socioeconomic status, and opium use, but not for BMI and physical activity. CRC cases reported higher dietary energy intake (2,406 kcal/day) compared to controls (2,319 kcal/day). Higher levels of FAs and cholesterol were reported by cases than controls (Table 1).

TABLE 1 Selected baseline demographic and lifestyle characteristics of study participants by colorectal cancer status, IROPICAN study.

	Controls	Cases		
		Colorectal*	Colon	Rectum
Overall	3,206	865	434	404
Province, *N* (%)				
Tehran	816 (25.45%)	165 (19.08%)	101 (23.27%)	64 (15.84%)
Fars	943 (29.41%)	248 (28.67%)	93 (21.43%)	155 (38.37%)
Kerman	525 (16.38%)	100 (11.56%)	49 (11.29%)	51 (12.62%)
Golestan	373 (11.63%)	149 (17.23%)	89 (20.51%)	53 (13.12%)
Mazandaran	136 (4.24%)	59 (6.82%)	34 (7.83%)	25 (6.19%)
Kermanshah	251 (7.83%)	68 (7.86%)	31 (7.14%)	35 (8.66%)
Mashhad	162 (5.05%)	76 (8.79%)	37 (8.53%)	21 (5.20%)
Gender, *N* (%)				
Women	1,003 (31.28%)	368 (42.54%)	193 (44.47%)	169 (41.83%)
Men	2,203 (68.71%)	497 (57.46%)	241 (55.53%)	235 (58.17%)
Age, years, *N* (%)				
<30	21 (0.66%)	8 (0.92%)	3 (0.69%)	5 (1.24%)
≥30 & <40	227 (7.08%)	60 (6.94%)	32 (7.37%)	27 (6.68%)
≥40 & <50	503 (15.69%)	126 (14.57%)	64 (14.75%)	58 (14.36%)
≥50 & <60	993 (30.97%)	242 (27.98%)	112 (25.81%)	123 (30.45%)
≥60 & <70	1,020 (31.82%)	258 (29.83%)	137 (31.57%)	112 (27.72%)
≥70	442 (13.79%)	171 (19.77%)	86 (19.82%)	79 (19.55%)
Socio-economic status (SES), *N* (%)				
Low	861 (26.86%)	337 (38.27%)	159 (36.64%)	161 (39.85%)
Moderate	1,078 (33.62%)	234 (27.05%)	118 (27.19%)	109 (26.98%)
High	1,267 (39.52%)	300 (34.68%)	157 (36.18%)	134 (33.17%)
Tobacco consumption, *N* (%)				
No	2,153 (67.16%)	629 (72.72%)	334 (76.96%)	274 (67.82%)
Yes	1,053 (32.84%)	236 (27.28%)	100 (23.04%)	130 (32.18%)
Opium consumption, *N* (%)				
No user	2,646 (82.53%)	731 (84.51%)	369 (85.02%)	340 (84.16%)
Regular user	432 (13.47%)	88 (10.17%)	40 (9.22%)	46 (11.39%)
Irregular user	128 (3.99%)	46 (5.32%)	25 (5.76%)	18 (4.46%)
Work-related physical activity, *N* (%)				
Sedentary	1,034 (32.27%)	287 (33.18%)	147 (33.87%)	132 (32.67%)
Moderate	701 (21.88%)	155 (17.92%)	78 (17.97%)	72 (17.82%)
Heavy	694(21.66%)	184 (21.27%)	87 (20.05%)	87 (21.53%)
Unknown	775 (24.19%)	239 (27.63%)	122 (28.11%)	113 (27.97%)
Family history, *N* (%)				
No	2,534 (79.04%)	653 (75.49%)	330 (76.04%)	304 (75.25%)
Yes	672 (20.96%)	212 (24.51%)	104 (23.96%)	100 (24.75%)
Aspirin use, *N* (%)				
No	2,469 (77%)	709 (81.97%)	358 (82.49%)	327 (80.94%)
Yes	737 (22.99 %)	156 (18.03%)	76 (17.51%)	77 (19.06%)
BMI*, kg/m^2, mean (±SD)	26.59 (± 4.72)	26.93 (±4.99)	26.91 (±5.07)	26.83 (±4.85)
Dietary intake, mean (±SD)				
Total processed meat (g/day)	1.99 (± 0.12)	2.16 (±0.26)	2.47 (±0.43)	1.83 (±0.31)
Fiber (g/day)	24.72 (±11.25)	25.86 (±12.38)	25.28 (±12.16)	26.34 (±12.73)

(Continued)

TABLE 1 (Continued)

	Controls	Cases		
		Colorectal*	Colon	Rectum
Calcium (mg/day)	860.35 (±6.61)	908.28 (±14.69)	919.66 (±20.89)	880.24 (±21.16)
Dietary energy intake (kcal/day)	2,319.45 (±878.09)	2,405.61 (±1,076.00)	2,387.21 (±1,081.89)	2,393.21 (±1,066.35)
Dietary intakes of Fatty acids, mean(±SD)				
Total fat (g/day)	68.52 (±29.92)	77.39 (±39.70)	79.40 (±39.71)	74.19 (±39.29)
Cholesterol (mg/day)	247.21 (±154.15)	275.53 (±174.84)	285.77 (±181.61)	263.41 (±169.04)
Total SFAs (g/day)**	24.31 (±11.28)	27.72 (±14.89)	28.52 (±14.44)	26.32 (±15.10)
14:0 (Myristic acid) (g/day)	2.51 (±1.26)	2.82 (±1.56)	2.90 (±1.52)	2.66 (±1.56)
15:0 (Pentanoic acid) (g/day)	0.094 (±0.071)	0.09 (±0.07)	0.108 (±0.086)	0.088 (±0.067)
16:0 (Palmitic acid) (g/day)	12.79 (±5.95)	14.73 (±8.05)	15.12 (±7.77)	14.04 (±8.25)
17:0 (Heptanoic acid) (g/day)	0.078 (±0.052)	0.08 (± 0.06)	0.091 (±0.062)	0.078 (±0.056)
18:0 (Stearic acid) (g/day)	5.52 (±2.81)	6.37 (±3.75)	6.56 (±3.62)	6.046 (±3.84)
Total MUFAs* (g/day)**	24.79 (±11.83)	28.38 (±15.83)	29.08 (±15.89)	27.27 (±15.62)
16:1n-7 cis (Palmitoleic acid) (g/day)	1.23 (±0.70)	1.50 (±0.99)	1.51 (±0.94)	1.45 (±1.05)
18:1n-9 cis (Oleic acid) (g/day)	22.95 (±11.01)	26.21 (±14.67)	26.88 (±14.76)	25.17 (±14.42)
Total PUFAs** (g/day)**	12.27 (±5.66)	13.44 (±6.83)	13.87 (±7.19)	12.90 (±6.44)

*Includes 27 cancers with unknown sub-site.
BMI, body mass index; **SFAs, saturated fatty acid; ***MUFAs, monounsaturated fatty acids; ****PUFAs, polyunsaturated fatty acids.

There was a statistically significant positive association between CRC and high intake (quartile 4) of dietary total fat ($mean_{Q4}$ = 111 g/day, OR_{Q4} = 1.77, 95% CI = 1.32–2.38), cholesterol ($mean_{Q4}$ = 437 mg/day, OR_{Q4} = 1.58, 95% CI = 1.22–2.05), and palmitoleic acid ($mean_{Q4}$ = 2.24 g/day, OR_{Q4} = 2.16, 95% CI = 1.19–3.91), as well as an inverse association with high intake of dietary heptanoic acid ($mean_{Q1}$: 0.147 g/day, OR_{Q4} = 0.33, 95% CI = 0.14, 0.79), low intake (quartile 2) of palmitic acid ($mean_{Q2}$ = 10.45 g/day, OR_{Q2} = 0.53, 95% CI = 0.31–0.88) (Table 2).

Additional analyses were performed on specific subsites of CRC cases. CRC were classified as colon, proximal or distal colon cancer, and rectum cancer. Based on stratified analyses by anatomical site, we identified a positive association between total fat and colon cancer [OR comparing highest to lowest quartile (Q4 vs. Q1) = 1.30, 95% CI = 1.14–1.48] as well as proximal [$OR_{Q4vs.Q1}$ = 1.43, 95% CI; 1.15–1.77], and distal colon [$OR_{Q4vs.Q1}$ = 1.25, 95% CI = 1.03–1.50].

Also, cholesterol intake was positively associated with colon [$OR_{Q4vs.Q1}$ = 1.22, 95% CI = 1.09–1.36] and proximal colon cancer risk [$OR_{Q4vs.Q1}$ = 1.25, 95% CI = 1.04–1.51].

Total SFAs intake was not associated with different sub-anatomical location of colon cancer, but we found a positive association for individual SFAs: pentanoic acid and colon cancer [$OR_{Q4vs.Q1}$ = 1.81, 95% CI = 1.14–2.87], myristic acid [$OR_{Q4vs.Q1}$ = 1.91, 95% CI = 1.09–3.34] and proximal colon cancer. Also, an inverse association was observed for heptanoic acid and colon cancer [$OR_{Q4vs.Q1}$ = 0.66, 95% CI = 0.47–0.94]. Intake of oleic acid, which is one of the important MUFAs, was inversely associated with colon [$OR_{Q4vs.Q1}$ = 0.70, 95% CI = 0.52–0.95] and proximal colon cancer risk [$OR_{Q4vs.Q1}$ = 0.50, 95% CI = 0.30–0.83]. Conversely, no significant associations were observed for total MUFAs and PUFAs. Rectal cancer was not associated with any FA (Table 3 and Figure 2). A further analysis between different types of FAs and all sub-anatomical locations of CRC according to different quartiles indicated a positive association between stearic acid and proximal colon cancer [ORQ4 = 8.33; 95% CI = 1.02–67.65].

According to the analyses stratified by age category, the statistically significant association persisted for total fat and CRC [$OR_{Q4vs.Q1}$ = 1.30, 95% CI = 1.16–1.46, p = 0.006 for the interaction], as well as for colon [$OR_{Q4vs.Q1}$ = 1.38, 95% CI = 1.18–1.61, p = 0.024 for the interaction] in subjects older than 50. Furthermore, a significant positive association was reported between cholesterol with CRC [$OR_{Q4vs.Q1}$ = 1.22, 95% CI = 1.11–1.35, p = 0.019 for the interaction], colon [$OR_{Q4vs.Q1}$ = 1.30, 95% CI = 1.14–1.48, p = 0.038 for the interaction]. There was no association between FAs intake and any of the cancer sub-sites among participants under 50 years old (Table 4).

Discussion

We found a positive relationship between total fat, cholesterol, myristic acid, pentanoic acid, and a high intake of palmitoleic acid, with CRC, with a stronger effect on colon

TABLE 2 Dietary estimates of fatty acids and risk of colorectal cancer.

Fatty acids type	Q1		Q2		Q3		Q4		OR (95% CI)*	*p*-trend
	Mean g/day	OR (95% CI)	Mean g/day	OR (95% CI)	Mean g/day	OR (95% CI)	Mean g/day	OR (95% CI)		
Total fat	37.4	1	56.49	0.95 (0.75–1.22)	72.26	0.91 (0.70–1.19)	110.74	**1.77 (1.32–2.38)**	**1.18 (1.07–1.30)**	**<0.001**
Cholesterol (mg/day)	115	1	188.38	0.90 (0.71–1.14)	254.03	0.89 (0.69–1.14)	437.32	**1.58 (1.22–2.05)**	**1.15 (1.06–1.25)**	**0.001**
Total SFAs	12.6	1	19.92	0.77 (0.57–1.05)	25.87	0.98 (0.67–1.43)	40.08	1.59 (0.98–2.57)	1.14 (0.98–1.34)	0.081
14:0 (Myristic acid)	1.17	1	2.01	1.19 (0.76–1.87)	2.72	1.26 (0.66–2.38)	4.23	1.31 (0.58–2.95)	1.14 (0.89–1.47)	0.28
15:0 (Pentanoic acid)	0.028	1	0.065	0.76 (0.39–1.47)	0.107	0.99 (0.34–2.89)	0.179	1.52 (0.45–5.14)	1.24 (0.86–1.77)	0.234
16:0 (Palmitic acid)	6.67	1	10.45	**0.53 (0.31–0.88)**	13.56	0.83 (0.40–1.69)	21.19	1.01 (0.40–2.52)	0.94 (0.71–1.25)	0.695
17:0 (Heptanoic acid)	0.029	1	0.059	0.76 (0.47–1.24)	0.082	0.59 (0.30–1.14)	0.147	**0.33 (0.14–0.79)**	**0.74 (0.57–0.97)**	**0.034**
18:0 (Stearic acid)	2.68	1	4.39	1.28 (0.78–2.09)	5.82	0.56 (0.28–1.10)	9.47	0.91 (0.39–2.12)	0.94 (0.73–1.22)	0.695
Total MUFAs	12.78	1	19.86	1.26 (0.93–1.72)	26.18	0.90 (0.59–1.37)	41.75	0.96 (0.57–1.64)	0.98 (0.82–1.16)	0.836
16:1n-7 cis (Palmitoleic acid)	0.55	1	0.93	1.34 (0.94–1.91)	1.31	1.49 (0.92–2.42)	2.24	**2.16 (1.19–3.91)**	**1.22 (1.02–1.47)**	**0.027**
18:1n-9 cis (Oleic acid)	11.79	1	18.34	1.39 (0.93–2.07)	24.23	0.96 (0.54–1.71)	38.72	0.73 (0.35–1.54)	0.88(0.70–1.10)	0.271
Total PUFAs	6.5	1	9.87	0.93 (0.71–1.22)	12.84	0.95 (0.69–1.31)	20.16	1.25 (0.85–1.84)	1.06 (0.94–1.20)	0.301

*OR for the continuous analysis across quartiles.
Adjusted by province, age, SES, gender, BMI, tobacco use, opium use, aspirin use, physical activity, processed meat, fiber intake, calcium, and energy intake.
The bold values indicates the statistically significant results with p values <0.05.

TABLE 3 Odds ratios and 95% confidence intervals of colorectal cancer and specific fatty acids intakes stratified by colorectal tumor location.

Fatty acids type	Anatomical cancer site			
	Colon OR (95% CI)*	Proximal colon OR (95% CI)*	Distal colon OR (95% CI)*	Rectum OR (95% CI)*
Total fat	**1.30 (1.14–1.48)**	**1.43 (1.15–1.77)**	**1.25 (1.03–1.50)**	1.07 (0.94–1.23)
Cholestrol	**1.22 (1.09–1.36)**	**1.25 (1.04–1.51)**	1.14 (0.97–1.35)	1.09 (0.97–1.22)
Total SFAs*	1.18 (0.95–1.46)	1.24 (0.87–1.77)	1.10 (0.81–1.50)	1.10 (0.89–1.37)
14:0 (Myristic acid)	1.35 (0.96–1.89)	**1.91 (1.09–3.34)**	1.33 (0.81–2.18)	0.91 (0.65–1.27)
15:0 (Pentanoic acid)	**1.81 (1.14–2.87)**	1.79 (0.85–3.77)	1.60 (0.79–3.23)	0.93 (0.55–1.55)
16:0 (Palmitic acid)	0.91 (0.62–1.34)	0.75 (0.39–1.46)	0.91 (0.52–1.57)	1.02 (0.70–1.50)
17:0 (Heptanoic acid)	**0.66 (0.47–0.94)**	0.73 (0.41–1.32)	0.71 (0.43–1.19)	0.79 (0.54–1.14)
18:0 (Stearic acid)	1.09 (0.77–1.54)	1.69 (0.92–3.08)	0.84 (0.51–1.38)	0.84 (0.59–1.19)
Total MUFAs	0.97 (0.77–1.22)	0.87 (0.59–1.26)	1.12 (0.80–1.56)	1.00 (0.79–1.26)
16:1n-7 cis (Palmitoleic acid)	1.22(0.96–1.57)	1.18 (0.78–1.77)	1.33 (0.94–1.90)	1.18 (0.92–1.50)
18:1n-9 cis (Oleic acid)	**0.70 (0.52–0.95)**	**0.50 (0.30–0.83)**	0.86 (0.56–1.32)	1.09 (0.80–1.48)
Total PUFAs	1.09 (0.92–1.29)	1.31 (0.99–1.72)	0.98 (0.77–1.25)	1.03 (0.87–1.22)

*OR for the continuous analysis across quartiles.
Adjusted by province, age, SES, gender, BMI, tobacco use, opium use, aspirin use, physical activity, processed meat, fiber intake, calcium, energy intake.
The bold values indicates the statistically significant results with p values <0.05.

and proximal colon cancer. The associations were stronger in subjects older than 50 and absent in younger ones. A high intake of heptanoic acid, Oleic acid, and a low intake of palmitic acid showed inverse associations with CRC and colon cancer. We couldn't find any relation between rectal cancer and different kinds of FAs. Total PUFAs did not appear to have a significant effect on CRC in our study.

High dietary fat intake resulted in an increase in CRC risk of about 60%. The effect appeared to be exerted on the colon rather than the rectum, especially on the proximal section rather than the distal. Studies also have shown that FAs have different effects depending on the anatomical region of the colon (proximal and distal) and the source of the fat (14, 20, 21, 30–32). For example, in our study, plant-sourced fats such as heptanoic acid

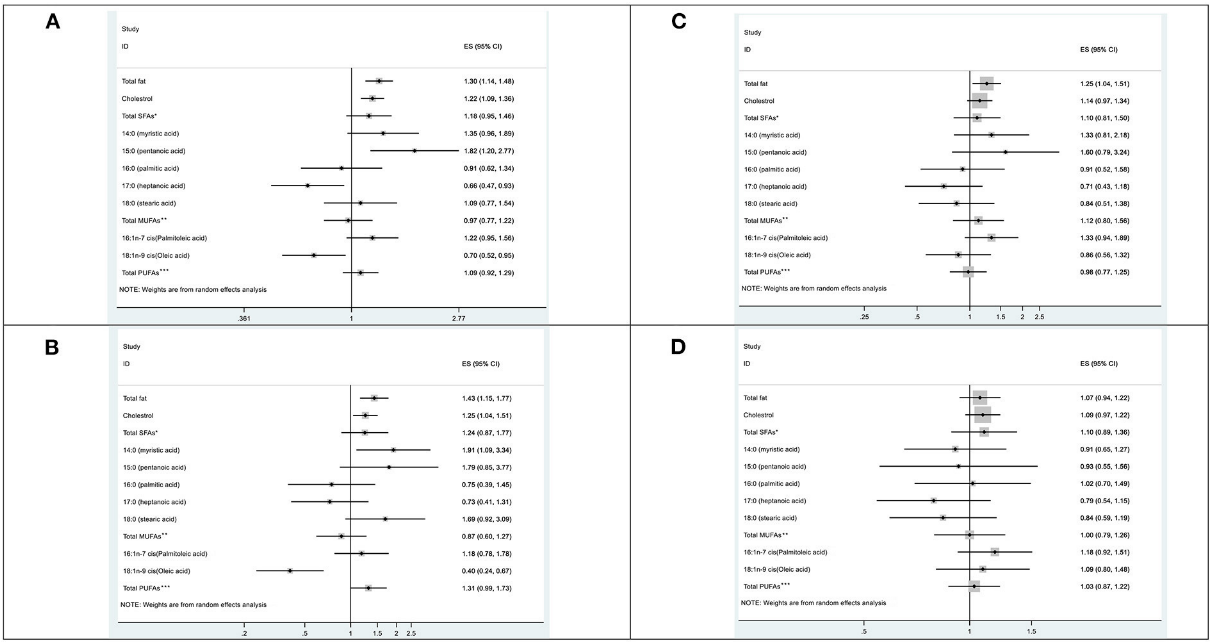

FIGURE 2
Forst plots according to the odds ratios, and 95% confidence intervals for colorectal cancer risk associated with different fat intake, by anatomical sub-site; **(A)** Colon cancer, **(B)** Proximal colon cancer, **(C)** Distal colon cancer, **(D)** Rectum cancer. *Saturated fatty acids; **Monounsaturated fatty acids; ***Polyunsaturated fatty acides.

and oleic acid, or animal fats such as palmitic acid, stearic acid, and myristic acid obtained from meat and dairy products, show different effect on sub-site of colon and rectum. Indeed, a large body of literature described the enhanced risk of colon cancer with high fat intake (16, 33, 34), despite several studies finding no association between FAs and CRC overall (35). A recent meta-analysis found weak evidence of a correlation between FAs and CRC in Chinese men (36). According to a world cancer research fund international (WCRF) report published in 2018, evidence of the association between fats and different fatty acid types is limited and requires further investigation (22).

A number of mechanisms contributed to the effect of FAs on CRC risk, such as (1) pro-inflammatory effects that may be triggered by interaction between dietary fat and gut microbiota, which play a role in the metabolism of bile acids (BA) (37, 38). In fact, BA supports the concept of CRC. Evidence of selective uptake of PUFAs from CRC cells have been provided (39). (2) Oils and fats as the highest sources of polycyclic aromatic hydrocarbons (PAH) (40) can damage DNA in several target tissues when consumed through saturated fat (41). (3) A higher intake of saturated fat has been associated with increased oxidative damage and lipid peroxidation based on the *in-vivo* and *in-vitro* studies (42, 43). (4) Lipids have also been shown to affect cell membrane structure and function, signaling pathways, and gene expression (44). (5) Moreover, obesity is a major risk factor for CRC, with a preponderant role of visceral adiposity (45). A double-blind trial reported subjects overfed with highly SFAs foods underwent more visceral adiposity accumulation than subjects overfed with foods rich in PUFAs showing a distinct effect on fat accumulation in humans, which can in turn be differently related to CRC (46).

Our results showed IROPICAN study population reported a higher daily intake of total fat (70 grams/day, 27% of kcal energy), cholesterol (253 mg/day), and saturated fat (25 grams/day, 10% of kcal energy) than recommendations, coupled with a lower intake of total PUFAs (5% of total kcal energy), reflecting previous studies regarding the amount of dietary fat from different sources in Iranian populations (47, 48). The benefit of unsaturated FA, PUFAs, and MUFAs derived from an overall positive metabolic effect, with inhibition of inflammation and balance of microbiota composition (49). Total MUFAs and total PUFAs do not appear to be associated with CRC in our study. Fish and oily fish are the main sources of ω3 PUFAs (50), while ω6 PUFAs are obtained from vegetable oil, nuts, and egg (51). In terms of fish and seafood consumption, there is a big difference between Iran and other countries, and most PUFAs in the Iranian diet are supplied from other sources such as liquid vegetable oils (Sunflower, maize oil) (52, 53). For human health, it is essential to have a balanced ratio between the two types of PUFAs (54, 55). In this study, we did not investigate the effect of different types of PUFAs on CRC, as we plan to address this topic in a separate paper.

TABLE 4 Odds ratios and 95% confidence intervals of colorectal cancer and specific fatty acids intakes stratified by age.

Fatty acids type	Cancer site	Age			
		Number of cases	≤50 $N = 1,077$ OR (95% CI)	Number of cases	>50 $N = 2,994$ OR (95% CI)
Total fat	**Colorectal**	206	0.89 (0.74–1.07)	659	**1.30 (1.16–1.46)**
	Colon	104	1.03 (0.80–1.32)	303	**1.38 (1.18–1.61)**
	Proximal colon	35	1.02 (0.67–1.55)	110	**1.62 (1.25–2.11)**
	Distal colon	43	1.00 (0.69–1.45)	142	**1.32 (1.05–1.65)**
	Rectum	97	0.79 (0.61–1.02)	307	**1.22 (1.04–1.44)**
Cholesterol	**Colorectal**	206	0.97 (0.81–1.16)	659	**1.22 (1.11–1.35)**
	Colon	104	0.99 (0.78–1.25)	303	**1.30 (1.14–1.48)**
	Proximal colon	35	0.97 (0.65–1.45)	110	**1.36 (1.10–1.69)**
	Distal colon	43	0.98 (0.68–1.41)	142	**1.21 (1.00–1.46)**
	Rectum	97	0.98 (0.77–1.25)	307	**1.14 (1.00–1.30)**
Total SFAs	**Colorectal**	206	1.13 (0.82–1.56)	659	1.16 (0.97–1.39)
	Colon	104	1.29 (0.83–2.01)	303	1.15 (0.90–1.48)
	Proximal colon	35	1.52 (0.71–3.23)	110	1.22 (0.81–1.84)
	Distal colon	43	1.42 (0.74–2.72)	142	1.01 (0.71–1.44)
	Rectum	97	0.96 (0.62–1.48)	307	1.19 (0.93–1.53)
Total MUFAs	**Colorectal**	206	0.79 (0.55–1.14)	659	1.04 (0.86–1.27)
	Colon	104	0.72 (0.45–1.17)	303	1.06 (0.81–1.38)
	Proximal colon	35	0.53 (0.23–1.21)	110	0.98 (0.63–1.51)
	Distal colon	43	0.73 (0.36–1.48)	142	1.28 (0.88–1.88)
	Rectum	97	0.96 (0.58–1.56)	307	1.01 (0.78–1.32)
Total PUFAs	**Colorectal**	206	1.01 (0.78–1.31)	659	1.07 (0.92–1.23)
	Colon	104	1.15 (0.82–1.62)	303	1.05 (0.86–1.27)
	Proximal colon	35	1.35 (0.76–2.38)	110	1.31 (0.95–1.79)
	Distal colon	43	1.17 (0.70–1.94)	142	0.90 (0.68–1.18)
	Rectum	97	0.84 (0.59–1.20)	307	1.09 (0.90–1.33)

The bold values indicates the statistically significant results with p values <0.05.
Adjusted by province, age, SES, gender, BMI, tobacco use, opium use, aspirin use, physical activity, processed meat, fiber intake, calcium, energy intake.

Over time, the type of oil available on the Iranian market has changed. According to a WHO report published in 2018, Iranian households consume a great deal of cooking oil made from partially hydrogenated vegetable oils, a major source of trans fatty acids (TFAs) (56). In recent years, many activities have been conducted with the goal of increasing awareness of solid/semisolid hydrogenated oils and reducing their consumption in Iran (57, 58). People who are 50 or older seem to use more of this type of fat than people who are younger. TFAs could influence cholesterol balance and the effect exerted by the amount of total fat intake (59). This can be seen in our results, where total fat increases the risk of CRC according to the proportion of TFAs intake. Nevertheless, this suggestion requires further studies.

To our knowledge, this is the first study to investigate the magnitude of different types of FAs on CRC in a large Iranian population from different provinces and in the EMRO region. Our data are characterized by high quality because (i) information were collected by trained interviewers, (ii) same standardized validated FFQs and questioning tools were used in the different centers, and (iii) all cases were provided with pathological confirmation and allowed us analyses by subsites.

Two potential limitations of our study include: (i) selection bias, because the controls were not chosen on a population-based approach in the primary study (IROPICAN) but were rather taken among the healthy visitors who did not have CRC or other diseases. However, our validation study showed that due to appropriate using healthy visitors instead of disease controls such bias is minimal (60); (ii) reporting and recall bias, especially regarding the FFQ, because of the dependence on memory and possibly case-control status. However, it is likely that this bias might have operated in a similar way in cases and controls, resulting in non-differential misclassification and underestimation of the associations.

Furthermore, diet might have changed among cases because of disease development. To allay this concern and risk of reverse causation bias, we collected dietary information one year before the data of cancer diagnosis among cases. Also, food composition tables may have some limitations, and matching is not always straightforward, so that the results may be impaired by residual confounding. Anyway, the different results between colon and rectal cancer argue against a strong role of selection or information bias. Finally, we could not report different group of FAs based on specific source such as animal, vegetables, seeds, so on. Future studies should explore the relationship between different type of FAs and CRC by considering the source intake. Also, comparing dietary and plasma levels of FAs can be interesting.

Conclusion

In this large CRC case-control study, total fat, cholesterol, and higher intake of myristic acid, palmitic acid, palmitoleic acid from animal sources were associated with increased risk of CRC, and some FAs from plant sources such as heptanoic acid or oleic acid- the main FA in olive oil- decreased particularly colon cancer risk, after accounting for major adjustments. Moreover, subgroup analyses by age revealed that participants older than 50 years had a higher risk of CRC due to consumption of a high FAs diet. This may be due to the cohort effect and changes on the amount, and type of FAs intake over time. Our study improves general knowledge on CRC epidemiology and offers important insights on CRC in Iranian population. These data may be useful for the identification of high-risk individuals and public awareness to promote prevention of CRC in Iran and other LMICs that facing the increasing pattern in the incidence of CRC. In line with international evidence, the promotion of a decrease in fat consumption, especially FAs from industrial and animal sources, may decrease the risk of CRC among the Iranian population. Along these lines, a number of restrictions have been imposed in Iran since 1025 on oil products, including trans and saturated fat, aimed at controlling and preventing non-communicable diseases, including CRC (61).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD) (Code: IR.NIMAD.REC.1394.027). Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MSS, KZ, and PB designed research. MSS, KZ, RA-N, RS-F, HR, and MH conducted research. MSS, GC, KZ, and PB analyzed data, performed statistical analysis, and wrote the paper. FK, AE, MG, VC, IH, and EP contributed in the editing of the preliminary results and draft. KZ had primary responsibility for final content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Mainul Haque,
National Defence University of Malaysia, Malaysia

REVIEWED BY
Prakash Doke,
Bharati Vidyapeeth Deemed University, India
Sonali Palkar,
Bharati Vidyapeeth Deemed University, India

*CORRESPONDENCE
Minjie Chu
✉ chuminjie@ntu.edu.cn

†These authors have contributed equally to this work

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Optimum birth interval (36–48 months) may reduce the risk of undernutrition in children: A meta-analysis

James Ntambara†, Wendi Zhang†, Anni Qiu, Zhounan Cheng and Minjie Chu*

Department of Epidemiology, School of Public Health, Nantong University, Nantong, Jiangsu, China

Background: Although some studies have highlighted short birth interval as a risk factor for adverse child nutrition outcomes, the question of whether and to what extent long birth interval affects better nutritional outcomes in children remains unclear.

Methods: In this quantitative meta-analysis, we evaluate the relationship between different birth interval groups and child nutrition outcomes, including underweight, wasting, and stunting.

Results: Forty-six studies with a total of 898,860 children were included in the study. Compared with a short birth interval of <24 months, birth interval of ≥24 months and risk of being underweight showed a U-shape that the optimum birth interval group of 36–48 months yielded the most protective effect (OR = 0.54, 95% CI = 0.32–0.89). Moreover, a birth interval of ≥24 months was significantly associated with decreased risk of stunting (OR = 0.61, 95% CI = 0.55–0.67) and wasting (OR = 0.63, 95%CI = 0.50–0.79) when compared with the birth interval of <24 months.

Conclusion: The findings of this study show that longer birth intervals (≥24 months) are significantly associated with decreased risk of childhood undernutrition and that an optimum birth interval of 36–48 months might be appropriate to reduce the prevalence of poor nutritional outcomes in children, especially underweight. This information would be useful to government policymakers and development partners in maternal and child health programs, especially those involved in family planning and childhood nutritional programs.

KEYWORDS

birth interval, undernutrition, underweight, stunting, wasting

Introduction

Despite significant progress in reducing child mortality attributed to undernutrition, childhood undernutrition remains a major public health concern in developing countries. Undernutrition is most often measured by anthropometry and evaluated in terms of underweight, stunting, and wasting (1). These undernutrition indices are classified according to the World Health Organization (WHO) classification using child growth standard medians in terms of standard deviations (SDs) (2). Weight-for-age, height-for-age, and weight-for-height provide different information about the cognitive growth and body composition of children. Stunting (low height-for-age) captures early chronic exposure to undernutrition, wasting (low weight-for-height) captures acute undernutrition, and underweight (low weight-for-age) is a composite indicator that includes elements of stunting and wasting (3). Undernutrition, especially stunting, in the first 1,000 days of life, is associated with fewer neural connections in the brain, leading to poor cognitive development, and this damage is irreversible (4). Therefore, more attention should be paid to undernourished children to avoid the adverse health effects of this irreversible damage on their future growth and development.

The WHO 2025 global nutrition target is to reduce the prevalence of stunting by 40% and wasting to <5% (5). However, the progress toward childhood malnutrition in developing countries has been deplorably slow. Globally, malnutrition among children under 5 years of age is estimated to contribute to more than one-third of all deaths, although it is rarely listed as the direct cause (6). The United Nations Children's Fund (UNICEF), WHO, and the World Bank Group reports recently revealed that globally, stunting affected an estimated 21.3% or 144 million children under the age of 5 years, and wasting continued to threaten the lives of an estimated 6.9%, or 47 million children under 5 years (7). Africa and Asia have the greatest burden of childhood undernutrition and account for 55 and 39% of global cases of undernutrition, respectively. In addition, more than half of all stunted children under 5 years live in Asia, whereas more than one-third live in Africa. More than two-thirds and more than one-quarter of wasted under 5 years of age live in Asia and Africa (8).

Adequate nutrition is essential for the healthy growth and development of children. The consumption of nutrients by children begins long before birth. Undernutrition during pregnancy stunts fetal growth and can lead to poor brain development, resulting in irreversible damage (9). During the growth period, especially in the first 5 years of a child's life, undernutrition can cause serious effects, such as wasting and stunting (10). In addition, undernutrition also has a negative effect on children's social skills and psychological development, such that underweight and stunted children are more likely to exhibit apathy, fewer positive emotions, and more insecure attachments (11). These children will have more problems with behavior, attention, and social relationships during their school years compared with non-stunted children (12). The intellectual and psychological deficits caused by undernutrition can persist into adolescence, which can negatively affect the nation's gross domestic product (13, 14). As a result, it is necessary to identify the underlying risk factors associated with malnutrition, based on the adopted WHO malnutrition framework model, so that governments and stakeholders can implement evidence-based policy and provide practical guidelines to improve childhood nutrition status (2).

Various studies have identified that low dietary intake, low birth weight, higher birth order, low parental education level, exclusive breastfeeding more than 6 months of age, illnesses such as diarrhea, and sex of child (male) are contributing factors to childhood undernutrition (15–18). However, the birth interval or the time interval between successive live births is a risk factor that has received little attention. According to a recent study conducted in 34 sub-Saharan countries, short birth intervals (<24 months) are strongly associated with childhood undernutrition and a 57% higher risk of infant mortality (19). Separate studies and reviews have also identified that short birth intervals could adversely affect the nutritional status of the mother and the child (20–23). However, the question of whether and to what extent long birth interval has on better nutritional outcomes in children remains unclear. Therefore, the present study aimed to carry out an in-depth analysis to evaluate different birth interval groups and child nutrition outcomes, including underweight, wasting, and stunting.

Abbreviations: WHO, World Health Organization; SD, standard deviation; UNICEF, United Nations Children's Fund; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis; DHS, demographic health surveys.

Materials and methods

Literature search strategies

This is a meta-analysis study and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guideline to examine the pooled odds ratio of the birth interval and its association with child undernutrition. A comprehensive literature search of research studies published before 30 June 2022 was conducted. Different search engines including PubMed, Web of Science, Science Direct, Google scholar, and Cochrane library were methodically searched. We tried to search for studies in different languages, but only English articles appeared to have relevant data about birth intervals and undernutrition, so we only used a single language for the search.

A further computerized search was conducted using a combination of medical subject headings or keyword terms for birth interval and child undernutrition and was used separately in combination using Boolean operators such as "OR" or "AND." Terms for birth intervals included birth interval, birth spacing, interpregnancy interval, interbirth interval, preceding birth interval, and subsequent birth interval, and for the child undernutrition, these terms were also used: undernutrition, malnutrition, nutrition status, nutrition outcomes, child growth, stunting, wasting, and underweight.

Inclusion and exclusion criteria

Studies included in this review had to meet the following criteria: "(1) cross-sectional, case–control, or cohort studies that evaluated the relationship between birth interval and any of the child undernutrition indicators, namely underweight, stunting, and wasting; and (2) original data were available. Studies were excluded if they were case series or reports, editorials, and reviews and if original data to calculate the association were unavailable.

Data extraction

Two authors independently extracted all necessary data. The full text of these potentially eligible studies was retrieved and assessed for eligibility by two review team members. Any discrepancies were resolved jointly. The data extraction format included the first author's name, publication year, country, region, sample size, study design, interval group, undernutrition indicators measured, and the quality score of each study.

Quality assessment

Two authors independently assessed the quality of the eligible studies and controlled for possible bias by adapting specific protocol/sample characteristics. The criteria proposed in the

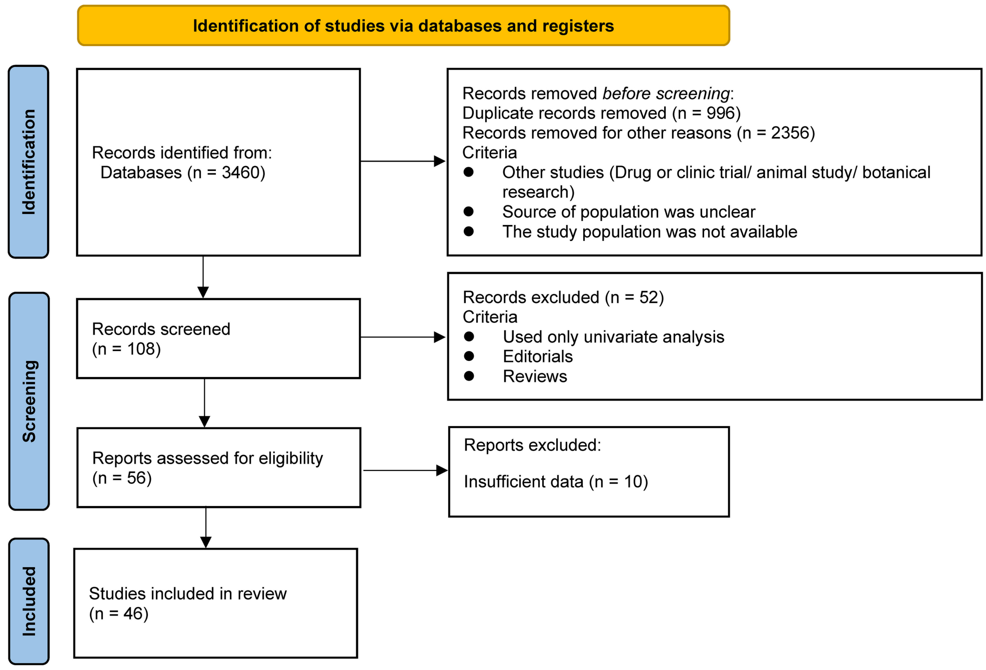

FIGURE 1
PRISMA flow diagram for the study selection process.

Newcastle–Ottawa Scale quality assessment tool were adapted and used to assess the quality of each study. Two authors independently assessed the quality of each original study using the tool. Discrepancies between the two authors were resolved jointly.

Statistical analysis

The effect size of the meta-analysis was an odds ratio of underweight, stunting, and wasting reported in each study about the birth interval applied, the pooled odds ratio with a confidence interval of underweight, stunting, and wasting, according to the birth intervals grouped into (<24 and ≥24) were estimated. When heterogeneity between studies was absent, we merged the results using fixed effect models. Otherwise, a random-effects model was chosen. Subgroup analyses were conducted for the studies according to regions and by considering the birth intervals, which were classified into 24–48 against <24 and ≥48 against <24 to determine the extent to which a certain birth interval used is considered a risk factor or protective according to the nutrition outcomes (underweight, stunting, and wasting). To determine the extent of publication bias, funnel plots were scattered and tested for asymmetry, and Begg's tests were computed. The analysis was performed using STATA version 15 statistical software (24).

Outcome definition

This study had three main outcomes; undernutrition was the main outcome and had three different indicators: underweight, stunting, and wasting. Each of the three indicators was measured independently according to WHO classification using child growth standard medians in terms of standard deviations (2). The first outcome was underweight, which was defined as a weight-for-age Z-score below minus two standard deviations (−2 SD) from the mean of the reference population. The second outcome was stunting, defined as a height-for-age Z-score of <-2 SD from the mean of the reference population. The third outcome was wasting, which was defined as a weight-for-height Z-score of <-2 SD from the mean of the reference population (25).

Results

Study selection

As shown in Figure 1, our literature search strategy identified 3,460 studies that were exported to the database; 3,352 studies were first excluded (996 of which were excluded because of duplication, 2,356 were excluded because the study type did not match, the population source was unclear, and the study population was not available), resulting in 108 studies with titles and abstracts screened for the relevance. Of these, 52 studies were removed because they used only univariate analysis or the type of literature was Editorials or Reviews. The remaining 56 relevant studies were evaluated, and 10 of them were excluded because of insufficient data on the relationship between birth spacing and child nutrition outcomes. Finally, 46 eligible studies were included in the analysis (1, 15, 19, 22, 23, 25–65). Regarding the child nutrition outcomes reported in the total 46 studies with data, 27 underweight data were reported, 23 stunting data were reported among all studies, and 13 wasting data were reported; seven studies reported all three undernutrition indicators in their result tables.

TABLE 1 Characteristics of literature included in the study.

Number	First author	Year	Country	Region	Sample size	Study design	Interval group (months)	Undernutrition indicators reported			Quality
								Underweight	Stunting	Wasting	Scores
1	Bater	2020	Uganda	Africa	3,337	DHS[b]	≤24; >24	√			8
2	Kahssay	2020	Ethiopia	Africa	269	Case-control	<24; ≥24		√		7
3	Yaya	2020	Multi[a]	Africa	171,371	DHS	<24; 24–47; ≥48		√		9
4	Das	2020	India	Asia	3,578	DHS	<24; ≥24		√		8
5	Ntenda	2019	Malawi	Africa	4,047	DHS	<24; 24–47; ≥48	√	√	√	8
6	Khatun	2019	Bangladesh	Asia	16,626	DHS	≤23; 24–47; ≥48		√	√	9
7	Takele	2019	Ethiopia	Africa	8,743	DHS	<24; 24–47; ≥48		√		8
8	Gupta	2019	Afghanistan	Asia	2,199	DHS	<24; 24–47; ≥48	√			7
9	Dessie	2019	Ethiopia	Africa	6,009	DHS	<24; 24–47; ≥48			√	8
10	Yaya	2019	Multi[a]	Africa	299,065	DHS	<24; 24–36; 37–59; ≥60	√	√	√	9
11	Fenta	2019	Ethiopia	Africa	7,830	DHS	<24; 24–35; 36–47; 48–59; ≥60		√		8
12	Fatemi	2018	Iran	Asia	172	Case-control	<24; 24–47; >48		√		7
13	Ansuya	2018	India	Asia	349	Case-control	<24; 24–47; >48	√			7
14	Talukder	2018	Bangladesh	Asia	7,102	DHS	<24; 24–47; >48		√		7
15	Talukder	2017	Bangladesh	Asia	7,102	DHS	<24; 24–47; ≥48	√			8
16	Remonja	2017	Madagascar	Africa	530	Case-control	<24; 24–47; ≥48		√		7
17	Pravana	2017	Nepal	Asia	277	Case-control	<24; ≥24			√	7
18	Kismul	2017	Congo	Africa	6,674	Case-control	<24; 24–47; ≥48		√		8
19	Mulugeta	2017	Ethiopia	Africa	321	DHS	<24; 24–48; >48	√	√	√	8

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TABLE 1 (Continued)

Number	First author	Year	Country	Region	Sample size	Study design	Interval group (months)	Undernutrition indicators reported			Quality
								Underweight	Stunting	Wasting	Scores
20	Darsene	2017	Ethiopia	Africa	811	DHS	<24; ≥24			√	7
21	Abera	2017	Ethiopia	Africa	342	DHS	<24; 24–35; 36–47; ≥48	√			7
22	Batiro	2017	Ethiopia	Africa	465	Case-control	≤24; >24		√		8
23	Olita'a	2014	Papua New Guinea	Oceania	68	Case-control	≤24; >24	√			7
24	Egata	2014	Ethiopia	Africa	2,199	Case-control	<24; ≥24			√	7
25	Khanal	2014	Nepal	Asia	3,490	DHS	<24; ≥24	√			8
26	Shahjada	2014	India	Asia	332	Case-control	<24; 24–48; >48	√	√	√	6
27	Adekanmbi	2013	Nigeria	Africa	2,8647	DHS	<24; ≥24		√		8
28	Ikeda	2013	Cambodia	Asia	7,453	DHS	<24; 24–47; ≥48	√	√	√	8
29	Sebayang	2012	Indonesia	Asia	8,568	Case-control	≤24; >24	√			9
30	Das	2011	Bangladesh	Asia	5,896	DHS	<24; 24–47; ≥ 48	√			8
31	Gribble	2009	El Salvador	America	3,852	DHS	<24; 24–35; 36–59; ≥60	√	√		8
32	Zottarelli	2007	Egypt	Africa	7,400	DHS	<23; 24–35; 36–47; ≥48	√	√	√	8
33	Som	2007	India	Asia	2,835	DHS	<24; ≥24		√		8
34	Som	2006	India	Asia	1,186	DHS	<24; 24–47; ≥ 48	√	√	√	7
35	Hosain	2006	Bangladesh	Asia	227	DHS	<24; ≥24	√			7
36	Aerts	2004	Brazil	America	3,289	Case-control	<24; >24		√		8
37	Kurup	2004	Oman	Asia	1,198	Case-control	<24; >24	√			8
38	Mozumder	2000	Bangladesh	Asia	1,562	DHS	<24; 25–36; 37–48; ≥49	√			8
39	BP Zhu	1999	USA	America	173,205	DHS	<24; 24–59; 60–119; ≥120	√			9
40	Basso	1998	Denmark	Europe	10,187	DHS	<24; 24–36; >36	√			8

(Continued)

TABLE 1 (Continued)

Number	First author	Year	Country	Region	Sample size	Study design	Interval group (months)	Undernutrition indicators reported			Quality
								Underweight	Stunting	Wasting	Scores
41	Basso	1998	Denmark	Europe	55,201	DHS	<24; 24–36; 36–60; >60	√			9
42	Adams	1997	Georgia	Europe	28,273	DHS	<24; 24–35; 36–47; ≥48	√			9
43	Hoa	1996	Vietnam	Asia	774	DHS	≤23; 24–35; ≥36	√			7
44	Huttly	1992	Brazil	America	3,586	DHS	<24; 24–35; 36–47; 48–71; >71	√			8
45	Thaver	1990	Pakistan	Asia	318	Case-control	<24; >24	√			7
46	Bertrand	1988	Zaire	Africa	1,895	DHS	<24; >24		√	√	8

[a]Including 34 sub-Saharan countries.
[b]Demographic health surveys.

Description of included studies

As shown in Table 1, 46 studies involving 898,860 children were included to examine the relationship between birth interval and child nutrition outcomes. Most of the included studies were cross-sectional studies; 32 of the 46 studies were demographic health survey (DHS)-based cross-sectional studies. Concerning the study regions, 18 studies were conducted in Africa, 20 studies in Asia, and eight studies in others. The quality score among the 46 included studies ranged from 6 to 9.

Quantitative synthesis

As shown in Figure 2, compared with the birth interval of <24 months, the birth interval of ≥24 months was significantly associated with a decreased risk of being underweight (OR = 0.78, 95% CI = 0.72–0.85). Furthermore, when we further divided the birth intervals into subgroups, birth intervals and risk of being underweight showed a U-shape. As shown in Figures 2, 3, compared with the birth interval of <24 months group, the birth interval group of 24–36 months was significantly associated with a 22% decreased risk of being underweight (OR = 0.78, 95% CI = 0.67–0.91), while the group of 36–48 months was 46% more protective (OR = 0.54, 95% CI = 0.32–0.89). However, there was no protective effect in the group with a birth interval of ≥60 months when compared with the birth interval of <24 months (OR = 1.07, 95% CI = 0.83–1.38). Interestingly, in contrast, the birth interval group of ≥120 months was significantly associated with a 115% increased risk of being underweight when compared with the birth interval of <24 months (OR = 2.15, 95% CI = 1.89–2.44). Meanwhile, in the subgroup analysis based on regions (Figure 2), the protective effect was significant in Africans (OR = 0.53, 95% CI = 0.36–0.78) and Asians (OR = 0.80, 95% CI = 0.71–0.90).

Moreover, as shown in Figures 4, 5, compared with a birth interval of <24 months, a birth interval of ≥24 months was significantly associated with a decreased risk of stunting (OR = 0.61, 95% CI = 0.55–0.67) and wasting (OR = 0.63, 95% CI = 0.50–0.79), respectively. We further divided the birth interval into subgroups, the birth interval group of <24 months was considered as the reference group, as shown in Figure 4, and the results showed that the birth interval group of 24–48 months was significantly associated with a decreased risk of stunting (OR = 0.82, 95% CI = 0.77—0.88), while the above 48 months groups yielded a clearer protective effect of stunting compared with a birth interval of <24 months (OR = 0.63, 95% CI = 0.57–0.71). In the subgroup analysis based on regions, the protective effects with a birth interval of ≥24 months for stunting were both significant in Africans and Asians, while similar results were observed for wasting in Africans.

Publication bias

We then utilized the funnel plot and Begg's test to evaluate potential publication bias in the literature. The funnel plots were symmetrical in all the studied undernutrition outcomes (Figure 6). Moreover, Begg's

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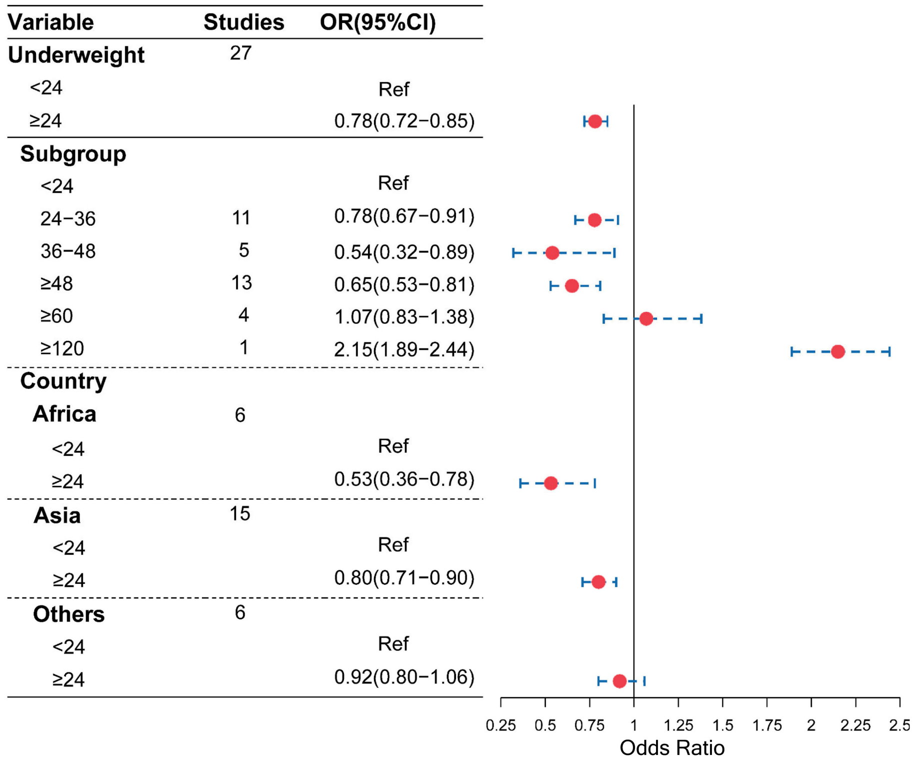

FIGURE 2
Association of the birth interval and child underweight.

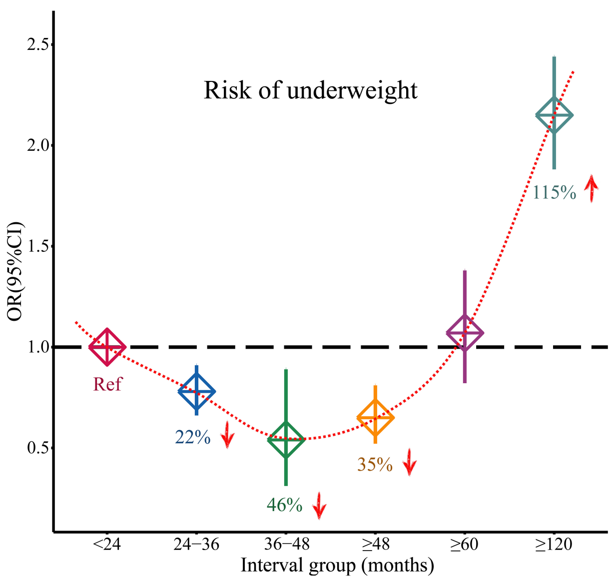

FIGURE 3
Changed effects of different birth interval groups and child underweight (<24 birth interval group was considered as the reference group; squares represent the ORs, and vertical lines represent the corresponding 95% CI).

test provided further statistical evidence for the absence of publication bias in all the studied undernutrition outcomes ($P > 0.05$).

Discussion

The results of our study show that a longer birth interval (≥24 months) is significantly associated with a reduced risk of childhood undernutrition. Moreover, birth interval of ≥24 months and risk of underweight showed a U-shape that the optimum birth interval group of 36–48 months had the most protective effect compared with the birth interval of <24 months.

The most important risk factors for child undernutrition have been proven to occur early in life, including inadequate breastfeeding and maternal undernutrition during pregnancy (13). If longer birth intervals are maintained appropriately, more time will be provided for the care of older children, including the possibility of extended breastfeeding. The mother will also have time to recover from the nutritional burden of the last pregnancy, reducing the risk of undernutrition during the next pregnancy. Our study shows that an optimum birth interval between 36 and 48 months is independently associated with a significantly decreased risk of a child being underweight. Although the results cannot be directly compared with some studies due to different birth spacing boundaries and definitions, most studies report similar associations between birth spacing and poor child health outcomes. A cross-sectional study found that compared with the birth interval of >24 months, the risk of undernutrition was 1.43 times higher in children with birth intervals of <24 months (66). Moreover, a meta-analysis also reported a 3-fold increase in the odds of low birth weight for infants born <24 months apart (67). Generally, the short birth interval plays a major role in pregnancy outcomes, particularly among

Variable	Studies	OR(95%CI)
Stunting	23	
<24		Ref
≥24		0.61(0.55−0.67)
Subgroup		
<24		Ref
24−48	13	0.82(0.77−0.88)
≥48	13	0.63(0.57−0.71)
Country		
Africa	13	
<24		Ref
≥24		0.58(0.51−0.66)
Asia	8	
<24		Ref
≥24		0.71(0.65−0.78)
Others	2	
<24		Ref
≥24		0.43(0.20−0.94)

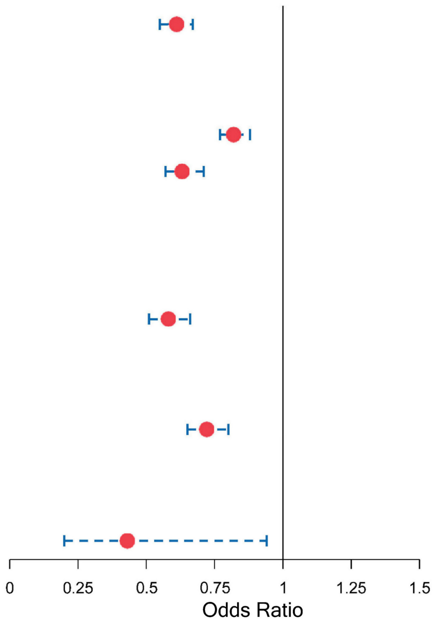

FIGURE 4
Association of birth interval and child stunting.

Variable	Studies	OR(95%CI)
Wasting	13	
<24		Ref
≥24		0.63(0.50−0.79)
Subgroup		
<24		Ref
24−48	8	0.86(0.70−1.05)
≥48	8	0.79(0.62−1.00)
Country		
Africa	8	
<24		Ref
≥24		0.54(0.37−0.79)
Asia	5	
<24		Ref
≥24		0.76(0.52−1.12)

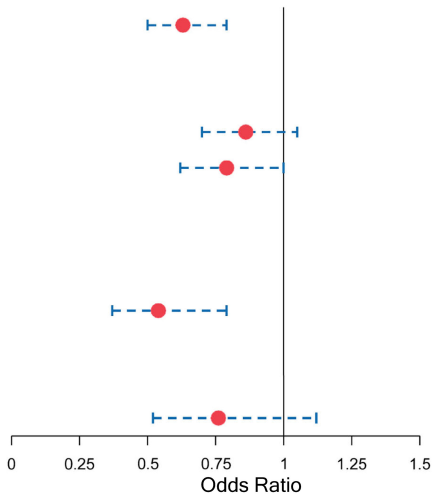

FIGURE 5
Association of birth interval and child wasting.

mothers with poor nutritional status, those with social-economic problems, and those with limited access to quality healthcare (68). The maternal nutrition depletion hypothesis states that a close sequence of pregnancies and periods of lactation worsens the mother's nutritional status (69, 70). This is because there is not enough time for the mother to recover from the physiological stresses of pregnancy before she is re-subjected to the stress. Our findings demonstrate that moderate birth intervals between 36 and 48 months would provide a mother with sufficient time to recover from the nutritional burden of pregnancy inherent during the prenatal period.

Some researchers have stipulated that having short birth intervals are caused by socioeconomic status, poorer lifestyles, failure to or inadequate use of healthcare services

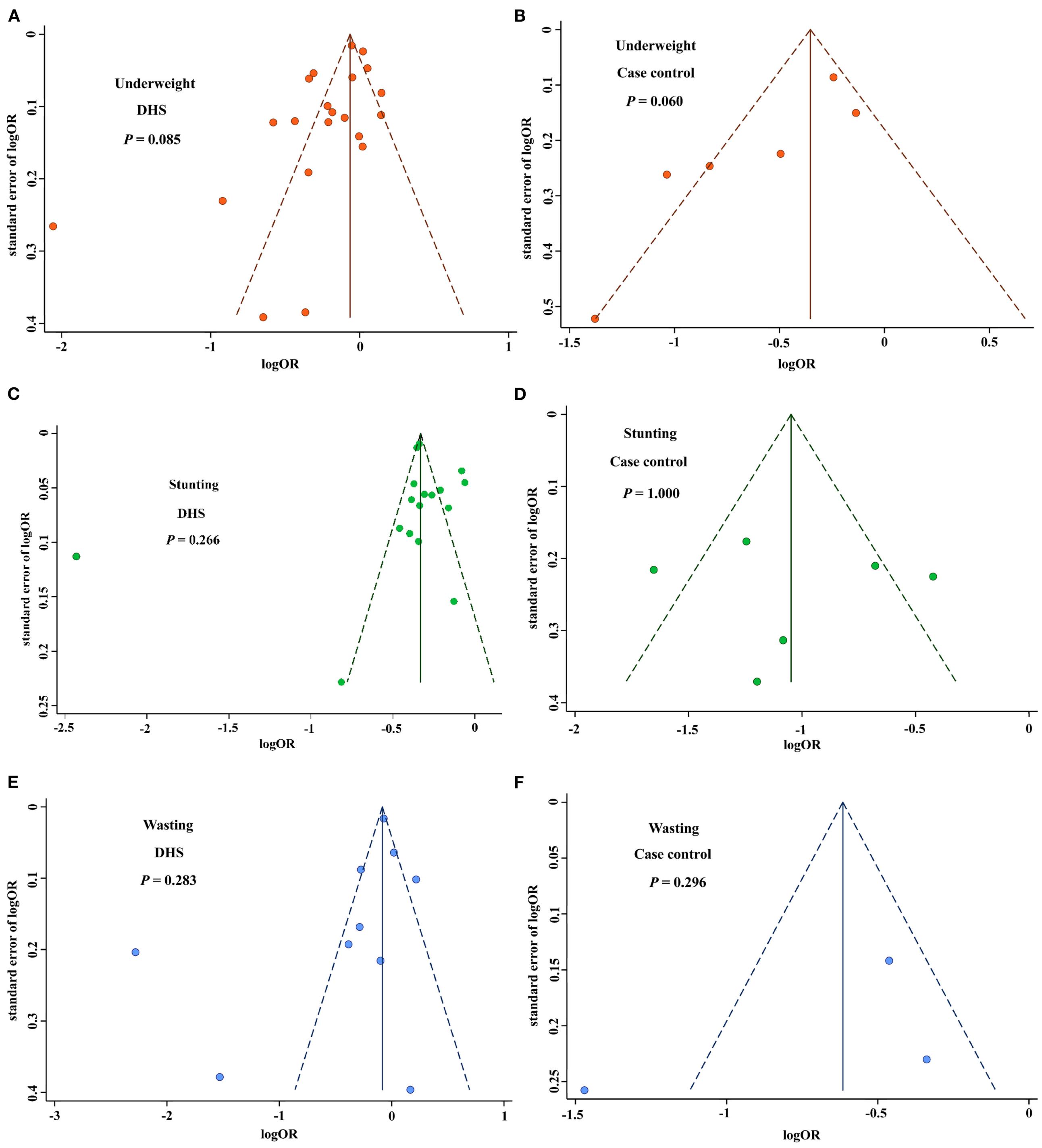

FIGURE 6
Funnel plot for publication bias of birth interval and childhood nutrition outcomes. **(A)** Funnel plot for publication bias of underweight based on the DHS studies. **(B)** Funnel plot for publication bias of underweight based on the case-control studies. **(C)** Funnel plot for publication bias of stunting based on the DHS studies. **(D)** Funnel plot for publication bias of stunting based on the case-control studies. **(E)** Funnel plot for publication bias of wasting based on the DHS studies. **(F)** Funnel plot for publication bias of wasting based on the case-control studies. DHS, demographic health surveys.

such as healthcare advice provided by healthcare advisers at community health centers, and other behavioral or physiological determinants, which will, in turn, lead to poorer pregnancy outcomes leading poor child nutrition outcomes (71, 72).

However, the effect of short birth intervals on children's nutritional status was not attenuated when socioeconomic and maternal characteristics were controlled (23, 73). This fact confirms that these confounding factors do not cause poor nutritional status endings, and short birth intervals are more likely to be an independent cause of poor nutritional status. Therefore, health policymakers should design appropriate policies to maintain desirable birth intervals, strengthen existing maternal and child nutrition interventions, and promote other relevant strategies to reduce child undernutrition, especially in developing countries.

This study had several strengths. First, our study presented a comparison between birth interval and all three undernutrition indicators: underweight, stunting, and wasting. Second, over 85% of the studies included in our meta-analysis were conducted in low-income and middle-income countries, which are mainly found in Africa and Asia, where the burden of child undernutrition is high. Therefore, this study supports the call to address the underlying causes of acute and chronic childhood undernutrition. Third, this study has identified areas where fellow researchers can design appropriate and strategic interventions to help the community to have healthy birth spacing based on our recommended birth interval.

There were some limitations to this study. First, there were few studies in developed countries, even though undernutrition is more prevalent in developing countries, so the results cannot be easily generalized. In addition, in many studies, assessing the relationship between birth interval and child nutritional outcomes was not a primary objective because birth interval was only one of the many variables examined. Most studies often lacked an assessment of all three nutritional indicators, namely, stunting, wasting, and underweight in their analysis. For three categories of child nutritional outcomes, further studies including a more comprehensive assessment of potentially confounding variables are needed to extract the complex factors involved in the relationship between birth interval and child nutritional outcomes.

Conclusion

Our study reveals that a longer birth interval ($\geq$24 months) is significantly associated with decreased risk of childhood undernutrition including underweight, stunting, and wasting. More importantly, the optimum birth interval of 36–48 months yielded the most protective effect for underweight, and this would allow for repletion prior to the next conception and conserves required nutrients for the baby's growth during and after the delivery, hence boosting further child nutrition status while reducing unacceptably high burden of child undernutrition.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JN, WZ, AQ, and ZC contributed to the literature search and painting of all figures. JN wrote the manuscript. WZ contributed to the critical revision of the manuscript. MC designed the study and had full access to all data in the study and take full responsibility for the accuracy of the analyses and their interpretation. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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