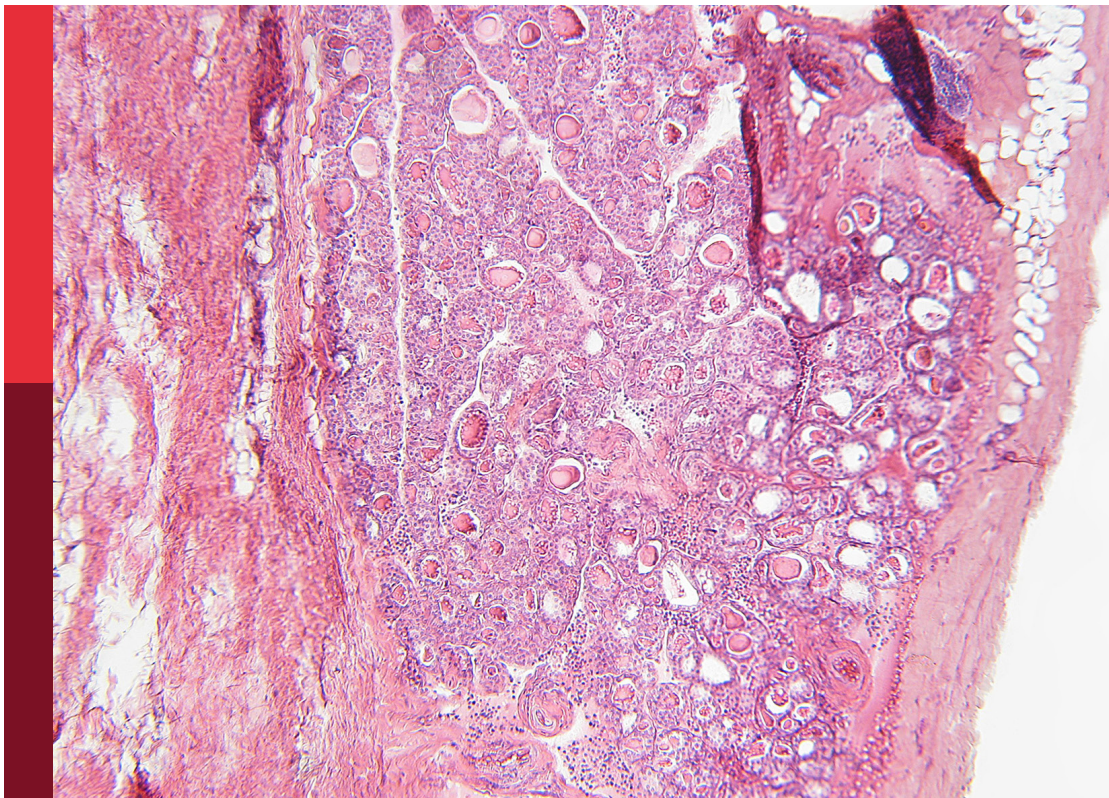
frontiers | Research Topics

Preventing cardiovascular complications of type 2 diabetes, volume II

Edited by
Caterina Pipino, Maria Pompea Antonia Baldassarre, Kyoungmin Park and Teresa Paolucci

Coordinated by
Nadia Di Pietrantonio

Published in
Frontiers in Endocrinology



FRONTIERS EBOOK COPYRIGHT STATEMENT

The copyright in the text of individual articles in this ebook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this ebook is the property of Frontiers.

Each article within this ebook, and the ebook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this ebook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or ebook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-8325-7502-4
DOI 10.3389/978-2-8325-7502-4

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Preventing cardiovascular complications of type 2 diabetes, volume II

Topic editors

Caterina Pipino — University of Studies G. d'Annunzio Chieti and Pescara, Italy

Maria Pompea Antonia Baldassarre — G. d'Annunzio University of Chieti and Pescara, Italy

Kyoungmin Park — Joslin Diabetes Center, Harvard Medical School, United States

Teresa Paolucci — University of Studies G. d'Annunzio Chieti and Pescara, Italy

Topic coordinator

Nadia Di Pietrantonio — Università degli Studi G. d'Annunzio Chieti e Pescara, Italy

Citation

Pipino, C., Baldassarre, M. P. A., Park, K., Paolucci, T., Di Pietrantonio, N., eds. (2026). *Preventing cardiovascular complications of type 2 diabetes, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7502-4

Table of contents

05 Editorial: Preventing cardiovascular complications of type 2 diabetes, volume II
Nadia Di Pietrantonio, Maria Pompea Antonia Baldassarre, Ilaria Cappellacci, Teresa Paolucci, Kyoungmin Park and Caterina Pipino

09 The triglyceride–glucose index is a promising predictor for the risk of cardiovascular disease in the diabetic population aged ≥60 years in the United States: a retrospective cohort study from NHANES (2007-2016)
Shu Yang and Zhenwei Wang

22 Evaluation of three mechanisms of action (SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas) in treating type 2 diabetes with heart failure: a systematic review and network meta-analysis of RCTs
Huize Gao, Qian Wei, Anqi Zou, Keying Yu, Da Song, Jian Li, Huize Han and Aidong Liu

38 Association between glycemia risk index and carotid intima-media thickness in type 2 diabetes
Lingyun Zhao, Hongyan Heng, Qinyuan Xie, Chenghong Liang, Sijia Guo, Ziyi Zhang and Huijuan Yuan

48 Establishment of a synthetic ECV model and its prognostic value in diabetes patients with acute myocardial infarction
Lei Chen, Bowen Qiu, Xinjia Du, Jiahua Liu, Yuan Lu, Wenliang Che and Wensu Chen

62 A decade of progress in type 2 diabetes and cardiovascular disease: advances in SGLT2 inhibitors and GLP-1 receptor agonists – a comprehensive review
David Aristizábal-Colorado, David Corredor-Rengifo, Santiago Sierra-Castillo, Carolina López-Corredor, David-Alexander Vernaza-Trujillo, Danilo Weir-Restrepo, Juan S. Izquierdo-Condoy, Esteban Ortiz-Prado, Jorge Rico-Fontalvo, Juan-Esteban Gómez-Mesa, Alin Abreu-Lomba and Wilfredo-Antonio Rivera-Martínez

77 Association of estimated glucose disposal rate with atrial fibrillation, heart failure and cardiovascular mortality in patients with diabetes: a prospective cohort study from the UK Biobank
Zhen Tan, Yijun Liu, Lei Liu, Shuang Li, Xinrui Xue, Xiaoping Li and Hongqiang Ren

92 Effectiveness and use of evidence-based cardiovascular preventive therapies in type 2 diabetes patients with established or high risk of atherosclerotic cardiovascular disease
Jian-Qing Tian, Zhi-Jun Zhang, Yi-Ting Peng, Jia-Wen Ye, Zhi-Yi Wang and Yu-Hao Lin

105 Association between the triglyceride-glucose index and hyperuricemia: potential role of obesity in patients with Type 2 diabetes mellitus
Dou Tang, Xi Gu, Yan Xuan, Fanfan Zhu, Ying Shen and Leiqun Lu

114 Association of blood urea nitrogen to serum albumin ratio with arterial stiffness in type 2 diabetes patients: a Chinese cross-sectional study
Shengqing He, Wanrui Meng, Miaoling Huang, Qingsong Fu and Jie Shen

124 Unveiling the anti-inflammatory potential of olive leaf phenolic extracts in diabetes-related endothelial dysfunction
Ilaria Cappellacci, Nadia Di Pietrantonio, Davide Viola, Gloria Formoso, Małgorzata Elżbieta Zujko, Beatriz Martín-García, Ana M. Gomez-Caravaca, Vito Verardo, Assunta Pandolfi and Caterina Pipino

139 Glycemic variability of glycated hemoglobin in patients with type 2 diabetes mellitus and the risk of cardiovascular diseases: a latest systematic review and meta-analysis
Chan Wu, Aijing Li, Qingyi Zhu, Jingyi Guo, Yincheng Li, Xin Gu, Anning Sun, Maoying Wei and Yanbing Gong

158 Coronary heart disease and type 2 diabetes metabolomic signatures in the Middle East
Mohamed Elshrif, Keivin Isufaj, Ayman El-Menyar, Ehsan Ullah, Alka Beotra, Mohammed Al-Maadheed, Vidya Mohamed-Ali, Mohamad Saad and Jassim Al Suwaidi

178 The association between residual cholesterol to high-density lipoprotein cholesterol ratio and type 2 diabetes risk in elderly populations
Jinting Zhang, Zhaoxiang Wang, Qianqian Wang, Yang Liu, Qi Shao, Ying Pan and Shao Zhong

frontiers | Frontiers in Endocrinology

TYPE Editorial
PUBLISHED 29 January 2026
DOI 10.3389/fendo.2026.1792059

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

*CORRESPONDENCE
Caterina Pipino
caterina.pipino@unich.it

RECEIVED 20 January 2026
ACCEPTED 21 January 2026
PUBLISHED 29 January 2026

CITATION
Di Pietrantonio N, Baldassarre MPA, Cappellacci I, Paolucci T, Park K and Pipino C (2026) Editorial: Preventing cardiovascular complications of type 2 diabetes, volume II. *Front. Endocrinol.* 17:1792059. doi: 10.3389/fendo.2026.1792059

COPYRIGHT
© 2026 Di Pietrantonio, Baldassarre, Cappellacci, Paolucci, Park and Pipino. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Preventing cardiovascular complications of type 2 diabetes, volume II

Nadia Di Pietrantonio[1,2], Maria Pompea Antonia Baldassarre[2,3], Ilaria Cappellacci[1,2], Teresa Paolucci[4,5], Kyoungmin Park[6] and Caterina Pipino[1,2]*

[1]Department of Medical, Oral and Biotechnological Sciences, G. d'Annunzio University, Chieti, Italy, [2]Center for Advanced Studies and Technology (CAST), G. d'Annunzio University, Chieti, Italy, [3]Department of Medicine and Aging Sciences, G. d'Annunzio University, Chieti, Italy, [4]Department of Medical, Oral and Biotechnological Sciences, Center of Rehabilitation, Sports and Disability (CARES), G. d'Annunzio University, Chieti, Italy, [5]BIND Center, Physical and Rehabilitation Medicine, G. d'Annunzio University, Chieti, Italy, [6]Research Division, Joslin Diabetes Center, Department of Medicine, Harvard Medical School, Boston, MA, United States

KEYWORDS

cardiovascular risk, glycemic variability, novel biomarkers, precision medicine, type 2 diabetes

Editorial on the Research Topic
Preventing cardiovascular complications of type 2 diabetes, volume II

Diabetes mellitus represents a major global health challenge, with a rapidly increasing prevalence worldwide, and is associated with a markedly elevated risk of adverse health outcomes, particularly cardiovascular disease (CVD) (1). Individuals with diabetes have a substantially higher likelihood of developing vascular complications, which are classified as microvascular—such as diabetic nephropathy and retinopathy—or macrovascular, including coronary artery disease, stroke, and peripheral artery disease. Consequently, substantial efforts are required to implement innovative technologies and strategies aimed at preventing cardiovascular complications in individuals with type 2 diabetes (T2D), through both lifestyle modification and early, accurate, and effective diagnosis.

Unveiling new risk markers for cardiovascular outcomes in diabetes

The search for new strategies to prevent diabetes and its cardiovascular complications increasingly emphasizes the identification of novel biomarkers and the re-evaluation of established ones, aiming to enable earlier and more precise risk assessment (2). One such area of interest is glycemic variability.

Wu et al. conducted a systematic review and meta-analysis to determine whether fluctuations in glycated hemoglobin (HbA1c) predict cardiovascular risk in patients with T2D. While mean HbA1c remains the standard measure of long-term glycemic control, it fails to capture short-term glucose swings and can be influenced by factors such as anemia or pregnancy. Evidence indicates that glycemic variability-measured through HbA1c

standard deviation, coefficient of variation, and indices like the HbA1c variability score or hemoglobin glycation index—may independently contribute to vascular outcomes. Wu et al. provide the first population-level evidence that HbA1c fluctuations themselves significantly increase cardiovascular risk, even when mean HbA1c levels are within target ranges, highlighting a new avenue for precision glycemic management.

Beyond glycemic variability, lipid-based markers are emerging as important predictors of both diabetes and cardiovascular complications. The remnant cholesterol to HDL-C ratio (RC/HDL-C) has recently gained attention as an indicator of metabolic disturbances. In a cohort of 7,655 Chinese adults aged ≥60 years, Tang et al. observed that elevated RC/HDL-C levels were independently associated with an increased risk of T2D. The results suggest that RC/HDL-C could enhance existing risk models. Zhang et al. similarly confirmed these findings, demonstrating that participants in the highest RC/HDL-C quartile had the greatest incidence of T2D, reinforcing its role as an independent risk factor in older adults and a potential tool for improving risk stratification in predictive models.

Another readily available biomarker is the Triglyceride–Glucose (TyG) index, a low-cost surrogate marker of insulin resistance. The TyG index appears to reflect aspects of dynamic glycemic instability that may contribute to vascular injury beyond chronic hyperglycemia. In a retrospective analysis of NHANES participants aged ≥60 years, S. Yang et al. found that both very low and very high TyG values were linked to elevated cardiovascular risk, highlighting the complexity of metabolic regulation in older individuals.

Collectively, these studies underscore the critical importance of dynamic metabolic markers in improving risk prediction for diabetes and its cardiovascular complications. Integrating these novel indicators with traditional measures could enable more individualized, precise strategies for early detection, prevention, and management of vascular risk in older adults with or at risk for T2D.

Integrating metabolomics to uncover cardiovascular risk diabetes

In recent years, cardiovascular phenotyping has advanced through the use of unbiased, high-throughput omics technologies capable of simultaneously analyzing genes, transcripts, proteins, and metabolites (3). These approaches have greatly expanded our understanding of disease pathways and potential biomarkers. In T2D and its cardiovascular complications, integrating multiple omics layers offers the opportunity to detect early endothelial dysfunction, clarify pathophysiological mechanisms, and identify novel predictive markers. Among these technologies, metabolomics is particularly valuable: it reflects both genetic and environmental influences such as diet, lifestyle, medication, microbiome. This makes it a promising tool for developing diagnostic, prognostic, and therapy-response biomarkers, ultimately supporting more personalized diabetes care.

Despite substantial progress, metabolomic interactions between T2D and coronary heart disease (CHD) remain poorly characterized in Middle Eastern populations, where T2D prevalence is among the highest globally. Addressing this gap, Elshrif et al. conducted the first large-scale metabolomics study of T2D and CHD in Qatar. Through univariate and multivariate analyses, pathway enrichment, machine learning, and metabolite-based risk scores, the authors identified marked metabolic differences between T2D patients with and without CHD. Metabolite risk scores showed strong predictive performance, underscoring its potential clinical practicality.

Overall, this work highlights distinct metabolic signatures associated with CHD in T2D patients and proposes candidate biomarkers for earlier detection, improved risk stratification, and future therapeutic targeting in an underrepresented population.

Natural compounds for preventing diabetic vascular dysfunction

Despite significant advances in diabetes care, lifestyle measures like healthy eating and regular exercise remain the foundation of managing T2D. However, these strategies alone are often not enough to prevent or reduce the vascular complications associated with diabetes, highlighting the need for additional therapeutic approaches. In this context, natural bioactive compounds, especially polyphenols, have attracted growing interest due to their strong anti-inflammatory, antioxidant, and heart-protective effects (4). Olive leaves, in particular, are a largely underutilized source of polyphenols, notably oleuropein, which can reduce oxidative stress, prevent blood clotting, and improve insulin sensitivity and blood sugar control.

The study by Cappellacci et al. observed that extracts from two spanish olive monocultivars, Picual and Changlot Real, reduce endothelial inflammation—a key factor in diabetes-related vascular problems. Using the *in vitro* model of human umbilical vein endothelial cells from women with gestational diabetes, the researchers showed that both extracts could influence the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)–Vascular cell adhesion protein 1 (VCAM-1) pathway, lowering inflammation and monocyte adhesion. These results suggest that olive leaf polyphenols may help protect against vascular complications in diabetes, highlight the potential of natural compounds, such as olive-derived polyphenols, to complement existing diabetes management strategies.

Protecting the diabetic heart: early risk to prevention

T2D significantly increases the risk of CVD by damaging the vascular endothelium and promoting processes that accelerate atherosclerosis and arterial stiffening. These changes contribute directly to the development of myocardial infarction, heart failure, and arrhythmias such as atrial fibrillation, making

cardiovascular complications the leading cause of morbidity and mortality in people with diabetes. This underscores the urgent need for early detection of individuals at high cardiac risk and for strategies aimed at protecting heart health in the context of T2D.

Several recent studies have explored practical, non-invasive markers to improve early risk stratification in T2D. Zhao et al. investigated the Glycemia Risk Index (GRI) in relation to carotid intima–media thickness (CIMT), a recognized indicator of subclinical atherosclerosis. In a cohort of 450 hospitalized adults with T2D, the study demonstrated that GRI correlates with CIMT, suggesting its potential as a convenient tool for detecting early macrovascular risk and complementing continuous glucose monitoring-based assessments.

Arterial stiffness represents another early and independent predictor of cardiovascular and renal outcomes. Using brachial–ankle pulse wave velocity (baPWV), He et al. examined its association with the blood urea nitrogen–to–albumin ratio (BAR) in 510 newly diagnosed, drug-naïve T2D patients. The study found a significant positive relationship, indicating that BAR may serve as a simple biomarker to identify early vascular changes in this population.

Insulin sensitivity also plays a key role in cardiovascular risk. Tan et al. evaluated the estimated glucose disposal rate (eGDR) in over 31,000 adults with diabetes from the UK Biobank. Higher eGDR was associated with substantially lower risks of atrial fibrillation, heart failure, and cardiovascular mortality, regardless of genetic risk. These findings position eGDR as a robust and clinically meaningful marker for predicting cardiovascular outcomes in diabetes.

Finally, myocardial fibrosis following acute myocardial infarction (AMI) is a critical determinant of prognosis but is difficult to assess directly during the acute phase. Chen et al. validated a synthetic extracellular volume (ECV) measure derived from cardiac magnetic resonance imaging, which does not require blood sampling. In patients with T2D and AMI, synthetic ECV closely matched conventional ECV measurements and independently predicted major adverse cardiovascular events, demonstrating its potential as a non-invasive prognostic tool.

Taken together, these studies highlight the critical need for early cardiovascular risk detection in diabetes. By incorporating novel heart-focused biomarkers—spanning glycemic instability, arterial stiffness, insulin sensitivity, and imaging markers of myocardial fibrosis—clinicians can more accurately identify individuals at heightened cardiac risk. This enables earlier, targeted interventions aimed at preventing the progression of diabetic heart disease.

Medical advances in the management of diabetes and vascular disease

Effective clinical management, particularly adequate glycemic control, is essential for preventing cardiovascular complications in diabetes (5). In 2015 when major trials showed that Glucagon Like Peptide-1 receptor agonists (GLP-1RAs) and Sodium/Glucose Transporter 2 (SGLT2) inhibitors significantly reduce cardiovascular and renal events. Along with ACEIs/ARBs, statins, and aspirin, these agents are now strongly recommended for cardiovascular risk reduction in T2D with established or high Atherosclerotic CVD risk.

Despite guideline support, the use of these therapies remains limited. In a large population-based cohort from Xiamen Humanity Hospital (2018–2023), Tian et al. found that patients using evidence-based cardioprotective therapies had lower risk of MACE, heart failure hospitalization, and a reduction in progression to advanced kidney disease compared with non-users.

Aristizábal-Colorado et al. emphasized individualized therapy selection: SGLT2 inhibitors are particularly beneficial in patients with heart or kidney disease, while GLP-1RAs may be preferable for obese individuals or those at high cardiometabolic risk. Importantly, combining both drug classes can offer additive cardiovascular and renal protection.

H. Gao et al. analyzed 14 trials in patients with T2D and heart failure, comparing the effects of different glucose-lowering drugs. Semaglutide showed the strongest overall cardiac benefit by reducing B-type natriuretic peptide. Licogliflozin caused the greatest weight loss, glimepiride reduced glycated hemoglobin the most, and dapagliflozin most improved left ventricular ejection fraction. Safety varied across drugs, with licogliflozin and ipragliflozin showing fewer side effects. Overall, semaglutide emerged as the most comprehensive cardiometabolic option.

Together, these findings reinforce the growing evidence that targeted glucose-lowering therapies, when appropriately selected and effectively implemented, have the potential modify cardiovascular outcomes in people with T2D.

Conclusion: A wake-up call for cardiovascular protection in diabetes

In conclusion, the contributions collected in this second volume highlight the urgent need for a multidimensional and anticipatory approach to cardiovascular prevention in T2D. By integrating dynamic metabolic markers, omics-based profiling, non-invasive cardiovascular phenotyping, lifestyle and nutraceutical strategies, and evidence-based pharmacological therapies, these studies move the field toward more precise and personalized risk assessment and intervention. Together, they reinforce the concept that effective cardiovascular protection in diabetes must begin early, be tailored to individual risk profiles, and leverage both technological innovation and clinical insight to reduce the global burden of diabetic cardiovascular disease.

Author contributions

ND: Formal Analysis, Writing – original draft, Methodology, Investigation, Conceptualization. MB: Writing – original draft. IC: Methodology, Writing – original draft. TP: Writing – original draft. KP: Writing – original draft. CP: Formal Analysis, Data curation, Writing – original draft, Conceptualization, Supervision.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. American Diabetes Association Professional Practice, C. Cardiovascular disease and risk management: standards of care in diabetes-2025. *Diabetes Care*. (2025) 48: S207–38. doi: 10.2337/dc25-S010

2. Baldassarre MPA, Pipino C, Pandolfi A, Consoli A, Di Pietro N, Formoso G. Old and new biomarkers associated with endothelial dysfunction in chronic hyperglycemia. *Oxid Med Cell Longev*. (2021) 2021:7887426. doi: 10.1155/2021/7887426

3. Di Pietrantonio N, Cappellacci I, Mandatori D, Baldassarre MPA, Pandolfi A, Pipino C. Role of epigenetics and metabolomics in predicting endothelial dysfunction in type 2 diabetes. *Adv Biol (Weinh)*. (2023) 7:e2300172. doi: 10.1002/adbi.202300172

4. Menezes RCR, Peres KK, Costa-Valle MT, Faccioli LS, Dallegrave E, Garavaglia J, et al. Oral administration of oleuropein and olive leaf extract has cardioprotective effects in rodents: A systematic review. *Rev Port Cardiol*. (2022) 41:167–75. doi: 10.1016/j.repc.2021.05.011

5. Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Signal Transduct Target Ther*. (2023) 8:152. doi: 10.1038/s41392-023-01400-z

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 21 February 2025
DOI 10.3389/fendo.2025.1475590

Check for updates

OPEN ACCESS

EDITED BY
Maria Pompea Antonia Baldassarre,
G. d'Annunzio University of Chieti and Pescara, Italy

REVIEWED BY
Klara Komici,
University of Molise, Italy
Xianjia Ning,
Tianjin Medical University General Hospital, China
Pengbo Wang,
China Medical University, China
Xintian Cai,
People's Hospital of Xinjiang Uygur Autonomous Region, China

*CORRESPONDENCE
Zhenwei Wang
1229445463@qq.com

RECEIVED 04 August 2024
ACCEPTED 31 January 2025
PUBLISHED 21 February 2025

CITATION
Yang S and Wang Z (2025) The triglyceride–glucose index is a promising predictor for the risk of cardiovascular disease in the diabetic population aged ≥60 years in the United States: a retrospective cohort study from NHANES (2007-2016).
Front. Endocrinol. 16:1475590.
doi: 10.3389/fendo.2025.1475590

COPYRIGHT
© 2025 Yang and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The triglyceride–glucose index is a promising predictor for the risk of cardiovascular disease in the diabetic population aged ≥60 years in the United States: a retrospective cohort study from NHANES (2007-2016)

Shu Yang[1] and Zhenwei Wang[2*]

[1]School of Medicine, Jiangsu University, Zhenjiang, China, [2]Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: The predictive value of triglyceride-glucose index (TyG) for cardiovascular disease (CVD) in the US elderly diabetic patients is ambiguous. This study aimed to investigate the association between TyG index and the risk of CVD in an older US population with diabetes.

Methods: The study examined data from the 2007-2016 National Health and Nutrition Examination Survey (NHANES). Univariate and multivariate regression analysis models were obtained to explore the association between baseline TyG index and the risk of CVD. Non-linear association were investigated using restricted cubic spline (RCS) regression. Subgroup analyses and interaction tests were constructed and a sensitivity analyses was carried out. The 10 - year CVD risk were evaluated via the Framingham Risk Score (FRS). Mediation analysis explored the mediating role of glycated hemoglobin in the above relationships.

Results: A total of 2987 subjects were included (977 CVD patients and 2010 non-CVD persons). CVD patients had higher TyG values (9.01 ± 0.58 vs. 8.94 ± 0.56, P=0.003), and the prevalence of CVD increased with TyG index (P=0.015). In a multifactorial regression model with gradual adjustment for all covariates, the risk of CVD associated with TyG increased by 48.0% in the highest quartile group (OR 1.480, 95% CI 1.171-1.871, P=0.001). The RCS curves showed a U-shaped association between TyG index and CVD risk (P for overall=0.013, P for nonlinear=0.043). Subgroup analyses showed that in the highest quartile group, individuals with body mass index (BMI) ≥24 kg/m^2, an estimated glomerular filtration rate (eGFR) <90 mL/1.73m^2/min, individuals without chronic kidney disease, and those with hypertension had significantly higher risks of CVD. Sensitivity analyses indicated that these associations were not associated with other significant confounders. Under different adjustment models, the TyG index exhibited significant correlations with the 10 - year risk of CVD (all P values < 0.05). Glycated hemoglobin mediated in the above relationships.

Conclusion: In a sample of US elderly diabetic patients, there is the U-shaped association of TyG index with CVD risk. This implies that TyG index can be regarded as an extremely important predictor for screening people at high risk of cardiovascular disease among elderly diabetic patients.

KEYWORDS

triglyceride-glucose index, cardiovascular disease, diabetes mellitus, elderly people, NHANES

Background

Cardiovascular disease (CVD) is regarded as one of the most seriously burdened health problems globally, and the latest epidemiologic reports of its prevalence are increasing every year (1, 2). It is worth noting that type 2 diabetes is prevalent among patients diagnosed with CVD and is associated with adverse outcomes (3). Therefore, early screening is of vital importance for the risk of cardiovascular death in diabetic patients to be reduced.

As a surrogate marker of insulin resistance derived from routine indicators, the triglyceride-glucose index (TyG) is more cost - effective, convenient and sensitive. It has been developed as a biochemical substitute for identifying insulin resistance in both diabetic and non - diabetic patients (4, 5). Numerous studies indicate that the TyG index serves as an independent predictor of future cardiovascular mortality and other subclinical cardiovascular diseases in the general population (6–8). Meanwhile, related research has confirmed the certain clinical value of the TyG index in relation to adverse cardiovascular events among both non - diabetic and diabetic patients (9). However, among diabetic patients of different age groups, the conclusion about using the TyG index to predict CVD risk remains controversial. Particularly in elderly diabetic patients, physical decline, co - morbidity of multiple chronic diseases, and intricate drug interactions alter their insulin - resistance patterns, blood - glucose fluctuation characteristics, as well as the structure and function of the cardiovascular system (10, 11). These result in differences in CVD pathogenesis and risk levels compared to other populations. Currently, targeted research in this regard is scarce.

Therefore, our study aimed to explore the association between the TyG index and the risk of CVD in elderly patients with diabetes, evaluate whether the TyG index has prognostic value for CVD risk in this population, and uncover the non - linear relationship between them.

Methods

Study population

National Health and Nutrition Examination Survey (NHANES) is a research program led by the National Center for Health Statistics (NCHS) of the CDC dedicated to measuring the health and nutritional status of Americans, adults, and children. Through integrated interviews and physical exams, it yields valuable insights on prevalent diseases, dietary and nutritional trends, and health-related behaviors, serving as a premier database for probing disease epidemiology and related risk factors. All participants provided written informed consent before participation in the survey. The data in this study were anonymized and de-identified before the analysis to ensure the privacy and confidentiality of the participants. In this retrospective observational study, a total of 50,588 participants were initially enrolled. Participants who did not attend, had unresolved status regarding diabetes (n=45,079), were under the age of 60 (n=2,218), or for whom the covariates were incomplete (n=236) were excluded. Participants with extreme values of the TyG index (mean ± 3 standard deviations) were also excluded (n=68). Ultimately, a total of 2987 participants with complete data were incorporated into this analysis (Figure 1).

Assessment of covariates

Demographic data included age, gender, race, education level, and marital status. Race was categorized as Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, and other races; education level was categorized as less than high school, high school or equivalent, and college or above; and marital status was categorized as married, widowed, divorced, and never married. Questionnaire data included smoking status, alcohol consumption, and medication use (insulin, hypoglycemics, antihypertensive drugs), etc. The smoking and alcohol consumption statuses were recorded as “yes” if the subjects agreed to smoke at least 100 cigarettes in a lifetime and drink at least 12 alcoholic per year, respectively. Blood pressure and body measurements were obtained from the examination data. Blood pressure were recorded as the maximum measurement, or the final value if there was only one measurement; body mass index (BMI) was calculated as weight (kg)/height (m) squared. In laboratory data, data on fasting blood glucose (FBG), glycated hemoglobin (HbA1c%), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and albumin and uric acid were collected. For more detailed measurement data, please visit the NHANES website.

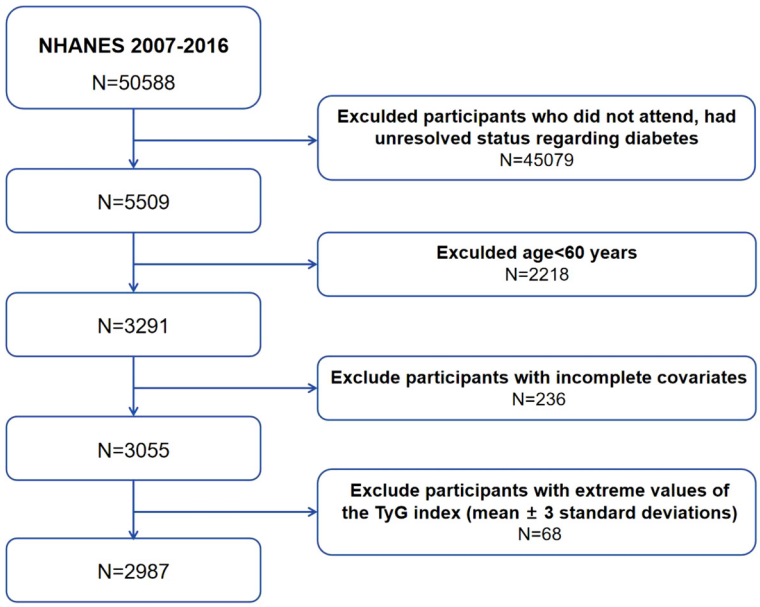


FIGURE 1
Flowchart of participants' selection. National Health and Nutrition Examination Survey (NHANES), The triglyceride-glucose index (TyG).

Data definitions

Diabetes mellitus was defined as satisfying any one of the following conditions: (1) FBG ≥ 7 mmol/L; (2) Random blood glucose or 2-hour oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L; (3) HbA1c ≥ 6.5%; and (4) Answering "yes" to one of the following questions: "Your doctor has ever told you that you have diabetes" "You are now taking insulin" "You are now taking hypoglycemic drugs". Subjects were considered to have CVD if they answered "yes" to the question "Have you ever suffered from congestive heart failure (CHF)/coronary heart disease (CHD)/angina/myocardial infarction/stroke" by a doctor or other health specialist. Hypertension was defined as being informed of hypertension or use of antihypertensive drugs or SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Chronic kidney disease (CKD) was determined by answering "yes" to the question, "Have you ever been told you have kidney failure?" or by calculating an estimated glomerular filtration rate (eGFR) of < 60 mL/1.73m^2/min, which was proposed based on the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (12).

Definitions of triglyceride-glucose index

TyG index as an exposure variable was calculated by the following formula: TyG = Ln[TG (mg/dL)*FBG (mg/dL)/2]. TyG index was divided into four groups, i.e., Q1 (≤ 8.67) 752 cases, Q2 (8.67-8.96) 729 cases, Q3 (8.96-9.20) 767 cases, and Q4 (≥ 9.20) 739 cases. Both triglyceride and fasting glucose concentrations were measured through an enzymatic assay using an automatic biochemistry analyzer. Serum triglyceride concentration was measured using the Roche Modular P and Roche Cobas 6000 chemistry analyzers while fasting plasma glucose was assessed through the hexokinase-mediated reaction using the Roche/Hitachi Cobas C 501 chemistry analyzer.

Cardiovascular disease risk

We employed the Framingham Risk Score (FRS) to evaluate participants' 10 - year CVD risk. This score gauges the 10 - year composite risk of coronary heart disease, stroke, peripheral arterial disease, and heart failure. The algorithm, based on age (years), sex (male/female), total and HDL cholesterol (mg/dL), SBP (mmHg), treated and untreated hypertension, smoking status (yes/no), and diabetes status (yes/no), calculates each participant's CVD risk score per sex - specific criteria. This score is then translated into a 10 - year CVD risk, expressed as FRS%. Specific scoring details are in Tables 5 - 8 of the reference (13).

Statistical analysis

Data in NHANES were sourced from the items in multiple sections, and inevitably some values are missing. In this study, the missing data issue was tackled via multiple imputation based on random forests. Through multiple samplings and predictions, we got imputed complete datasets, better preserving info, correcting biases, and boosting statistical power. Continuous variables were reported as mean ± standard deviation (SD) using the independent samples T test when they conformed to a normal distribution, and as median (25th-75th percentile) using the Mann-Whitney U test for non-normal distribution. Categorical variables were reported as frequencies and percentages using chi-square and Fisher's exact

tests. Besides, TyG index was divided the into quartile groups to compare their baseline characteristics. One-way analysis of variance (ANOVA), Kruskal-Wallis H test, and chi-square and Fisher's exact tests were performed.

Univariate and multivariate logistic regression models were developed to investigate the relationship between TyG index and the risk of CVD at continuous and categorical variables. Model 1 was not adjusted for covariates. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, race, education level, marital status, smoking status, and DBP. Model 4 was adjusted for all covariates, including age, sex, race, education level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, CKD, antihypertensive drugs. For subgroup analyses, the groups were separated by sex (male/female), BMI (< 24/≥ 24 kg/m^2), eGFR (< 90/≥ 90 mL/1.73m^2/min), CKD (Yes/No), and Hypertension (Yes/No). Ratio ratios (ORs) of the different strata were compared by interaction testing to determine the presence of an interaction effect. Concurrently, the p-value corresponding to the interaction was computed for statistical examination to investigate the potential moderating impacts of TyG on the CVD risk. Finally, to explore whether there was a potential non-linear relationship between TyG index and the risk of CVD, several restricted cubic spline curve (RCS) regression models were constructed based on the complete adjustment model, and four knots were placed at the 5th, 35th, 65th, and 95th percentiles. In addition, though the same method, the sex-stratified curves separately were graphed to further explore whether sex differences would have an impact on the predictive value of TyG. Linear regression models were employed to assess the association between the Tyg index and the 10 - year CVD risk, as well as to adjust for potential confounding factors. Sensitivity analyses were conducted, adjusting for eGFR<30mL/1.73m^2/min, to assess the stability of the results with adjustments for all variables. Mediation analyses were used to investigate whether the relevance of TyG to cardiovascular disease could be explained by glycated hemoglobin after adjusting for factors in Model 4.

The above analyses were performed using SPSS 26.0 and R 4.4.0. Two-tailed P<0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

As is shown in Table 1, a total of 2987 subjects were included in this study with a mean age of 70.17 ± 6.78 years. Among them, 52.2% were male and 47.8% were female, with an overall prevalence of 32.7%. Compared with the non-CVD population, the CVD population had a higher percentage of males, smokers, hypertensive, and taking antihypertensive drugs (P < 0.05). Race, education level, and marital status were statistically significant differences (P < 0.05). In terms of laboratory indicators, CVD patients had higher levels of FBG, TG, TC, LDL-C, and uric acid, and lower levels of HDL-C, albumin, and eGFR (P < 0.05). Notably, the CVD group exhibited a significantly higher TyG index than the non-CVD group (9.01 vs 8.94, P < 0.05).

Furthermore, we undertook in - depth explorations within five discrete subgroups of CVD by implementing a uniform methodological approach. The prevalence rates were as follows: 11.4% for CHF, 14.0% for CHD, 8.1% for angina, 12.8% for myocardial infarction, and 11.1% for stroke. Notably, the TyG index in the CHD group exhibited a significantly higher value compared to that in the non - CHD group (9.05 vs 8.95, P < 0.05). Conversely, no discernible statistical differences were detected among the remaining four groups (Supplementary Tables S1-S5).

To further investigate the correlation between TyG index and CVD, the baseline table with TyG index was charted as quartile groups (Table 2). The risk of CVD prevalence increased as TyG index grew in each group (Q1: 30.2%; Q2: 30.6%; Q3: 32.9%; and Q4: 37.2%). Various factors including age, sex, race, smoking status, CKD, BMI, FBG, HbA1c%, TG, TC, HDL-C, LDL-C, uric acid, and eGFR demonstrated significant differences between the four quartiles of the TyG index (P < 0.05).

Association between TyG index and the risk of CVD

After performing univariate logistic regression analyses (Table 3), the correlation between TyG index and the risk of CVD can be found through multivariate logistic regression models. The results demonstrated that the higher the TyG index, the higher the risk of CVD in both continuous and categorical variables. In Model 1, the OR for CVD increased with TyG index (OR = 1.235, 95% Cl 1.078-1.414, P = 0.002). In Model 2, age and sex were adjusted (OR = 1.291, 95% Cl 1.124-1.484, P < 0.001), and Model 3 gradually adjusted for more covariates (OR = 1.222, 95% Cl 1.019-1.465, P = 0.030), with all results found to be significant. After adjusting for all covariates, the positive correlation between TyG index and CVD remained consistent (OR = 1.222, 95% Cl 1.016-1.469, P = 0.033), indicating that each unit increased in TyG index was associated with a 22.2% increase in the risk of developing CVD. In the perfectly adjusted model, when the TyG index was divided into quartiles, subjects in the highest quartile group had a significant 48.0% increased risk of CVD compared to the lowest one (OR = 1.480, 95% Cl 1.171-1.871, P = 0.001).

Subgroup analysis

Subgroup analyses and interaction tests were performed for the association of TyG quartile groups with CVD risk in different subgroups (Table 4). The results showed that in the BMI ≥ 24 kg/m^2 subgroup (OR 1.433, 95% Cl 1.110-1.851, P = 0.006), in the eGFR < 90 mL/1.73m^2/min subgroup (OR 1.543, 95% Cl 1.165-2.042, P = 0.002), and the subgroups without chronic kidney disease (OR 1.505, 95% Cl 1.111 -2.037, P = 0.008), and with hypertension (OR 1.449, 95% Cl 1.122-1.872, P = 0.004), individuals in the highest TyG quartile group presented a higher risk of CVD compared with individuals in the lowest TyG Quartile group. There was a statistically significant interaction among individuals without hypertension in groups Q2 and Q3. Interaction was presented for the BMI subgroup in group Q2 and the CKD

TABLE 1 Baseline characteristics of the CVD and non-CVD groups.

Variable	Overall	CVD	Non-CVD	P value
N(%)	2987	977(32.7)	2010(67.3)	
Age, years	70.17(6.78)	71.69(6.70)	69.43(6.70)	<0.001
Sex, n(%)				<0.001
Male	1560(52.2)	560(57.3)	1000(49.8)	
Female	1427(47.8)	417(42.7)	1010(50.2)	
Race, n(%)				<0.001
Mexican American	505(16.9)	129(13.2)	376(18.7)	
Non-Hispanic Black	699(23.4)	204(20.9)	495(24.6)	
Non-Hispanic White	1185(39.7)	482(49.3)	703(35.0)	
Other Hispanic	349(11.7)	98(10.0)	251(12.5)	
Other Race	249(8.3)	64(6.6)	185(9.2)	
Educational level, n(%)				0.018
Less than high school	672(22.5)	206(21.1)	466(23.2)	
High school or equivalent	1206(40.4)	430(44.0)	776(38.6)	
Some college or above	1109(37.1)	341(34.9)	768(38.2)	
Marital status, n(%)				0.003
Married	1633(54.7)	501(51.3)	1132(56.3)	
Widowed	687(23.0)	260(26.6)	427(21.2)	
Divorced	361(12.1)	127(13.0)	234(11.6)	
Never married	306(10.2)	89(9.1)	217(10.8)	
Smoking status, n(%)	1566(35.4)	580(42.0)	986(32.3)	<0.001
Alcohol consumption, n(%)	1703(57.0)	575(58.9)	1128(56.1)	0.214
Hypertension, n(%)				<0.001
Yes	2346(78.5)	820(83.9)	1526(75.9)	
No	641(21.5)	157(16.1)	484(24.1)	
Antihypertensive drugs, n(%)				<0.001
Yes	2134(71.4)	761(77.9)	1373(68.3)	
No	853(28.6)	216(22.1)	637(31.7)	
CKD, n(%)				<0.001
Yes	909(30.4)	399(40.8)	510(25.4)	
No	2078(69.6)	578(59.2)	1500(74.6)	
SBP, mmHg	133.97(32.12)	132.55(33.94)	134.66(31.18)	0.102
DBP, mmHg	65.78(18.35)	63.68(19.00)	66.80(17.94)	<0.001
BMI, kg/m^2	30.18(8.15)	30.30(9.03)	30.11(7.69)	0.575
FBG, mmol/L	7.15(2.43)	7.30(2.51)	7.08(2.39)	0.022
HbAlc, %	6.99(1.51)	7.06(1.53)	6.96(1.49)	0.102
TG, mmol/L	7.36(5.50,8.94)	7.50(5.65,9.18)	7.28(5.40,8.89)	0.019
TC, mmol/L	4.65(1.11)	4.40(1.14)	4.77(1.08)	<0.001
HDL-C, mmol/L	1.28(0.39)	1.22(0.37)	1.31(0.39)	<0.001

(Continued)

TABLE 1 Continued

Variable	Overall	CVD	Non-CVD	P value
LDL-C, mmol/L	2.71(0.69)	2.60(0.72)	2.76(0.67)	<0.001
Albumin, g/L	41.37(3.53)	40.88(3.39)	41.61(3.31)	<0.001
Uric acid, μmol/L	354.02(94.63)	371.17(105.06)	345.69(87.95)	<0.001
eGFR, mL/1.73m^2/min	76.28(56.74,99.52)	68.08(48.73,92.86)	80.10(60.90,102.27)	<0.001
TyG	8.96(0.57)	9.01(0.58)	8.94(0.56)	0.003
TyG group				0.015
Q1(<8.67)	752(25.2)	227(23.2)	525(26.1)	
Q2(8.67-8.96)	729(24.4)	223(22.8)	506(25.2)	
Q3(8.96-9.20)	767(25.7)	252(25.8)	515(25.6)	
Q4(>9.20)	739(24.7)	275(28.1)	464(23.1)	

Values are number (percentage), or median (25th-75th percentile).
CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glucated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated-glomerular filtration rate.

TABLE 2 Baseline characteristics according to TyG index quartiles.

Variable	Quartiles of TyG index				P value
	Q1(<8.67)	Q2(8.67-8.96)	Q3(8.96-9.20)	Q4(>9.20)	
N(%)	752(25.2)	729(24.4)	767(25.7)	739(24.7)	
Age, years	70.91(6.87)	70.16(6.79)	69.90(6.62)	69.71(6.79)	0.003
Sex, n(%)					
Male	354(47.1)	343(47.1)	460(60.0)	403(54.5)	<0.001
Female	398(52.9)	386(52.9)	307(40.0)	336(45.5)	
Race, n(%)					<0.001
Mexican American	101(13.4)	125(17.1)	135(17.6)	144(19.5)	
Non-Hispanic Black	262(34.8)	177(24.3)	151(19.7)	109(14.7)	
Non-Hispanic White	251(33.4)	267(36.6)	327(42.6)	340(46.0)	
Other Hispanic	83(11.0)	85(11.7)	86(11.2)	95(12.9)	
Other Race	55(7.3)	75(10.3)	68(8.9)	51(6.9)	
Educational level, n(%)					
Less than high school	159(21.1)	168(23.0)	169(22.0)	176(23.8)	0.256
High school or equivalent	312(41.5)	274(37.6)	305(39.8)	315(42.6)	
Some college or above	281(37.4)	287(39.4)	293(38.2)	248(33.6)	
Marital status, n(%)					0.071
Married	393(52.3)	372(51.0)	450(58.7)	418(56.6)	
Widowed	186(24.7)	193(26.5)	151(19.7)	157(21.2)	
Divorced	91(12.1)	91(12.5)	87(11.3)	92(12.4)	
Never married	82(10.9)	73(10.0)	79(10.3)	72(9.7)	
Smoking status, n(%)	365(31.7)	379(35.1)	406(35.8)	416(39.2)	<0.001
Alcohol consumption, n(%)	432(57.4)	408(56.0)	450(58.7)	413(55.9)	0.465

(Continued)

TABLE 2 Continued

Variable	Quartiles of TyG index				P value
	Q1(<8.67)	Q2(8.67-8.96)	Q3(8.96-9.20)	Q4(>9.20)	
Hypertension, n(%)					0.207
Yes	608(80.9)	557(76.4)	605(78.9)	576(77.9)	
No	144(19.1)	172(23.6)	162(21.1)	163(22.1)	
Hypotensive drugs, n(%)					0.4
Yes	552(73.4)	506(69.4)	550(71.7)	526(71.2)	
No	200(26.6)	223(30.6)	217(28.3)	213(28.8)	
CKD, n(%)					0.016
Yes	261(34.7)	224(30.7)	214(27.9)	210(28.4)	
No	491(65.3)	505(69.3)	553(72.1)	529(71.6)	
SBP, mmHg	134.13(34.65)	134.01(31.71)	132.17(30.13)	135.65(31.82)	0.218
DBP, mmHg	65.34(19.44)	65.68(18.86)	65.79(17.54)	66.31(17.70)	0.782
BMI, kg/m^2	29.39(8.02)	29.92(8.22)	30.99(7.95)	30.39(8.35)	0.001
FBG, mmol/L	6.16(1.10)	6.54(1.33)	6.68(1.24)	9.25(3.66)	<0.001
HbAlc, %	6.60(1.21)	6.91(1.34)	7.03(1.41)	7.44(1.87)	<0.001
TG, mmol/L	4.49(3.56,5.24)	6.83(6.20,7.36)	8.42(8.00,9.02)	10.28(8.89,12.78)	<0.001
TC, mmol/L	4.55(1.04)	4.60(1.09)	4.56(1.07)	4.88(1.22)	<0.001
HDL-C, mmol/L	1.63(0.44)	1.32(0.22)	1.10(0.26)	1.08(0.31)	<0.001
LDL-C, mmol/L	2.56(0.67)	2.72(0.59)	2.79(0.48)	2.77(0.93)	<0.001
Albumin, g/L	41.21(3.49)	41.40(3.32)	41.44(3.33)	41.43(3.27)	0.499
Uric acid, μmol/L	342.37(92.85)	352.38(93.61)	362.22(92.86)	358.98(98.13)	<0.001
eGFR, mL/1.73m^2/min	72.63(51.89,94.19)	75.38(56.04,98.35)	78.17(59.27,101.02)	79.96(58.82,103.19)	<0.001
Cardiovascular disease, n(%)					0.015
Yes	227(30.2)	223(30.6)	252(32.9)	275(37.2)	
No	525(69.8)	506(69.4)	515(67.1)	464(62.8)	

Values are number (percentage), or median (25th-75th percentile).
CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glucated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated-glomerular filtration rate.

TABLE 3 Logistic regression results showing association between the TyG index and CVD.

	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
TyG continuous	1.235 (1.078-1.414)	0.002	1.291 (1.124-1.484)	<0.001	1.222 (1.019-1.465)	0.030	1.222 (1.016-1.469)	0.033
TyG categories								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	1.019 (0.817-1.272)	0.866	1.063 (0.848-1.331)	0.597	1.047 (0.831-1.318)	0.698	1.046 (0.827-1.323)	0.705
Q3	1.132 (0.911-1.405)	0.263	1.157 (0.927-1.443)	0.197	1.171 (0.934-1.469)	0.172	1.126 (0.893-1.420)	0.317
Q4	1.371 (1.105-1.701)	0.004	1.445 (1.160-1.801)	0.001	1.540 (1.225-1.937)	<0.001	1.480 (1.171-1.871)	0.001

Model 1: Unadjusted.
Model 2: Adjusted for age, sex.
Model 3: Adjusted for age, sex, race, educational level, marital status, smoking status, DBP.
Model 4: Adjusted for age, sex, race, educational level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, Hypotensive drugs, Chronic kidney disease.

TABLE 4 Subgroup analysis for the association between the TyG index and the risk of CVD.

Subgroups	Q1	Q2		Q3		Q4	
	OR (95%CI)	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Sex							
Male	Ref.	1.288 (0.919-1.803)	0.142	1.151 (0.832-1.592)	0.396	1.538 (1.108-2.135)	0.010
Female		0.905 (0.644-1.272)	0.565	1.164 (0.818-1.656)	0.399	1.409 (0.998-1.988)	0.051
P interaction			0.790		0.804		0.897
BMI, kg/m^2							
< 24	Ref.	1.441 (0.807-2.573)	0.216	1.056 (0.535-2.084)	0.876	1.500 (0.770-2.924)	0.234
≥ 24		1.009 (0.776-1.312)	0.946	1.129 (0.875-1.458)	0.350	1.433 (1.110-1.851)	0.006
P interaction			0.035		0.086		0.166
eGFR, mL/ 1.73m^2/min							
< 90	Ref.	1.158 (0.879-1.525)	0.299	1.160 (0.878-1.531)	0.296	1.543 (1.165-2.042)	0.002
≥ 90		0.863 (0.535-1.391)	0.545	1.090 (0.691-1.718)	0.711	1.372 (0.979-2.146)	0.165
P interaction			0.076		0.588		0.778
CKD							
Yes	Ref.	0.908 (0.622-1.328)	0.620	1.036 (0.704-1.525)	0.856	1.407 (0.957-2.069)	0.082
No		1.181 (0.868-1.607)	0.289	1.219 (0.900-1.652)	0.201	1.505 (1.111-2.037)	0.008
P interaction			0.700		0.014		0.733
Hypertension							
Yes	Ref.	0.891 (0.686-1.158)	0.389	1.035 (0.800-1.339)	0.791	1.449 (1.122-1.872)	0.004
No		2.464 (1.350-4.498)	0.003	1.972 (1.055-3.688)	0.033	1.853 (0.978-3.510)	0.058
P interaction			0.848		0.875		0.812

Each subgroup analysis was adjusted for age, sex, race, educational level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, Hypotensive drugs, Chronic kidney disease.

subgroup in group Q3, and no significant interaction was found among the remaining subgroups (all P for interaction > 0.05).

RCS analysis

Figure 2A showed a significant nonlinear relationship between the TyG index and CVD risk in the form of a U-shaped curve (with an overall P-value of 0.013, a nonlinear P-value of 0.043, and an inflection point at 8.63). To the left of the inflection point, the TyG index was uncorrelated with CVD risk but positively correlated to the right.

Figure 2B indicated that the TyG index was nonlinearly associated with CVD risk in both genders, aligning with the pattern in the total population. The inflection points of TyG levels for men and women were 8.61 (nonlinear P = 0.039) and 8.68 (nonlinear P = 0.047), respectively. There was no association to the left of these points, but a positive link existed on the right.

Sensitivity analysis

In Table 5, the stability of the aforesaid research finding were verified s via sensitivity analysis. Considering that severely impaired

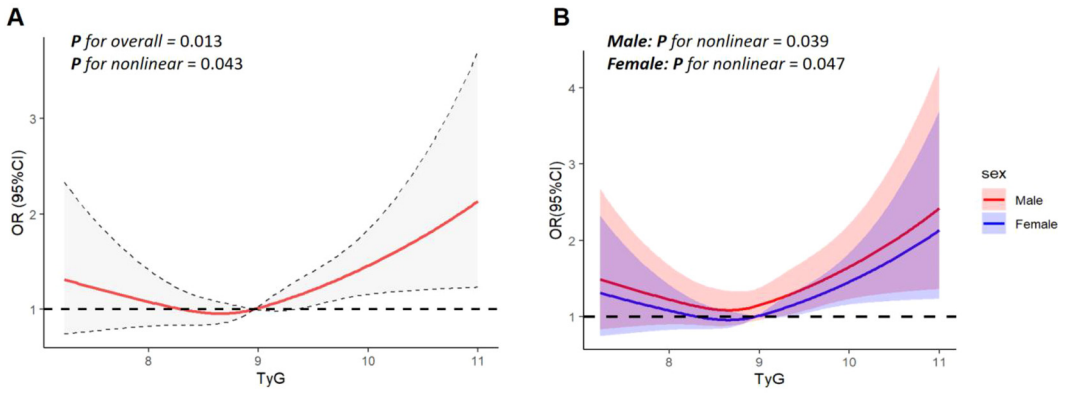


FIGURE 2
The restricted cubic spline (RCS) analysis of the association between the TyG index and the risk of CVD. **(A)** RCS curve of the association between TyG index and CVD risk in the total population; **(B)** RCS curves of the association between TyG index and CVD risk among males and females. The association was adjusted for age, sex, race, educational level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, Hypotensive drugs, Chronic kidney disease.

kidney function may influence the evaluation of the cardiovascular risk in diabetic patients, subjects with eGFR < 30 mL/1.73m^2/min were excluded when adjusting confounding factors. Multivariate logistic regression analysis demonstrated that the TyG index was significantly correlated with CVD risk (P < 0.05) both as a continuous and categorical variable in Model 1 and Model 2. In Model 3, a one-unit increase in the TyG index led to a 21.0% rise in CVD risk (OR = 1.210, 95% CI 1.042 - 1.406, P = 0.012). Additionally, the CVD risk in the Q4 group was 1.279 times that of the Q1 group (OR = 1.279, 95% CI 1.010 - 1.619, P = 0.041). In the fully adjusted Model 4, a higher TyG index was still significantly associated with a higher CVD risk (continuous variable: OR = 1.222, 95% CI 1.008 - 1.480, P = 0.041; Q4 vs Q1: OR = 1.436, 95% CI 1.124 - 1.835, P = 0.004), emphasizing the high credibility and robustness of results.

The association of the TyG index with 10 - year risk of CVD

Table 6 demonstrated the associations between the TyG index and 10 - year CVD risk via four distinct linear regression models, incrementally adjusting potential confounding factors. Remarkably, a consistently significant positive correlation emerged. Across all models, the data clearly showed that as the TyG index rose, the 10 - year CVD risk increased substantially. In the fully adjusted Model 4, the corresponding regression coefficients of TyG index were 0.228 (95%CI 0.098 - 0.357, P = 0.001) for 10 - year CVD risk.

Mediation analysis of TyG with CVD risk

Mediation analysis showed that HbA1c mediated the correlation between TyG and the risk of CVD. The percentage of the indirect effect of the correlation between TyG and CVD risk mediated by HbA1c was 12.5% (Supplementary Figure S1).

Discussion

Here, the relationship between TyG index and the risk of CVD in 2987 diabetic patients aged 60 years and above was investigated based on information from the NAHANES database from the period 2007 to 2016. Excitingly, there is a significant nonlinear relationship between the TyG index and CVD, and there seemingly exists a threshold effect. This reveals that both overly high and low TyG values will elevate the CVD risk. Moreover, this study has verified that a pronounced U-shaped association between the TyG index and CVD risk prevails in both genders. The inflection points have been pinpointed as 8.61 for men and 8.68 for women. This implies that in clinical practice, the TyG index can function as a crucial predictor for gauging the CVD occurrence risk in the elderly diabetic population and facilitate the formulation of targeted CVD prevention and personalized treatment strategies.

The TyG index, a new indicator for evaluating insulin resistance, is widely applied in multiple fields, such as the screening of the general population, the management of diabetic patients, and the monitoring of cardiovascular diseases. A longitudinal cohort study showed that the TyG index could serve as a useful indicator for predicting the glycemic conversion outcome in people with prediabetes. This study demonstrated a negative, non - linear link between the TyG index and glucose status conversion from prediabetes to normoglycemia (14). Gao et al., through a cross-sectional study, were the first to discover a positive correlation between the TyG index and impaired cardiovascular fitness among 3,364 non-diabetic young people (15). The study by Zhang et al. observed a positive correlation between the TyG index and both CVD mortality and all - cause mortality in CVD patients with diabetes or pre - diabetes. Specifically, when the TyG index exceeds certain thresholds (8.5 for CVD mortality and 8.2 for all - cause mortality), the risk of death increases significantly (16). A study conducted in Italy showed that, among elderly hypertensive individuals with prediabetes, the TyG index served as a valuable reference for predicting the risks of both cognitive and physical impairments, and even frailty (17). Revealed by Zhao et al.'s research, the TyG index

TABLE 5 Sensitivity analysis.

	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
TyG continuous	1.209 (1.050-1.392)	0.008	1.258 (1.088-1.455)	0.002	1.210 (1.042-1.406)	0.012	1.222 (1.008-1.480)	0.041
TyG categories								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.955 (0.758-1.203)	0.696	0.994 (0.786-1.257)	0.959	0.970 (0.764-1.232)	0.806	1.011 (0.789-1.295)	0.932
Q3	1.087 (0.869-1.361)	0.463	1.094 (0.870-1.376)	0.442	1.061 (0.839-1.340)	0.622	1.099 (0.861-1.404)	0.448
Q4	1.315 (1.052-1.645)	0.016	1.377 (1.095-1.730)	0.006	1.279 (1.010-1.619)	0.041	1.436 (1.124-1.835)	0.004

Excluded subjects with eGFR < 30 mL/1.73m^2/min.
Model 1: Unadjusted.
Model 2: Adjusted for age, sex.
Model 3: Adjusted for age, sex, race, educational level, marital status, smoking status, DBP.
Model 4: Adjusted for age, sex, race, educational level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, Hypotensive drugs, Chronic kidney disease.

TABLE 6 Linear regression models of associations between the TyG index and 10-year risk of CVD.

10-year risk of CVD	Model 1		Model 2		Model 3		Model 4	
	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
	0.241 (0.020-0.461)	0.033	0.335 (0.148-0.521)	<0.001	0.286 (0.138-0.434)	<0.001	0.228 (0.098-0.357)	0.001

Model 1: Unadjusted.
Model 2: Adjusted for age, sex.
Model 3: Adjusted for age, sex, race, educational level, marital status, smoking status, DBP.
Model 4: Adjusted for age, sex, race, educational level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, Hypotensive drugs, Chronic kidney disease.

exhibited a positive correlation with the incidence of chest pain and was capable of predicting the all-cause mortality of patients suffering from chest pain (18). Wu et al.'s longitudinal survey of 4,710 middle-aged and elderly people aged over 45 showed that participants with a higher baseline TyG level had a higher incidence of stroke (19). As was demonstrated, the TyG index served as an important predictor and therapeutic target for heart failure (HF) as well, with a positive correlation to the risk of HF (20). In addition, it was indicated by Xue et al.'s research that high clinical value was also possessed by TyG-related parameters in identifying liver diseases closely associated with metabolic disorders, such as non-alcoholic fatty liver disease (NAFLD) and metabolic associated fatty liver disease (MAFLD) (21).

More significantly, the nonlinear association between the TyG index and CVD risk has currently been explored across various populations. A prospective cohort study involving 7,851 subjects observed a U-shaped association between the TyG index and cardiovascular mortality in the general population, with a threshold of 8.7. After exceeding this threshold, a positive correlation between the TyG index and CVD risk was only detected in male subjects (22). Mengjie Zhao et al. also identified this particular U-shaped association among middle-aged and elderly diabetic patients aged 45 and above and concluded that there was a significant correlation between TyG and CVD mortality in men at the TyG > 9 (23). Sangsang Li et al.'s retrospective analysis of 6,078 subjects aged 60 and above also suggested a nonlinear relationship between the TyG index and CVD risk. Conversely, they found that when the TyG value was greater than the threshold (9.53), TyG was a stronger risk factor for CVD in women compared to men (24). Generally, a higher TyG index indicates higher insulin resistance in the body and can trigger a series of pathophysiological reactions such as elevated blood glucose, abnormal increase in triglycerides, and enhanced inflammatory response, thus substantially increasing the risk of CVD (25–27). Meanwhile, individuals with a low TyG level may have an increased CVD risk due to reasons like sympathetic nerve stimulation caused by hypoglycemia (28, 32). However, there is no definite mechanism to explain how gender differences regulate the impact of TyG on CVD risk. Moreover, the results are inconsistent due to variations in sample size, follow-up duration, and target populations. It has been reported that it may be related to the protective effect of sex steroid hormones, especially estrogen, in women (30). Therefore, it is of significant clinical importance to explore the impact of the TyG index on CVD risk and determine its threshold, especially in the elderly diabetic population, as it can help reduce the occurrence risk of CVD to some extent.

Furthermore, according to our subgroup analysis, this study reveals the correlations of the TyG index among the populations with cardiovascular comorbidities or other pathologies, including overweight, renal impairment, and the presence or absence of CKD or hypertension. The strong associations remain even after adjusting for confounding factors, suggesting that the findings are applicable to most people. It emphasizes that the TyG index can serve as a valuable marker for assessing cardiovascular risks in diverse populations, consistent with other studies. A longitudinal study by Xin et al. with 15,056 physical examinees as samples and a 12-year follow-up found that the trajectories of participants whose TyG indices showed "moderate increasing" and "high stable" were closely related to the risk of hypertension (31). A cohort study of 6,114 Chinese aged 45 years or older by Ye Zixiang et al. showed that increased TyG index enhanced the association between diabetes and CVD in middle-aged and older adults (32). Their subgroup analysis found that subjects with concomitant hypertension had an increased CVD risk, consistent with the results of this study. Delightfully, Wanlu Su precisely confirmed this in a prospective observational study of 4,434 people with diabetes complicated by hypertension, stating that those with higher TyG index levels were more likely to have increased incidences of T2DM-HTN comorbidities (33). This may imply that the metabolic pathways of hypertension and the TyG index interact with each other and cause synergistic damage to the cardiovascular system (28, 29). Mengjie Zhao et al. noted a significant positive correlation between the TyG index and CVD risk in the subgroup with BMI ≥ 25 kg/m^2, which is also concluded in this study (34). This fully demonstrates that high BMI may lead to increased insulin resistance and abnormal fat metabolism, thus affecting the TyG level. Conversely, a high TyG index indicates abnormal glucose and lipid metabolism in the body, prompting abnormal fat accumulation and resulting in high BMI. The interaction between the two significantly increases an individual's risk of CVD. Cancan Cui et al. illustrated in a prospective cohort study of 6496 subjects, through stratified analysis, that in diabetic patients, the combination of a higher TyG index and a lower eGFR level (eGFR < 60 mL/1.73m^2/min) was associated with the risk of cardiovascular disease, consistent with this study (34). Therefore, it can be speculated that renal impairment can significantly mediate the association between the TyG index and cardiovascular risk. This may be related to the renal metabolic feedback mechanism. In CKD patients, the kidney's clearance ability for substances decreases, leading to elevated levels of triglycerides and glucose in the blood. Meanwhile, persistently high TyG index may lead to renal

microangiopathy, which further impairs renal function (35). In summary, understanding the interactions between TyG and hypertension, BMI, and CKD helps to stratify patients' risks more precisely, comprehensively assess the risks of adverse events such as cardiovascular diseases and kidney disease progression, and provide effective treatment strategies to control the conditions, thereby alleviating the progression of kidney diseases and preventing cardiovascular complications (36–39). This also means that the TyG index can be a powerful predictor of the risk of cardiovascular diseases in elderly diabetic patients.

Although most studies and ours have consistently confirmed the correlation between TyG and CVD, the mechanisms involved require further discussion. Presently, the published papers unanimously agree on the following mechanisms: (1) The body's sensitivity to insulin is reduced, causing chronic hyperglycemia, which induces chronic fibrosis of myocardial tissue and myocardial remodeling, leading to the development of cardiovascular disease (32); (2) Hyperinsulinemia makes fat ineffectively used, causing dyslipidemia (33), exacerbating inflammatory responses and oxidative stress, producing lipotoxicity in the heart, damaging endothelial cells and vascular function (34), and even causing heart failure (34); (3) At the same time, the inflammatory response will increase platelet aggregation, promote thrombosis and hypercoagulable state of the body (35), cause atherosclerotic dyslipidemia (36), and further deterioration of cardiovascular disease; (4) Elevated insulin levels help to excite the sympathetic nervous system, resulting in increased adrenaline secretion, higher blood pressure, renal sodium storage, and increased cardiac load, leading to cardiovascular and renal damage (37, 38); (5) Furthermore, insulin resistance may promote the development and progression of cardiovascular diseases through subclinical conditions (39); (6) Favorable insulin sensitivity is conducive to the maintenance of normal glycometabolism, attenuates the adverse effects of hyperglycemia on the cardiovascular system, confers a protective function on the cardiovascular apparatus, and mitigates myocardial damage (34, 40); and (7) Potential confounding factors not included in the study may also influence the relationship between TyG and CVD risk. Individuals who follow a high-sugar and high-fat diet for a long time are prone to obesity and abnormal blood glucose and lipid levels, directly elevating the TyG index (41, 42). Regular exercise can improve insulin sensitivity, reduce the TyG index, and simultaneously enhance cardiovascular function and lower CVD risk (43). Constraints like financial difficulties can lead to inadequate preventive care and may also affect the CVD risk in the diabetic population (44).

Despite the meaningful findings of our study, some limitations remain unavoidable: (1) This is a retrospective observational study without prospective design and interventions, thus the causal association between TyG and CVD cannot be confirmed, which needs further exploration; (2) The data in this study were obtained from NHANES Epidemiological Survey, and the subjects were generally healthy community population, which was different from clinical data, and most of them may have HDL-C in normal range. Therefore, further validation of hospital cohort data is still needed before clinical application; (3) As mentioned above, NHANES, as a multiple sampling design, needs to be reweighted if it is intended to be representative of the U.S. population as a whole. However, in our study, we did not perform any data adjustments because we were analyzing in deeper subgroups and adjusting the weights could have missed some important effects, which also means that our findings may not be sustainable for the entire U.S. population; (4) Although this study included as many variables as it could and adjustment for confounders was made wherever possible in the regression analyses, potential confounders, such as genetic susceptibility, genetic variation, dietary and environmental factors and mental health and social factors, were still unavoidable; (5) Finally, the diagnoses of diabetes and CVD partly relied on NHANES participants' recall during interviews, causing recall bias. When assessing the TyG-CVD relationship, patients may misremember onset time, treatment, or lifestyle changes, distorting the true link. Individual differences in memory and attention levels are large. High-stress individuals often recall inaccurately due to overlooking details, making the results uncertain; (6) The cross-sectional nature of NHANES data may affect the results. It is unclear whether TyG fluctuations precede or follow the latent changes of CVD, making it difficult to prove causality. Also, it is hard to capture the short-term impacts of seasons and sudden incidents. Geographically, metabolic fluctuation patterns vary among populations in regions with different climates and social rhythms. Thus, the results cannot align with the actual TyG-CVD dynamics everywhere, weakening their generalizability; and (7) The lack of external validation is a key constraint. Future studies need to replicate these findings in independent cohorts to confirm the robustness of the conclusions.

Conclusions

There is an independent correlation between TyG index and cardiovascular disease in elderly diabetic subjects. TyG index can be introduced into the routine screening and management of elderly diabetic patients for early detection, diagnosis, and treatment. In clinical practice, physicians can stratify the risk of CVD for elderly diabetic patients based on the relationship between the TyG index and CVD. For patients whose TyG index is close to or exceeds the inflection point value, the risk of CVD occurrence should be monitored more closely, and proactive intervention measures should be taken. Additionally, it is advisable to combine the TyG index with other CVD risk factors such as age, blood pressure, blood lipids, blood glucose control status, and lifestyle to construct a more accurate CVD risk prediction model. This will enhance the predictive ability for CVD occurrence in the elderly diabetic population, thereby quickly and effectively reducing the impact of the TyG index on CVD and decreasing the morbidity and mortality of CVD.

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

This study was conducted in accordance with the principles of the Declaration of Helsinki. The NHANES protocol was reviewed and approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. All participants provided written informed consent before participation in the survey. The data used in this study were anonymized and de-identified prior to analysis to ensure the privacy and confidentiality of the participants. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ZW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1475590/full#supplementary-material

SUPPLEMENTARY TABLE 1
Baseline characteristics of the CHF and non-CHF groups.

SUPPLEMENTARY TABLE 2
Baseline characteristics of the CHD and non-CHD groups.

SUPPLEMENTARY TABLE 3
Baseline characteristics of the Angina and non-Angina groups.

SUPPLEMENTARY TABLE 4
Baseline characteristics of the myocardial infarction and non-myocardial infarction groups.

SUPPLEMENTARY TABLE 5
Baseline characteristics of the Stroke and non-Stroke groups.

SUPPLEMENTARY FIGURE 1
Mediation analysis of TyG with CVD risk. Adjusted for age, sex, race, educational level, marital status, smoking status, DBP, TC, HDL-C, LDL-C, albumin, eGFR, uric acid, Hypertension, Hypotensive drugs, Chronic kidney disease.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019:update from the GBD 2019 study. *J Am Coll Cardiol*. (2020) 76:2982–3021. doi: 10.1016/j.jacc.2020.11.010

2. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol*. (2019) 16:203–12. doi: 10.1038/s41569-018-0119-4

3. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC guidelines on diabetes, prediabetes, and Cardiovascular Diseases developed in collaboration with the EASD: the Task Force for diabetes, pre-diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J*. (2020) 41:255–323. doi: 10.1093/eurheartyj/ehz486

4. Park HM, Lee HS, Lee Y-J, Lee J-H. The triglyceride–glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 Diabetes Mellitus than the homeostatic model assessment of insulin resistance. *Diabetes Res Clin Pract*. (2021) 180:109042. doi: 10.1016/j.diabres.2021.109042

5. Tahapary DL, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index. *Diabetes Metab Syndr*. (2022) 16:102581. doi: 10.1016/j.dsx.2022.102581

6. Hu Y, Wang X, Xiao S, Sun N, Huan C, Wu H, et al. A clinical nomogram based on the triglyceride-glucose index to predict contrast-induced acute kidney injury after percutaneous intervention in patients with acute coronary syndrome with diabetes mellitus. *Cardiovasc Ther*. (2022) 2022:5443880. doi: 10.1155/2022/5443880

7. Peng Z, Zhao R, Yang Y, Hua K, Yang X. Predictive value of the CT-based visceral adiposity tissue index and triglyceride-glucose index on new-onset atrial fibrillation after off-pump coronary artery bypass graft: analyses from a longitudinal study. *Rev Cardiovasc Med*. (2023) 24:338. doi: 10.31083/j.rcm2411338

8. Zhao J, Fan H, Wang T, Yu B, Mao S, Wang X, et al. TyG index is positively associated with risk of CHD and coronary atherosclerosis severity among NAFLD patients. *Cardiovasc Diabetol*. (2022) 21:123. doi: 10.1186/s12933-022-01548-y

9. Zhang Y, Chu C, Zhong Z, Luo YB, Ning FF, Guo N. High triglyceride-glucose index is associated with poor cardiovascular outcomes in Chinese acute coronary

syndrome patients without diabetes mellitus who underwent emergency percutaneous coronary intervention with drug-eluting stents. *Front Endocrinol (Lausanne)*. (2023) 14:1101952. doi: 10.3389/fendo.2023.1101952

10. Li J, Zhang R, Wu Z, Guo J, Wang Z, Li S, et al. Blood glucose fluctuation in older adults with diabetes mellitus and end-stage renal disease on maintenance hemodialysis: an observational study. *Diabetes Ther*. (2022) 13:1353–65. doi: 10.1007/s13300-022-01274-4

11. Kucukseymen S, Neisius U, Rodriguez J, Tsao CW, Nezafat R. Negative synergism of diabetes mellitus and obesity in patients with heart failure with preserved ejection fraction: a cardiovascular magnetic resonance study. *Int J Cardiovasc Imaging*. (2020) 36:2027–38. doi: 10.1007/s10554-020-01915-4

12. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. (2021) 385:1737–49. doi: 10.1056/NEJMoa2102953

13. D'Agostino RBSr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. (2008) 117:743–53. doi: 10.1161/CIRCULATIONAHA.107.699579

14. Chen X, Liu D, He W, Hu H, Wang W. Predictive performance of triglyceride glucose index (TyG index) to identify glucose status conversion: a 5-year longitudinal cohort study in Chinese pre-diabetes people. *J Transl Med*. (2023) 21:624. doi: 10.1186/s12967-023-04402-1

15. Guo D, Wu Z, Xue F, Chen S, Ran X, Zhang C, et al. Association between the triglyceride-glucose index and impaired cardiovascular fitness in non-diabetic young population. *Cardiovasc Diabetol*. (2024) 23:39. doi: 10.1186/s12933-023-02089-8

16. Zhang Q, Xiao S, Jiao X, Shen Y. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001-2018. *Cardiovasc Diabetol*. (2023) 22:279. doi: 10.1186/s12933-023-02030-z

17. Santulli G, Visco V, Varzideh F, Varzideh F, Guerra G, Kansakar U, et al. Prediabetes increases the risk of frailty in prefrail older adults with hypertension: beneficial effects of metformin. *Hypertension*. (2024) 81:1637–43. doi: 10.1161/HYPERTENSIONAHA.124.23087

18. Zhao Y, Gu Y, Zhang B. Associations of triglyceride-glucose (TyG) index with chest pain incidence and mortality among the U.S. population. *Cardiovasc Diabetol*. (2024) 23:111. doi: 10.1186/s12933-024-02209-y

19. Wu Y, Yang Y, Zhang J, Liu S, Zhuang W. The change of triglyceride-glucose index may predict incidence of stroke in the general population over 45 years old. *Cardiovasc Diabetol*. (2023) 22:132. doi: 10.1186/s12933-023-01870-z

20. Zhang F, Hou X. Association between the triglyceride glucose index and heart failure: NHANES 2007-2018. *Front Endocrinol (Lausanne)*. (2024) 14:1322445. doi: 10.3389/fendo.2023.1322445

21. Xue Y, Xu J, Li M, Gao Y. Potential screening indicators for early diagnosis of NAFLD/MAFLD and liver fibrosis: Triglyceride glucose index-related parameters. *Front Endocrinol (Lausanne)*. (2022) 13:951689. doi: 10.3389/fendo.2022.951689

22. Yu Y, Wang J, Ding L, Huang H, Cheng S, Deng Y, et al. Sex differences in the nonlinear association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. *Diabetol Metab Syndr*. (2023) 15:136. doi: 10.1186/s13098-023-01117-7

23. Zhao M, Xiao M, Tan Q, Lu F. Triglyceride glucose index as a predictor of mortality in middle-aged and elderly patients with type 2 diabetes in the US. *Sci Rep*. (2023) 13:16478. doi: 10.1038/s41598-023-43512-0

24. Li S, Guo B, Chen H, Shi Z, Li Y, Tian Q, et al. The role of the triglyceride (triacylglycerol) glucose index in the development of cardiovascular events: a retrospective cohort analysis. *Sci Rep*. (2019) 9:7320. doi: 10.1038/s41598-019-43776-5

25. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. *Metabolism*. (2021) 119:154766. doi: 10.1016/j.metabol.2021.154766

26. Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. *Diabetes Metab J*. (2022) 46:15–37. doi: 10.4093/dmj.2021.0280

27. Li T, Wang P, Wang X, Liu Z, Zhang Z, Zhang Y, et al. Inflammation and insulin resistance in diabetic chronic coronary syndrome patients. *Nutrients*. (2023) 15:2808. doi: 10.3390/nu15122808

28. Limberg JK, Soares RN, Padilla J. Role of the autonomic nervous system in the hemodynamic response to hyperinsulinemia-implications for obesity and insulin resistance. *Curr Diabetes Rep*. (2022) 22:169–75. doi: 10.1007/s11892-022-01456-1

29. Kelem A, Adane T, Shiferaw E. Insulin resistance-induced platelet hyperactivity and a potential biomarker role of platelet parameters: A narrative review. *Diabetes Metab Syndr Obes*. (2023) 16:2843–53. doi: 10.2147/DMSO.S425469

30. Yang K, Liu W. Triglyceride and glucose index and sex differences in relation to major adverse cardiovascular events in hypertensive patients without diabetes. *Front Endocrinol (Lausanne)*. (2021) 12:761397. doi: 10.3389/fendo.2021.761397

31. Xin F, He S, Zhou Y, Jia X, Zhao Y, Zhao H. The triglyceride glucose index trajectory is associated with hypertension: a retrospective longitudinal cohort study. *Cardiovasc Diabetol*. (2023) 22:347. doi: 10.1186/s12933-023-02087-w

32. Ye Z, Xie E, Jiao S, Gao Y, Li P, Tu Y, et al. Triglyceride glucose index exacerbates the risk of future cardiovascular disease due to diabetes: evidence from the China Health and Retirement Longitudinal Survey (CHARLS). *BMC Cardiovasc Disord*. (2022) 22:236. doi: 10.1186/s12872-022-02673-y

33. Su W, Wang J, Chen K, Yan W, Gao Z, Tang X, et al. A higher TyG index level is more likely to have enhanced incidence of T2DM and HTN comorbidity in elderly Chinese people: a prospective observational study from the reaction study. *Diabetol Metab Syndr*. (2024) 16:29. doi: 10.1186/s13098-024-01258-3

34. Cui C, Liu L, Zhang T, Fang L, Mo Z, Qi Y, et al. Triglyceride-glucose index, renal function and cardiovascular disease: a national cohort study. *Cardiovasc Diabetol*. (2023) 22:325. doi: 10.1186/s12933-023-02055-4

35. Zhu Q, Chen Y, Cai X, Cai L, Hong J, Luo Q, et al. The non-linear relationship between triglyceride-glucose index and risk of chronic kidney disease in hypertensive patients with abnormal glucose metabolism: A cohort study. *Front Med (Lausanne)*. (2022) 9:1018083. doi: 10.3389/fmed.2022.1018083

36. Cai X, Hu J, Zhu Q, Wang M, Liu S, Dang Y, et al. Relationship of the metabolic score for insulin resistance and the risk of stroke in patients with hypertension: A cohort study. *Front Endocrinol (Lausanne)*. (2022) 13:1049211. doi: 10.3389/fendo.2022.1049211

37. Hu J, Cai X, Li N, Wen W, Hong J, Zhang D, et al. Association between triglyceride glucose index-waist circumference and risk of first myocardial infarction in chinese hypertensive patients with obstructive sleep apnea: an observational cohort study. *Nat Sci Sleep*. (2022) 14:969–80. doi: 10.2147/NSS.S362101

38. Zhao J, Cai X, Hu J, Song S, Zhu Q, Shen D, et al. J-shaped relationship between weight-adjusted-waist index and cardiovascular disease risk in hypertensive patients with obstructive sleep apnea: A cohort study. *Diabetes Metab Syndr Obes*. (2024) 17:2671–81. doi: 10.2147/DMSO.S469376

39. Wen W, Cai X, Zhu Q, Hu J, Hong J, Zhang X, et al. Linear relationship between hepatic steatosis index and major adverse cardiovascular events in hypertensive patients with obstructive sleep apnea: A real-world cohort study from China. *Rev Cardiovasc Med*. (2023) 24:280. doi: 10.31083/j.rcm2410280

40. Liang S, Wang C, Zhang J, Liu Z, Bai Y, Chen Z, et al. Triglyceride-glucose index and coronary artery disease: a systematic review and meta-analysis of risk, severity, and prognosis. *Cardiovasc Diabetol*. (2023) 22:170. doi: 10.1186/s12933-023-01906-4

41. Zhao S, Wang Z, Qing P, Li M, Liu Q, Pang X, et al. Comprehensive analysis of the association between triglyceride-glucose index and coronary artery disease severity across different glucose metabolism states: a large-scale cross-sectional study from an Asian cohort. *Cardiovasc Diabetol*. (2024) 23:251. doi: 10.1186/s12933-024-02355-3

42. Chen X, Zhuo S, Zhu T, Yao P, Yang M, Mei H, et al. Fpr2 deficiency alleviates diet-induced insulin resistance through reducing body weight gain and inhibiting inflammation mediated by macrophage chemotaxis and M1 polarization. *Diabetes*. (2019) 68:1130–42. doi: 10.2337/db18-0469

43. Clavero-Jimeno A, Dote-Montero M, Migueles JH, Camacho-Cardenosa A, Oses M, et al. Impact of lifestyle moderate-to-vigorous physical activity timing on glycemic control in sedentary adults with overweight/obesity and metabolic impairments. *Obes (Silver Spring)*. (2024) 32:1465–73. doi: 10.1002/oby.24063

44. Malik AO, Chen H, Tang F, Chan PS, Cooper A, Gomes MB, et al. Association of country economy and socioeconomic factors on risk factor control for primary prevention of cardiovascular disease in patients with diabetes mellitus: Insights from the DISCOVER study. *Indian Heart J*. (2022) 74:398–405. doi: 10.1016/j.ihj.2022.07.008

frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 10 June 2025
DOI 10.3389/fendo.2025.1562815

Check for updates

OPEN ACCESS

EDITED BY
Åke Sjöholm,
Gävle Hospital, Sweden

REVIEWED BY
Per M. Hellström,
Uppsala University, Sweden
Aikaterini Andreadi,
University of Rome Tor Vergata, Italy

*CORRESPONDENCE
Aidong Liu
laddoc8808@163.com

RECEIVED 18 January 2025
ACCEPTED 23 May 2025
PUBLISHED 10 June 2025

CITATION
Gao H, Wei Q, Zou A, Yu K, Song D, Li J, Han H and Liu A (2025) Evaluation of three mechanisms of action (SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas) in treating type 2 diabetes with heart failure: a systematic review and network meta-analysis of RCTs.
Front. Endocrinol. 16:1562815.
doi: 10.3389/fendo.2025.1562815

COPYRIGHT
© 2025 Gao, Wei, Zou, Yu, Song, Li, Han and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Evaluation of three mechanisms of action (SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas) in treating type 2 diabetes with heart failure: a systematic review and network meta-analysis of RCTs

Huize Gao[1], Qian Wei[2], Anqi Zou[1], Keying Yu[3], Da Song[1], Jian Li[1], Huize Han[1] and Aidong Liu[2*]

[1]Changchun University of Chinese Medicine, Changchun, Jilin, China, [2]The Third Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin, China, [3]The Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin, China

Objective: We aimed to evaluate and compare the efficacy and safety of three antidiabetic drug classes—SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas—in patients with type 2 diabetes mellitus (T2DM) complicated by heart failure (HF). We focused on their differential effects on both cardiovascular outcomes (e.g., heart failure biomarkers and cardiac function) and metabolic outcomes (e.g., glycemic control and body weight), aiming to determine whether the newer agents offer superior cardiometabolic benefits. A network meta-analysis was conducted to integrate available evidence and compare all interventions simultaneously.

Methods: A comprehensive literature search was performed in PubMed, EMBASE, and the Cochrane Library. encompassing all available records up to December 10, 2024. Fourteen RCTs were included. A Bayesian network meta-analysis was utilized to integrate direct and indirect evidence, facilitating a comparative ranking of various SGLT2 inhibitors—canagliflozin (CANA), ipragliflozin (IPRA), empagliflozin (EMPA), remogliflozin (REMO), licogliflozin (LICO), and dapagliflozin (DAPA)—as well as one GLP-1 receptor agonist—semaglutide (SEMA)—and a sulfonylurea—glimepiride (GLIM)—with respect to their efficacy and safety profiles.

Results: SEMA (SMD = −0.22, 95% CI: −1.31 to 0.87) demonstrated the most favorable outcome in reducing BNP levels. LICO (SMD = −0.91, 95% CI: −1.76 to −0.06) ranked highest for body weight reduction, indicating the greatest impact. GLIM (SMD = −0.64, 95% CI: −1.12 to −0.17) showed the strongest effect on lowering HbA1c, while DAPA (SMD = 0.34, 95% CI: −0.97 to 1.65) was the top-ranked agent for improving LVEF. Safety analysis indicated that LICO and IPRA had the lowest incidence of adverse events. GLIM was associated with an increased risk of hypoglycemia, whereas DAPA was linked to a higher risk of urinary tract infections.

Conclusion: SEMA significantly improves both metabolic control and BNP levels, making it suitable for patients requiring comprehensive management of metabolic abnormalities and heart failure. LICO offers a distinct advantage in weight management, particularly benefiting individuals with obesity. DAPA demonstrates notable efficacy in optimizing HbA1c and LVEF, making it a preferred option for patients needing more intensive cardiac support. Despite its moderate efficacy, GLIM remains a viable choice for certain patients due to its favorable safety profile and cost-effectiveness. Collectively, these findings provide essential evidence-based insights to guide individualized therapeutic strategies in type 2 diabetes complicated by heart failure.

KEYWORDS

type 2 diabetes with heart failure, SGLT2 inhibitors, GLP-1 receptor agonists, efficacy and safety, network meta-analysis

1 Introduction

Heart failure (HF) is among the most prevalent and fatal cardiovascular diseases worldwide, affecting an estimated 64.3 million individuals globally (1). The five-year mortality rate for HF patients can reach up to 50%, underscoring its significance as a primary clinical concern (2). Diabetes mellitus is a prevalent comorbidity in heart failure, affecting approximately 40% of patients with heart failure with reduced ejection fraction (HFrEF) and 45% of those with heart failure with preserved ejection fraction (HFpEF) (3). This association is largely due to hyperglycemia-induced metabolic disturbances such as oxidative stress, endothelial dysfunction, and advanced glycation end product accumulation, all of which contribute to cardiomyocyte injury and ventricular remodeling (4). Consequently, managing diabetes in patients with heart failure presents a complex and critical challenge, necessitating therapeutic agents that can simultaneously enhance both cardiac function and metabolic status. Current pharmacotherapies for heart failure include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor blockers (ARBs), β-blockers, mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitors (ARNIs) such as sacubitril/valsartan (5). However, these standard therapies present limitations for heart failure patients with concurrent diabetes. For instance, conventional hypoglycemic agents, including sulfonylureas, have been linked to an elevated risk of heart failure in certain studies (6). Therefore, there is a need to develop comprehensive therapeutic strategies with enhanced cardiovascular protective effects. Novel agents, such as sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, are considered to provide potential benefits for patients with heart failure due to their unique mechanisms of action (7). SGLT2 inhibitors lower blood glucose levels and reduce blood volume by inhibiting the reabsorption of glucose and sodium in the renal tubules. Studies have demonstrated that they can significantly decrease hospitalization rates for heart failure and all-cause mortality. In addition, they improve myocardial energy metabolism, enhance diuresis and natriuresis, and exhibit anti-inflammatory and anti-fibrotic effects, collectively reducing cardiac preload and afterload (8). GLP-1 receptor agonists, including liraglutide and semaglutide, regulate blood glucose levels by enhancing insulin secretion, suppressing glucagon release, and delaying gastric emptying (9, 10). Furthermore, they provide additional cardiometabolic benefits, including reductions in body weight and improvements in blood pressure and lipid profiles. Emerging evidence also supports their antioxidative and anti-inflammatory effects on the vascular endothelium, which may contribute to attenuating atherosclerosis and improving cardiac outcomes (4).

Despite existing studies demonstrating some benefits of SGLT2 inhibitors and GLP-1 receptor agonists in patients with heart failure, most randomized controlled trials (RCTs) have been limited to comparisons of single or a few medications, lacking comprehensive evaluations across multiple drug classes.

To address this evidence gap, we performed a Bayesian network meta-analysis to compare the efficacy and safety of SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas in patients with T2DM and HF. This method allows for the integration of both direct and indirect comparisons across multiple therapies, and provides probabilistic rankings that are particularly valuable for clinical decision-making.

We hypothesized that SGLT2 inhibitors and GLP-1 receptor agonists would demonstrate superior cardiometabolic outcomes compared to sulfonylureas in patients with T2DM and HF.

2 Materials and methods

This network meta-analysis (NMA) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network

meta-analyses (Supplementary Table 1). Given the limited availability of direct head-to-head randomized controlled trials (RCTs) comparing different drug classes in patients with type 2 diabetes mellitus (T2DM) and heart failure (HF),a Bayesian network meta-analysis framework was adopted to integrate both direct and indirect evidence across a connected network of interventions. This method enables the estimation of relative treatment effects and treatment rankings even when direct comparisons are sparse or unavailable. Compared to conventional pairwise meta-analysis, the Bayesian approach offers greater flexibility in modeling multi-arm comparisons, incorporates prior distributions, and provides probabilistic statements regarding the likelihood of each treatment being optimal. This analytic strategy is particularly suitable for decision-making involving multiple competing treatments, such as the three drug classes under investigation. Accordingly, we applied this approach to estimate and compare the relative efficacy and safety of SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas. To ensure transparency, reliability, and novelty, the study protocol was registered in the Prospective Register of Systematic Reviews (CRD42025630552).

2.1 Data sources and search strategy

A systematic literature search was performed in PubMed, EMBASE, and the Cochrane Library. The search terms included "heart failure," "cardiac failure," "myocardial failure," "heart decompensation," "randomized clinical trial," "RCT," "type 2 diabetes mellitus," "T2DM," "non-insulin dependent diabetes," "type 2 diabetes," "maturity onset diabetes," "noninsulin dependent diabetes mellitus," "adult-onset diabetes mellitus," and "ketosis-resistant diabetes mellitus." The search period spanned from the inception of each database up to December 10, 2024. The search strategy employed a combination of free-text terms and controlled vocabulary, with no restrictions on language.

2.2 Selection criteria

Inclusion Criteria

(1)RCTs: Studies involving adult patients with a confirmed diagnosis of T2DM and concurrent HF.(2)Interventions: RCTs evaluating monotherapy or combination therapy with SGLT2 inhibitors, GLP-1 receptor agonists, or sulfonylureas.(3) Comparators: RCTs comparing the specified interventions with placebo, SOC, or other pharmacological treatments.(4)Outcome Measures: RCTs reporting at least one of the following outcomes, BNP Levels: Changes in brain natriuretic peptide (BNP) concentrations or other related biomarkers. Body Weight: Alterations in body weight or weight-related metrics. Glycated Hemoglobin (HbA1c): Changes in HbA1c levels. Left Ventricular Ejection Fraction (LVEF): Modifications in LVEF. Common Adverse Events: Incidence of mild to moderate adverse events, including but not limited to headache, nausea, diarrhea, and hypoglycemia.

Exclusion Criteria:

(1)Non-Randomized Studies: Observational studies, retrospective studies, and other non-RCT designs.(2)Multiple Phases: RCTs investigating different stages of the same patient cohort.(3)Ineligible Interventions: Studies involving medications outside the specified classes (i.e., non-SGLT2 inhibitors, non-GLP-1 receptor agonists, or non-sulfonylurea drugs).(4)Unclear Outcomes: RCTs that do not clearly define or report the specified outcome measures.(5)Non-Original Research: Reviews, case reports, and other studies that do not present original data. This structured approach ensures the inclusion of high-quality evidence relevant to the comparative efficacy and safety of SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas in managing patients with T2DM and HF, while excluding studies that do not meet the rigorous standards necessary for a robust network meta-analysis.

2.3 Data extraction and quality assessment

Three researchers independently extracted data from the RCTs in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In instances of discrepancies, a fourth author was consulted to achieve consensus. The extracted data from each study encompassed the first author's name, sample size, year of publication, randomization method, median age in both the intervention and control groups, gender distribution within each group, and the treatment regimens administered to the intervention and control cohorts.

The quality of the included RCTs was evaluated using the Cochrane Risk of Bias Tool (Version 2.0). This instrument assesses five domains:(1)Risk of bias arising from the randomization process (2)Risk of bias due to deviations from intended interventions (3)Risk of bias from missing outcome data (4)Risk of bias in the measurement of the outcome (5)Risk of bias in the selection of the reported result.

Each RCT was assigned a risk level of low, high, or "some concerns" for each domain. This thorough quality assessment ensures the reliability and validity of the findings obtained from the network meta-analysis.

2.4 Statistical analysis

Bayesian network meta-analyses were performed using Stata 17.0. For dichotomous outcomes, odds ratios (ORs) were utilized as the effect size metric, whereas continuous outcomes were expressed as mean differences (MDs) with corresponding 95% confidence intervals (CIs). When continuous variables were assessed using different units, standardized mean differences (SMDs) were calculated to reduce heterogeneity.

In constructing the network evidence diagrams, the size of each node represented the sample size of the respective intervention, and

the thickness of the connecting lines indicated the number of RCTs comparing the two interventions. For networks exhibiting an open-loop structure, a consistency model was applied. In contrast, for closed-loop structures, inconsistency tests were conducted to evaluate the coherence of outcome measures. A p-value greater than 0.05 suggested satisfactory consistency between direct and indirect evidence, thereby justifying the use of a consistency model.

Although the overall inconsistency tests yielded $p \geq 0.05$, suggesting acceptable coherence, subgroup analyses and meta-regression were not feasible due to the limited number of included studies with stratified subgroups (e.g., HFrEF *vs*. HFpEF).

This limitation was acknowledged, and caution was taken when interpreting potential heterogeneity across treatment classes.

Subsequently, cumulative probability ranking plots were generated based on the surface under the cumulative ranking (SUCRA) values to determine the most efficacious treatment regimen. For networks with closed-loop structures, loop-specific inconsistency tests were implemented to assess the consistency within each loop. A 95% confidence interval for the inconsistency factor that included zero indicated good concordance between direct and indirect evidence.

Finally, comparison-adjusted funnel plots were employed to assess potential publication bias and the presence of small-study effects. Visual inspection and symmetry of funnel plots were used to evaluate the likelihood of reporting bias.

3 Results

3.1 Systematic review and characteristics of the included studies

The initial literature search yielded a total of 5,875 records from the databases. After screening abstracts to eliminate duplicates and irrelevant studies, 379 articles were deemed eligible for full-text review. Ultimately, 14 (11–24) studies met our inclusion criteria (Figure 1).

This analysis included 6,931 patients who were randomly assigned to receive one of the following treatment regimens: canagliflozin (CANA), ipragliflozin (IPRA), empagliflozin (EMPA), remogliflozin (REMO), licogliflozin (LICO), semaglutide (SEMA), dapagliflozin (DAPA), or standard of care (SOC). The control groups comprised glimepiride (GLIM) and other conventional treatments. Detailed information for all included studies is provided in Table 1. Quality assessment was conducted using the Cochrane Risk of Bias Tool (ROB 2.0). Among the 14 studies evaluated, 10 were assessed as having a low overall risk of bias, while 4 were categorized as having "some concerns." Detailed quality assessment results are presented in Figure 2.

3.2 Network meta-analyses

3.2.1 BNP outcome

Nine studies reported changes in BNP levels, encompassing eight different treatment modalities within the network meta-analysis. The network diagram illustrating the various drug interventions for the included subjects is presented in Figure 3A. The BNP network formed a closed loop. An inconsistency test of the overall network yielded a p-value ≥ 0.05, indicating no significant inconsistency; therefore, a consistency model was utilized for the analysis. Loop-specific inconsistency tests revealed that the 95% confidence intervals included zero and that the inconsistency factors were minimal, suggesting good homogeneity. Ultimately, both direct and indirect comparisons demonstrated consistent results.

SEMA (SMD = −0.22, 95% CI: −1.31 to 0.87) and CANA (SMD = −0.04, 95% CI: −1.20 to 1.12) showed some efficacy in improving BNP levels compared to SOC, although these differences were not statistically significant. CANA exhibited a slight advantage over SOC; however, this difference did not reach statistical significance. GLIM (SMD = 0.74, 95% CI: −0.59 to 2.07) did not demonstrate any benefit compared to SOC. Details are provided in Figures 3A, 4A.

3.2.2 Permission to reuse and copyright

Six studies reported changes in body weight, encompassing six distinct treatment modalities within the network meta-analysis. The network diagram illustrating the various drug interventions among the included subjects is presented in Figure 3B. The body weight network formed a closed loop. An inconsistency test of the overall network yielded a p-value ≥ 0.05, indicating no significant inconsistency; therefore, a consistency model was employed for the analysis. Loop-specific inconsistency tests revealed that the 95% confidence intervals included zero and that the inconsistency factors were minimal, suggesting good homogeneity. Consequently, both direct and indirect comparisons demonstrated consistent results.

LICO (SMD = −0.91, 95% CI: −1.76 to −0.06) and SEMA (SMD = −0.52, 95% CI: −1.01 to −0.03) showed efficacy in reducing body weight compared to SOC, with LICO reaching statistical significance. CANA (SMD = 0.09, 95% CI: −0.71 to 0.89) did not demonstrate any significant advantage over SOC in terms of body weight reduction.

3.2.3 Glycated hemoglobin outcome

Five studies reported changes in HbA1c levels, encompassing six distinct treatment modalities within the network meta-analysis. The network diagram illustrating the various drug interventions among the included subjects is presented in Figure 3C. The HbA1c network formed a closed loop. An inconsistency test of the overall network yielded a p-value ≥ 0.05, indicating no significant inconsistency; therefore, a consistency model was employed for the analysis. Loop-specific inconsistency tests revealed that the 95% confidence intervals included zero and that the inconsistency factors were minimal, suggesting good homogeneity. Consequently, both direct and indirect comparisons demonstrated consistent results.

GLIM (SMD = −0.64, 95% CI: −1.12 to −0.17) and DAPA (SMD = −0.60, 95% CI: −1.11 to −0.08) showed significant advantages in improving HbA1c levels compared to SOC. Additionally, GLIM (SMD = −0.30, 95% CI: −0.48 to −0.11) also demonstrated a significant advantage over CANA. Details are provided in Figures 3C, 4B.

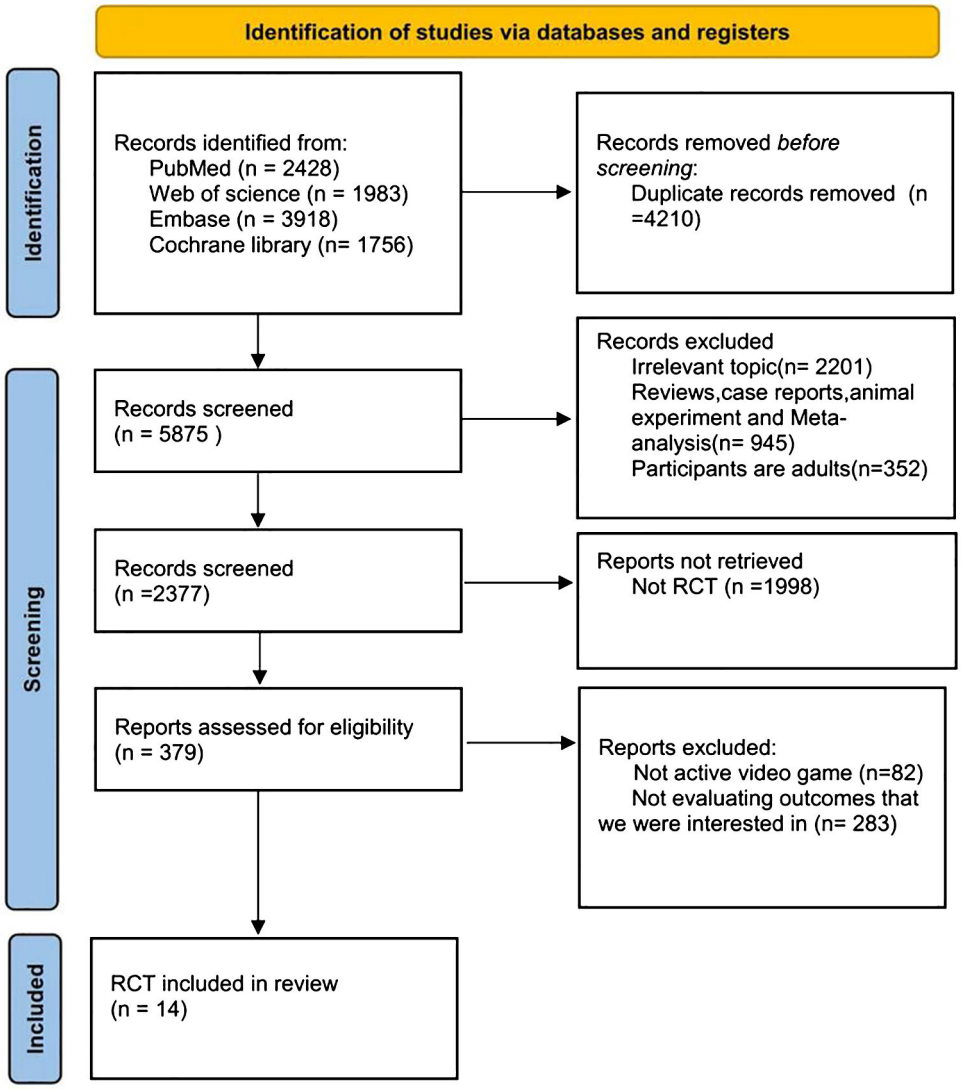


FIGURE 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for selection and inclusion of the studies via databases. Latest search date: Dec, 2024.

3.2.4 Left ventricular ejection fraction outcome

Three studies reported changes in left ventricular ejection fraction (LVEF) levels, encompassing three distinct treatment modalities within the network meta-analysis. The network diagram illustrating the various drug interventions among the included studies is presented in Figure 3D. The LVEF network formed an open loop; therefore, a consistency model was employed.

DAPA (SMD = 0.34, 95% CI: −0.97 to 1.65) demonstrated the best performance among all treatment regimens, although the difference compared to SOC did not reach statistical significance. Furthermore, other treatment regimens did not show significant improvements in LVEF when compared with SOC or with each other, with no statistically significant differences observed. Details are provided in Figures 3D, 4B.

3.2.5 Safety and toxicity

The incidence of adverse reactions varied among the different treatment regimens, with statistically significant differences observed in the following comparisons: IPRA versus SEMA (OR = 0.26, 95% CI: 0.09–0.80), SEMA versus GLIM (OR = 0.46, 95% CI: 0.28–0.75), and GLIM versus SOC (OR = 0.67, 95% CI: 0.18–2.44). These findings indicate that IPRA is associated with a significantly lower incidence of adverse reactions compared to SEMA, while SEMA exhibits a significantly lower risk of adverse reactions compared to GLIM. Additionally, no statistically significant differences were observed between SOC and SOTA (OR = 0.49, 95% CI: 0.19–1.61) and between DAPA and EMPA (OR = 0.55, 95% CI: 0.06–5.16). No new safety concerns were identified in the included studies.

TABLE 1 Baseline characteristics of studies included in the network meta-analysis.

First Author	Sample Size	Year	Randomization	Median age (Experimental Group)	Median age (Control Group)	Male/Famale (Experimental Group)	Male/Famale (Control Group)	Intervention Arm	Control Arm
Kazuki Shiina	113/120	2020	1:1	68.3 ± 9.8	68.9 ± 10.4	78/35	84/36	Canagliflozin	Glimepiride
Kenya Kusunose	113/120	2021	1:1	69 ± 9	69 ± 9	88/25	86/34	Canagliflozin	Glimepiride
Shunsuke Tamaki	30/29	2021	1:1	80	82	18/12	18/11	Empagliflozin	Conventional glucose-lowering therapy
Shantanu Sengupta	125/125	2024	1:1					Remogliflozine	Empagliflozine
Ueda T	42/40	2021	1:1	76.5	75.9	28/14	27/13	Canagliflozin	Standard Diabetic Therapy
Rudolf A. de Boer	30/30/33	2024	1:1	66	68.5	28/2	24/6	Licogliflozin	Empagliflozin
			1:1		71		26/7		Placebo
Mikhail N Kosiborod	310/306	2024	1:1	64	65	195/115	186/120	Semaglutide	Placebo
M.N. Kosiborod	310/306	2024	1:1	69	70	128/182	145/161	semaglutide	Placebo
Ibrahim A	50/50	2020	1:1	62.02 ± 8.8	60.64 ± 9.9	28/22	26/24	Dapagliflozin, furosemide, and other convent-ional anti-HF treatments.	Insulin for blood glucose control, furosemide, and other conventional anti-HF treatments
Mark C. Petrie	573/572	2024	1:1	70	72	192/192	215/163	Semaglutide	Placebo
Fu	30/30	2023	1:1	70.7	70.4	9/21	8/22	Dapagliflozin	Placebo
Daisaku Nakatani	109/117	2023	1:1	68.6	69.1	85/24	85/32	Canagliflozin	Glimepiride
Singh	28/28	2020	1:1	67.1	67.1	19/9	19/9	Dapagliflozin	Placebo

10.3389/fendo.2025.1562815



FIGURE 2
Detailed quality assessment results.

Common adverse events included hypoglycemia, urinary tract infections, gastrointestinal reactions, and hypotension (Figure 5). Details are provided in Figure 4C.

3.4 Rank analysis

3.4.1 BNP outcome

Bayesian ranking analysis (Figure 6) revealed that SEMA is most likely to achieve the highest rank in improving BNP levels, with a cumulative probability of 31.3%, thereby demonstrating superior performance among the evaluated treatments. CANA follows with a 22.9% probability of attaining the top rank, while IPRA ranks third at 17.5%. LICO exhibits lower efficacy in BNP improvement, with only a 3.2% likelihood of securing the highest position. In contrast, GLIM performs the poorest, showing a 46.1% probability of being ranked last among all treatment options, indicating the least favorable outcome in BNP.

3.4.2 Body weight outcome

Bayesian ranking analysis (Figure 7) revealed that LICO is most likely to achieve the highest rank in improving body weight, with a cumulative probability of 70.9%, demonstrating the most significant effect among the evaluated treatments. SEMA follows, ranking second with a 17.3% probability of attaining the top position. DAPA (7.0%), EMPA (2.7%), and CANA (2.1%) exhibit lower probabilities of securing the first rank, while SOC shows no likelihood of ranking first (0.0%).

In terms of the worst rankings, CANA performs the least favorably, with a 44.9% probability of being ranked last. In contrast, LICO and SEMA have minimal probabilities of occupying the lowest ranks, at only 0.3% and 0.6%, respectively. These findings further underscore the

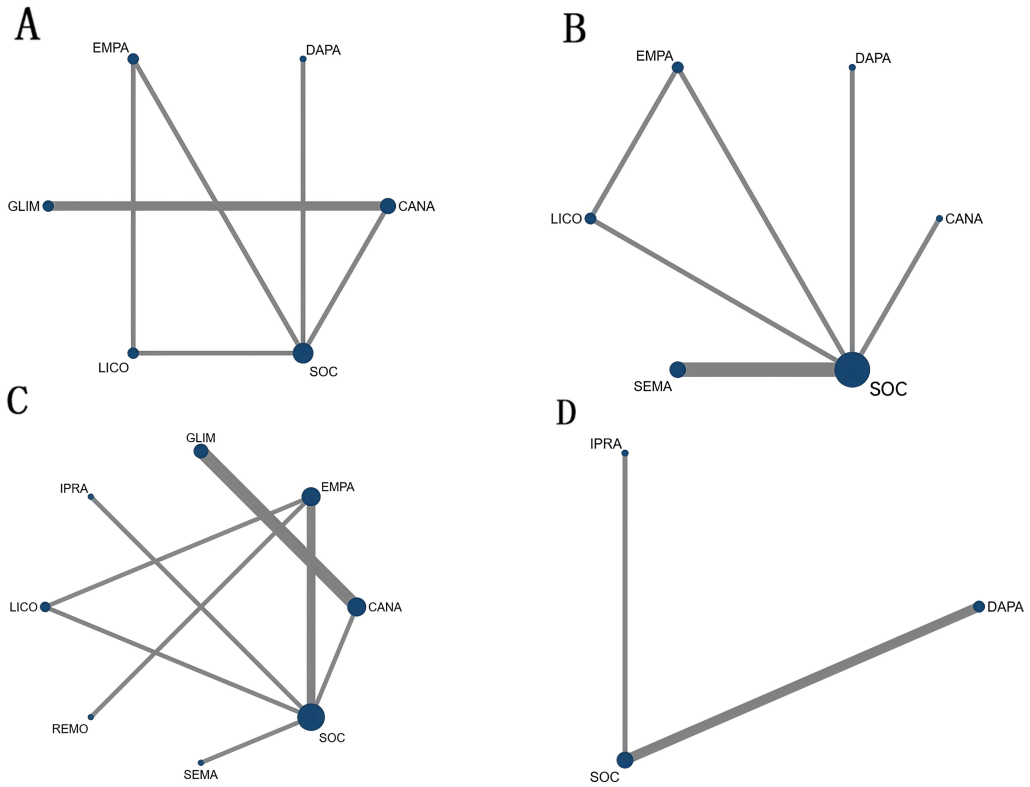


FIGURE 3
Network diagrams illustrating different drug interventions for the included subjects: **(A)** BNP network diagram. **(B)** Body weight network diagram.**(C)** HbA1c network diagram.**(D)** LVEF network diagram.

favorable efficacy and safety profiles of LICO and SEMA in managing body weight among patients with T2DM and HF.

3.4.3 Glycated Hemoglobin outcome

Bayesian ranking analysis (Figure 8) indicated that GLIM is most likely to achieve the highest rank in improving HbA1c levels, with a cumulative probability of 43.2%, thereby demonstrating the best performance among the evaluated treatments. DAPA closely follows, with a 36.1% probability of attaining the top rank, while LICO ranks third with a 14.5% probability. CANA and SOC were the least effective in improving HbA1c, each exhibiting a 0.0% probability of securing the first rank.

Regarding the worst rankings, SOC displayed the most unfavorable performance, with an 81.1% probability of being ranked last. In contrast, GLIM showed no likelihood of being the worst performer (0.0%), underscoring its consistent efficacy in improving HbA1c levels.

3.4.4 Left ventricular ejection fraction outcome

Bayesian ranking analysis (Figure 9) revealed that DAPA demonstrated the most significant improvement in LVEF, achieving the highest probability of ranking first with a cumulative probability of 68.0%. IPRA ranked second, possessing a 29.2% probability of attaining the top position. In contrast, SOC exhibited the poorest performance, with only a 2.8% probability of ranking first and a substantial 58.2% probability of being ranked last. These findings highlight SOC's inferior efficacy in enhancing LVEF compared to the other treatment options.

3.4.5 Adverse event incidence analysis

Bayesian ranking analysis (Figure 10) demonstrated that LICO exhibited the highest efficacy in controlling adverse events, with a 69.1% probability of ranking first. This indicates an exceptionally low risk of adverse event occurrence for LICO. IPRA followed with a 20.9% probability of attaining the top rank. In contrast, DAPA (41.9%) and EMPA (51.2%) showed higher probabilities of being ranked worst, reflecting a greater incidence of adverse events. Additionally, SOC and SOTA were present in the lower rankings, with SOC at 0.4% and SOTA at 2.6%. However, their performance was relatively better compared to DAPA and EMPA.

3.4.6 Publication bias

Funnel plots were generated for BNP, body weight, HbA1c, and drug safety outcomes to assess the presence of publication bias (Figure 11). The results demonstrated a symmetrical distribution of study points without any scattered outliers, indicating a minimal likelihood of publication bias in this study.

4 Discussion

This study is the first to systematically integrate three distinct classes of drugs—SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas—and compare their efficacy and safety in patients with

10.3389/fendo.2025.1562815

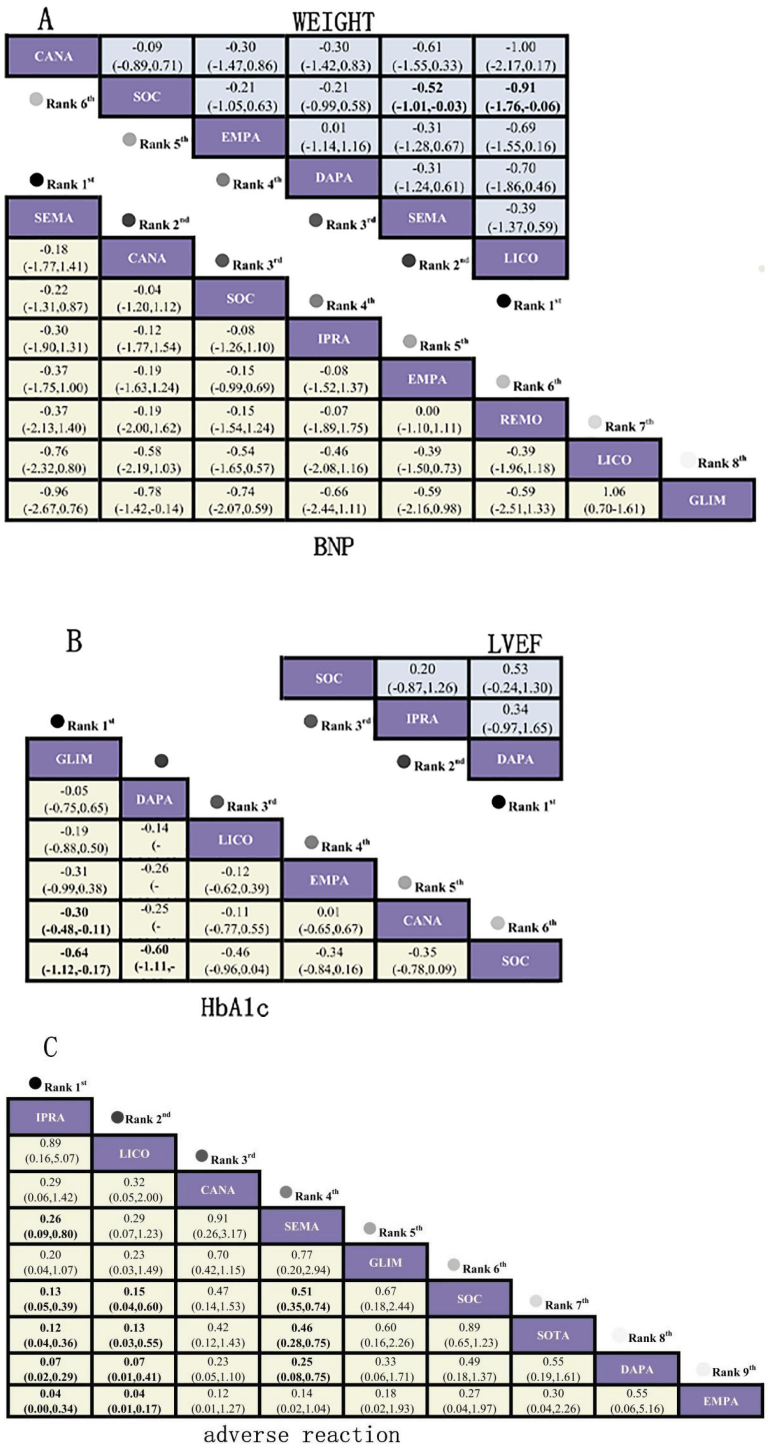


FIGURE 4
Rankograms illustrating comparative efficacy and safety of different medications across various outcome measures based on Bayesian network meta-analysis. **(A)** SMD and 95% CI for BNP (yellow lower triangle region) and body weight (blue upper triangle region). **(B)** SMD and 95% CI for HbA1c and LVEF. An SMD < 0.00 indicates a better survival benefit. **(C)** OR and 95% CI for Adverse Drug Reactions (ADRs).Note: SMD < 0.00 signifies a more favorable outcome in terms of survival benefits. OR < 1.00 signifies a reduced risk of adverse drug reactions, indicating better safety profiles.

T2DM and heart failure through a network meta-analysis. Unlike previous randomized controlled trials or traditional meta-analyses, our research consolidates multiple direct and indirect sources of evidence, providing a comprehensive therapeutic evaluation for this complex patient population. The results suggest that SEMA may be associated with improvements in BNP levels and body weight; however, these findings were not consistently statistically significant across comparisons, and should be interpreted as indicative trends rather than definitive effects. This suggests potential utility for patients needing both metabolic and cardiac support, but

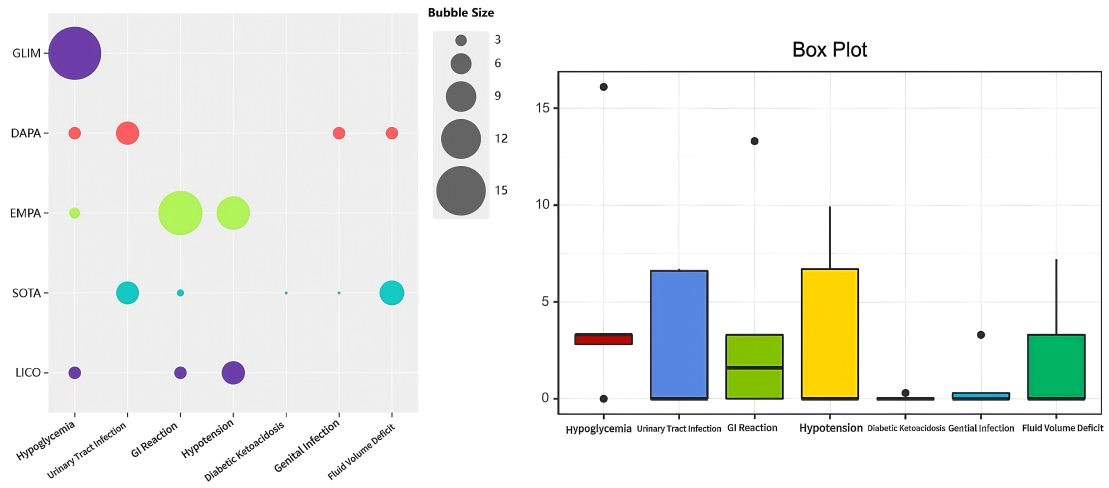


FIGURE 5
Safety profiles of various treatment regimens: Based on the results from the bubble plots and box plots, GLIM was found to be the most likely to induce hypoglycemia. DAPA and standard of therapy A (SOTA) were associated with an increased risk of urinary tract infections, whereas EMPA primarily manifested gastrointestinal reactions and a tendency towards hypotension. In contrast, LICO and IPRA exhibited relatively lower overall rates of adverse events, indicating a higher safety profile. However, the safety of DAPA and EMPA still requires further attention.

additional comparative trials are warranted to establish clinical superiority. Our findings are consistent with the meta-analysis by Barbagelata, which also confirmed the positive effects of SEMA on BNP reduction and weight improvement (25). However, this analysis included only six randomized controlled trials (RCTs), primarily comparing SEMA with placebo, and did not encompass drugs with other mechanisms of action. Additionally, Kristensen's meta-analysis further supports that semaglutide significantly reduces BNP levels

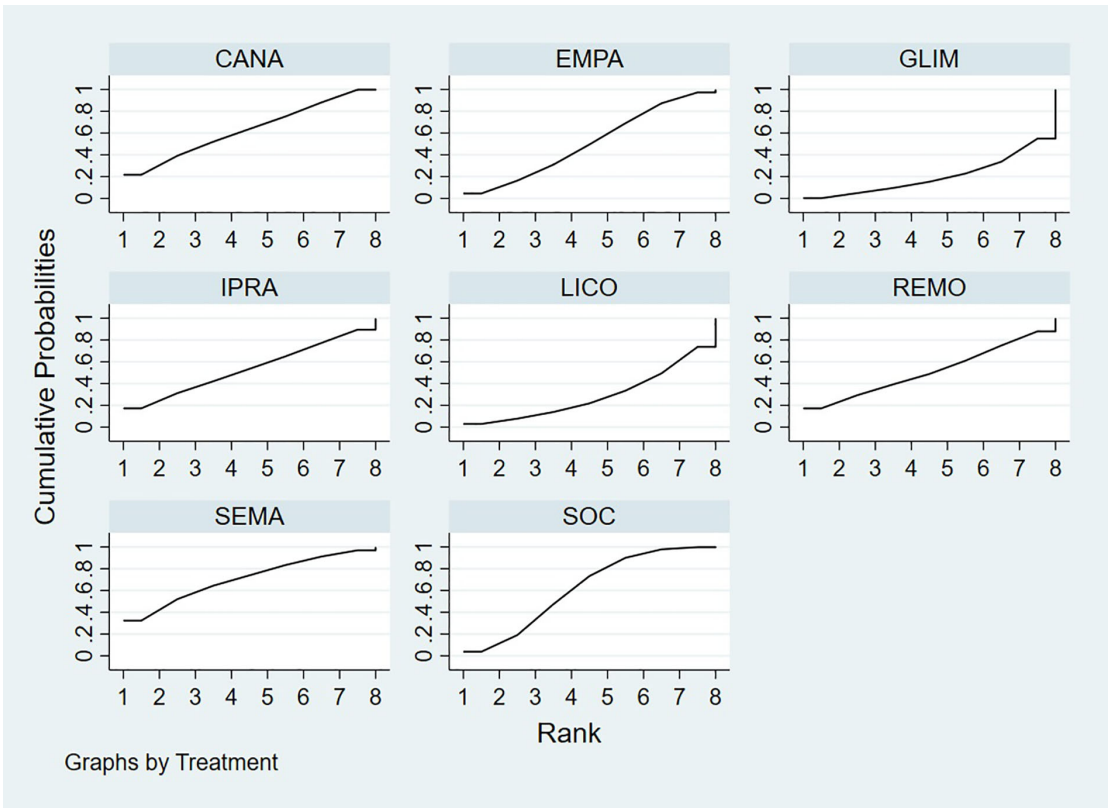


FIGURE 6
Bayesian rankogram illustrating the efficacy of different medications on BNP levels in patients.

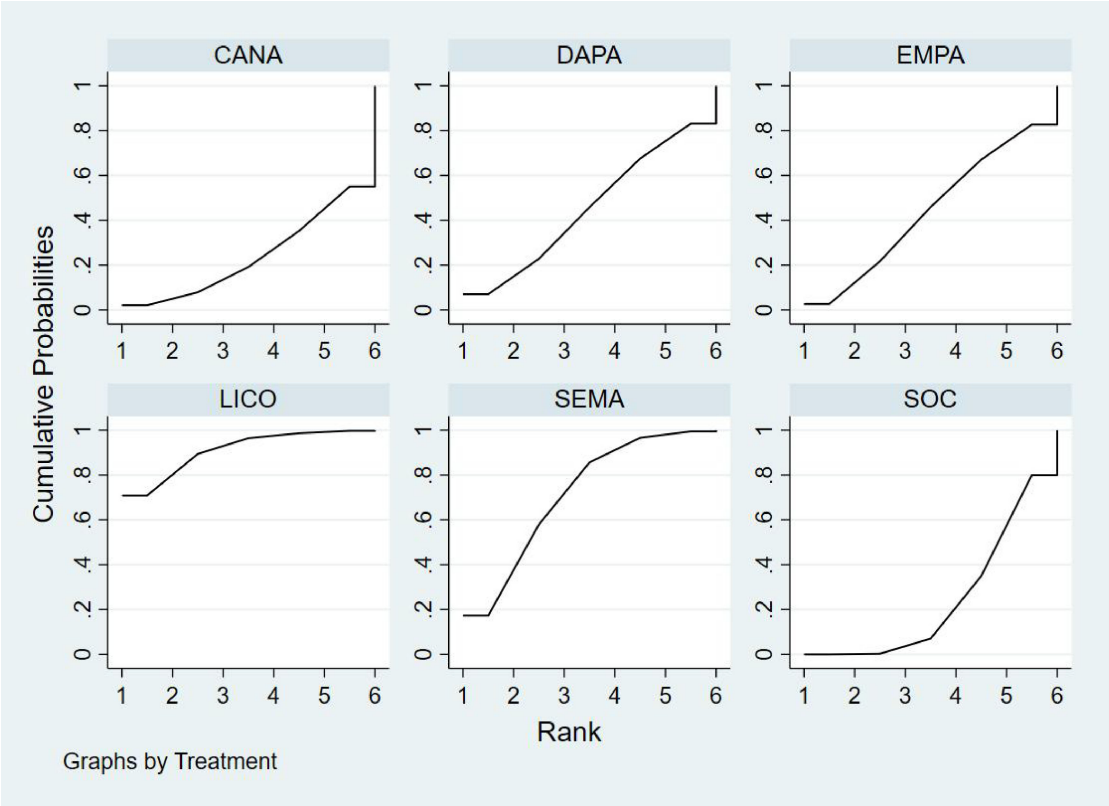


FIGURE 7
Bayesian rankogram illustrating the efficacy of different medications on body weight outcomes in patients.

and body weight (26). However, this analysis included only six RCTs, primarily comparing SEMA with placebo, and did not encompass drugs with other mechanisms of action. Additionally, Kristensen's meta-analysis further supports that semaglutide significantly reduces BNP levels and body weight. By incorporating additional drug classes such as SGLT2 inhibitors and sulfonylureas, our analysis extends the comparative framework and validates SEMA's effects across a broader therapeutic landscape. It further validated the advantages of SEMA across multiple outcomes, addressing the limitations of existing research.

LICO ranked first in body weight improvement, demonstrating its unique role in metabolic control, particularly suitable for patients with T2DM and heart failure who are also obese. Our findings are consistent with Cheong's meta-analysis, which confirmed the significant effect of LICO in weight management and highlighted the potential advantages of combined SGLT1/SGLT2 inhibition in reducing body weight (27). However, this study did not directly compare LICO with GLP-1 receptor agonists or other medications that operate through different mechanisms of action.

Furthermore, the results of this study are consistent with those of Teo's meta-analysis, which also demonstrated a significant effect of LICO in weight management. However, Teo's study primarily focused on comparisons with placebo or other single SGLT2 inhibitors, without including medications with different mechanisms of action (28). This limitation is addressed in our study by incorporating a broader range of medications and more comprehensive outcome measures, thereby expanding the potential application value of LICO in weight management and metabolic improvement. Finally, Zaki's meta-analysis further confirmed the dose-dependent effect of LICO in weight management, particularly at higher doses (150 mg once daily), where weight reduction was most significant (−4.20 kg) (29). However, the current study did not encompass a comprehensive comparison of LICO with other medications that operate through different mechanisms of action. In contrast, our study provides broader clinical evidence support through a multi-drug comparative analysis.

DAPA was associated with the highest probability of improving LVEF in Bayesian ranking analysis. However, However, the credible intervals crossed the null line, indicating no statistical significance; thus, this should be interpreted as a potential trend rather than a confirmed therapeutic advantage. These findings may reflect underlying hemodynamic and metabolic effects of DAPA, although further head-to-head trials are needed to confirm its superiority. Our findings are consistent with those of Jhund, whose analysis validated the efficacy of DAPA in enhancing cardiac function and metabolic parameters (30). However, their study was limited to comparisons between DAPA and placebo, without including other SGLT2 inhibitors or medications with different mechanisms of action. Additionally, Zannad's meta-analysis highlighted that DAPA significantly improved LVEF in

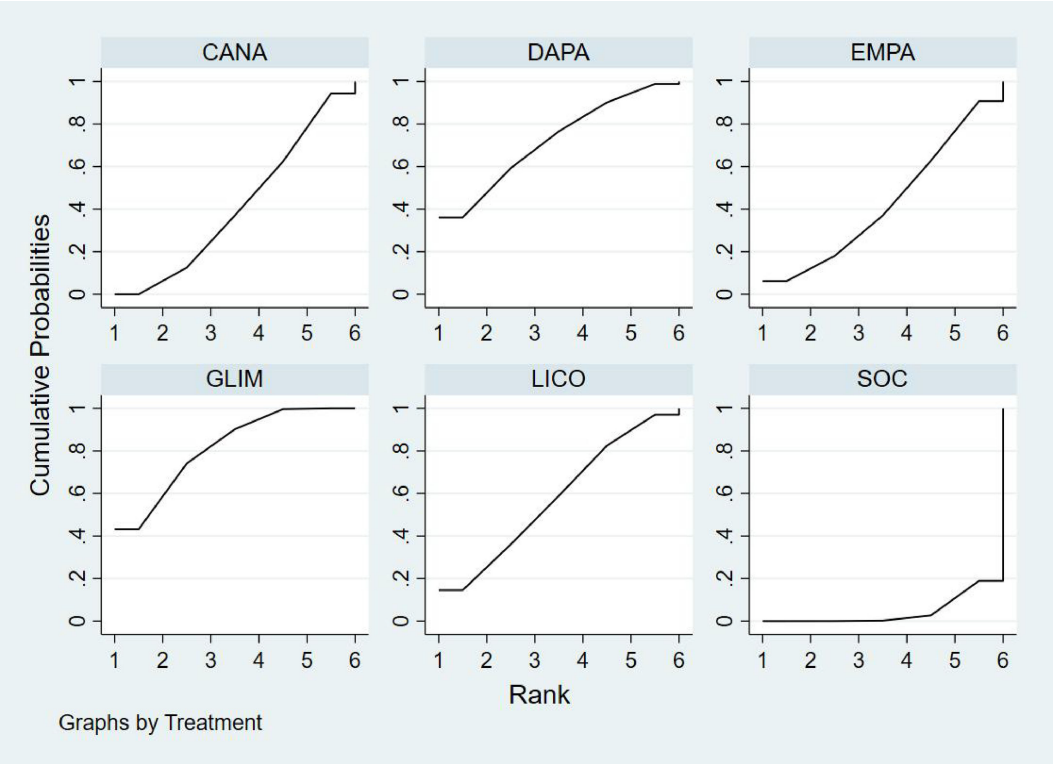


FIGURE 8
Bayesian rankogram illustrating the efficacy of different medications on HbA1c outcomes in patients.

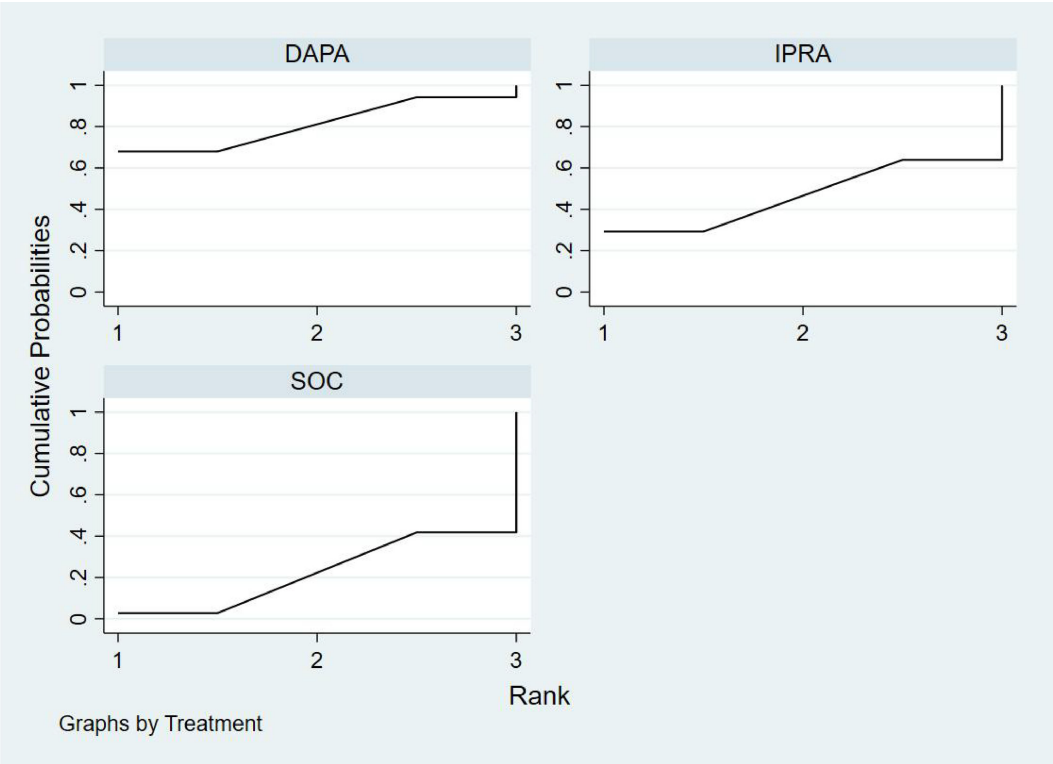


FIGURE 9
Bayesian rankogram illustrating the efficacy of different medications on LVEF outcomes in patients.

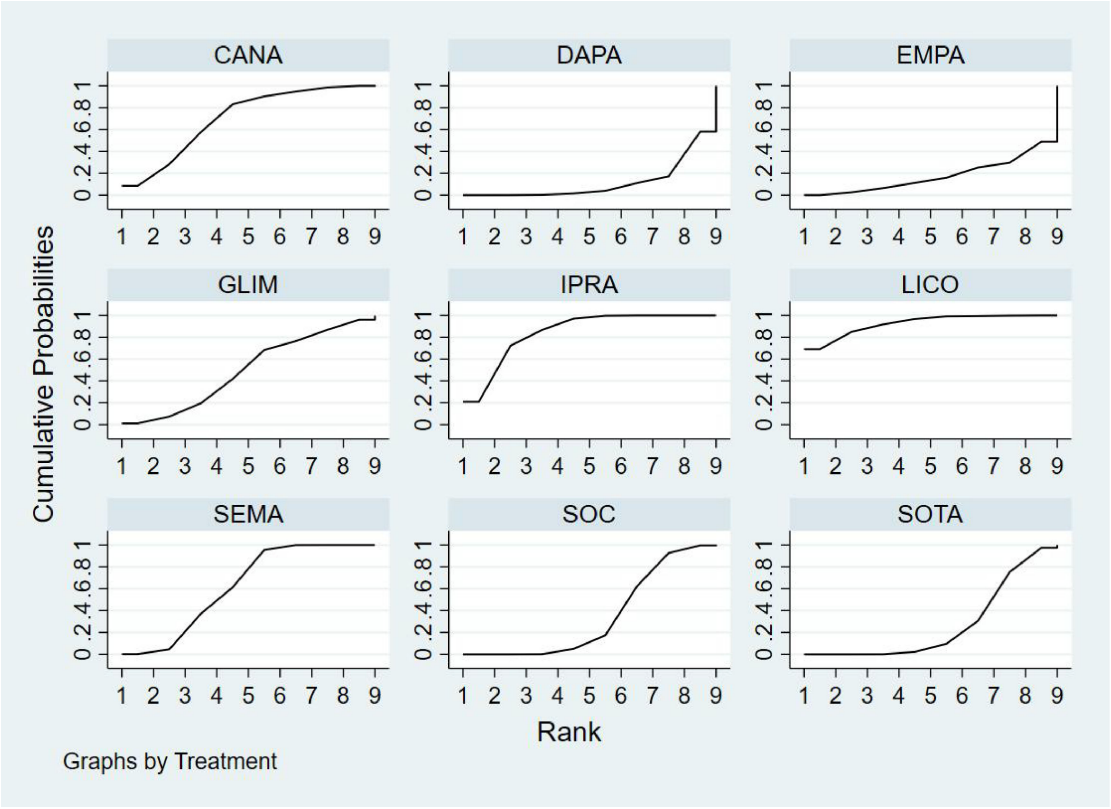


FIGURE 10
Bayesian rankogram illustrating the safety of different medications used in patients.

patients with HFrEF and reduced the risk of heart failure hospitalization (31). Nevertheless, their research did not cover a wider range of SGLT2 inhibitors nor involve direct comparisons with GLP-1 receptor agonists or other classes of medications. By incorporating multiple drugs and analyzing a broader spectrum of outcome measures, our study not only expands the research scope but also addresses the limitations of single-trial analyses, thereby providing more comprehensive evidence to support clinical decision-making.

GLIM exhibited moderate efficacy in glycemic control, consistent with its insulin-stimulating mechanism. However, it showed a higher likelihood of hypoglycemia and lacked additional cardiovascular benefits, limiting its suitability for heart failure patients. Its lower cost may still make it a practical option under economic considerations.

Interestingly, SEMA showed significant performance in metabolic improvement, contrasting sharply with its limited effect on cardiac function. This discrepancy may suggest different regulatory mechanisms between metabolic outcomes and cardiac function improvements, warranting further investigation in future studies.

The strengths of this study lie in the inclusion of multiple SGLT2 inhibitors (such as CANA, IPRA, EMPA, REMO, LICO, and DAPA), which comprehensively reflect the overall efficacy and safety profiles of this drug class, thereby avoiding the limitations associated with single-drug studies. Additionally, this study simultaneously evaluated three classes of drugs with different mechanisms of action—SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas—systematically analyzing their efficacy and safety. Compared to previous studies that focused on a single mechanism or a limited range of drugs, our research offers broader coverage, providing more comprehensive evidence-based guidance for clinical practice.

Nonetheless, this study has certain limitations. First, the included RCTs predominantly involved patients from Europe, North America, and Asia, limiting the generalizability of the findings to underrepresented populations, such as those from Africa or Latin America. Future studies should aim to include more diverse patient populations. Second, the study lacked data on patient-reported quality of life outcomes, thereby preventing a comprehensive assessment of the potential impact of these medications on patients' quality of life. Furthermore, most trials had relatively short follow-up periods, which are inadequate to fully reveal the long-term efficacy and safety of the medications. In addition, due to the limited number of trials reporting heart failure subtypes, we were unable to analyze outcomes separately for patients with preserved versus reduced ejection fraction. Given the distinct pathophysiology and treatment responses of HFrEF and HFpEF, this represents an important area for future research. Addressing these gaps will require studies with longer follow-up

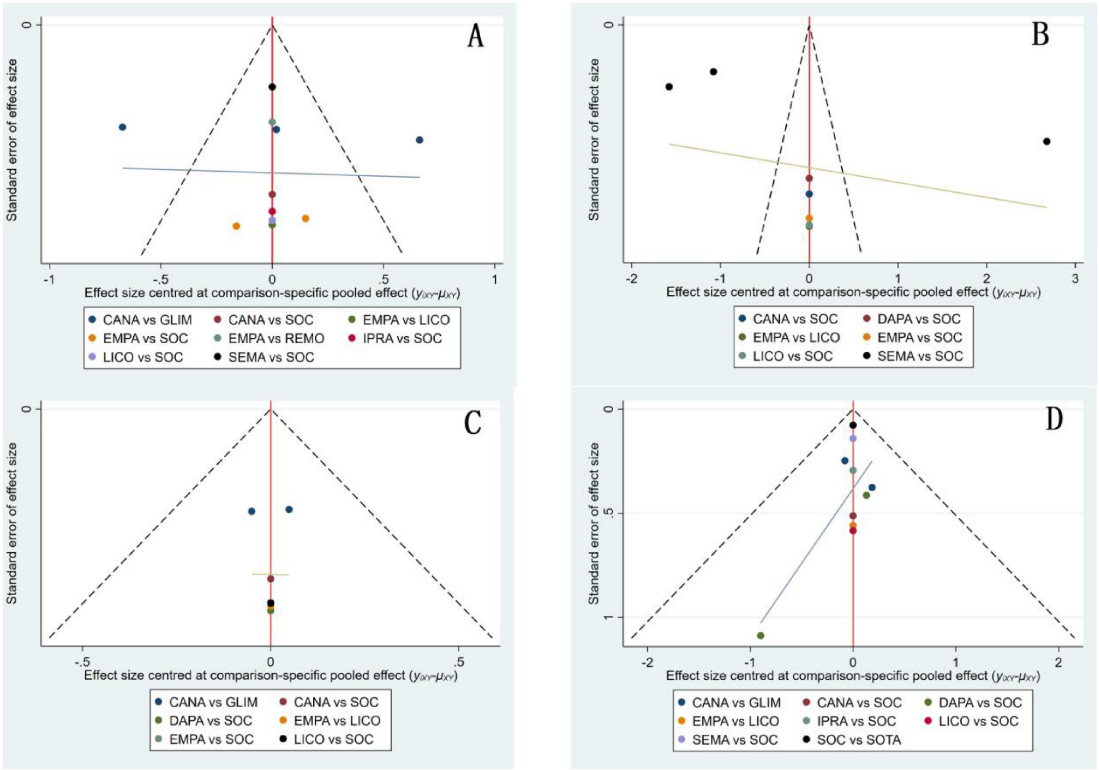


FIGURE 11
Funnel plots for patients using various medications. **(A)** BNP funnel plot; **(B)** Body weight funnel plot; **(C)** HbA1c funnel plot; **(D)** Drug safety funnel plot.

durations to provide a more thorough understanding of the long-term effects.

5 Conclusion

This study compared the efficacy and safety of SGLT2 inhibitors, GLP-1 receptor agonists, and sulfonylureas in managing type 2 diabetes with heart failure. SEMA demonstrated a trend toward improving metabolic control and BNP levels, LICO ranked highest in weight reduction probability, while DAPA exhibited potential in enhancing both HbA1c and LVEF, though these results did not always reach statistical significance. LICO and IPRA were associated with more favorable safety profiles, while GLIM had a higher risk of hypoglycemia.

These findings provide a comparative overview that may assist clinicians in tailoring treatment strategies according to individual patient profiles and comorbidities.

However, further studies are needed to assess long-term outcomes, especially in underrepresented populations, and to determine the consistency of treatment effects across various heart failure phenotypes.

Author contributions

HG: Writing – original draft, Writing – review & editing. QW: Writing – original draft. AZ: Data curation, Writing – review & editing. KY: Data curation, Writing – review & editing. DS: Investigation, Visualization, Writing – review & editing. JL: Writing – review & editing. HH: Writing – review & editing. AL: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1562815/full#supplementary-material

References

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1789–858. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0140673618322797 (Accessed December 01, 2024).

2. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail*. (2019) 21:1306–25. doi: 10.1002/ejhf.1594

3. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol*. (2012) 59:998–1005. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0735109711053617 (Accessed December 01, 2024).

4. Andreadi A, Muscoli S, Tajmir R, Meloni M, Muscoli C, Ilari S, et al. Recent pharmacological options in type 2 diabetes and synergic mechanism in cardiovascular disease. *IJMS*. (2023) 24:1646. Available online at: https://www.mdpi.com/1422-0067/24/2/1646 (Accessed December 01, 2024).

5. Bao J, Kan R, Chen J, Xuan H, Wang C, Li D, et al. Combination pharmacotherapies for cardiac reverse remodeling in heart failure patients with reduced ejection fraction: A systematic review and network meta-analysis of randomized clinical trials. *Pharmacol Res*. (2021) 169:105573. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S1043661821001572 (Accessed December 01, 2024).

6. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. *Lancet*. (2015) 385:2107–17. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0140673614614021 (Accessed December 01, 2024).

7. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet*. (2021) 398:262–76. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0140673621005365 (Accessed December 01, 2024).

8. Muscoli S, Barillà F, Tajmir R, Meloni M, Della Morte D, Bellia A, et al. The new role of SGLT2 inhibitors in the management of heart failure: Current evidence and future perspective. *Pharmaceutics*. (2022) 14:1730. Available online at: https://www.mdpi.com/1999-4923/14/8/1730 (Accessed December 01, 2024).

9. Baggio LL, Drucker DJ. iology of incretins: GLP-1 and GIP. *Gastroenterology*. (2007) 132:2131–57. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S001650850700580X (Accessed December 01, 2024).

10. Hammoud R, Drucker DJ. Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nat Rev Endocrinol*. (2023) 19:201–16. Available online at: https://www.nature.com/articles/s41574-022-00783-3 (Accessed December 01, 2024).

11. De Boer RA, Núñez J, Kozlovski P, Wang Y, Proot P, Keefe D. Effects of the dual sodium–glucose linked transporter inhibitor, licogliflozin vs placebo or empagliflozin in patients with type 2 diabetes and heart failure. *Brit J Clin Pharma*. (2020) 86:1346–56. doi: 10.1111/bcp.14248

12. Tanaka A, Hisauchi I, Taguchi I, Sezai A, Toyoda S, Tomiyama H, et al. Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial (CANDLE). *ESC Heart Failure*. (2020) 7:1585–94. doi: 10.1002/ehf2.12707

13. Akasaka H, Sugimoto K, Shintani A, Taniuchi S, Yamamoto K, Iwakura K, et al. Effects of ipragliflozin on left ventricular diastolic function in patients with type 2 diabetes and heart failure with preserved ejection fraction: The EXCEED randomized controlled multicenter study. *Geriatrics Gerontology Int*. (2022) 22:298–304. doi: 10.1111/ggi.14363

14. Kusunose K, Imai T, Tanaka A, Dohi K, Shiina K, Yamada T, et al. Effects of canagliflozin on NT-proBNP stratified by left ventricular diastolic function in patients with type 2 diabetes and chronic heart failure: a sub analysis of the CANDLE trial. *Cardiovasc Diabetol*. (2021) 20:186. doi: 10.1186/s12933-021-01380-w

15. Tamaki S, Yamada T, Watanabe T, Morita T, Furukawa Y, Kawasaki M, et al. Effect of empagliflozin as an add-on therapy on decongestion and renal function in patients with diabetes hospitalized for acute decompensated heart failure: A prospective randomized controlled study. *Circ: Heart Failure*. (2021) 14:e007048. doi: 10.1161/CIRCHEARTFAILURE.120.007048

16. Ueda T, Kasama S, Yamamoto M, Nakano T, Ueshima K, Morikawa Y, et al. Effect of the sodium-glucose cotransporter 2 inhibitor canagliflozin for heart failure with preserved ejection fraction in patients with type 2 diabetes. *Circ Rep*. (2021) 3:440–8. Available online at: https://www.jstage.jst.go.jp/article/circrep/3/8/3_CR-21-0030/_article (Accessed December 01, 2024).

17. Nakatani D, Dohi T, Hikoso S, Tanaka A, Nanasato M, Shimizu W, et al. Relationship between canagliflozin, sodium glucose cotransporter 2 inhibitor, and hematopoietic effects in patients with diabetes and mild heart failure: results from the CANDLE trial. *J Cardiovasc Pharmacol*. (2023) 82:61–8. doi: 10.1097/FJC.0000000000001430

18. Kosiborod MN, Deanfield J, Pratley R, Borlaug BA, Butler J, Davies MJ, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. *Lancet*. (2024) 404:949–61. doi: 10.1016/S0140-6736(24)01643-X

19. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N Engl J Med*. (2024) 390:1394–407. doi: 10.1056/NEJMoa2313917

20. Ibrahim A, Ghaleb R, Mansour H, Hanafy A, Mahmoud NM, Abdelfatah Elsharef M, et al. Safety and efficacy of adding dapagliflozin to furosemide in type 2 diabetic patients with decompensated heart failure and reduced ejection fraction. *Front Cardiovasc Med*. (2020) 7:602251/full. doi: 10.3389/fcvm.2020.602251/full

21. Petrie MC, Borlaug BA, Butler J, Davies MJ, Kitzman DW, Shah SJ, et al. Semaglutide and NT-proBNP in obesity-related HFpEF. *J Am Coll Cardiol*. (2024) 84:27–40. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0735109724070207 (Accessed December 01, 2024).

22. Fu Q, Zhou L, Fan Y, Liu F, Fan Y, Zhang X, et al. Effect of SGLT-2 inhibitor, dapagliflozin, on left ventricular remodeling in patients with type 2 diabetes and HFrEF. *BMC Cardiovasc Disord*. (2023) 23:544. doi: 10.1186/s12872-023-03591-3

23. Singh JSS, Mordi IR, Vickneson K, Fathi A, Donnan PT, Mohan M, et al. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the REFORM trial. *Diabetes Care*. (2020) 43:1356–9. doi: 10.2337/dc19-2187

24. Sengupta S, Jayagopal PB, Sawhney JPS, Mehta A, Suryavanshi SC, Jamwal N, et al. Effect of remogliflozin on biomarkers compared to empagliflozin inpatients of type 2 diabetes mellitus with chronic heart failure (Remit hf). *J Am Coll Cardiol*. (2024) 83:549. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0735109724025397 (Accessed December 01, 2024).

25. Barbagelata L, Masson W, Lobo M, Bluro I. Semaglutide and heart failure: Updated meta-analysis. *Curr Problems Cardiol*. (2024) 49:102721. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S0146280624003591 (Accessed December 01, 2024).

26. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. (2019) 7:776–85. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S2213858719302499 (Accessed December 01, 2024).

27. Cheong AJY, Teo YN, Teo YH, Syn NL, Ong HT, Ting AZH, et al. SGLT inhibitors on weight and body mass: A meta-analysis of 116 randomized-controlled trials. *Obesity*. (2022) 30:117–28. doi: 10.1002/oby.23331

28. Teo YN, Ting AZH, Teo YH, Chong EY, Tan JTA, Syn NL, et al. Effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors and combined SGLT1/2 inhibitors on cardiovascular, metabolic, renal, and safety outcomes in patients with diabetes: A network meta-analysis of 111 randomized controlled trials. *Am J Cardiovasc Drugs*. (2022) 22:299–323. Available online at: https://link.springer.com/10.1007/s40256-022-00528-7 (Accessed December 01, 2024).

29. Zaki AM, Abo-Elnour DE, Abdalla YE, Hassan RY, Salama MK, Elboraay T, et al. Dose-dependent efficacy and safety of licogliflozin on obese adults: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Syndrome: Clin Res Rev*. (2022) 16:102657. Available online at: https://linkinghub.elsevier.com/retrieve/pii/S1871402122002715 (Accessed December 01, 2024).

30. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. (2022) 28:1956–64. Available online at: https://www.nature.com/articles/s41591-022-01971-4 (Accessed December 01, 2024).

31. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. (2020) 396:819–29. doi: 10.1016/S0140-6736(20)31824-9

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 19 June 2025
DOI 10.3389/fendo.2025.1563734

Check for updates

OPEN ACCESS

EDITED BY
Yun Shen,
Pennington Biomedical Research Center,
United States

REVIEWED BY
Ajay Vikram Singh,
Federal Institute for Risk Assessment (BfR),
Germany
Rossana C. Zepeda,
Universidad Veracruzana, Mexico

*CORRESPONDENCE
Huijuan Yuan
hjyuan@zzu.edu.cn

RECEIVED 20 January 2025
ACCEPTED 28 May 2025
PUBLISHED 19 June 2025

CITATION
Zhao L, Heng H, Xie Q, Liang C, Guo S, Zhang Z and Yuan H (2025) Association between glycemia risk index and carotid intima-media thickness in type 2 diabetes. *Front. Endocrinol.* 16:1563734. doi: 10.3389/fendo.2025.1563734

COPYRIGHT
© 2025 Zhao, Heng, Xie, Liang, Guo, Zhang and Yuan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Association between glycemia risk index and carotid intima-media thickness in type 2 diabetes

Lingyun Zhao[1,2], Hongyan Heng[2], Qinyuan Xie[1,2], Chenghong Liang[1,2], Sijia Guo[1,2], Ziyi Zhang[1,2] and Huijuan Yuan[1,2]*

[1]Department of Endocrinology, Zhengzhou University People's Hospital, Zhengzhou, China, [2]Department of Endocrinology, Henan Provincial Key Medicine Laboratory of Intestinal Microecology and Diabetes, Diabetes Microecology Diagnosis and Treatment and Transformation Engineering Research Center of Henan Province, Henan Provincial People's Hospital, Zhengzhou, China

Objective: To investigate the association between the Glycemic Risk Index (GRI) and carotid intima-media thickness (CIMT) in type 2 diabetes mellitus (T2DM) patients and evaluate the clinical utility of GRI for early vascular risk assessment.

Methods: This retrospective study included 450 previously untreated patients with T2DM prior to hospitalization. We calculated GRI using CGM data and assessed CIMT with high-resolution ultrasound. Multiple linear and logistic regression analyses assessed the association between GRI and CIMT. Receiver operating characteristic (ROC) curve analyses evaluated GRI's predictive performance.

Results: There was a significant positive correlation between GRI and CIMT ($r = 0.42$, $P < 0.001$). After adjusting for confounders, GRI remained an independent predictor of CIMT thickening (OR = 7.226, 95% CI: 5.597–8.856, $P < 0.001$). ROC analysis revealed that GRI alone predicted abnormal CIMT with an AUC of 0.869.

Conclusion: GRI is a robust marker for predicting CIMT thickening in T2DM patients, providing a novel approach for cardiovascular risk stratification. This study underscores the potential of integrating GRI into routine diabetes management to improve vascular outcomes.

KEYWORDS

glycemia risk index, type 2 diabetes, carotid intima-media thickness, cardiovascular diseases, continuous glucose monitoring

Introduction

Type 2 diabetes mellitus (T2DM) is a significant global public health challenge, with its prevalence projected to reach 12.2% by 2045, affecting approximately 783.2 million individuals worldwide (1). Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in T2DM, imposing a substantial economic burden (2). Persistent hyperglycemia-induced vascular endothelial damage is a core pathological mechanism driving diabetic vascular complications, accelerating atherosclerosis, arterial stiffness, and macrovascular dysfunction (3, 4).

Carotid intima-media thickness (CIMT) is a well-established, non-invasive marker of subclinical atherosclerosis and an independent predictor of cardiovascular events (5). Numerous longitudinal studies have validated CIMT as a robust and independent predictor of future cardiovascular events—particularly stroke and myocardial infarction—even after adjustment for conventional risk factors (6–8). In individuals with T2DM, elevated CIMT indicates subclinical atherosclerosis and is also associated with the advancement of microvascular and macrovascular complications. These findings underscore the prognostic value of CIMT and support its clinical utility as a surrogate marker for early vascular risk stratification and timely intervention in diabetic populations (9).

While optimal glycemic control is essential for mitigating vascular risk, traditional glycemic indices offer only a limited perspective on glucose dynamics. Glycated hemoglobin (HbA1c), although long considered the gold standard, reflects average glucose levels over several months and fails to capture short-term fluctuations or glycemic excursions that may trigger oxidative stress and vascular injury (10). Time-in-range (TIR), derived from continuous glucose monitoring (CGM), has gained popularity as a more dynamic indicator; however, it primarily reflects the proportion of time spent within a target glucose range and does not comprehensively quantify the burden of hypoglycemia or hyperglycemia (11).

The Glycemia Risk Index (GRI) is a novel composite metric that addresses these limitations by integrating the frequency, magnitude, and duration of hypo- and hyperglycemic episodes based on CGM data (12). Unlike HbA1c and TIR, GRI provides a continuous, risk-weighted measure of glycemic instability, capturing the full spectrum of glycemic excursions. Studies have demonstrated that GRI captures glucose variability and the associated metabolic burden more effectively than conventional indices. It has shown enhanced prognostic utility for identifying microvascular complications, such as retinopathy and albuminuria (13–15). More recently, a study by Cai et al. reported an independent association between elevated GRI and arterial stiffness, suggesting its potential relevance for macrovascular outcomes in T2DM (16). Furthermore, comparative analyses have shown that GRI outperforms traditional CGM-derived indices—such as TIR and the coefficient of variation—in identifying deleterious glycemic profiles associated with endothelial dysfunction and oxidative stress (17–19).

Despite this growing body of evidence supporting GRI as a valuable glycemic risk metric, its relationship with carotid structural alterations—particularly CIMT thickening—remains poorly characterized. Given that CIMT reflects early-stage atherosclerosis and is a robust predictor of stroke and myocardial infarction, elucidating its association with GRI may offer novel insights into the vascular consequences of glycemic instability and further refine cardiovascular risk assessment in diabetes care.

Therefore, this study aims to investigate the association between the Glycemia Risk Index (GRI) and carotid intima-media thickness (CIMT) in patients with type 2 diabetes mellitus (T2DM) to improve cardiovascular risk stratification and advance the clinical application of CGM-derived metrics in diabetes management.

Methods

Data source and study population

This study included 450 type 2 diabetes mellitus (T2DM) patients hospitalized in the Department of Endocrinology, Henan Provincial People's Hospital, Zhengzhou University, from January 2019 to September 2021. Inclusion criteria were: (1) diagnosis of T2DM based on 1999 WHO criteria; (2) age ≥ge years; (3) no hypoglycemic drug use within 3 months before admission; (4) no history of severe cardiovascular disease, which was defined as prior myocardial infarction, or previous coronary revascularization procedures including percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); and (5) completion of continuous glucose monitoring (CGM) and carotid ultrasound. Exclusion criteria included: (1) type 1, special types, gestational, or unclear diabetes; (2) severe organ dysfunction, malignancy, or infection; and (3) incomplete CGM data (<3 days). The study was approved by the Ethics Committee of Henan Provincial People's Hospital (NO. 2018048) and adhered to the 2008 Declaration of Helsinki.

Clinical and biochemical information

Demographic and clinical data, including gender, age, BMI, diabetes duration, blood pressure, and smoking status, were collected. Biochemical analyses of fasting blood samples measured total cholesterol (TC), triglycerides (TG), LDL-C, HDL-C, and HbA1c. Urine samples were analyzed for creatinine to estimate the glomerular filtration rate (eGFR).

Continuous glucose monitoring and glycemia risk index

CGM data were collected using the FreeStyle Libre-CGM system (Abbott). Sensors placed on the upper arm recorded blood glucose every 5 minutes for two weeks. Glycemic variability metrics included coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE), largest amplitude of glycemic excursions (LAGE), and mean daily difference (MODD). Time below range (TBR), time above range (TAR), very-low glucose (VLow), low

glucose (Low), high glucose (High), and very-high glucose (VHigh) were also recorded.

The GRI was calculated as follows (20–22):

$$\text{Hypoglycemia component} = \text{VLow} + (0.8 \times \text{Low})$$
$$\text{Hyperglycemia component} = \text{VHigh} + (0.5 \times \text{High})$$
$$\text{GRI} = (3.0 \times \text{hypoglycemia component}) + (1.6 \times \text{hyperglycemia component})$$

Carotid Doppler ultrasonography

Carotid Doppler ultrasonography conducted using an ACUSON Sequoia 512 device (10 MHz probe), measured CIMT 10 mm below the bifurcation of both carotid arteries. The average CIMT was calculated from both sides, with abnormal CIMT defined as ≥1.0 mm (6, 7).

Statistical analysis methods

We divided participants into two groups based on CIMT (≥1.0 mm or <1.0 mm) and further stratified them by GRI quartiles. Continuous variables were tested for normality using the Kolmogorov-Smirnov test and reported as mean ± standard deviation or median (interquartile range). Categorical variables were summarized as frequency (percentage) and compared using t-tests, Mann-Whitney U tests, or $\chi 2$ tests, as appropriate.

Spearman correlation analysis assessed relationships between GRI, glycemic variability metrics, and CIMT. Linear regression explored the association between GRI and CIMT, adjusting for confounders across three models: Model 1 (unadjusted), Model 2 (adjusted for age and sex), and Model 3 (further adjusted for BMI, diabetes duration, smoking, SBP, TG, HDL-C, and LDL-C). Variance inflation factor (VIF) analysis confirmed no multicollinearity.

Binary logistic regression analyzed associations between GRI quartiles and CIMT thickening (≥ 1.0 mm), presenting odds ratios (OR) with 95% CI using the same three models. Subgroup analyses examined GRI-CIMT interactions by stratifying participants by sex, age (< 40, 40–50, ≥50 years), BMI (< 25, ≥25 kg/m^2), and diabetes duration (≤3, >3 years), adjusting for confounders except for the stratification variable.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of various glycemic metrics in identifying carotid intima-media thickening (CIMT ≥ 1.0 mm) (21). The area under the curve (AUC) was calculated for the glycemic risk index (GRI), HbA1c ≥ 7%, and time in range (TIR < 70%). GRI was analyzed as a continuous variable, and the optimal cutoff value was determined by maximizing Youden's index. At this threshold, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. HbA1c and TIR were treated as binary variables based on clinical guideline recommendations.

We conducted all statistical analyses using R (v4.3.1), SPSS (v26), and GraphPad Prism (9.0), considering $P < 0.05$ statistically significant.

Results

Clinical features

The study included 450 participants, divided into two groups based on carotid intima-media thickness (CIMT): a normal CIMT group (n = 193) and an abnormal CIMT group (n = 257). Table 1

TABLE 1 Characteristics of study participants are analyzed according to CIMT status

Characteristic	Total (n=450)	Normal CIMT(n=193)	Abnormal CIMT(n=257)	P-Value
Age, years	47(39, 54)	42 (34-51)	50 (45-56)	<0.001*
Duration of disease, years	3(1-5)	3(1-5)	3(1-5)	0.641
	13437.00 (10544.25 - 17800.50)			
BMI, kg/m^2	25.25 (23.72 - 27.04)	25.25 (23.14,26.58)	25.25 (24.34,27.43)	0.003*
Systolic blood pressure, mmHg	130.00 (120.00 - 141.75)	130.00 (119.00-141.00)	130.00 (120.00-142.00)	0.334
Diastolic blood pressure, mmHg	80.00 (73.25 - 87.00)	80.00 (72.00-87.00)	80.00 (74.00-86.00)	0.722
Pulse rate	80.00 (75.00 - 85.00)	80.00 (74.00-85.00)	80.00 (75.00-84.00)	0.834
Total cholesterol, mmol/L	4.48 (3.79 - 5.20)	4.50 (3.78-5.29)	4.48 (3.83-5.14)	0.197
Triglycerides, mmol/L	1.69 (1.22 - 2.64)	1.69 (1.36-2.75)	1.69 (1.16-2.52)	0.034*
HDL cholesterol, mmol/L	1.05 (0.94 - 1.21)	1.05 (0.94-1.21)	1.05 (0.94-1.20)	0.94
LDL cholesterol, mmol/L	2.42 (1.92 - 3.02)	2.42 (1.90-3.15)	2.42 (1.93-2.93)	0.197
FPG, mmol/L	7.58 (5.99 - 9.48)	7.58 (5.96-9.17)	7.58 (6.00-9.66)	0.483

(Continued)

10.3389/fendo.2025.1563734

TABLE 1 Continued

Characteristic	Total (n=450)	Normal CIMT(n=193)	Abnormal CIMT(n=257)	P-Value
HbA1c (%)	8.10 (7.40 - 9.20)	8.10 (7.00-8.70)	8.10 (7.80-9.40)	0.001*
CV, %	31 (27-35)	28 (25-31)	33 (29-37)	<0.001*
MAGE, mmol/L	5.25 (4.38 - 6.32)	4.71 (3.87-5.54)	5.84 (4.81-6.85)	<0.001*
MODD, mmol/L	0.63 (0.48 - 0.78)	0.73 (0.61-0.89)	0.56 (0.42-0.71)	<0.001*
LAGE, mmol/L	13.05 (10.60 - 15.80)	11.70 (9.40-13.80)	14.40 (12.00-16.60)	<0.001*
TIR (3.9–10 mmol/L), %	81 (70 - 89)	90 (82-93)	74 (63-82)	<0.001*
TBR (<3.9 mmol/L), %	1 (0 - 4)	1 (0-3)	2 (0-6)	<0.001*
TAR (>10 mmol/L), %	15 (6 - 27)	8 (4-16)	22 (11-33)	<0.001*
GRI, %		12 (8-20)	32 (22-45)	<0.001*
Scr, umol/L	58.00 (51.00-68.00)	58.00 (51.00-69.00)	58.00 (51.00-66.00)	0.554
Uric acid, umol/L	312.00 (256.00 - 364.75)	312.00 (269.00-372.00)	312.00 (247.00-354.00)	0.096
Urea to creatinine ratio	0.09 (0.09 - 0.11)	0.09 (0.08-0.10)	0.09 (0.09-0.11)	0.06
EGFR, mL/min	14.00 (14.00 - 14.00)	14.00 (14.00-14.00)	14.00 (14.00-14.00)	0.899
Male, n(%)				
Female	148 (32.89%)	126 (65.28%)	176 (68.48%)	0.48
Male	302 (67.11%)	67 (34.72%)	81 (31.52%)	
Current smoking, n (%)				
No	288 (64.00%)	74 (38.34%)	88 (34.24%)	0.374
YES	162 (36.00%)	119 (61.66%)	169 (65.76%)	
Alcohol consumption, n (%)				
No	293 (65.11%)	63 (32.64%)	94 (36.58%)	0.424
YES	157 (34.89%)	130 (67.36%)	163 (63.42%)	
Family history of genetic diseases, n (%)				
No	289 (64.22%)	68 (35.23%)	93 (36.19%)	0.843
YES	161 (35.78%)	125 (64.77%)	164 (63.81%)	
Hypertension ,n (%)				
No	235 (52.22%)	90 (46.63%)	125 (48.64%)	0.703
YES	215 (47.78%)	103 (53.37%)	132 (51.36%)	
Hyperlipidemia history, n (%)				
No	358 (79.56%)	49 (25.39%)	43 (16.73%)	0.025*
YES	92 (20.44%)	144 (74.61%)	214 (83.27%)	

Data for continuous variables were expressed as median (quartile distance), data for categorical variables as numerical (percentage) CIMT, carotid intima-media thickening; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FPG, fasting blood glucose; HbA1c, glycosylated hemoglobin; CV, coefficient of variation; MAGE, the average amplitude of blood sugar fluctuations; MODD: average daily difference; TIR, range of time; TAR, out-of-range time; GRI, glycemia risk index; TBR, time below range; LAGE, the maximum value of blood sugar fluctuations.

summarizes the general clinical characteristics of the two groups. The abnormal CIMT group showed significantly higher GRI and glycemic variability metrics (CV, MAGE, MODD, LAGE). Additionally, the abnormal CIMT group demonstrated older age, higher BMI, greater hospitalization costs, and a higher prevalence of hypertension. No significant differences were observed between the groups for lipid levels (total cholesterol, triglycerides, HDL-C, LDL-C) or blood pressure. These findings suggest that GRI and glycemic fluctuations may play critical roles in CIMT thickening.

Then, to explore the relationship between different GRI levels and CIMT, participants were further divided into four groups (Q1–Q4) based on GRI quartiles (Table 2). Higher GRI levels were

10.3389/fendo.2025.1563734

TABLE 2 Study participants were grouped according to GRI quartile characteristics

Characteristic	GRI,%				P
	Q1(n=113) (0.0081,0.7947)	Q2(n=112) (0.81, 12.58)	Q3(n=112) (12.58, 22.52)	Q4(n=113) (22.52, 34.84)	
Age, years	46.26 ± 10.36	45.68 ± 11.19	45.44 ± 10.75	50.01 ± 9.41	0.003*
Duration of disease, years	3(1-5)	3(1-5)	3(1-5)	3(1-5)	0.914
Cost, RMB	12616.00 (8747.00 - 16564.00)	13437.00 (10929.75 - 16726.00)	12795.50 (10370.75 -17499.75)	15711.00 (12420.00 -20107.00)	<0.001*
BMI, kg/m^2	25.25 (25.56, 27.25)	25.25 (24.43, 27.70)	25.25 (24.13, 26.30)	25.25 (23.08, 26.42)	0.355
Systolic blood pressure, mmHg	130.00 (120.00 - 141.00)	129.00 (120.00 - 140.25)	130.00 (120.00 - 140.00)	131.00 (122.00 - 146.00)	<0.001*
Diastolic blood pressure, mmHg	80.00 (73.00 - 90.00)	80.00 (74.00 - 88.00)	79.00 (72.00 - 85.00)	80.00 (74.00 - 86.00)	<0.001*
Pulse rate	80.00 (76.00 - 85.00)	80.00 (74.00 - 84.25)	80.00 (75.00 - 84.00)	80.00 (75.00 - 86.00)	<0.001*
Total cholesterol, mmol/L	4.48 (3.69 - 5.29)	4.62 (3.93 - 5.21)	4.48 (3.77 - 5.13)	4.48 (3.91 - 5.10)	<0.001*
Triglycerides, mmol/L	1.72 (1.36 - 2.86)	1.73 (1.42 - 2.73)	1.58 (1.16 - 2.42)	1.69 (1.06 - 2.07)	<0.001*
HDL cholesterol, mmol/L	1.05 (0.92 - 1.22)	1.05 (0.96 - 1.16)	1.04 (0.92 - 1.21)	1.06 (0.95 - 1.26)	<0.001*
LDL cholesterol, mmol/L	2.42 (1.80 - 3.18)	2.42 (1.98 - 3.08)	2.42 (1.93 - 2.94)	2.42 (1.91 - 2.97)	<0.001*
CIMT, mm	0.90 (0.80 - 0.90)	0.90 (0.80 - 1.10)	1.10 (0.90 - 1.10)	1.20 (1.10 - 1.20)	<0.001*
FPG, mmol/L	7.47 (5.70 - 8.20)	7.58 (6.37 - 10.24)	7.58 (6.04 - 8.99)	7.58 (6.24 - 10.50)	<0.001*
HbA1c, %	7.90 (6.50 - 8.10)	8.10 (7.47 - 9.20)	8.10 (7.80 - 9.12)	8.10 (8.10 - 9.90)	<0.001*
CV, %	26 (22 - 29)	30 (27 - 33)	33 (30 - 36)	36 (31 - 40)	<0.001*
MAGE, mmol/L	4.13 (3.54 - 4.82)	5.15 (4.59 - 5.95)	5.83 (4.80 - 6.55)	6.43 (5.49 - 7.78)	<0.001*
MODD, mmol/L	0.82 (0.72 - 0.96)	0.65 (0.55 - 0.74)	0.59 (0.47 - 0.71)	0.43 (0.35 - 0.59)	<0.001*
LAGE, mmol/L	10.00 (8.70 - 12.20)	13.10 (11.03 - 14.62)	13.85 (12.40 - 15.80)	16.20 (13.10 - 18.50)	<0.001*
TIR (3.9–10 mmol/L), %	93 (90 - 96)	84 (80 - 88)	75 (71 - 82)	61 (52 - 67)	<0.001*
TBR (<3.9 mmol/L), %	1 (0 - 2)	1 (0 - 3)	2 (0- 6)	3 (1 - 9)	<0.001*
TAR (>10 mmol/L), %	6 (3 - 9)	15 (9 - 20)	23 (11 - 28)	36 (22 - 45)	<0.001*
Scr, umol/L	58.00 (51.00 - 66.00)	58.00 (50.75 - 68.00)	57.00 (48.00 - 65.00)	59.00 (52.00 - 72.00)	<0.001*
Uric acid, umol/L	312.00 (281.00 - 376.00)	312.00 (260.50 - 358.75)	312.00 (243.75 - 350.25)	311.00 (242.00 - 369.00)	<0.001*
Urea to creatinine ratio	0.09 (0.08 - 0.10)	0.09 (0.09 - 0.11)	0.09 (0.09 - 0.11)	0.09 (0.09 - 0.10)	<0.001*
EGFR, mL/min	14.00 (14.00 - 14.00)	14.00 (14.00 - 14.00)	14.00 (14.00 - 14.00)	14.00 (14.00 - 14.00)	<0.001*
Sex, n(%)					
Female	37 (32.74%)	36 (32.14%)	40 (35.71%)	35 (30.97%)	0.891
Male	76 (67.26%)	76 (67.86%)	72 (64.29%)	78 (69.03%)	0.891
Current smoking, n(%)					
No	72 (63.72%)	68 (60.71%)	75 (66.96%)	73 (64.60%)	0.808
YES	41 (36.28%)	44 (39.29%)	37 (33.04%)	40 (35.40%)	0.808
Alcohol consumption, n (%)					
No	66 (58.41%)	77 (68.75%)	76 (67.86%)	74 (65.49%)	0.352
YES	47 (41.59%)	35 (31.25%)	36 (32.14%)	39 (34.51%)	0.352
Family history of genetic diseases, n (%)					
No	72 (63.72%)	73 (65.18%)	72 (64.29%)	72 (63.72%)	0.995

(Continued)

TABLE 2 Continued

Characteristic	GRI,%				P
YES	41 (36.28%)	39 (34.82%)	40 (35.71%)	41 (36.28%)	0.995
Hypertension, n (%)					
No	64 (56.64%)	57 (50.89%)	59 (52.68%)	55 (48.67%)	0.673
YES	49 (43.36%)	55 (49.11%)	53 (47.32%)	58 (51.33%)	0.673
Hyperlipidemia history, n (%)					
No	87 (76.99%)	89 (79.46%)	89 (79.46%)	93 (82.30%)	0.806
YES	26 (23.01%)	23 (20.54%)	23 (20.54%)	20 (17.70%)	0.806
	(0.81, 12.58)	(12.58, 22.52)	(22.52, 34.84)	(34.84, 79.47)	

Data for continuous variables are expressed as median (interquartile distance), age is expressed as mean SD categorical variables are expressed as numerical (percentage) CIMT, carotid intima-media thickening; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FPG, fasting blood glucose; HbA1c, glycosylated hemoglobin; CV, coefficient of variation; MAGE, the average amplitude of blood sugar fluctuations; MODD: average daily difference; TIR, range of time; TAR, out-of-range time; GRI, blood glucose risk index; TBR, time below range; LAGE, the maximum value of blood sugar fluctuations.

associated with significantly increased age, hospitalization costs, fasting plasma glucose (FPG), and HbA1c levels, along with elevated glycemic variability indices (CV, MAGE, MODD). However, lipid levels and other metabolic markers did not differ significantly across quartiles. Similarly, clinical features such as smoking history, alcohol consumption, family history of genetic disease, hypertension, and hyperlipidemia were not significantly different. Further analyses indicated that the prevalence of carotid intimal thickening increased progressively with GRI quartiles ($P < 0.001$, Supplementary Figure S1).

Correlation between CIMT and GRI

Spearman correlation analysis (Supplementary Table S2) found a significant positive correlation between CIMT and GRI, in addition, CIMT was also correlated with other indicators of blood glucose fluctuation. Multiple linear regression analysis (Table 3) confirmed GRI as an independent predictor of CIMT across all models. In the fully adjusted model (Model 3), GRI showed a strong association with CIMT (β = 0.488, 95% CI: 0.413–0.563, $P < 0.001$). Age was also positively associated with CIMT (β = 0.022, 95% CI: 0.018–0.026, $P < 0.001$), while gender, BMI, diabetes duration, lipid indices, and smoking history were not significantly associated ($P > 0.05$). These findings underline the importance of GRI as a robust marker of CIMT thickening.

Logistic regression analysis

Logistic regression analysis further evaluated the relationship between GRI quartiles and CIMT thickening risk (Table 4). After adjusting for confounders (Model 3), participants in the higher GRI quartiles had significantly increased odds of CIMT thickening compared to the lowest quartile (Q2: OR = 2.631, 95% CI: 1.734–3.528, P < 0.001; Q3: OR = 4.675, 95% CI: 3.636–5.714, P < 0.001; Q4: OR = 7.226, 95% CI: 5.597–8.856, P < 0.001). Age (β = 0.136, 95% CI: 0.097–0.174, P < 0.001) and BMI (β = 0.347, 95% CI: 0.218–0.477, P < 0.001) were also significantly associated with CIMT thickening, whereas gender showed no significant association. These results highlight the relationship between GRI and CIMT risk, suggesting the potential utility of GRI in identifying at-risk populations.

Subgroup analysis

Since age, BMI, and disease duration are recognized as risk factors for CIMT thickening, these variables were included in the regression

TABLE 3 Multivariate linear regression analysis of the relationship between GRI and CIMT

Variable	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
const	-0.006 (-0.149, 0.137)	0.936	-0.006 (-0.149, 0.137)	0.936	-0.006 (-0.149, 0.137)	0.936
GRI	0.488 (0.413, 0.563)	<0.001*	0.488 (0.413, 0.563)	<0.001*	0.488 (0.413, 0.563)	<0.001*
Age			0.006 (0.005, 0.007)	<0.001*	0.006 (0.005, 0.007)	<0.001*
Sex			0.025 (-0.008, 0.059)	0.135	0.025 (-0.008, 0.059)	0.135
BMI					0.022 (0.018, 0.026)	<0.001*

The data were expressed as regression coefficient (95% CI) Model 1 adjusted for sex and age Model 2 further adjusted for BMI diabetes course current smoking status triglyceride HDL cholesterol and LDL cholesterol CIMT, carotid indium-media thickened; GRI, blood glucose risk index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

10.3389/fendo.2025.1563734

TABLE 4 logistic regression analysis of different GRI levels and CIMT thickening

Variable	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
const	-2.040 (-2.618, -1.462)	<0.001*	-8.890 (-10.907, -6.873)	<0.001*	-18.451 (-23.205, -13.698)	<0.001*
Q1		<0.001*		<0.001*		<0.001*
Q2	1.897 (1.210, 2.584)	<0.001*	2.483 (1.677, 3.288)	<0.001*	2.631 (1.734, 3.528)	<0.001*
Q3	3.092 (2.376, 3.808)	<0.001*	4.175 (3.257, 5.094)	<0.001*	4.675 (3.636, 5.714)	<0.001*
Q4	5.345 (4.192, 6.498)	<0.001*	6.090 (4.790, 7.390)	<0.001*	7.226 (5.597, 8.856)	<0.001*
Age			0.130 (0.096, 0.165)	<0.001*	0.136 (0.097, 0.174)	<0.001*
Sex			0.343 (-0.254, 0.939)	0.260	0.279 (-0.518, 1.077)	0.493
BMI					0.347 (0.218, 0.477)	<0.001*

The data were expressed as regression coefficient (95% CI) Model 1 adjusted for sex and age Model 2 further adjusted for BMI diabetes course current smoking status triglyceride HDL cholesterol and LDL cholesterol CIMT, carotid indium-media thickened; GRI, blood glucose risk index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

model as interaction terms for analysis. The results (Supplementary Table S3) indicated no significant interactions between GRI and variables such as gender, age, BMI, and disease duration in predicting CIMT thickening. However, further subgroup analysis (Figure 1) revealed significant differences in the association between GRI and CIMT thickening across various demographic and clinical subgroups.

Male patients exhibited a higher odds ratio (OR = 2.03, 95% CI: 1.60–2.47) compared to females (OR = 1.72, 95% CI: 1.16–2.28), suggesting a stronger association between GRI and CIMT thickening in men. Among age groups, the 40–50 age group showed the highest risk (OR = 2.93, 95% CI: 1.97–3.88), followed by patients aged ≥50 years (OR = 2.08, 95% CI: 1.43–2.73). For BMI, patients with BMI ≥25 kg/m² had a significantly greater risk of CIMT thickening (OR = 2.04, 95% CI: 1.56–2.51) compared to those with BMI <25 kg/m² (OR = 1.85, 95% CI: 1.34–2.36).

The influence of diabetes duration was relatively smaller, with patients having a disease duration ≤3 years showing a slightly higher odds ratio (OR = 2.03, 95% CI: 1.55–2.51) compared to those with >3 years (OR = 1.86, 95% CI: 1.36–2.37). These findings

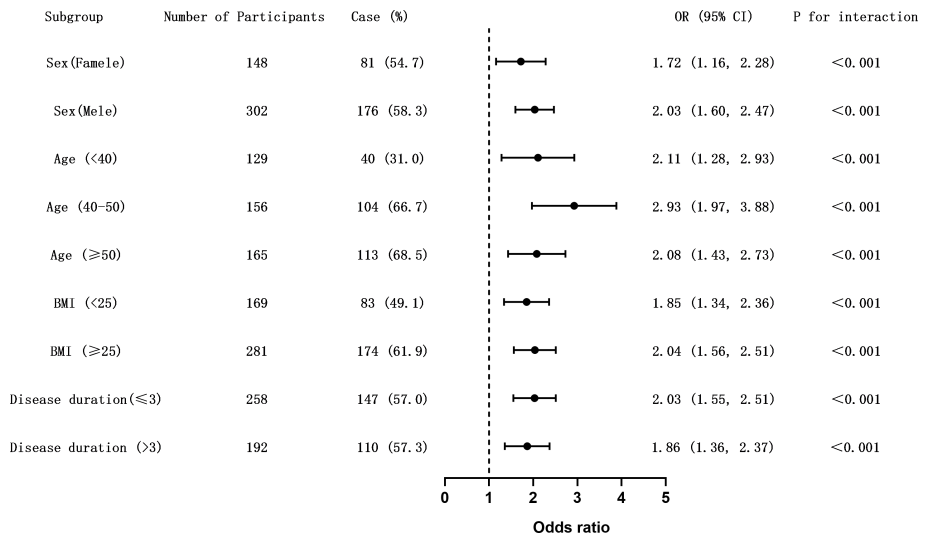


FIGURE 1
Subgroup analysis of the association between GRI and carotid intima-media thickness (CIMT) thickening. Forest plot showing odds ratios (ORs) and 95% confidence intervals (CIs) for the association between elevated glycemia risk index (GRI) and CIMT thickening (CIMT ≥ 1.0 mm) across predefined clinical subgroups. Horizontal lines represent 95% CIs. The dashed vertical line indicates the null value (OR = 1.0). Interaction p-values were calculated to assess effect modification. The association remained consistent across all subgroups without evidence of effect heterogeneity.
Figure 1. Subgroup analysis of the association between GRI and carotid intima-media thickness (CIMT) thickening. Forest plot showing odds ratios (ORs) and 95% confidence intervals (CIs) for the association between elevated glycemia risk index (GRI) and CIMT thickening (CIMT ≥ 1.0 mm) across predefined clinical subgroups. Horizontal lines represent 95% CIs. The dashed vertical line indicates the null value (OR = 1.0). Interaction p-values were calculated to assess effect modification. The association remained consistent across all subgroups without evidence of effect heterogeneity.

10.3389/fendo.2025.1563734

underscore the importance of gender, age, and BMI as critical stratified factors influencing the risk of CIMT abnormalities. Meanwhile, the association between GRI and CIMT thickening remains significant across different diabetes duration groups, highlighting its robust predictive value.

ROC curve analysis

To evaluate the diagnostic performance of GRI and other glycemic indices for predicting carotid intima-media thickness (CIMT ≥ 1.0 mm), receiver operating characteristic (ROC) curve analysis was conducted (Figure 2A; Supplementary Table S4). Among the individual markers, GRI demonstrated the highest discriminative ability, with an area under the curve (AUC) of 0.869, sensitivity of 0.802, and specificity of 0.788. In contrast, HbA1c ≥ 7% and TIR < 70% showed inferior performance, with AUCs of 0.495 and 0.678, respectively. While HbA1c exhibited high sensitivity (0.872), its specificity was markedly low (0.119); conversely, TIR had high specificity (0.948) but poor sensitivity (0.409), indicating imbalanced classification performance.

To further explore the incremental value of clinical variables, we constructed combined models incorporating traditional risk factors. As shown in Figure 2B, the combination of GRI and Age increased the AUC to 0.913, and the addition of BMI further improved the AUC to 0.937. Notably, the positive predictive value (PPV) also increased from 0.834 (GRI alone) to 0.892 (GRI + Age + BMI), indicating a substantial gain in classification robustness. These results suggest that integrating GRI with conventional clinical parameters significantly enhances its predictive value for subclinical atherosclerosis in patients with type 2 diabetes.

Discussion

This study evaluated the clinical applicability of the Glycemic Risk Index (GRI) for predicting subclinical macrovascular complications in individuals with type 2 diabetes mellitus (T2DM). Although prior studies have demonstrated that GRI is significantly associated with microvascular complications such as diabetic retinopathy and proteinuria (12, 14), its role in macrovascular pathology remains insufficiently studied. Our results show that elevated GRI levels are significantly associated with increased carotid intima-media thickness (CIMT), suggesting its potential utility as a noninvasive, integrative biomarker for early cardiovascular risk assessment in patients with T2DM.

These findings align with a Japanese cohort study, which examined the association between GRI and various markers of atherosclerosis. While no significant relationship was observed between GRI and mean CIMT, the study identified strong associations between GRI and longer diabetes duration, higher HbA1c levels, elevated mean glucose concentrations, brachial-ankle pulse wave velocity (baPWV), and the gray-scale median (GSM) of the carotid artery wall—even after adjustment for conventional cardiovascular risk factors (22). The authors proposed that GRI may reflect vascular remodeling and overall atherosclerotic burden beyond arterial wall thickness alone. By focusing on CIMT as a structural indicator of subclinical atherosclerosis, our study extends the evidence base for GRI as a predictor of early macrovascular changes. This complementary relationship may reflect differences in population characteristics, disease stages, endpoint definitions, or methods of GRI calculation.In addition, another investigation found an inverse and independent association between Time in Range (TIR)—a CGM-derived glycemic variability metric—and CIMT, reinforcing the relevance of CGM-based parameters in vascular risk evaluation (23). Compared with single glycemic indices such as TIR and HbA1c, GRI integrates the burden of both hypo- and hyperglycemia, offering a more holistic measure of glycemic instability.

Previous studies have demonstrated that intermittent hyperglycemia activates the NADPH oxidase system, leading to excessive production of reactive oxygen species (ROS), which in turn reduces the bioavailability of nitric oxide (NO) and impairs endothelial vasodilation (19, 24). In parallel, ROS also triggers the NF-κB signaling cascade, resulting in the upregulation of pro-inflammatory cytokines (e.g., IL-6 and TNF-α), enhanced leukocyte adhesion, endothelial apoptosis, and foam cell formation—all hallmark processes in the development of atherosclerosis (25).As an integrated measure of overall glycemic

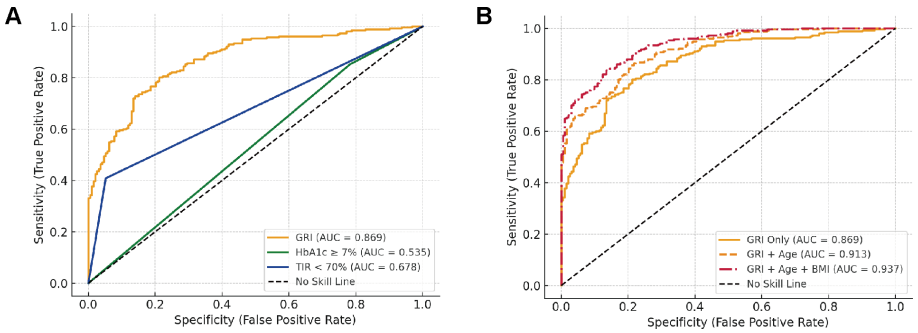


FIGURE 2
Receiver operating characteristic (ROC) curves for predicting CIMT thickening. **(A)** Comparative diagnostic performance of glycemic metrics including the Glycemia Risk Index (GRI), HbA1c ≥ 7%, and Time in Range (TIR < 70%) in identifying CIMT thickening (CIMT ≥ 1.0 mm). **(B)** Predictive performance of GRI alone and in combination with traditional risk factors.

variability, an elevated GRI may exacerbate metabolic disturbances and amplify oxidative and inflammatory responses, thereby accelerating macrovascular injury in patients with diabetes mellitus; (26).

Subgroup analyses suggested that sex, age, and body mass index (BMI) may significantly influence the relationship between GRI and CIMT. Men are more prone to insulin resistance and dyslipidemia due to the absence of estrogen-mediated vascular protection (27–29), while postmenopausal women may experience accelerated vascular aging owing to hormonal decline (30, 31);. Additionally, aging-related β-cell dysfunction and arterial stiffness further heighten the risk of atherosclerosis (32);. Obesity, a key component of metabolic syndrome, may promote CIMT progression via persistent low-grade inflammation and endothelial dysfunction (29, 33);.Because GRI dynamically captures fluctuations in both hyperglycemia and hypoglycemia, it may offer greater clinical value than traditional static glycemic measures such as HbA1c. Regular monitoring of GRI —at intervals of 3 to 6 months—could facilitate earlier cardiovascular risk stratification, particularly in high-risk individuals such as those with inadequate glycemic control, obesity, or advanced age. Persistent elevations in GRI may act as early warning signals, prompting clinicians to intensify glucose-lowering therapy, initiate statin treatment, or recommend lifestyle interventions in a timely, personalized manner.

This study has several limitations. First, as a single-center retrospective analysis, selection bias and missing data may affect the generalizability of our findings. Moreover, the GRI algorithm has not yet been standardized, and the absence of consensus thresholds for cardiovascular risk stratification may compromise inter-study comparability and reproducibility. Future multicenter, prospective, and interventional trials are essential to validate the predictive robustness of GRI and to better define its role in guiding cardiovascular risk management.Second, we did not assess lifestyle variables such as diet, physical activity, or sleep behaviors, which may confound the observed association between GRI and CIMT. Future research should integrate standardized lifestyle questionnaires or wearable technologies to better account for behavioral confounders, improve model accuracy, and support more rigorous causal inference.Third, this study did not stratify female participants based on menopausal status, potentially underestimating the effects of hormonal changes on vascular risk. Future studies should consider including sex hormone measurements and menopausal classification to improve the precision of sex-specific risk assessments.

Conclusion

This study identifies GRI as an independent predictor of CIMT thickening in type 2 diabetes. As a noninvasive, CGM-derived metric, GRI may enable early identification of high-risk patients and support timely, individualized interventions—such as optimizing glycemic control or initiating statin therapy—to slow the progression of subclinical atherosclerosis.

Data availability statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request. Requests to access these datasets should be directed to HY, hjyuan@zzu.edu.cn.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Henan Provincial People's Hospital (NO. 792018048). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. 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

LZ: Data curation, Writing – original draft, Writing – review & editing. HH: Conceptualization, Data curation, Writing – review & editing. QX: Data curation, Writing – original draft. CL: Conceptualization, Formal analysis, Writing – original draft. SG: Formal analysis, Writing – review & editing. ZZ: Data curation, Writing – original draft. HY: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National natural science foundation of China (82270865), Henan provincial key research and development projects (231111313200) and Henan provincial medical science and technology research program-the provincial and ministerial major projects(SBGJ202301002).

Acknowledgments

This study is supported by several research groups, and thanks to the technicians of Abbott Company for exporting the blood glucose monitoring data.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1563734/full#supplementary-material

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. (2019) 157:107843. doi: 10.1016/j.diabres.2019.107843

2. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S Diabetes 2030: insights from yesterday, today, and future trends. *Popul Health Manag*. (2017) 20:6–12. doi: 10.1089/pop.2015.0181

3. Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. *BMJ (Clinical Res ed)*. (2020) 370:m2297. doi: 10.1136/bmj.m2297

4. Rask-Madsen C, King GL Vascular complications of diabetes: mechanisms of injury and protective factors. *Cell Metab*. (2013) 17:20–33. doi: 10.1016/j.cmet.2012.11.012

5. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. *Circulation*. (2016) 133:2459–502. doi: 10.1161/circulationaha.116.022194

6. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. (2000) 151:478–87. doi: 10.1093/oxfordjournals.aje.a010233

7. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol*. (1997) 146:483–94. doi: 10.1093/oxfordjournals.aje.a009302

8. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100–667 patients. *Circulation*. (2020) 142:621–42. doi: 10.1161/circulationaha.120.046361

9. Cardoso CRL, Salles GC, Leite NC, Salles GF Prognostic impact of carotid intima-media thickness and carotid plaques on the development of micro- and macrovascular complications in individuals with type 2 diabetes: the Rio de Janeiro type 2 diabetes cohort study. *Cardiovasc Diabetol*. (2019) 18:2. doi: 10.1186/s12933-019-0809-1

10. American Diabetes Association Professional Practice Committee. Glycemic targets: standards of medical care in diabetes-2022. *Diabetes Care*. (2022) 45:S83–s96. doi: 10.2337/dc22-S006

11. Kim JY, Yoo JH, Kim JH Comparison of glycemia risk index with time in range for assessing glycemic quality. *Diabetes Technol Ther*. (2023) 25:883–92. doi: 10.1089/dia.2023.0264

12. Klonoff DC, Wang J, Rodbard D, Kohn MA, Li C, Liepmann D, et al. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. *J Diabetes Sci Technol*. (2023) 17:1226–42. doi: 10.1177/19322968221085273

13. Nathiya D, Singh M, Suman S, Bareth H, Pal N, Jain A, et al. Albuminuria, glycemic variability and effect of flash glucose monitoring based decision making on short term glycemic variability in Indian type 2 diabetes patients: Indi-GlyVar study. *Front Endocrinol (Lausanne)*. (2022) 13:1011411. doi: 10.3389/fendo.2022.1011411

14. Wang Y, Lu J, Ni J, Wang M, Shen Y, Lu W, et al. Association between glycaemia risk index (GRI) and diabetic retinopathy in type 2 diabetes: A cohort study. *Diabetes Obes Metab*. (2023) 25:2457–63. doi: 10.1111/dom.15068

15. Dehghani Firouzabadi F, Poopak A, Samimi S, Deravi N, Nakhaei P, Sheikhy A, et al. Glycemic profile variability as an independent predictor of diabetic retinopathy in patients with type 2 diabetes: a prospective cohort study. *Front Endocrinol (Lausanne)*. (2024) 15:1383345. doi: 10.3389/fendo.2024.1383345

16. Cai L, Shen W, Li J, Wang B, Sun Y, Chen Y, et al. Association between glycemia risk index and arterial stiffness in type 2 diabetes. *J Diabetes Investig*. (2024) 15:614–22. doi: 10.1111/jdi.14153

17. Hjort A, Iggman D, Rosqvist F Glycemic variability assessed using continuous glucose monitoring in individuals without diabetes and associations with cardiometabolic risk markers: A systematic review and meta-analysis. *Clin Nutr*. (2024) 43:915–25. doi: 10.1016/j.clnu.2024.02.014

18. Papachristoforou E, Lambadiari V, Maratou E, Makrilakis K Association of glycemic indices (Hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. *J Diabetes Res*. (2020) 2020:7489795. doi: 10.1155/2020/7489795

19. Pérez-López P, Férnandez-Velasco P, Bahillo-Curieses P, de Luis D, Díaz-Soto G Impact of glucose variability on the assessment of the glycemia risk index (GRI) and classic glycemic metrics. *Endocrine*. (2023) 82:560–8. doi: 10.1007/s12020-023-03511-7

20. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. (2017) 40:1631–40. doi: 10.2337/dc17-1600

21. Chandrasekar V, Mohammad S, Aboumarzouk O, Singh AV, Dakua SP Quantitative prediction of toxicological points of departure using two-stage machine learning models: A new approach methodology (NAM) for chemical risk assessment. *J Hazard Mater*. (2025) 487:137071. doi: 10.1016/j.jhazmat.2024.137071

22. Torimoto K, Okada Y, Mita T, Tanaka K, Sato F, Katakami N, et al. Association of glycaemia risk index with indices of atherosclerosis: A cross-sectional study. *J Diabetes*. (2025) 17:e70065. doi: 10.1111/1753-0407.70065

23. Lu J, Ma X, Shen Y, Wu Q, Wang R, Zhang L, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther*. (2020) 22:72–8. doi: 10.1089/dia.2019.0251

24. Kawano N, Emoto M, Mori K, Yamazaki Y, Urata H, Tsuchikura S, et al. Association of endothelial and vascular smooth muscle dysfunction with cardiovascular risk factors, vascular complications, and subclinical carotid atherosclerosis in type 2 diabetic patients. *J Atheroscler Thromb*. (2012) 19:276–84. doi: 10.5551/jat.10629

25. Chee YJ, Dalan R, Cheung C The interplay between immunity, inflammation and endothelial dysfunction. *Int J Mol Sci*. (2025) 26(4):1708. doi: 10.3390/ijms26041708

26. Wilmot EG, Choudhary P, Leelarathna L, Baxter M Glycaemic variability: The under-recognized therapeutic target in type 1 diabetes care. *Diabetes Obes Metab*. (2019) 21:2599–608. doi: 10.1111/dom.13842

27. Klimontov VV, Saik OV, Korbut AI Glucose variability: how does it work? *Int J Mol Sci*. (2021) 22(15):7783. doi: 10.3390/ijms22157783

28. Xue C, Chen K, Gao Z, Bao T, Dong L, Zhao L, et al. Common mechanisms underlying diabetic vascular complications: focus on the interaction of metabolic disorders, immuno-inflammation, and endothelial dysfunction. *Cell Commun Signal*. (2023) 21:298. doi: 10.1186/s12964-022-01016-w

29. Sharma G, Hu C, Brigman JL, Zhu G, Hathaway HJ, Prossnitz ER GPER deficiency in male mice results in insulin resistance, dyslipidemia, and a proinflammatory state. *Endocrinology*. (2013) 154:4136–45. doi: 10.1210/en.2013-1357

30. An Y, Xu BT, Wan SR, Ma XM, Long Y, Xu Y, et al. The role of oxidative stress in diabetes mellitus-induced vascular endothelial dysfunction. *Cardiovasc Diabetol*. (2023) 22:237. doi: 10.1186/s12933-023-01965-7

31. Finan B, Yang B, Ottaway N, Stemmer K, Müller TD, Yi CX, et al. Targeted estrogen delivery reverses the metabolic syndrome. *Nat Med*. (2012) 18:1847–56. doi: 10.1038/nm.3009

32. Zhu M, Liu X, Liu W, Lu Y, Cheng J, Chen Y β cell aging and age-related diabetes. *Aging (Albany NY)*. (2021) 13:7691–706. doi: 10.18632/aging.202593

33. Mihuta MS, Paul C, Borlea A, Roi CM, Velea-Barta OA, Mozos I, et al. Unveiling the silent danger of childhood obesity: non-invasive biomarkers such as carotid intima-media thickness, arterial stiffness surrogate markers, and blood pressure are useful in detecting early vascular alterations in obese children. *Biomedicines*. (2023) 11(7):1841. doi: 10.3390/biomedicines11071841

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 25 June 2025
DOI 10.3389/fendo.2025.1534236

Check for updates

OPEN ACCESS

EDITED BY
Manoj Kumar Mahata,
Belle Vue Clinic, India

REVIEWED BY
Alexander E Berezin,
Paracelsus Medical University, Austria
Hanqing Liu,
Zhejiang University, China

*CORRESPONDENCE
Yuan Lu
xyfyluyuan@163.com
Wensu Chen
chen.wensu@163.com
Wenliang Che
chewenliang@tongji.edu.cn

†These authors have contributed equally to this work

RECEIVED 25 November 2024
ACCEPTED 04 June 2025
PUBLISHED 25 June 2025

CITATION
Chen L, Qiu B, Du X, Liu J, Lu Y, Che W and Chen W (2025) Establishment of a synthetic ECV model and its prognostic value in diabetes patients with acute myocardial infarction. *Front. Endocrinol.* 16:1534236. doi: 10.3389/fendo.2025.1534236

COPYRIGHT
© 2025 Chen, Qiu, Du, Liu, Lu, Che and Chen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Establishment of a synthetic ECV model and its prognostic value in diabetes patients with acute myocardial infarction

Lei Chen[1,2†], Bowen Qiu[1†], Xinjia Du[1], Jiahua Liu[1], Yuan Lu[1*], Wenliang Che[2*] and Wensu Chen[1*]

[1]Department of Cardiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [2]Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

Background: Extracellular volume (ECV) is an important marker of myocardial fibrosis. However, the prognostic role of ECV in diabetes patients is unknown. In addition, synthetic ECV without blood sampling has not been reported in diabetes cohorts. This study investigated the establishment and validation of synthetic ECV and its prognostic value in type 2 diabetes mellitus (T2DM) patients with acute myocardial infarction (AMI).

Methods: This single-center retrospective study included T2DM patients with AMI who completed cardiac magnetic resonance (CMR) during hospitalization. The patients were randomly divided into a derivation group and a validation group. MACE included all-cause death, recurrent MI, stroke, or heart failure. ECV in integral (Integral ECV), non-myocardial infarction region (NMI-ECV), and myocardial infarction region (MI-ECV) was obtained by CMR.

Results: The study included 157 patients, with a median time from admission to CMR of 4 days. Bland-Altman and Pearson analysis showed good consistency and correlation between conventional ECV and synthetic ECV. Cox regression showed that Integral ECV (HR=1.07; 95%CI: 1.01 ~ 1.13, p = 0.023), MI-ECV (HR=1.03; 95%CI: 1.00 ~ 1.07, p = 0.024), and NMI-ECV (HR=1.07; 95%CI: 1.00 ~ 1.14, p = 0.039) were independently associated with MACE in different models. Kaplan-Meier analysis indicated that patients with a high synthetic ECV had a significantly higher MACE risk.

Conclusions: Synthetic ECV is strongly consistent and correlated with conventional ECV in T2DM patients with AMI. Elevated synthetic ECV is an independent risk factor for MACE in T2DM patients with AMI.

KEYWORDS

cardiac magnetic resonance, synthetic extracellular volume, diabetes, acute myocardial infarction, major adverse cardiac events

Introduction

Acute myocardial infarction (AMI) is one of the leading causes of death in the population worldwide, and type 2 diabetes mellitus (T2DM) is a major risk factor for AMI (1). Patients with diabetes have a higher risk of major adverse cardiovascular events (MACE) after AMI compared to patients without diabetes (2, 3). Although the pathophysiology of diabetes leading to cardiovascular disease is not fully understood, what can be confirmed is that myocardial fibrosis plays a key role (4). Myocardial fibrosis has been found to occur in diabetic patients in previous autopsy studies even in the absence of signs of ischemic heart disease (5, 6). Thus, myocardial fibrosis may play an important role in T2DM patients with AMI.

Histology remains the gold standard for myocardial fibrosis. However, endomyocardial biopsy is an invasive procedure that is neither reasonable nor feasible in the acute phase of AMI (7). Among the various noninvasive imaging modalities, cardiac magnetic resonance (CMR) has emerged as the most powerful tool for characterizing structural and functional changes in tissues. Extracellular volume (ECV) allows quantification of the extracellular matrix with good reproducibility and is termed "noninvasive" or "virtual biopsy" (8–10). As an alternative to myocardial fibrosis, ECV has been shown to independently predict MACE risk in a variety of diseases, including diabetes (11).

Conventional ECV measurements need to be combined with hematocrit (HCT), but HCT is highly individualized and is affected by several factors such as time of day and body position (12–14). To minimize the interference of variability, the Society for Cardiovascular Magnetic Resonance (SCMR) recommends blood collection within 24 hours of the CMR scan, which limits the routine clinical application of ECV measurement (15). In addition, conventional ECV is estimated from venous blood HCT, whereas ideally ECV calculations should be obtained from a left ventricular blood pool representing arterial blood (16). Indeed, a linear relationship between HCT and blood pool R1 (1/T1) has been extensively described (16–19). Based on this linear relationship, a method to determine synthetic ECV without blood sampling has been proposed. In these studies, good agreement was demonstrated between synthetic and conventional ECV (16, 20–22). However, the establishment and validation of synthetic ECV in diabetes patients have not been reported, and the prognostic value of different regional ECV in diabetes patients is unclear.

The main objectives of this study were as follows: First, to investigate the establishment and validation of synthetic ECV without blood sampling in T2DM patients with AMI; Second, to investigate the prognostic value of ECV from different regions in T2DM patients with AMI.

Methods

Study population

This retrospective study included T2DM patients with AMI at the Affiliated Hospital of Xuzhou Medical University from May 2019 to June 2024. Inclusion criteria: 1. Underwent CMR with T1 mapping sequences during hospitalization; 2. Underwent coronary angiography (CAG) and successful revascularization therapy (TIMI ≥ 2). Exclusion criteria: 1. Without HCT within 24 hours of the CMR examination; 2. Poor image quality; 3. History of myocardial infarction; 4. Malignancy, or inflammatory disease; 5. Severe renal insufficiency; 6.Blood disease. The Institutional Review Board (IRB) approved the study protocol (XYFY2023-KL199-01). Considering this was a retrospective study with no risk to patients, the informed consent was waived by the IRB. The patients were randomly divided into a derivation group (n = 80) and a validation group (n = 77). The clinical data, relevant laboratory indexes, and medications were obtained from the patient's clinical records. Peak values of high-sensitivity troponin T (hs-TnT), high-sensitivity C-reactive protein (hs-CRP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) during hospitalization were collected. Infarct-related arteries (IRA) were recorded based on CAG. Considering the interference of stress glucose elevation, only patients diagnosed with T2DM before the current AMI were included in this study (Supplementary Figure 1).

Cardiac MRI protocol and cardiac MRI-related parameters

The median time to CMR completion was 4 (3.5, 6) days after hospitalization. The detailed parameters of CMR have been described in our earlier publications (23, 24). CMR assessments were conducted using 3.0 T imaging systems (Ingenia, Philips, The Netherlands). A balanced turbo field echo (BTFE) sequence was implemented. Scan parameters: slice thickness = 7 mm, no interlayer gap; echo time (TE) = 1.47 ms, repetition time (TR) = 2.94 ms; flip angle = 60°, field of view (FOV) = 300 × 300 mm, matrix = 280 × 240 mm and voxel size = 1.22 × 1.22 × 8.0 mm^3. Following the administration of a gadolinium-based contrast agent (0.1 mmol/kg), short-axis images encompassing the left ventricle (LV) were obtained with 3 to 5 slices, and T1-mapping (MOLLI) was performed 10 to 15 minutes both before and after the application of the contrast medium. The CVI42 (cvi42® version 5.13.5, Circle Cardiovascular Imaging, Canada) was used for image analysis. The analysis of CMR images was carried out independently by two skilled physicians who did not know this study. End-diastolic volume (EDV), end-systolic volume (ESV), and left ventricular ejection fraction (LVEF) values were automatically derived and adjusted for body surface area (BSA). CMR feature tracking was used to measure the global longitudinal strain (GLS). Microvascular obstruction (MVO) and late gadolinium enhancement (LGE) were adjusted for the total left ventricular myocardial mass. The endocardial, epicardial, and blood pool were identified on a short-axis view to evaluate the T1 relaxation time. Average relaxation times (≥1 cm^2) for two regions of interest (ROI) were recorded at both the myocardial infarction region and the non-infarction region. The limbic area and papillary muscles were meticulously avoided. The T1 value concerning the blood pool was derived from the left ventricle. Conventional ECV was computed

using previously established equations: ECV = (1-HCT) × (1/Myocardial enhanced T1 -1/Myocardial native T1)/(1/Blood pool enhanced T1 -1/Blood pool native T1). ECV in integral (Integral ECV), non-myocardial infarction region (NMI-ECV), and myocardial infarction region (MI-ECV) was obtained (Supplementary Figure 2).

Calculation of synthetic ECV

Within the derivation group, an analysis was conducted on the reciprocal longitudinal relaxation time of blood (R1 = 1/T1) and HCT to explore their linear correlation, resulting in a formula for synthetic HCT. In the validation group, the synthetic ECV was then calculated by applying the synthetic HCT values. The synthetic ECV was verified by the analysis with conventional ECV in the validation group. In all patients, synthetic ECV from different regions was calculated to investigate the prognostic value in patients with AMI combined with diabetes.

Clinical outcomes and follow-up

Patients were followed up from their discharge via outpatient appointments and/or telephone communications utilizing a standardized questionnaire. In cases where the patient was unreachable, pertinent information was obtained from the patient's family members or healthcare provider. The main follow-up endpoint was MACE, which included all-cause mortality, recurrent myocardial infarction (MI), stroke, or heart failure. The diagnosis of recurrent MI and heart failure was made following the latest guidelines from the European Society of Cardiology (ESC) (25, 26). Stroke was characterized as neurological impairment and cerebrovascular damage resulting from either cerebral ischemia or hemorrhage (27). Any patients who could not be followed up were confirmed deceased through the local official household registry.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM, Chicago, USA). To evaluate the normality of the data, the Kolmogorov-Smirnov test was used. Continuous variables that followed a normal distribution were represented as mean ± standard deviation (SD), with subsequent analysis performed using Student's t-test. Continuous variables that did not conform to normal distribution were summarized as median (Q25, Q75), and analyzed using a nonparametric test. Categorical variables were depicted in terms of frequencies and percentages, and analyzed through the chi-square test (count >5) or Fisher test (count ≤5). For the derivation group, linear regression analysis was conducted to derive the synthetic HCT formula. In the validation group, a Bland-Altman analysis was executed to evaluate the consistency between synthetic and conventional ECV. The Pearson correlation coefficient was calculated to assess relationships among continuous variable gates. To examine the association of ECV with MACE, Cox regression models were utilized. Variables associated with MACE ($p < 0.1$) in univariate analysis were incorporated into the multivariate model using a stepwise forward approach. To eliminate collinear interference, Integral ECV, NMI-ECV, and MI-ECV were analyzed in separate multivariate Cox regression models. Receiver operating characteristic (ROC) curve was applied to evaluate the capability of ECV in identifying MACE. Based on the cut-off values derived from the ROC analysis, all patients were stratified into two groups for Kaplan-Meier curve analysis. All P values are from two-sided tests and results were considered statistically significant at $p < 0.05$.

Results

Establishment of an ECV model without blood sampling

The derivation group was used to calculate the linear regression equation of synthetic HCT and ECV. There were no statistical differences in baseline characteristics between the derivation and validation groups (Supplementary Table 1). In the derivation group, R1 and conventional HCT had a linear correlation ($R^2 = 0.29$, $p < 0.001$). Through linear regression analysis, R1 was used to derive the formula to estimate synthetic HCT: HCT=697.95* (1/Blood pool T1) + 0.03207 (Supplementary Figure 3).

Validation of an ECV model without blood sampling

In the validation group, the formula was used to calculate the synthetic HCT. Then, the synthetic HCT was used to calculate synthetic ECV. In the validation group, there was no statistical difference between conventional HCT and synthetic HCT. Also, there was no statistical difference between conventional ECV and synthetic ECV from different regions (Figure 1; Table 1). Bland-Altman analysis showed good consistency between the conventional HCT and the synthetic HCT (Bias = 0.38). The synthetic ECV and conventional ECV in Integral, NMI, and MI also showed high consistency in the verification group (Bias = -0.16, -0.15, and -0.01, respectively) (Figure 2). In addition, the conventional HCT and the synthetic HCT showed a linear correlation ($R^2 = 0.33$, $p<0.001$); the synthetic ECV and conventional ECV in Integral, NMI, and MI also showed a good linear correlation ($R^2 = 0.89$, $p<0.001$; $R^2 = 0.92$, $p<0.001$; $R^2 = 0.86$, $p<0.001$; respectively) (Figure 3).

Baseline characteristics of patients

A total of 157 AMI patients were enrolled in this study, including 102 patients with STEMI. There were 41 (26.1%)

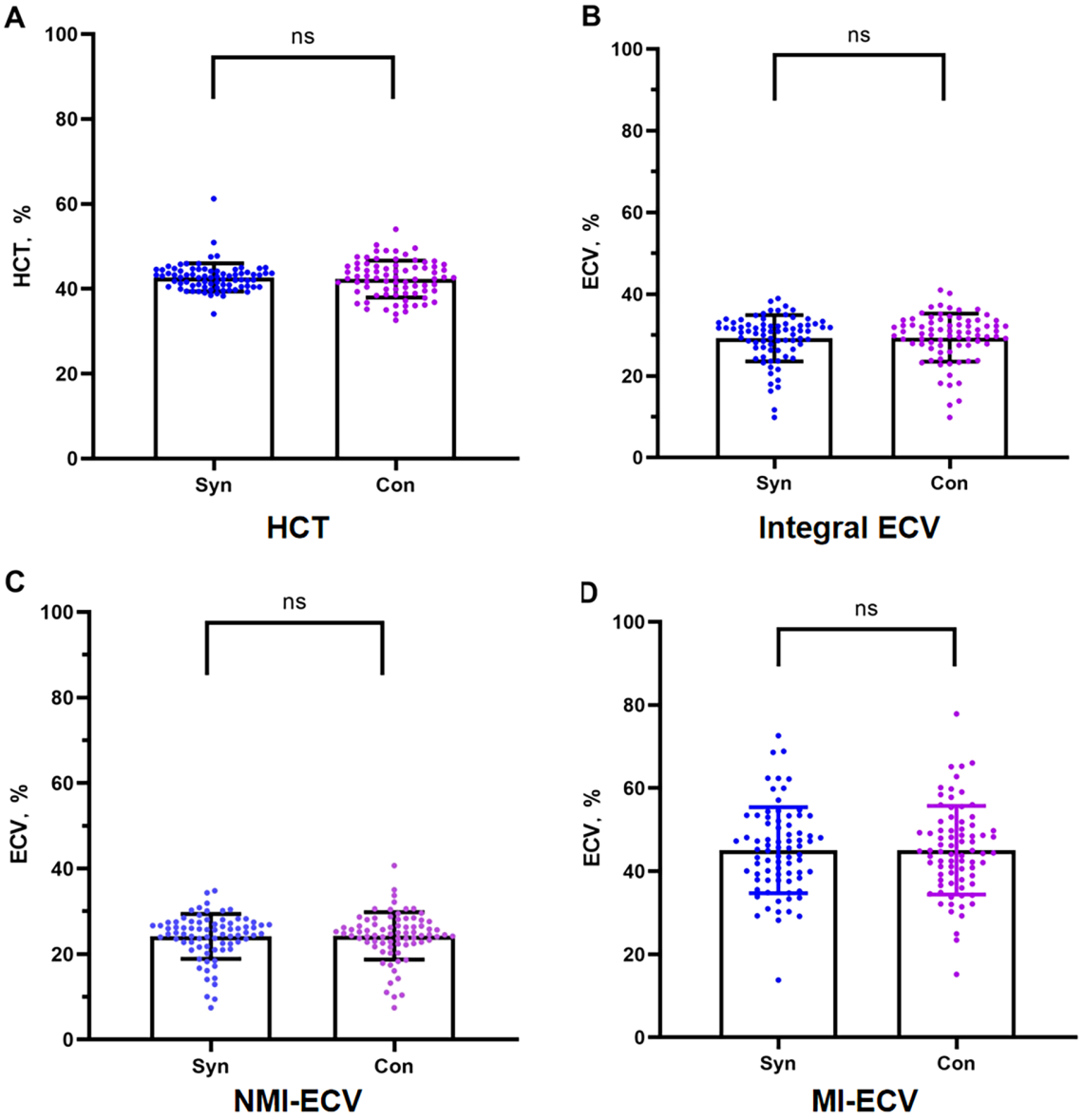


FIGURE 1
Comparison between conventional ECV and synthetic ECV. **(A)** Comparison between conventional HCT and synthetic HCT; **(B)** Comparison between conventional ECV and synthetic ECV in the integral myocardium; **(C)** Comparison between conventional NMI-ECV and synthetic NMI-ECV in NMI; **(D)** Comparison between conventional ECV and synthetic ECV at MI. NMI, non-myocardial infarction regions; MI, myocardial infarction regions; ECV, extracellular volume; HCT, hematocrit.

TABLE 1 Comparison of Pearson correlation coefficients of ECV.

Validation (n=77)	Conventional	Synthetic	P
HCT, %	42.02 ± 4.20	42.66 ± 3.32	0.294
Integral ECV, %	29.52 ± 6.10	29.21 ± 5.67	0.743
NMI-ECV, %	24.42 ± 5.93	24.11 ± 5.24	0.731
MI-ECV, %	45.28 ± 10.70	45.05 ± 10.36	0.893

HCT, haematocrit; ECV, extracellular volume; NMI, non-myocardial myocardial infarction; MI, myocardial infarction.

patients with MACE after a median time of 26.6 (17.1, 38.1) months of follow-up (Supplementary Table 2). Compared with No MACE group, patients with MACE had higher age, hs-TnT, NT-proBNP, LGE%, and MVO%, lower LVEF and GLS. In addition, the MI-ECV (50.52 ± 10.49% vs. 45.37 ± 10.24%, p = 0.007), NMI-ECV (26.06 ± 5.91% vs. 23.82 ± 5.18%, p = 0.023), and Integral ECV (32.73 ± 5.85% vs. 29.42 ± 6.25%, p = 0.003) in the MACE group were significantly higher than those in the No MACE group (Table 2).

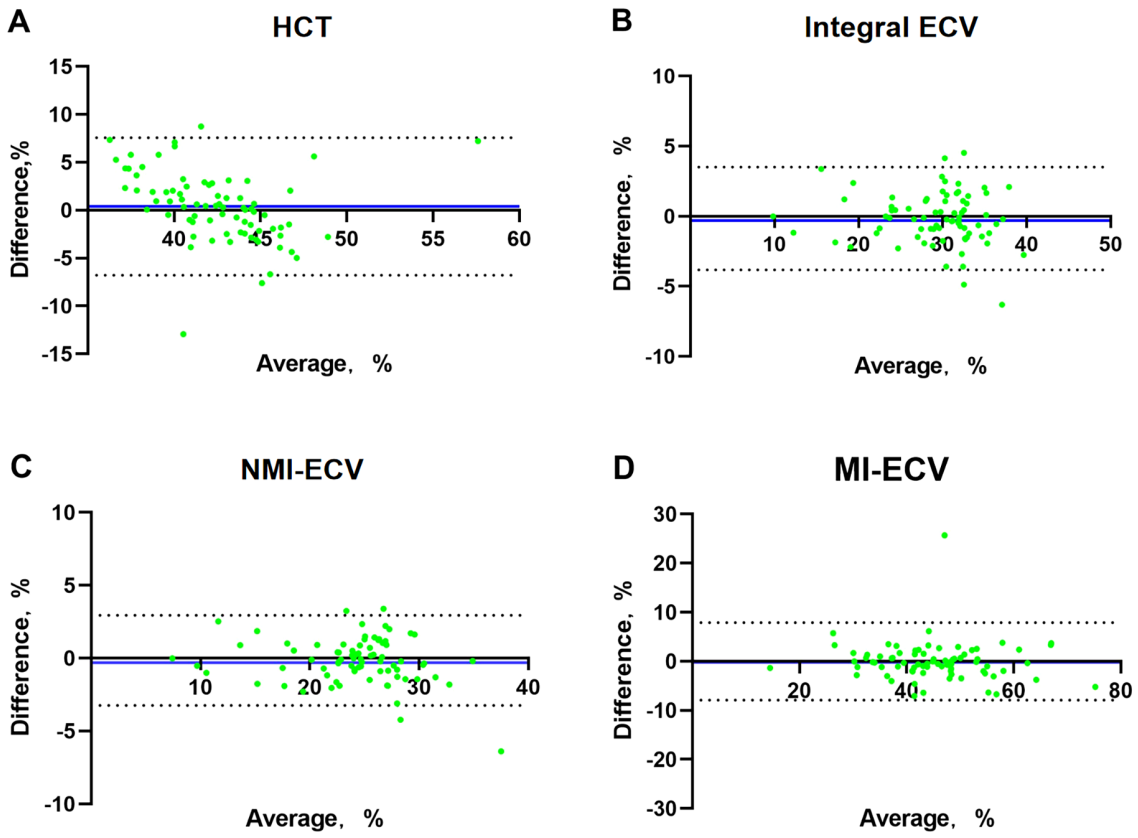


FIGURE 2
Bland-Altman analysis between conventional ECV and synthetic ECV. **(A)** Bland-Altman analysis between conventional HCT and synthetic HCT; **(B)** Bland-Altman analysis between conventional ECV and synthetic ECV in the integral myocardium; **(C)** Bland-Altman analysis between conventional ECV and synthetic ECV in NMI; **(D)** Bland-Altman analysis between conventional ECV and synthetic ECV in MI. The X-axis represents the mean value, The Y-axis represents Bias, The blue line is Bias. NMI, non-myocardial infarction regions; MI, myocardial infarction regions; ECV, extracellular volume; HCT, hematocrit.

Relationship between synthetic ECV and MACE

Univariate COX regression analysis identified hs-TnT, NT-proBNP, MI-ECV, NMI-ECV, Integral ECV, GLS, LVEF, LGE%, and MVO% associated with MACE. Integral ECV, NMI-ECV, and MI-ECV were included in model 1, model 2, and model 3, respectively. After adjusting for confounding factors, it was found that hs-TnT, GLS, MVO%, Integral ECV (HR=1.07; 95%CI: 1.01 ~ 1.13, p = 0.023), and NMI-ECV (HR=1.07; 95%CI: 1.00 ~ 1.14, p = 0.039) were independently associated with MACE in model 1 and model 2. In model 3, it was found that hs-TnT, GLS, and MI-ECV (HR=1.03; 95% CI: 1.00 ~ 1.07, p = 0.024) were independently associated with MACE (Table 3, 4). GLS was moderately correlated with Integral ECV (r = -0.388, p < 0.001), weakly correlated with NMI-ECV (r = -0.266, p < 0.001) and NMI-ECV (r = -0.226, p = 0.004) (Figure 4).

Value of synthetic ECV for predicting MACE

ROC was used to analyze the predictive value of synthetic ECV for MACE. The results showed that the area under the curve (AUC) of MI-ECV for MACE was 0.639 (95% CI 0.537 ~ 0.741, p = 0.008) with a cut-off value of 48.18%, the AUC of Integral ECV for MACE was 0.633 (95% CI 0.533 ~ 0.733, p = 0.011) with a cut-off value of 33.16%, and the AUC of NMI-ECV for MACE was 0.562 (95% CI 0.455 ~ 0.670, p = 0.236) with a cut-off value of 30.16% (Figure 5; Table 5). Based on the cut-off value of synthetic ECV, all patients were stratified into two groups for Kaplan-Meier curve analysis. Kaplan-Meier curve showed that compared with the AMI patients with low synthetic ECV, the patients with high synthetic ECV had a significantly higher long-term risk of MACE (both log-rank P < 0.05) (Figure 6).

Discussion

To the best of our knowledge, there are currently no relevant data in the diabetes cohort to demonstrate the consistency and correlation between synthetic and conventional ECV. The prognostic value of different regional ECV in diabetes patients is unclear. The main findings of this study are as follows. First, Synthetic ECV was strongly consistent and correlated with conventional ECV in T2DM patients with AMI. Second, Elevated synthetic ECV was an independent risk factor for MACE in T2DM

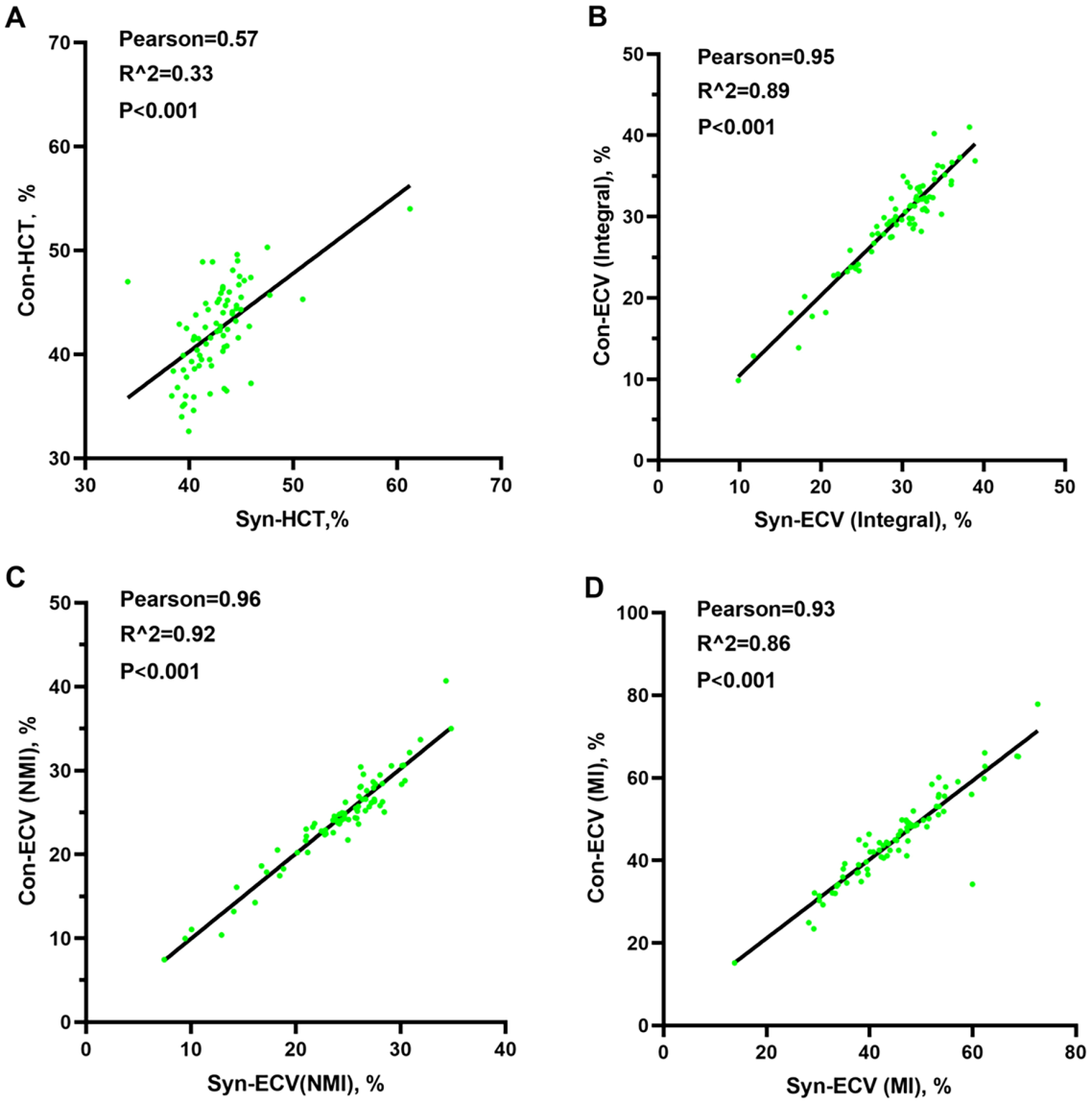


FIGURE 3
Pearson analysis between conventional ECV and synthetic ECV. **(A)** Pearson analysis between conventional HCT and synthetic HCT; **(B)** Pearson analysis between conventional ECV and synthetic ECV in the integral myocardium; **(C)** Pearson analysis between conventional ECV and synthetic ECV in NMI; **(D)** Pearson analysis between conventional ECV and synthetic ECV in MI. NMI, non-myocardial infarction region; MI, myocardial infarction regions; ECV, extracellular volume; HCT, hematocrit.

patients with AMI. Third, Patients with high synthetic ECV had a significantly higher long-term risk of MACE.

ECV in T2DM patients with AMI

T2DM is a high-risk factor for MI and is associated with a high prevalence of diastolic dysfunction and congestive heart failure (28). A potential contributing factor is the accelerated accumulation of diffuse myocardial fibrosis and stiffness (29). Although biopsy remains the gold standard for assessing myocardial fibrosis, this invasive test is difficult to perform in the acute phase of AMI. ECV assessed by CMR is a marker of cardiac remodeling in the early stages of a variety of cardiac diseases and is associated with poor clinical outcomes (11, 30). Therefore, ECV may be of significant value in patients with AMI combined with diabetes. In a previous study of patients with T2DM, ECV levels were lower than in our study (27.9 ± 2.6% vs. 30.44 ± 6.5%) (11, 30). This may be because all patients included in our study combined with AMI, and acute myocardial injury may have additionally increased ECV levels.

Establishment and validation of an ECV model without blood sampling

HCT is crucial for the calculation of conventional ECV. Due to the high temporal variability of HCT, it should be as close as

10.3389/fendo.2025.1534236

TABLE 2 Patient characteristics.

Variables	No MACE (n = 116)	MACE (n = 41)	P
Age, years	56.84 ± 11.26	61.41 ± 11.54	0.028
Female, n (%)	22 (19.0)	5 (12.2)	0.323
BMI, kg/m^2	25.96 ± 3.38	25.5 ± 2.71	0.426
Smoker, n (%)	54 (46.6)	18 (43.9)	0.770
Hypertension, n (%)	53 (45.7)	16 (39.0)	0.460
Stroke, n (%)	17 (14.7)	7 (17.1)	0.712
STEMI, n (%)	72 (62.1)	30 (73.2)	0.200
SBP, mmHg	130.8 ± 19.71	125.68 ± 16.88	0.141
DBP, mmHg	79.8 ± 13.39	79.15 ± 13.85	0.790
Heart rate, bpm	80.39 ± 14.19	79.71 ± 16.12	0.799
Total cholesterol, mmol/L	4.27 ± 1.08	4.52 ± 0.82	0.183
Triglycerides, mmol/L	1.94 ± 1.55	1.84 ± 1.24	0.713
HDL cholesterol, mmol/L	0.96 ± 0.24	0.94 ± 0.2	0.666
LDL cholesterol, mmol/L	2.63 ± 0.94	2.91 ± 0.83	0.091
HbA1c, %	6.58 ± 1.25	6.68 ± 0.84	0.630
FBG, mmol/L	8.85 ± 3.49	9.09 ± 3.08	0.698
eGFR, mL/min/ 1.73 m^2	109.81 ± 16.69	106.31 ± 16.65	0.249
hs-CRP, mg/L	13.75 (4.23, 47)	17.4 (7.25, 53.25)	0.342
hs-TnT, ng/L	2392.5 (773.4, 5072.8)	4942.0 (2480.5, 8388.5)	0.002
NT-proBNP, pg/mL	950.0 (545.0, 1932.3)	2155.0 (784.5, 3250.5)	0.003
Antiplatelet, n (%)	115 (99.1)	41 (100.0)	1.000
Statins, n (%)	112 (96.6)	38 (92.7)	0.326
Dapagliflozin, n (%)	84 (72.4)	31 (75.6)	0.691
Insulin, n (%)	42 (36.2)	18 (43.9)	0.383
ACEI/ARB, n (%)	76 (65.5)	25 (61.0)	0.602
β-Blockers, n (%)	101 (87.1)	34 (82.9)	0.511
Spironolactone, n (%)	12 (10.3)	6 (14.6)	0.469
Killip class, n (%)			0.768
I	106 (91.4)	36 (87.8)	
II	6 (5.2)	3 (7.3)	
III	1 (0.9)	0 (0.0)	
IV	3 (2.6)	2 (4.9)	
IRA, n (%)			
LCX	26 (22.4)	10 (24.4)	0.796
LAD	51 (44.0)	14 (34.1)	0.273
RCA	38 (32.8)	15 (36.6)	0.656
Others	1 (0.9)	2 (4.9)	0.167
Integral ECV, %	29.42 ± 6.25	32.73 ± 5.85	0.003
NMI-ECV, %	23.82 ± 5.18	26.06 ± 5.91	0.023
MI-ECV, %	45.37 ± 10.24	50.52 ± 10.49	0.007
GLS, %	13.79 ± 4.22	10.97 ± 4.27	<0.001
LVEF, %	46.71 ± 10.56	42.04 ± 11.01	0.017
LV-EDVi, mL/m^2	77.49 ± 17.83	78.27 ± 24.24	0.827
LV-ESVi, mL/m^2	43.73 ± 15.97	48.18 ± 20.53	0.158
MVO, n (%)	62 (53.4)	27 (65.9)	0.168
MVO%	0.21 (0, 3.19)	2.82 (0, 9.70)	0.007
LGE%	22.20 (15.25, 30.77)	31.34 (18.50, 42.20)	0.013

BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; GFR, glomerular filtration rate; ECV, extracellular volume; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LV, left ventricular; EDVi, end-diastolic volume index; LGE, late gadolinium enhanced; MVO, microvascular obstruction; ESVi, end-systolic volume index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left atrial diameter; LCX, left circumflex artery; RCA, right coronary artery; ACEI, angiotensin-converting-enzyme inhibitor; IRA, infarct-related artery; ARB, angiotensin II receptor blocker; HDL-C, high-density leptin cholesterol; LDL-C, low-density leptin cholesterol; Others, left main coronary artery and intermediate branch; hs-CRP, high sensitivity C-reactive protein; hs-TnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MI, myocardial infarction; NMI, non-myocardial infarction.

possible to the CMR scan time (12–15). However, this is still not an immediate HCT. It has been reported that HCT levels may even change within a few hours (12). Thus, these factors limit the applicability of ECV in routine clinical work. Recently, synthetic ECV without blood sampling has received considerable attention. The calculation of synthetic ECV is based on a linear relationship between the native R1 (1/T1) and HCT (16–19). In contrast to conventional HCT, synthetic HCT is measured during CMR scanning and is calculated from the R1 of LV blood. Thus, it somewhat avoids potential variability caused by differences in LV and peripheral venous blood or changes in body position and time that may affect conventional HCT measurements (32–34). Although some synthetic ECV models have been previously established and validated (16, 20–23), no relevant reports have been seen for diabetic patients. In this study, we established and validated the first synthetic ECV model containing only T2DM patients with AMI. Similar to previous studies, synthetic HCT was only moderately correlated with conventional HCT (16, 20, 21, 35, 36). However, the performance of synthetic ECV was favorable. The close correlation between synthetic ECV and conventional ECV may be attributed to the four additional terms (myocardial and ventricular blood R1 before and after contrast injection) that remained constant in the ECV calculations, and these constants

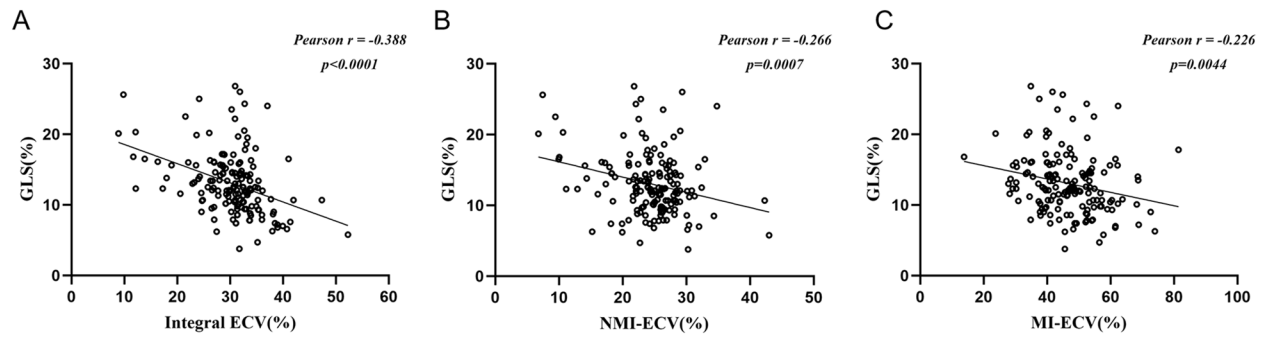


FIGURE 4
Pearson analysis between synthetic ECV and GLS. **(A)** Pearson analysis between GLS and synthetic ECV in the integral myocardium; **(b)** Pearson analysis between GLS and synthetic ECV in NMI; **(C)** Pearson analysis between GLS and synthetic ECV in MI. GLS, global longitudinal strain; NMI, non-myocardial infarction regions; MI, myocardial infarction regions; ECV, extracellular volume.

may have partially offset the greater variability in HCT. In contrast, the differences between HCT may be related to the following reasons. First, there is high variability in HCT itself as described above. Second, blood iron outside hemoglobin has been reported to have a substantial effect on T1 relaxation time, and the R1/HCT relationship may be broken in patients with iron overload, especially those with thalassemia (37). In addition, conventional HCT is measured in peripheral venous blood, whereas synthetic HCT is derived from the T1 relaxation time of left ventricular arterial blood. Differences between arterial and venous blood may also introduce interference. In our study, we successfully established and validated a synthetic ECV model in T2DM patients with AMI. Based on the unique value of ECV for myocardial fibrosis, the role of this "pragmatic" ECV in patient prognosis is equally attractive. However, given the characteristics of HCT, the synthesis of HCT and ECV needs to be repeatedly verified in different subpopulations.

Prognostic value of synthetic ECV in T2DM patients with AMI

Elevated ECV is associated with poor prognosis in previous diabetes cohorts and animal studies (11, 38). In our study, it was found that elevated synthetic ECV was an independent risk factor for MACE in T2DM patients with AMI, patients with high synthetic ECV had a significantly higher long-term risk of MACE. Although the exact mechanism of action is unknown, myocardial fibers may be an important cause. Specifically, myocardial fibrosis is one of the core mechanisms of myocardial remodeling and poor prognosis. In diabetic patients, myocardial fibrosis can be promoted through various pathways such as inflammation and oxidative stress. ECV, as a marker of myocardial fibrosis, may account for the findings of this study (38, 39). In addition, we found that GLS was also an independent risk factor for MACE in patients with AMI, and Integral ECV, NMI-ECV, and NMI-ECV were all significantly correlated with GLS, which quantifies systolic function by measuring LV deformation and is independent of geometric factors (40, 41). Even in the presence of normal LVEF, ECV, and GLS can detect LV disease and stratify risk (40, 42). Indeed, correlations between ECV and GLS have been demonstrated in other diseases (43, 44). These may also partly explain the results of the present study. In a previous study that included 47 patients with T2DM, high HbA1c was shown to be associated with increased ECV (45). In contrast, in a larger study, the association between HbA1c and ECV was not confirmed (31), which is consistent with our findings. The different results may be related to several reasons. First, sample size limitations may have led to some bias. In addition, the study populations were different. All T2DM patients in our study were combined with AMI, and it is known that myocardial necrosis is also an important factor in myocardial fibrosis. In another cohort that includes non-diabetic patients with AMI, ECV was also proven to be a powerful predictor of heart failure and all - cause mortality (46). Given the crucial role of myocardial fibrosis, it appears that ECV is closely associated with prognosis in both diabetic and non - diabetic AMI patients.

Role of NMI-ECV in T2DM patients with AMI

In recent years, myocardial fibrosis in non-infarcted regions has received increasing attention. In the early stages of AMI, myocardial necrosis and systemic inflammatory responses can cause collagen deposition and remodeling in non-infarcted regions (47, 48). In a mouse animal model, Tsuda et al. (49) found pathological evidence of myocardial fibrosis in the non-infarcted regions in the early stages of AMI. In clinical studies, it was also found that diffuse myocardial fibrosis could occur in non-infarcted myocardium in the early stages of AMI and that elevated NMI-ECV was associated with poor LV remodeling in the chronic phase (50, 51). Consistent with these findings, we found that elevated NMI-ECV was an independent risk factor for MACE in T2DM patients with AMI. However, it is

TABLE 3 Association of patient characteristics With MACE: univariate and multivariate analysis.

Variables	Univariate		Multivariate	
			Integral ECV (Model 1)	
	HR (95%CI)	P	HR (95%CI)	P
Age, years	1.02 (0.99 ~ 1.05)	0.173		
Female, n (%)	0.65 (0.25 ~ 1.65)	0.360		
BMI, kg/m^2	0.97 (0.88 ~ 1.07)	0.524		
Current smoker, n (%)	0.86 (0.46 ~ 1.62)	0.644		
Hypertension, n (%)	0.76 (0.41 ~ 1.44)	0.405		
Stroke, n (%)	0.49 (0.15 ~ 1.59)	0.235		
STEMI, n (%)	1.67 (0.76 ~ 3.66)	0.203		
SBP, mmHg	0.99 (0.97 ~ 1.00)	0.172		
DBP, mmHg	1.00 (0.97 ~ 1.02)	0.714		
Heart rate, bpm	1.00 (0.98 ~ 1.02)	0.764		
Total cholesterol, mmol/L	1.18 (0.87 ~ 1.61)	0.294		
Triglycerides, mmol/L	1.00 (0.78 ~ 1.27)	0.983		
HDL cholesterol, mmol/L	0.61 (0.15 ~ 2.42)	0.478		
LDL cholesterol, mmol/L	1.26 (0.90 ~ 1.78)	0.179		
HbA1c, %	1.04 (0.83 ~ 1.32)	0.726		
FBG, mmol/L	1.02 (0.93 ~ 1.11)	0.699		
eGFR, mL/min/1.73 m^2	0.99 (0.98 ~ 1.01)	0.524		
hs-CRP, mg/L	1.00 (0.99 ~ 1.01)	0.989		
hs-TnT, ng/L	1.62 (1.18 ~ 2.23)	0.003	1.57 (1.14 ~ 2.16)	0.006
NT-proBNP, pg/mL	1.41 (1.04 ~ 1.91)	0.028		
Statins, n (%)	0.62 (0.19 ~ 2.01)	0.427		
Dapagliflozin, n (%)	1.07 (0.52 ~ 2.20)	0.846		
Insulin, n (%)	1.38 (0.67 ~ 2.84)	0.384		
ACEI/ARB, n (%)	0.92 (0.48 ~ 1.75)	0.800		
β-Blockers, n (%)	0.98 (0.41 ~ 2.33)	0.959		
Spironolactone, n (%)	1.37 (0.58 ~ 3.27)	0.474		
Killip ≥2, n (%)	1.47 (0.47 ~ 4.60)	0.505		
IRA-LCX, n (%)	0.95 (0.45 ~ 2.00)	0.898		
IRA-LAD, n (%)	0.73 (0.38 ~ 1.41)	0.351		
IRA-RCA, n (%)	1.23 (0.65 ~ 2.34)	0.525		
Integral ECV, %	1.11 (1.05 ~ 1.18)	<0.001	1.07 (1.01 ~ 1.13)	0.023
NMI-ECV, %	1.10 (1.03 ~ 1.18)	0.007	Not in model	
MI-ECV, %	1.04 (1.02 ~ 1.07)	0.002	Not in model	
GLS, %	0.84 (0.77 ~ 0.92)	<0.001	0.90 (0.81 ~ 0.99)	0.033
LVEF, %	0.97 (0.94 ~ 0.99)	0.025		
LV-EDVi, mL/m^2	1.00 (0.99 ~ 1.02)	0.662		

(Continued)

TABLE 3 Continued

Variables	Univariate		Multivariate	
			Integral ECV (Model 1)	
	HR (95%CI)	P	HR (95%CI)	P
LV-ESVi, mL/m^2	1.01 (1.00 ~ 1.03)	0.137		
MVO, n (%)	1.33 (0.69 ~ 2.55)	0.390		
MVO%	1.08 (1.03 ~ 1.13)	0.002	1.06 (1.01 ~ 1.11)	0.023
LGE%	1.02 (1.01 ~ 1.04)	0.024		

BMI, body mass index; GFR, glomerular filtration rate; STEMI, ST-segment elevation myocardial infarction; ECV, extracellular volume; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LV, left ventricular; EDVi, end-diastolic volume index; LGE, late gadolinium enhanced; MVO, microvascular obstruction; ESVi, end-systolic volume index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left atrial diameter; LCX, left circumflex artery; RCA, right coronary artery; ACEI, angiotensin-converting-enzyme inhibitor; IRA, infarct-related artery; ARB, angiotensin II receptor blocker; HDL-C, high-density leptin cholesterol; LDL-C, low-density leptin cholesterol; Others, left main coronary artery and intermediate branch; hs-CRP, high sensitivity C-reactive protein; hs-TnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MI, myocardial infarction; NMI, non-myocardial infarction.

TABLE 4 Association of patient characteristics with MACE: multivariate analysis.

Variables	NMI-ECV (Model 2)		MI-ECV (Model 3)	
	HR (95%CI)	P	HR (95%CI)	P
hs-TnT, ng/L	1.57 (1.14 ~ 2.15)	0.006	1.56 (1.13 ~ 2.15)	0.007
NT-proBNP, pg/mL				
Integral ECV, %	Not in model		Not in model	
NMI-ECV, %	1.07 (1.00 ~ 1.14)	0.039	Not in model	
MI-ECV, %	Not in model		1.03 (1.00 ~ 1.07)	0.024
GLS%	0.88 (0.80 ~ 0.97)	0.009	0.86 (0.78 ~ 0.94)	0.001
LVEF, %				
MVO%	1.07 (1.01 ~ 1.12)	0.013		
LGE%				

ECV, extracellular volume; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LGE, late gadolinium enhanced; MVO, microvascular obstruction; hs-TnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MI, myocardial infarction; NMI, non-myocardial infarction.

TABLE 5 ROC of parameters for MACE.

Variables	AUC	95%CI	P	Cut-off	Sensitivity	Specificity
GLS	0.702	0.604 ~ 0.801	<0.001	11.45	0.390	0.716
MVO	0.637	0.530 ~ 0.744	0.009	1.91	0.585	0.707
hs-TnT	0.659	0.565 ~ 0.753	0.002	2450.5	0.780	0.509
Integral ECV	0.633	0.533 ~ 0.733	0.011	33.16	0.439	0.793
NMI-ECV	0.562	0.455 ~ 0.670	0.236	30.16	0.244	0.966
MI-ECV	0.639	0.537 ~ 0.741	0.008	48.18	0.610	0.655

GLS, global longitudinal strain; MVO, microvascular obstruction; hs-TnT, high sensitivity troponin T; MI, myocardial infarction; NMI, non-myocardial myocardial infarction.

noteworthy that in the ROC analysis, the results showed no statistical significance between NMI-ECV and MACE. Indeed, the prognosis value of myocardial fibrosis in the non-infarcted regions is inadequate and controversial for the prognosis of patients. In a previous study, Marijianowski et al. (52) found that myocardial fibrosis in non-infarct regions was not associated with LV remodeling after MI in patients with end-stage heart failure. Therefore, the prognostic value of NMI-ECV in T2DM patients with AMI may be worth further investigation.

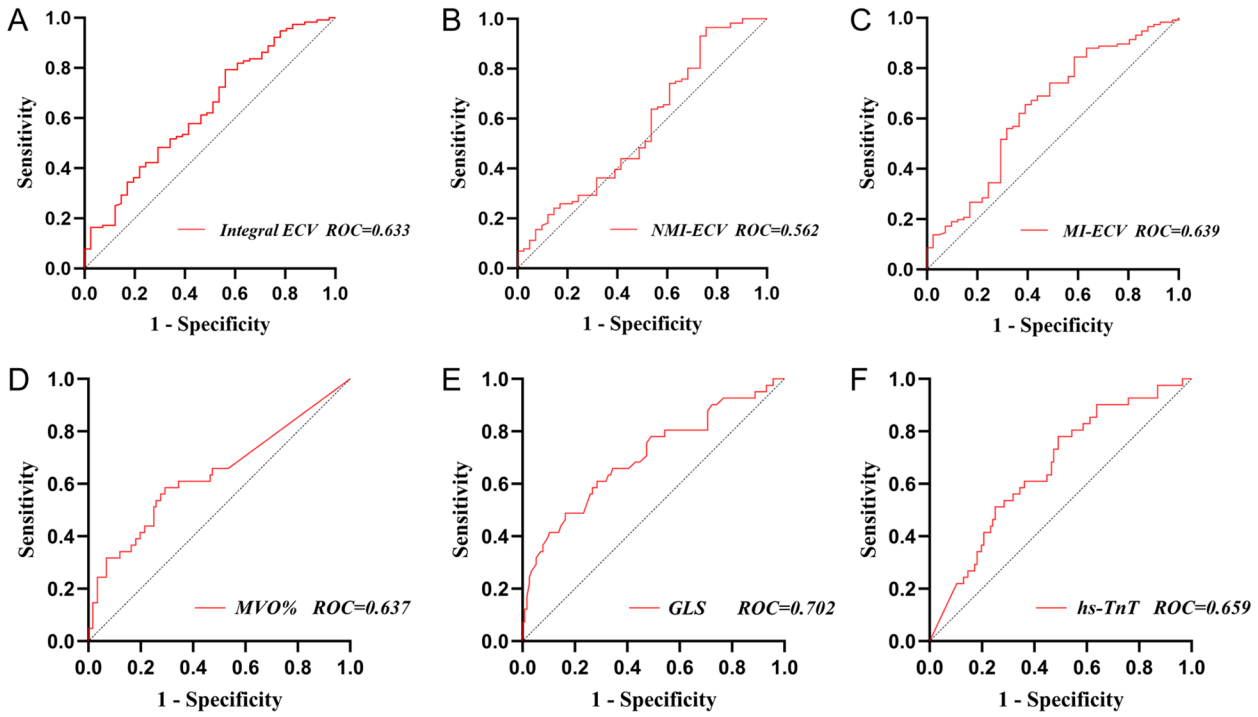


FIGURE 5
Receiver operating characteristic analysis of synthetic ECV for MACE. **(A)** ROC analysis of synthetic Integral ECV for MACE; **(B)** ROC analysis of synthetic NMI-ECV for MACE; **(C)** ROC analysis of synthetic MI-ECV for MACE; **(D)** ROC analysis of MVO for MACE; **(E)** ROC analysis of GLS for MACE; **(F)** ROC analysis of hs-TnT for MACE. GLS, global longitudinal strain; NMI, non-myocardial infarction regions; MI, myocardial infarction regions; ECV, extracellular volume; MVO, microvascular obstruction; hs-TnT, high sensitivity troponin T; MACE, major adverse cardiovascular events; ROC, receiver operating characteristic analysis.

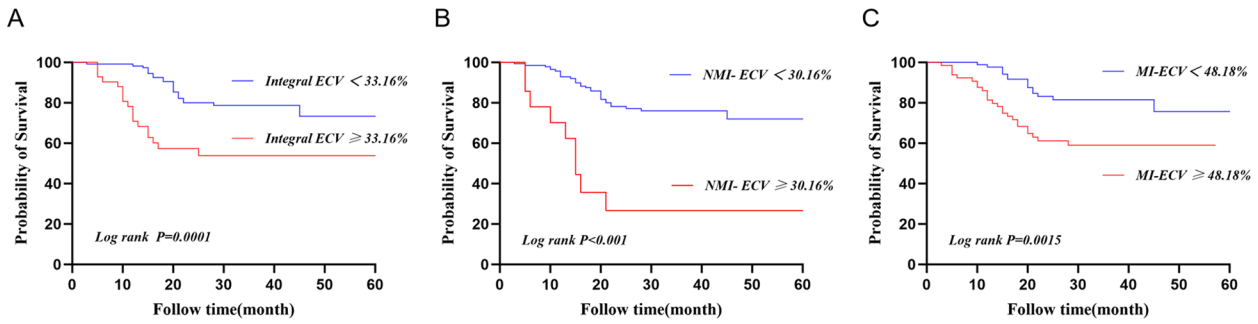


FIGURE 6
Kaplan-Meier curve for patients based on the cut-off values of synthetic ECV. **(A)** Kaplan-Meier curve of synthetic Integral ECV for MACE; **(B)** KaplanMeier curve of synthebtic NMI-ECV for MACE; **(C)** Kaplan-Meier curve of synthetic MI-ECV for MACE. ECV, extracellular volume; MACE, major adverse cardiovascular events.

Clinical implications

One of the major advantages of synthetic ECV is that it provides CMR laboratories with the convenience of ECV measurement without the blood samples. In addition, this study emphasizes the prognostic importance of synthetic ECV (including Integral ECV, NMI-ECV, and MI-ECV) in T2DM patients with AMI. These findings increase the potential of ECV in routine clinical CMR, which could facilitate the widespread use of CMR-ECV. Certainly, there are some potential barriers to implementing synthetic ECV in routine clinical practice. For instance, differences in CMR protocols among various institutions, cost concerns, or a lack of technical expertise.

Limitations

First, the single-center, retrospective design limits generalizability. There is a potential selection bias due to exclusion of patients with poor imaging or severe comorbidities. Second, in our study, there is a lack of histopathological validation for ECV, especially considering the known heterogeneity of myocardial fibrosis in diabetic patients. Third, the sample size of this study is limited, and the follow-up time is relatively short. Longer-term data will strengthen the claims regarding prognosis. Fourth, there is high variability in HCT, so further studies after matching for age, BMI, and gender are expected. Fifth, our study included patients with AMI combined with T2DM, so some of the results may need to be replicated and validated in other diseases.

Conclusions

Synthetic ECV is strongly consistent and correlated with conventional ECV in T2DM patients with AMI. Elevated synthetic ECV is an independent risk factor for MACE in T2DM patients with AMI.

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 humans were approved by The Institutional Review Board (IRB) of the Affiliated Hospital of Xuzhou Medical University approved this study protocol. The studies were conducted in accordance with the local legislation and institutional requirements. The requirement for signed written consent was waived owing to the no risk to the patient in accordance with the relevant IRB regulatory guidelines.

Author contributions

LC: Writing – original draft, Writing – review & editing. BQ: Writing – original draft. XD: Writing – original draft. JL: Writing – original draft. WLC: Writing – review & editing. WSC: Writing – original draft. YL: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (Grant No.2024ZD0524000).

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1534236/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Workflow.

SUPPLEMENTARY FIGURE 2
Measurement of ECV. **(A)** Native T1 map; **(B)** Enhanced T1 map; **(C)** Generate ECV images; **(D)** The distribution coefficient λ generates the image; Red circle marks the endocardium, green circle marks the epicardium, ROI (yellow) marks the blood pool, ROI (pink) marks the non-myocardial infarction sites, ROI (blue) marks the myocardial infarction site.

SUPPLEMENTARY FIGURE 3
Linear regression analysis between hematocrit (HCT) and blood pool T1.

SUPPLEMENTARY FIGURE 4
Pearson analysis between synthetic ECV and HbA1c. NMI, non-myocardial infarction regions; MI, myocardial infarction regions; ECV, extracellular volume.

References

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes [published correction appears in Eur Heart J. 2024 Apr 1;45(13):1145. doi: 10.1093/eurheartj/ehad870. *Eur Heart J.* (2023) 44:3720–826. doi: 10.1093/eurheartj/ehad191

2. Arnold SV, Spertus JA, Jones PG, McGuire DK, Lipska KJ, Xu Y, et al. Predicting adverse outcomes after myocardial infarction among patients with diabetes mellitus. *Circ Cardiovasc Qual Outcomes*. (2016) 9:372–9. doi: 10.1161/CIRCOUTCOMES.115.002365

3. Divakaran S, Singh A, Biery D, Yang J, DeFilippis EM, Collins BL, et al. Diabetes is associated with worse long-term outcomes in young adults after myocardial infarction: the partners YOUNG-MI registry. *Diabetes Care*. (2020) 43:1843–50. doi: 10.2337/dc19-0998

4. Biernacka A, Cavalera M, Wang J, Russo I, Shinde A, Kong P, et al. Smad3 signaling promotes fibrosis while preserving cardiac and aortic geometry in obese diabetic mice. *Circ Heart Fail*. (2015) 8:788–98. doi: 10.1161/CIRCHEARTFAILURE.114.001963

5. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol*. (1972) 30:595–602. doi: 10.1016/0002-9149(72)90595-4

6. Lundbaek K. Diabetic angiopathy: a specific vascular disease. *Lancet*. (1954) 266:377–9. doi: 10.1016/s0140-6736(54)90924-1

7. Connelly KA, Sarak B. Diabetes and myocardial fibrosis: is CMR the force leading to the rise of "Scar wars"? *JACC Cardiovasc Imaging*. (2022) 15:809–11. doi: 10.1016/j.jcmg.2022.01.015

8. Kramer CM, Chandrashekhar Y, Narula J. T1 mapping by CMR in cardiomyopathy: a noninvasive myocardial biopsy? *JACC Cardiovasc Imaging*. (2013) 6:532–4. doi: 10.1016/j.jcmg.2013.02.002

9. Fontana M, White SK, Banypersad SM, Sado DM, Maestrini V, Flett AS, et al. Comparison of T1 mapping techniques for ECV quantification. Histological validation and reproducibility of ShMOLLI versus multibreath-hold T1 quantification equilibrium contrast CMR. *J Cardiovasc Magn Reson*. (2012) 14:88. doi: 10.1186/1532-429X-14-88

10. Lurz JA, Luecke C, Lang D, Besler C, Rommel KP, Klingel K, et al. CMR-derived extracellular volume fraction as a marker for myocardial fibrosis: the importance of coexisting myocardial inflammation. *JACC Cardiovasc Imaging*. (2018) 11:38–45. doi: 10.1016/j.jcmg.2017.01.025

11. Wong TC, Piehler KM, Kang IA, Kadakkal A, Kellman P, Schwartzman DS, et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. *Eur Heart J*. (2014) 35:657–64. doi: 10.1093/eurheartj/eht193

12. Sennels HP, Jørgensen HL, Hansen AL, Goetze JP, Fahrenkrug J. Diurnal variation of hematology parameters in healthy young males: the Bispebjerg study of diurnal variations. *Scand J Clin Lab Invest*. (2011) 71:532–41. doi: 10.3109/00365513.2011.602422

13. Thirup P. Haematocrit: within-subject and seasonal variation. *Sports Med*. (2003) 33:231–43. doi: 10.2165/00007256-200333030-00005

14. Engblom H, Kanski M, Kopic S, Nordlund D, Xanthis CG, Jablonowski R, et al. Importance of standardizing timing of hematocrit measurement when using cardiovascular magnetic resonance to calculate myocardial extracellular volume (ECV) based on pre- and post-contrast T1 mapping. *J Cardiovasc Magn Reson*. (2018) 20:46. doi: 10.1186/s12968-018-0464-9

15. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI) [published correction appears in J Cardiovasc Magn Reson. 2018 Feb 7;20(1):9. doi: 10.1186/s12968-017-0408-9. . *J Cardiovasc Magn Reson*. (2017) 19:75. doi: 10.1186/s12968-017-0389-8

16. Chen W, Doeblin P, Al-Tabatabaee S, Klingel K, Tanacli R, Jakob Weiß K, et al. Synthetic extracellular volume in cardiac magnetic resonance without blood sampling: a reliable tool to replace conventional extracellular volume. *Circ Cardiovasc Imaging*. (2022) 15:e013745. doi: 10.1161/CIRCIMAGING.121.013745

17. Piechnik SK, Ferreira VM, Lewandowski AJ, Ntusi NA, Banerjee R, Holloway C, et al. Normal variation of magnetic resonance T1 relaxation times in the human population at 1.5 T using ShMOLLI. *J Cardiovasc Magn Reson*. (2013) 15:13. doi: 10.1186/1532-429X-15-13

18. Li W, Grgac K, Huang A, Yadav N, Qin Q, van Zijl PC. Quantitative theory for the longitudinal relaxation time of blood water. *Magn Reson Med*. (2016) 76:270–81. doi: 10.1002/mrm.25875

19. Spees WM, Yablonskiy DA, Oswood MC, Ackerman JJ. Water proton MR properties of human blood at 1.5 Tesla: magnetic susceptibility, T(1), T(2), T*(2), and non-Lorentzian signal behavior. *Magn Reson Med*. (2001) 45:533–42. doi: 10.1002/mrm.1072

20. Treibel TA, Fontana M, Maestrini V, Castelletti S, Rosmini S, Simpson J, et al. Automatic measurement of the myocardial interstitium: synthetic extracellular volume quantification without hematocrit sampling. *JACC Cardiovasc Imaging*. (2016) 9:54–63. doi: 10.1016/j.jcmg.2015.11.008

21. Fent GJ, Garg P, Foley JRJ, Swoboda PP, Dobson LE, Erhayiem B, et al. Synthetic myocardial extracellular volume fraction. *JACC Cardiovasc Imaging*. (2017) 10:1402–4. doi: 10.1016/j.jcmg.2016.12.007

22. Kammerlander AA, Duca F, Binder C, Aschauer S, Zotter-Tufaro C, Koschutnik M, et al. Extracellular volume quantification by cardiac magnetic resonance imaging without hematocrit sampling: Ready for prime time? *Wien Klin Wochenschr*. (2018) 130:190–6. doi: 10.1007/s00508-017-1267-y

23. Chen L, Zhang Z, Du X, Liu J, Liu Z, Chen W, et al. Establishment and validation of an extracellular volume model without blood sampling in ST-segment elevation myocardial infarction patients. *Eur Heart J Imaging Methods Pract*. (2024) 2:qyae053. doi: 10.1093/ehjimp/qyae053

24. Chen L, Zhang M, Chen W, Li Z, Wang Y, Liu D, et al. Cardiac MRI left atrial strain associated with new-onset atrial fibrillation in patients with ST-segment elevation myocardial infarction. *J Magn Reson Imaging*. (2023) 58:135–44. doi: 10.1002/jmri.28491

25. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. (2019) 40:237–69. doi: 10.1093/eurheartj/ehy462

26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in Eur Heart J. 2021 Dec 21;42(48):4901. doi: 10.1093/eurheartj/ehab670. . *Eur Heart J*. (2021) 42:3599–726. doi: 10.1093/eurheartj/ehab368

27. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol*. (2018) 71:1021–34. doi: 10.1016/j.jacc.2017.12.048

28. Gao Y, Xu HY, Guo YK, Wen XL, Shi R, Li Y, et al. Impact of myocardial scars on left ventricular deformation in type 2 diabetes mellitus after myocardial infarction by contrast-enhanced cardiac magnetic resonance. *Cardiovasc Diabetol*. (2021) 20:215. doi: 10.1186/s12933-021-01407-2

29. Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. *J Mol Cell Cardiol*. (2016) 90:84–93. doi: 10.1016/j.yjmcc.2015.12.011

30. Jin C, Weber J, Singh H, Gliganic K, Cao JJ. The association of reduced left ventricular strains with increased extracellular volume and their collective impact on clinical outcomes [published correction appears in J Cardiovasc Magn Reson. 2021 Nov 18;23(1):128. doi: 10.1186/s12968-021-00826-0. . *J Cardiovasc Magn Reson*. (2021) 23:93. doi: 10.1186/s12968-021-00776-7

31. Bojer AS, Sørensen MH, Gæde P, Madsen PL. Myocardial extracellular volume expansion in type 2 diabetes is associated with ischemic heart disease, autonomic neuropathy, and active smoking. *Diabetes Care*. (2022) 45:3032–9. doi: 10.2337/dc22-0942

32. Su MY, Huang YS, Niisato E, Chow K, Juang JJ, Wu CK, et al. Is a timely assessment of the hematocrit necessary for cardiovascular magnetic resonance-derived extracellular volume measurements? *J Cardiovasc Magn Reson*. (2020) 22:77. doi: 10.1186/s12968-020-00689-x

33. Jacob G, Raj SR, Ketch T, Pavlin B, Biaggioni I, Ertl AC, et al. Postural pseudoanemia: posture-dependent change in hematocrit. *Mayo Clin Proc*. (2005) 80:611–4. doi: 10.4065/80.5.611

34. Chen W, Faragli A, Goetze C, Zieschang V, Weiss KJ, Hashemi D, et al. Quantification of myocardial extracellular volume without blood sampling. *Eur Heart J Imaging Methods Pract*. (2023) 1:qyad022. doi: 10.1093/ehjimp/qyad022

35. Raucci FJ Jr, Parra DA, Christensen JT, Hernandez LE, Markham LW, Xu M, et al. Synthetic hematocrit derived from the longitudinal relaxation of blood can lead to clinically significant errors in measurement of extracellular volume fraction in pediatric and young adult patients. *J Cardiovasc Magn Reson*. (2017) 19:58. doi: 10.1186/s12968-017-0377-z

36. Lim EH, Le TT, Bryant J, Chung YC, Su B, Gan J, et al. Importance of sex-specific regression models to estimate synthetic hematocrit and extracellular volume fraction. *JACC Cardiovasc Imaging*. (2018) 11:1366–7. doi: 10.1016/j.jcmg.2017.11.035

37. Rosmini S, Bulluck H, Abdel-Gadir A, Treibel TA, Culotta V, Thompson R, et al. The effect of blood composition on T1 mapping. *JACC Cardiovasc Imaging*. (2019) 12:1888–90. doi: 10.1016/j.jcmg.2019.03.018

38. Shi C, Zhang H, Zhang N, Liu D, Fan Z, Sun Z, et al. The dynamic characteristics of myocardial contractility and extracellular volume in type 2 diabetes mellitus mice investigated by 7.0T cardiac magnetic resonance. *J Clin Med*. (2022) 11:4262. doi: 10.3390/jcm11154262

39. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. *Circulation*. (2016) 133:2459–502. doi: 10.1161/CIRCULATIONAHA.116.022194

40. Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL, et al. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. *Eur J Heart Fail*. (2014) 16:1301–9. doi: 10.1002/ejhf.154

41. Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, et al. Geometry as a confounder when assessing ventricular systolic function: comparison between ejection fraction and strain. *J Am Coll Cardiol*. (2017) 70:942–54. doi: 10.1016/j.jacc.2017.06.046

42. Schelbert EB, Sabbah HN, Butler J, Gheorghiade M. Employing extracellular volume cardiovascular magnetic resonance measures of myocardial fibrosis to foster novel therapeutics. *Circ Cardiovasc Imaging*. (2017) 10:e005619. doi: 10.1161/CIRCIMAGING.116.005619

43. Bojer AS, Sørensen MH, Madsen SH, Broadbent DA, Plein S, Gæde P, et al. The independent association of myocardial extracellular volume and myocardial blood flow

with cardiac diastolic function in patients with type 2 diabetes: a prospective cross-sectional cohort study. *Cardiovasc Diabetol*. (2023) 22:78. doi: 10.1186/s12933-023-01804-9

44. Fröjdh F, Fridman Y, Bering P, Sayeed A, Maanja M, Niklasson L, et al. Extracellular volume and global longitudinal strain both associate with outcomes but correlate minimally. *JACC Cardiovasc Imaging*. (2020) 13:2343–54. doi: 10.1016/j.jcmg.2020.04.026

45. Al-Badri A, Hashmath Z, Oldland GH, Miller R, Javaid K, Syed AA, et al. Poor glycemic control is associated with increased extracellular volume fraction in diabetes. *Diabetes Care*. (2018) 41:2019–25. doi: 10.2337/dc18-0324

46. Black N, Bradley J, Schelbert EB, Bonnett LJ, Lewis GA, Lagan J, et al. Remote myocardial fibrosis predicts adverse outcome in patients with myocardial infarction on clinical cardiovascular magnetic resonance imaging. *J Cardiovasc Magn Reson*. (2024) 26:101064. doi: 10.1016/j.jocmr.2024.101064

47. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. *J Cardiovasc Magn Reson*. (2013) 15:91. doi: 10.1186/1532-429X-15-91

48. Moon JC, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M, et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson*. (2013) 15:92. doi: 10.1186/1532-429X-15-92

49. Tsuda T, Gao E, Evangelisti L, Markova D, Ma X, Chu ML. Post-ischemic myocardial fibrosis occurs independent of hemodynamic changes. *Cardiovasc Res*. (2003) 59:926–33. doi: 10.1016/s0008-6363(03)00519-4

50. Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, et al. Automated extracellular volume fraction mapping provides insights into the pathophysiology of left ventricular remodeling post-reperfused ST-elevation myocardial infarction. *J Am Heart Assoc*. (2016) 5:e003555. doi: 10.1161/JAHA.116.003555

51. Carrick D, Haig C, Rauhalammi S, Ahmed N, Mordi I, McEntegart M, et al. Pathophysiology of LV remodeling in survivors of STEMI: inflammation, remote myocardium, and prognosis. *JACC Cardiovasc Imaging*. (2015) 8:779–89. doi: 10.1016/j.jcmg.2015.03.007

52. Marijianowski MM, Teeling P, Becker AE. Remodeling after myocardial infarction in humans is not associated with interstitial fibrosis of noninfarcted myocardium. *J Am Coll Cardiol*. (1997) 30:76–82. doi: 10.1016/s0735-1097(97)00100-9

frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 07 July 2025
DOI 10.3389/fendo.2025.1605746

Check for updates

OPEN ACCESS

EDITED BY
Tatsuya Sato,
Sapporo Medical University, Japan

REVIEWED BY
Nina Japundzic-Zigon,
University of Belgrade, Serbia
Jennifer E. Richard,
University of Gothenburg, Sweden

*CORRESPONDENCE
Juan S. Izquierdo-Condoy
juan1izquierdo11@gmail.com

RECEIVED 03 April 2025
ACCEPTED 20 June 2025
PUBLISHED 07 July 2025
CORRECTED 15 August 2025

CITATION
Aristizábal-Colorado D, Corredor-Rengifo D, Sierra-Castillo S, López-Corredor C, Vernaza-Trujillo D-A, Weir-Restrepo D, Izquierdo-Condoy JS, Ortiz-Prado E, Rico-Fontalvo J, Gómez-Mesa J-E, Abreu-Lomba A and Rivera-Martínez W-A (2025) A decade of progress in type 2 diabetes and cardiovascular disease: advances in SGLT2 inhibitors and GLP-1 receptor agonists – a comprehensive review. *Front. Endocrinol.* 16:1605746. doi: 10.3389/fendo.2025.1605746

COPYRIGHT
© 2025 Aristizábal-Colorado, Corredor-Rengifo, Sierra-Castillo, López-Corredor, Vernaza-Trujillo, Weir-Restrepo, Izquierdo-Condoy, Ortiz-Prado, Rico-Fontalvo, Gómez-Mesa, Abreu-Lomba and Rivera-Martínez. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A decade of progress in type 2 diabetes and cardiovascular disease: advances in SGLT2 inhibitors and GLP-1 receptor agonists – a comprehensive review

David Aristizábal-Colorado[1,2], David Corredor-Rengifo[1,2], Santiago Sierra-Castillo[3], Carolina López-Corredor[4], David-Alexander Vernaza-Trujillo[2,5,6], Danilo Weir-Restrepo[7], Juan S. Izquierdo-Condoy[8]*, Esteban Ortiz-Prado[8], Jorge Rico-Fontalvo[9,10], Juan-Esteban Gómez-Mesa[11,12], Alin Abreu-Lomba[13] and Wilfredo-Antonio Rivera-Martínez[2,14]

[1]Internal Medicine Department, Universidad Libre, Cali, Colombia, [2]Grupo Interinstitucional de Medicina Interna (GIMI1), Universidad Libre, Cali, Colombia, [3]Epidemiology Department, Universidad Centros de Estudios en Salud (CES), Medellín, Colombia, [4]Medicine Program, Universidad Santiago de Cali, Cali, Colombia, [5]Department of Public Health, Pontificia Universidad Javeriana, Cali, Colombia, [6]Clinical Research Center, Clínica Imbanaco, Cali, Colombia, [7]Internal Medicine Department, Universidad Centros de Estudios en Salud (CES), Medellin, Colombia, [8]One Health Research Group, Universidad de las Américas, Quito, Ecuador, [9]Department of Nephrology, Faculty of Medicine, Universidad Simón Bolívar, Barranquilla, Colombia, [10]Latin American Society of Nephrology and Arterial Hypertension (SLANH), Ciudad de Panama, Panama, [11]Cardiology Department, Fundación Valle del Lili, Cali, Colombia, [12]Department of Health Sciences, Universidad Icesi, Cali, Colombia, [13]Endocrinology Department, Clínica Imbanaco, Cali, Colombia, [14]Endocrinology Department, Universidad de Antioquia, Medellín, Colombia

Cardiovascular and renal complications remain leading causes of morbidity and mortality among individuals with type 2 diabetes mellitus (T2DM). Since 2015, large-scale cardiovascular outcome trials (CVOTs) have demonstrated that sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) significantly reduce the risk of major adverse cardiovascular events, cardiovascular mortality, and heart failure hospitalization in patients with T2DM and established cardiovascular disease or high-risk profiles. These findings—originating from landmark trials such as EMPA-REG OUTCOME, LEADER, and SUSTAIN-6—have led to substantial revisions in international guidelines from the European Society of Cardiology, American College of Cardiology, and American Heart Association, which now recommend the use of SGLT2i or GLP-1 RAs, often in conjunction with metformin. SGLT2i have shown robust effects in reducing heart failure hospitalization and slowing the progression of chronic kidney disease, while GLP-1 RAs have demonstrated superior efficacy in reducing atherothrombotic events, particularly non-fatal stroke. Additionally, emerging data supports the complementary use of both drug classes, revealing additive benefits on cardiovascular and renal outcomes without increased toxicity. This narrative

review summarizes the mechanisms of action, clinical efficacy, safety profiles, and sex-specific outcomes associated with SGLT2i and GLP-1 RAs. It also highlights key evidence supporting their combined use and underscores their critical role in optimizing long-term outcomes in patients with T2DM and cardiovascular disease.

KEYWORDS

cardiovascular outcomes, SGLT2 inhibitors, GLP-1 agonists, combination therapy, heart failure, renal outcomes

1 Introduction

Cardiovascular disease (CVD) continues to be a significant global health concern, with ischemic stroke and acute myocardial infarction ranking as the second and third leading causes of death worldwide in 2019 (1). In 2020, an estimated 523 million people were affected by CVD, resulting in approximately 19 million deaths —an 18.7% increase compared to 2010 (2). In parallel, type 2 diabetes mellitus (T2DM) continues to rise, with 536.6 million individuals affected globally in 2021. This figure is projected to increase to 783.2 million by 2045 (3). The CALIBER UK study highlights that peripheral arterial disease (16.2%), heart failure, stable angina, non-fatal myocardial infarction, and cerebrovascular accidents are common cardiovascular complications in T2DM patients after 5.5 years of follow-up (4).

The complex interaction between diabetes mellitus (DM) and cardiovascular events complicates patient management. Individuals with T2DM frequently have multiple cardiovascular risk factors, including obesity (32.9%), hypertension (32-80%), and dyslipidemia (39%) (5–8). Moreover, factors such as oxidative stress, hypercoagulability, endothelial dysfunction, and autonomic neuropathy contribute significantly to CVD risk in T2DM patients (5).

The association between glycemic control and cardiovascular outcomes in DM patients has been long studied (9–11). However, recent evidence shows conflicting results regarding the benefits of strict glycemic control on reducing cardiovascular events. Although stringent glycemic targets (HbA1c ≤ 6.5%) may yield benefits on microvascular complications, their impact on cardiovascular mortality remains uncertain (12, 13). Moreover, pursuing overly strict control may increase the risk of hypoglycemia, weight gain, and all-cause mortality (14, 15).

To address these challenges, novel pharmacological therapies such as sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged, offering cardioprotective benefits (16, 17). These agents have been shown to reduce cardiovascular mortality, slow chronic kidney disease (CKD) progression, and decrease heart failure (HF) hospitalizations (17–19). Leading clinical guidelines now recommend the combined or monotherapy use of SGLT-2i and GLP-1 RAs in patients with T2DM and CVD or those at high cardiovascular risk (20, 21).

The aim of this review is to enhance our understanding of the role of SGLT-2i and GLP-1 RAs in managing patients with T2DM and CVD. By highlighting key findings and clinical implications, this review aims to provide valuable information for healthcare professionals involved in the care of these patients.

2 Material and methods

This narrative literature review examines the use of SGLT-2 inhibitors and GLP-1 RAs in patients with T2DM and CVD. The review included a comprehensive search of peer-reviewed articles published between January 2010 and November 2024 conducted using the PubMed and Medline databases, supplemented by the inclusion of relevant studies from earlier periods when clinically justified. Articles were primarily selected based on clinical relevance and their inclusion in current international guidelines for the management of patients with CVD and T2DM. The search strategy incorporated the following Boolean logic; (SGLT-2 inhibitors) AND (GLP-1 receptor agonists) AND (type 2 diabetes mellitus) AND (cardiovascular diseases).

The review process comprised three distinct stages:

1. An exhaustive search of documentary material using PubMed and Medline databases.
2. Classification and selection of the most relevant articles based on predefined evaluation criteria.
3. Detailed analysis and synthesis of the extracted data.

The initial search yielded 564 articles. Inclusion criteria were studies involving adult patients (≥18 years) with T2DM and CVD; evaluation of SGLT-2 inhibitors or GLP-1 receptor agonists; and reporting of cardiovascular or renal outcomes. Eligible study designs included randomized controlled trials, observational studies (cohort or case-control), systematic reviews, and meta-analyses. Only peer-reviewed, indexed publications were considered. Data extraction and review were independently conducted by three authors (DAC, DCR, and SSC) using a standardized data collection form. A total of 407 records were excluded based on title and abstract screening, and 113 full-text articles were assessed for eligibility. The final manuscript was

reviewed by experts in endocrinology, nephrology, and cardiology, who provided critical feedback and ensured comprehensive bibliographic coverage.

3 Results

3.1 Mechanism of action and clinical impact

3.1.1 Mechanism of action of SGLT2 inhibitors

Phlorizin, a botanical extract, is a non-specific inhibitor of sodium-glucose transporter proteins. Its discovery traces back over 150 years to research on glucosuria (22). Since then, various types of SGLT proteins have been identified. SGLT2i, in particular, target the sodium-glucose cotransporter 2, which is primarily located in the proximal tubular epithelium. This protein is responsible for roughly 90% of renal glucose reabsorption, and by inhibiting it, SGLT2i effectively disrupt this reabsorption process (23).

By blocking sodium-glucose cotransporter 2 in the S1 and S2 segments of the proximal tubule, SGLT2i significantly reduce glucose reabsorption, promoting urinary glucose excretion. This creates a state of "relative hypoglycemia," which has several beneficial effects, including reductions in both systolic and diastolic blood pressure through decreased circulating volume and improved glomerular hyperfiltration control. Additionally, SGLT2i can lower HbA1c levels by 0.5-1.0% and support weight loss (24, 25). Increased natriuresis and sodium delivery to the distal nephron, induced by SGLT2 inhibition, are key in renal protection, normalizing the tubuloglomerular feedback mechanism, a principal driver of hyperfiltration (17, 19, 25).

Studies have indicated that increased expression of the sodium-hydrogen exchanger isoform 1 (NHE-1) is linked to heart failure and may contribute to the development of hypertrophy and cardiac injury during ischemia and reperfusion (26, 27). SGLT2i have been shown to reduce myocardial fibrosis, a critical factor in heart failure progression. Additionally, they may promote the use of ketone bodies as an alternative energy source for the myocardium, potentially reducing the production of reactive oxygen species (ROS) (24, 26).

Of note, long-term use of SGLT2i may lead to a reduction in glycosuric efficacy, without a corresponding decline in cardiovascular benefits. This phenomenon is thought to result from compensatory mechanisms, such as increased SGLT1 activity and upregulation of SGLT2 expression. These findings support the rationale for dual SGLT1/SGLT2 inhibition as a potential therapeutic strategy (28–30).

3.2 Complications and side effects of SGLT2 inhibitors

The most common side effect of SGLT-2 inhibitors is polyuria, resulting from osmotic diuresis. Genital tract infections, affecting approximately 10-15% of women and less frequently in men, are another potential adverse effect (31, 32). Euglycemic diabetic ketoacidosis (euDKA), a rare but serious complication, has been primarily reported in patients with type 1 diabetes and may be precipitated by acute illnesses, inappropriate insulin dose reductions, or omissions (31).

Skin infections, such as Fournier's gangrene, have been reported; their association with SGLT-2 inhibitors requires further confirmation through large, randomized trials (31). Genital fungal infections are up to four times more common in patients using SGLT-2 inhibitors (31, 32). The results of the CANVAS study showed a possible increased risk of amputations; however, neither this result nor the increased risk of fractures has been documented in other clinical trials of canagliflozin or other SGLT2 inhibitors, so further studies are required to establish a definitive link (32–35).

SGLT2 inhibitors should be discontinued in specific clinical scenarios to mitigate potential adverse events. Severe or recurrent genital mycotic infections and urinary tract infections warrant treatment suspension if they become problematic (36, 37). Patients presenting with euglycemic diabetic ketoacidosis require immediate cessation of SGLT2i therapy (36). Furthermore, it is recommended that SGLT2 inhibitors be discontinued during the perioperative period due to the risk of euDKA. This risk increases during the physiological stress associated with surgery and preoperative fasting, which can precipitate euDKA even in the absence of significant hyperglycemia. Additionally, treatment should be halted in elderly or frail individuals experiencing severe dehydration or orthostatic hypotension (36, 38).

Canagliflozin specifically should be discontinued in patients with a heightened risk of amputations, including those with a history of amputations, severe peripheral neuropathy, severe peripheral arterial disease, or active lower-limb ulcers or infections, as well as in individuals with an increased fracture risk, particularly those with previous osteoporotic fractures (34, 36, 37, 39). Although SGLT2 inhibitors do not typically increase the risk of AKI, their use should be halted during episodes of acute renal impairment (39). Although rare, cases of Fournier's gangrene also necessitate immediate discontinuation of SGLT2 inhibitors to prevent further complications.

3.3 Mechanism of action of GLP1 receptor agonists

GLP-1 is a hormone belonging to the incretins that is produced in the gastrointestinal tract, by L cells, in response to the intake of nutrients, especially fat and glucose (40). Its release stimulates an increase in insulin secretion when stimulated by glucose at sufficient plasma levels (40). The effects of GLP-1 are not limited to the endocrinological component; there are receptors for these at the brain, liver, and gastrointestinal tract (41). It can influence renal function by increasing diuresis and natriuresis, and it can impact cardiac function by enhancing contractility and promoting cardiomyocyte survival. Additionally, GLP-1 can improve muscle

insulin sensitivity and glucose uptake (42). These effects, including hemodynamic, metabolic, and anti-inflammatory actions, contribute to the cardio and renoprotective properties of GLP-1 RAs. By reducing intraglomerular pressure, decreasing inflammation, and mitigating oxidative stress, GLP-1 RAs can help preserve renal function, independent of glycemic control (43).

GLP-1 RAs like liraglutide and semaglutide, offer a therapeutic advantage over native GLP-1 by being resistant to degradation by dipeptidyl peptidase-4 (DPP-4). This resistance allows for prolonged exposure to GLP-1, resulting in sustained physiological effects. By activating GLP-1 receptors in the hypothalamus and brainstem, these analogs promote satiety, leading to reduced food intake and weight loss (40, 44).

Studies as Network Meta-analysis and clinical trials have shown that GLP1-RA can achieve a statistically significant decrease in HbA1C compared to placebo, as well as a weight reduction ranging between 1.3 and 8.65 kg (40, 45, 46). Furthermore, these analogues have the ability to stimulate natriuresis by inhibiting sodium reabsorption by decreasing the activity of sodium-hydrogen exchanger 3 (NHE3), resulting in a reduction in blood pressure in patients with diabetes (40, 46). In animal models, a modulatory effect has also been observed at the level of the carotid sinus, suggesting that this pharmacological class may influence sympathetic tone regulation during hyperglycemic states (47).

With regard to cardioprotection, several mechanisms have been proposed. GLP-1 RAs reduce macrophage adhesion to the endothelium, thereby inhibiting the formation of atherosclerotic plaques; they also suppress platelet activity, which may further contribute to cardiovascular protection (40). Moreover, these agents enhance cardiac glucose uptake and ATP production by increasing GLUT-1 translocation (40), and they modulate antioxidant, anti-inflammatory, and anti-apoptotic pathways (48).

3.4 Complications and side effects of GLP-1 RAs

Common side effects associated with GLP-1 receptor agonists (GLP-1 RAs) include gastrointestinal symptoms such as nausea (25–60%), diarrhea, and vomiting (5–15%) (16, 46). Although these adverse effects can be bothersome, they rarely lead to treatment discontinuation. Importantly, clinical trials have not demonstrated an increased risk of hypoglycemia with GLP-1 RAs compared to placebo (16). Less frequent side effects include injection site reactions, headaches, and nasopharyngitis (16).

While some studies have suggested a possible association between GLP-1 RAs and acute kidney injury (AKI), this has not been confirmed and appears to occur primarily in patients with underlying risk factors such as dehydration or severe gastrointestinal symptoms (49). Reports of preneoplastic pancreatic ductal disease exist, but experimental findings in mice have not been consistently replicated in human clinical trials. Although a potential association between GLP-1 RAs and gastrointestinal tumors has been proposed, current evidence does not support an increased risk of colorectal neoplasia (50).

GLP-1 RA therapy should be discontinued under specific clinical conditions to minimize risk. While a definitive causal relationship has not been established, the occurrence of acute pancreatitis necessitates immediate drug withdrawal, as recommended by the American Diabetes Association and the American College of Cardiology (37, 51). These agents are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, based on findings from preclinical studies (21).

Treatment cessation should also be considered in patients who develop gallbladder complications, such as acute cholecystitis. Caution and close monitoring are warranted in individuals with preexisting diabetic retinopathy, due to a higher incidence of retinopathy-related complications observed in clinical trials, particularly with semaglutide (21, 37). In rare instances, severe hypersensitivity reactions, including anaphylaxis, require immediate discontinuation of GLP-1 RA therapy (52). Additionally, although uncommon, reported cases of diabetic ketoacidosis (DKA) associated with GLP-1 RAs also warrant prompt treatment cessation (53).

4 Cardiovascular results

4.1 Evidence of SGLT2 inhibitors in patients with DM2

The management of DM requires a long-term perspective, emphasizing the importance of medication safety over time. The Food and Drug Administration (FDA) mandates that clinical trials demonstrate the cardiovascular safety of anti-diabetic medications. To assess this, randomized trials typically evaluate the primary outcome of "major adverse cardiovascular events" (MACE), which includes cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction (MI). This rigorous evaluation has led to the accelerated recognition of the cardioprotective, renoprotective, and vasoprotective effects of SGLT2i (54, 55) (Figure 1).

4.1.1 Cardiovascular outcomes in SGLT2 inhibitors: safety studies

The EMPA-REG OUTCOME trial, which included 7020 patients with T2DM, was the first to demonstrate the cardiovascular protective effects of empagliflozin (54, 56). Patients were randomized to receive empagliflozin 10 mg, 25 mg, or placebo. After 3.1 years of follow-up, the trial showed a significant 14% reduction in the relative risk (RR) of MACE. Secondary outcomes included a 38% reduction in hospitalizations for HF and a 32% reduction in all-cause mortality (56).

Subsequent trials, such as CANVAS and DECLARE-TIMI 58, have further confirmed the cardiovascular benefits of SGLT-2 inhibitors. CANVAS demonstrated a 14% reduction in MACE in patients with T2DM and a high cardiovascular risk (34). CANVAS demonstrated a 14% reduction in MACE in patients with T2DM and a high cardiovascular risk. DECLARE-TIMI 58, which included a larger population with a lower baseline risk of CVD, did not show a significant reduction in MACE overall but did demonstrate a 27%

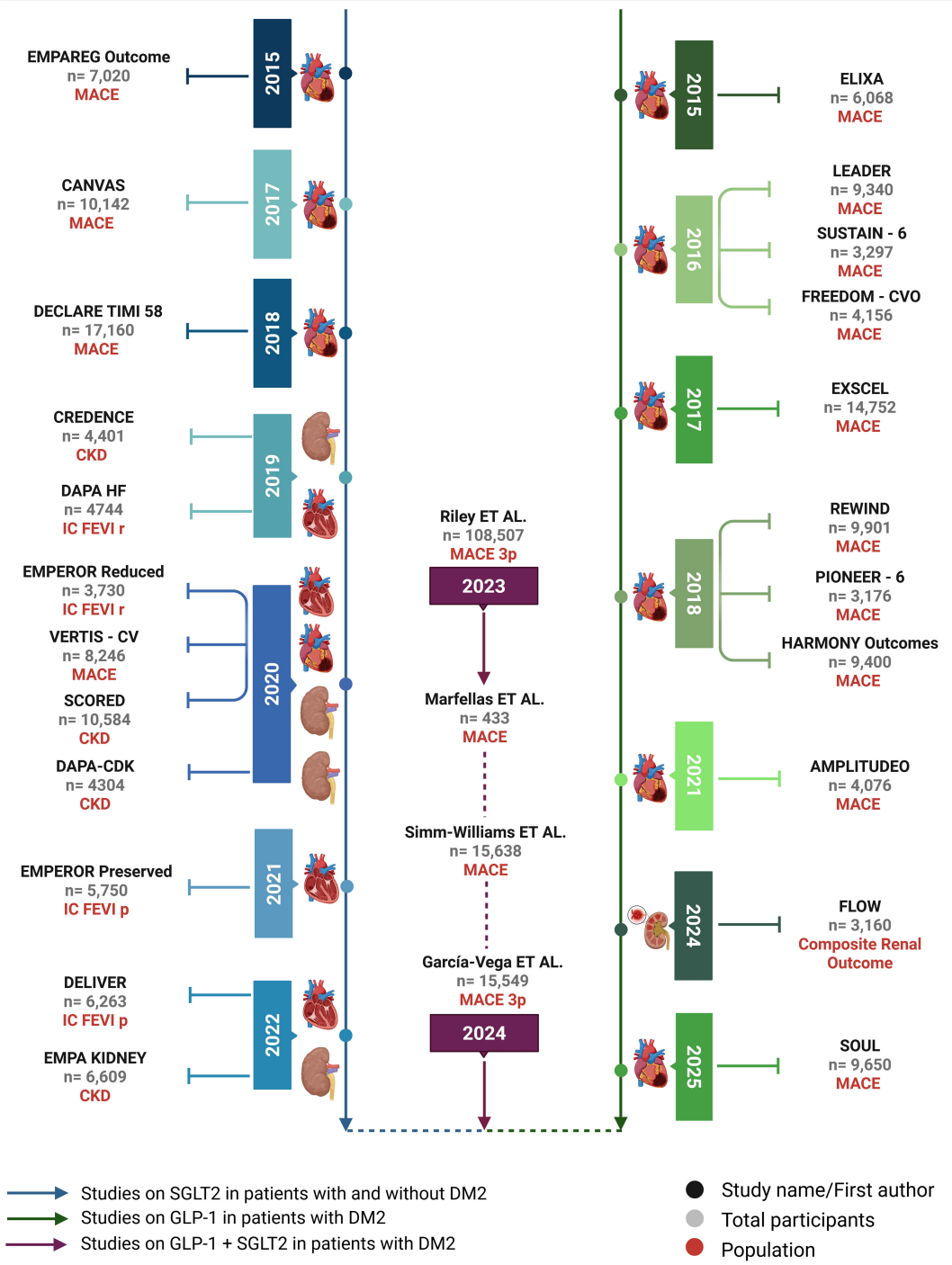


FIGURE 1
Timeline of major studies on SGLT-2i and GLP-1. The left axis displays key cardiovascular and renal outcome trials involving SGLT2 inhibitors, including studies in patients with and without T2DM. The right axis presents pivotal trials assessing GLP-1 receptor agonists in T2DM populations. The central column highlights observational studies and meta-analyses investigating the combined use of both drug classes. Study populations, primary outcomes (e.g., MACE, CKD, HF), and sample sizes are indicated for each trial.

reduction in hospitalizations for HF in a subgroup of patients with a history of myocardial infarction (54, 57). The explanation for the discrepancy in the reduction of MACE in patients treated with SGLT2i in DECLARE-TIMI 58 suggests that the benefits of SGLT2i may be more pronounced in patients with a higher risk of cardiovascular disease.

4.1.2 Cardiovascular results in studies aimed at CVD

The CREDENCE clinical trial evaluated the effects of canagliflozin (100 mg daily) versus placebo in 4,401 patients with T2DM and CKD. While primarily designed to assess renal

outcomes, the trial also demonstrated significant cardiovascular benefits. A 20% relative risk reduction in MACE, including myocardial infarction, stroke, and cardiovascular death and a 30% relative risk reduction in hospitalizations for HF (58).

The VERTIS trial, involving 8246 patients with T2DM, compared ertugliflozin 5 mg or 15 mg daily to placebo for 3.5 years. While ertugliflozin did not outperform placebo for MACE, it significantly reduced hospitalizations for HF by 30% (59).

The SCORED clinical study, which included 10,584 patients with T2DM and an estimated glomerular filtration rate (eGFR) of 25–60 ml/m²/1.73 m², evaluated the effects of sotagliflozin on cardiovascular death and hospitalization for HF. After 16 months, sotagliflozin demonstrated a significant reduction in the primary endpoint (HR: 0.74; 95% CI: 0.63 - 0.88; P<0.001) (60).

A meta-analysis of five double-blind placebo-controlled trials involving 46,969 patients showed that SGLT-2 inhibitors were associated with a 14% reduction in all-cause mortality and a 9% reduction in MACE. Hospitalizations for HF were also reduced by 31% compared to placebo. However, SGLT-2 inhibitors were associated with an increased risk of diabetic ketoacidosis (RR 2.59 CI95% 1.57, 4.27) and genital infections (RR 3.50 CI95% 3.09, 3.95) (17).

4.2 SGLT2i outcomes in patients with HF

The cardiovascular benefits of SGLT-2i are particularly evident in reducing the risk of hospitalization for HF, both in patients with and without T2DM. The DAPA-HF trial, which included 4744 patients with LVEF ≤40%, demonstrated a 26% reduction in the RR of hospitalization or emergency room visits for HF within 28 days of randomization (54, 61). The cardiovascular benefits of SGLT-2i are particularly evident in reducing the risk of hospitalization for HF, both in patients with and without T2DM. The DAPA-HF trial, which included 4744 patients with LVEF ≤40%, demonstrated a 26% reduction in the RR of hospitalization or emergency room visits for HF within 28 days of randomization. Furthermore, patients treated with dapagliflozin experienced a lower rate of cardiovascular death (9.6% vs. 11.5%), reflecting an 18% reduction in RR. In addition to these objective outcomes, the DAPA-HF study assessed quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and found a significant improvement in the dapagliflozin-treated group compared to placebo, indicating a positive impact on patient-reported symptoms (62).

The EMPEROR-REDUCED trial, which included 3730 patients with HF and a left ventricular ejection fraction (LVEF) ≤40%, demonstrated a 25% reduction in the RR of cardiovascular death and HF hospitalization with empagliflozin 10 mg daily compared to placebo; hospitalization from IC was reduced approximately 30% (RR 0,70; IC del 95%, 0,58 a 0,85; P <0,001). While empagliflozin did not significantly reduce all-cause mortality, it improved renal outcomes, with a slower decline in GFR compared to placebo (63). Regarding renal outcomes, the decline in GFR was slower in the empagliflozin group, with an estimated −0.55 ml per minute per 1.73 m², compared with placebo, which was −2.28 ml per minute per year. This led to a reduction in the incidence of the composite renal outcome, defined as chronic dialysis, kidney transplantation, and a sustained decline in GFR (63).

Another trial that evaluated the efficacy and safety of empagliflozin was EMPEROR-Preserved; it included 5,988 patients with heart failure with preserved left ventricular ejection fraction, regardless of whether the patients had T2DM. Participants were randomly assigned to receive empagliflozin 10 mg or placebo once daily. There was a reduction in the RR in the primary outcome (cardiovascular death and hospitalization for heart failure) (RR 0.79, 95% CI 0.69-0.90). Highlighting the decrease in hospitalization for HF (0.71; 95% CI 0.60-0.83). In this study, it was unclear whether these benefits were preserved in subgroups of patients with higher left ventricular ejection fraction (>60%), as the result was not statistically significant (RR 0.87; 95% CI; 0.69-1.10) (64). It is also unclear whether this benefit was retained in patients who started treatment during the subacute phase, or in patients with an improved LVEF (54, 64).

In the DELIVER trial, in which participants were randomly assigned to receive dapagliflozin 10 mg or placebo once daily, 6263 patients with HF with LVEF >40% were enrolled. A significant reduction in RR was observed in the primary outcomes, such as cardiovascular death or worsening of HF, compared with placebo in the overall population (RR 0.82, 95% CI 0.73 to 0.92). Worsening of HF in the group of patients receiving dapagliflozin was 23% lower. These results were consistent both in patients with LVEF of 60% or more and in those <60%. In addition, the results were similar in prespecified subgroups, including patients with or without diabetes (65).

The SOLOIST-WHF trial evaluated the efficacy and safety of sotagliflozin in 1,222 patients with HF who were recently hospitalized for worsening of their baseline condition. This study demonstrated a significant risk reduction in a composite of cardiovascular death and worsening of HF (RR 0.67; 95% CI 0.52 to 0.85). Regarding hospitalizations and emergency department visits, the decrease in RR was 36%. These results were independent of LVEF (>50% or ≤50%) (66).

The DAPA-HF, EMPEROR-REDUCED, EMPEROR-Preserved, DELIVER and other trials mentioned above consistently demonstrate the efficacy of SGLT-2i in patients with HF, regardless of LVEF or the presence of diabetes. These studies establish SGLT-2i as a cornerstone therapy for HF across the disease spectrum (54, 61). Multiple meta-analyses performed on the most important studies have confirmed a significant risk reduction for a composite of cardiovascular death and hospitalization for heart failure, with the risk reduction for hospitalization being greater (67–69). In addition to the positive cardiovascular outcomes demonstrated in the studies discussed, early initiation of SGLT-2i is increasingly emphasized to reduce associated complications. This approach is supported by evidence on the results of studies such as the EMPULSE trial and the DICTATE-AHF trial (70–75).

SGLT2i have consistently demonstrated cardiovascular benefits in meta-analyses and recent studies, confirming their robust efficacy regardless of ejection fraction or the presence of diabetes. These findings support their role as a cornerstone therapy in the management of heart failure across the entire clinical spectrum (Table 1).

TABLE 1 Summary of the main studies with SGLT-2i.

Study/ clinical trial	Drug (SGLT2)	Number of patients	Duration (years)	Primary outcomes	MACE reduction (%)	Hospitalization for HF reduction (%)	AlL-CAuse mortality (%)
EMPAREG	Empagliflozin	702	3.1	MACE, hospitalization for HF	14%	38%	32%
CANVAS	Canagliflozin	10,142	2.4	MACE, albuminuria reduction	14%	N/A	N/A
DECLARE-TIMI 58	Dapagliflozin	1,716	4.2	MACE, hospitalization for HF	Not significant	27%	N/A
CREDENCE	Canagliflozin	4,401	2.6	MACE, composite renal outcome	20%	N/A	N/A
VERTIS	Ertugliflozin	8,246	3.5	MACE, hospitalization for HF	Not significant	30%	N/A
SCORED	Sotagliflozin	10,584	1.5	CV death, hospitalization for HF	26%	N/A	N/A
DAPA-HF	Dapagliflozin	4,744	2.1	MACE, hospitalization for HF, CV death	26%	26%	18%
EMPA-KIDNEY	Empagliflozin	6,609	2	MACE, composite renal outcome	N/A	N/A	N/A
EMPEROR-REDUCED	Empagliflozin	3,730	1.9	Hospitalization for HF, CV death	25%	30%	N/A
EMPEROR-PRESERVED	Empagliflozin	2,997	2.2	Hospitalization for HF, CV death	21%	29%	N/A
DAPA CKD	Dapagliflozin	4,304	2.4	Decrease in eGFR, CV or Renal deaths	N/A	N/A	31%
DELIVER	Dapagliflozin	6,263	N/A	CV death, hospitalization for HF	23%	N/A	N/A
SOLOIST-WHF	Sotagliflozin	1,222	N/A	CV death, hospitalization for HF	36%	N/A	N/A

N/A, Not Available.

4.3 GLP-1 RAs in patients with DM2

Several randomized clinical trials have demonstrated the cardiovascular benefits of GLP-1 RAs in patients with T2DM. Five of these trials have shown superiority in reducing MACE compared to placebo, while all have confirmed the cardiovascular safety of GLP-1 RAs (76).

4.3.1 Cardiovascular outcomes in GLP-1 RAs studies

The ELIXA trial, which included 6068 patients, was the first to investigate the cardiovascular effects of GLP-1 RAs. While lixisenatide 20 µg once daily did not demonstrate a significant reduction in the primary outcome of four-point MACE (RR1.02; 95% CI, 0.89–1.17), it was shown to be non-inferior to placebo in terms of cardiovascular safety (77).

The first study to demonstrate superiority over placebo was the LEADER study, in which 9,340 patients were assigned to either liraglutide or placebo. There was a significant reduction in the risk of MACE of 3 points (RR 0.87; 95% CI, 0.78-0.97). Regarding the cardiovascular mortality rate in patients with liraglutide, it was lower compared to placebo (RR 0.78; 95% CI, 0.66-0.93), and when analyzed in mortality due to any cause, it was also lower in the liraglutide group with a reduction of the RR by 15%. The rate of non-fatal stroke, non-fatal MI, and hospitalization for HF did not show significant differences (78). Semaglutide injection and CV impact was evaluated using the SUSTAIN-6 trial (designed as a non-inferiority trials), which primarily showed a reduction in the rate of non-fatal stroke events (RR 0.61; 95% CI, 0.38–0.99), as well as a decrease in the rate of MACE by 26% (79).

Other contemporary studies, such as the EXSCEL and FREEDOM trials evaluated the cardiovascular effects of exenatide, a GLP-1 RA (80, 81). EXSCEL found a 9% reduction in the relative risk (RR) of three-point MACE. While there were reductions in cardiovascular death (12%) and all-cause mortality (14%), the rates of fatal myocardial infarction (MI) and hospitalization for MI were not significantly different (80). The FREEDOM trial, with a median follow-up of 1.33 years, did not demonstrate a statistically significant difference in four-point MACE (RR 1.21; 95% CI, 0.90–1.63) (81).

The REWIND trial investigated the cardiovascular benefits of dulaglutide, a GLP-1 receptor agonist, in a population of 9,901 patients with T2DM aged 50+ and either established CVD or risk factors. The primary outcome was the first occurrence of a

composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Dulaglutide significantly reduced the risk of this primary composite outcome by 12% compared to placebo (p=0.026). Gastrointestinal adverse events during follow-up were statistically significant (82).

Oral semaglutide has been studied in PIONEER 6 (designed as a non-inferiority trials), with a mean follow-up of 1.3 years and positive results for the primary endpoint: the MACE rate was reduced by 21% but did not achieve statistically significant differences. Furthermore, an important reduction in the number of deaths due to stroke was observed in the semaglutide treatment group (RR 0.49; 95% CI, 0.27-0.92). Regarding non-fatal myocardial infarction, there was no statistically significant difference (RR 1.18; 95% CI, 0.73-1.90) (83). For this drug, the ongoing SOUL trial has shown promising preliminary results, indicating a 14% reduction in the risk of MACE (84). The results of this study are expected in 2025.

The AMPLITUDE-O trial, which studied Efpeglenatide versus placebo with a mean follow-up of 1.81 years, demonstrated a significant 27% reduction in MACE. It also showed a reduction in heart failure (RR 0.61; 95% CI, 0.38–0.98) and cardiovascular mortality (RR 0.72; 95% CI, 0.50–1.03) (85).

Another study evaluating cardiovascular outcomes of GLP-1RAs was the HARMONY study. Albiglutide 30 mg was administered once weekly and enrolled a total of 9463 subjects aged ≥40 years with T2DM and established CVD. The albiglutide-treated group had a 3-point lower risk of MACE (0.78; 95% CI, 0.68–0.90). There was also a positive result for the rate of nonfatal myocardial infarction events, which was lower for the albiglutide group (RR 0.75; 0.61–0.90). However, the results were not positive for cardiovascular death (RR 0.93; 95% CI, 0.73–1.19) or stroke (RR 0.86; 95% CI, 0.66–1.14). It should be noted that this study did not evaluate hospitalization for HF (86).

A comprehensive meta-analysis by Giugliano et al. (2021) evaluated the cardiovascular benefits of GLP-1 RAs in patients with T2DM. The analysis, which included several of the above-mentioned, demonstrated a 14% reduction in the relative risk (RR) of MACE with GLP-1 RAs compared to placebo (87). Another meta-analysis also demonstrated that GLP-1s have a robust effect in reducing MACE (RR 0.87; 95% CI, 0.81-0.94) and death from any cause (RR 0.89; 95% CI, 0.83-0.95) (88). Positive results have also been found on HF, where GLP-1RAs could significantly reduce the incidence of hospital admission for heart failure by 11% (89).

Recent evidence has further substantiated the cardiovascular benefits of GLP-1 RAs. The SOUL trial (2025), a large-scale, double-blind, placebo-controlled study, evaluated once-daily oral semaglutide in 9,650 patients with T2DM and established atherosclerotic cardiovascular disease, chronic kidney disease, or both. Over a median follow-up of 49.5 months, oral semaglutide reduced the risk of MACE by 14% compared to placebo (HR 0.86; 95% CI, 0.77–0.96; p = 0.006), primarily driven by reductions in non-fatal MI and major adverse limb events. Approximately 27% of participants were on background SGLT2 inhibitor therapy at baseline; however, no significant interaction was observed, suggesting complementary cardiovascular protection mechanisms (90).

GLP-1 RAs significantly reduce the risk of MACE. Systematic reviews and meta-analyses confirm their overall cardiovascular benefits, demonstrating reductions in the relative risk of MACE, all-cause mortality, and hospitalizations for heart failure.

4.4 Role of GLP-1 RAs in arrhythmias and stroke

A meta-analysis by Liu et al. (2022) suggests that GLP-1 RAs may be associated with a reduced risk of atrial arrhythmias. This analysis included five trials with a total of 31,314 patients. While the study found that semaglutide specifically reduced the risk of atrial arrhythmias and atrial fibrillation (AF), other studies have reported conflicting results regarding the arrhythmia risk associated with GLP-1 RAs (91).

GLP-1RAs have been shown to significantly reduce postprandial levels of triglycerides, apolipoprotein (Apo) B48 and ApoC-III, independently of gastric emptying. In addition, liraglutide has been shown to significantly modify lipoprotein metabolism by reducing chylomicron production. Additionally, they exert a neuroprotective effect independently of blood glucose levels (92). Some of the antiatherosclerotic effects that contribute to stroke prevention are increased plaque stability, reduced vascular smooth muscle proliferation, and increased nitric oxide, all of which translate into improved endothelial function (92). This effect has been observed in several cardiovascular outcome clinical trials. GLP-1RAs have been shown to exert a protective factor by reducing stroke (RR 0.84; 95% CI, 0.77-0.93) (93) (Table 2).

4.5 Impact of SGLT-2 inhibitors and GLP-1 receptor agonists on kidney function

Multiple clinical trials have demonstrated the renoprotective effects of SGLT-2i and GLP-1 RAs in patients with T2DM and CKD. Studies such as EMPA-REG, CANVAS and DECLARE-TIMI 58, while not primarily focused on renal outcomes, have consistently shown that these medications can help preserve renal function (89, 94). In the EMPA-REG study, empagliflozin significantly reduced the risk for the composite renal outcome, which included doubling of serum creatinine, progression of macroalbuminuria, initiation of renal replacement therapy, or renal death (56). The CANVAS trial was a cardiovascular safety study; however, it suggested the presence of the renoprotective effects of canagliflozin in patients with T2DM and CKD. Canagliflozin-treated patients experienced a slower decline in GFR and an 18% reduction in the urea-albumin-creatinine ratio. Additionally, the risk of sustained doubling of serum creatinine, end-stage renal disease, and renal death was lower in the canagliflozin group (34).

Subsequent studies, such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY, were specifically designed to investigate the renoprotective effects of SGLT-2i. The CREDENCE clinical trial evaluated the effects of canagliflozin 100 mg daily versus placebo in 4401 patients with T2DM and chronic kidney disease (CKD). With a mean follow-up of 2.6 years, the study demonstrated a 34% reduction in the relative risk (RR) of a composite renal outcome,

10.3389/fendo.2025.1605746

TABLE 2 Summary of the main studies with GLP1-AR.

Study	Drug	Number of patients	Duration (years)	Primary outcomes	MACE reduction (%)	Cardiovascular mortality reduction (%)	Heart Failure hospitalization reduction (%)
ELIXA	Lixisenatide	6,068	N/A	No significant effect on MACE	Not significant	Not significant	Not evaluated
LEADER	Liraglutide	934	N/A	3-point MACE reduction	13%	22%	Not significant
SUSTAIN-6	Semaglutide	N/A	N/A	Reduction of non-fatal stroke, MACE	26%	N/A	Not evaluated
EXSCEL	Exenatide	N/A	3.2	3-point MACE risk reduction	9%	12%	Not significant
REWIND	Dulagluitde	9,901		3-point MACE risk reduction	12%	Not significant	Not significant
PIONEER 6	Semaglutide	N/A	1.3	Significant MACE reduction	21%	51%	Not evaluated
AMPLITUDE-O	Efpeglenatide	N/A	1.81	Reduction of MACE, Heart Failure	27%	28%	39%
HARMONY	Albiglutide	9,463	N/A	3-point MACE reduction	22%	Not significant	Not evaluated
SOUL	Oral Semaglutide	9650	4.1	MACE risk reduction	14%	Not significant	Not evaluated

N/A, Not Available.

including dialysis requirement, a decline in glomerular filtration rate (GFR) <15 ml/m²/1.73 m², kidney transplant requirement, doubling of creatinine, and cardiovascular or renal death (58).

The DAPA-CKD trial, which specifically evaluated the efficacy of dapagliflozin in patients with CKD, regardless of T2DM status, found a 39% reduction in the relative risk of a composite renal outcome, including a decline in GFR by at least 50%, end-stage renal disease, or renal or cardiovascular death. Dapagliflozin-treated patients had a lower incidence of these events 6.6% vs. 11.3% in the placebo group (0.61; 95% CI, 0.51 to 0.72) (95).

The results of the EMPA-KIDNEY study showed that its primary endpoint was the first occurrence of the composite outcome of kidney disease progression, defined as end-stage kidney disease, a sustained decline in eGFR to <10 mL per minute per 1.73 m², a sustained decline in eGFR of ≥40% from baseline, renal death, or cardiovascular death. The study included 6,609 patients, who were followed for 2.0 years. Emplagliflozin demonstrated a 28% reduction in the risk of the primary endpoint. In addition, it also showed a reduction in the risk of kidney disease progression by 29% (0.71; 95% CI; 0.62–0.81) (96).

Regarding GLP-1 RAs, the LEADER, SUSTAIN-6, REWIND, PIONEER 6 and AMPLITUDE-O studies have shown nephroprotective effect, especially in preventing the occurrence of macroalbuminuria. In the LEADER study, the group treated with liraglutide had a lower risk of nephropathy, with a reduction of 26% (78). In the SUSTAIN-6 trial, it was observed that semaglutide reduced the risk of nephropathy in patients treated with the drug compared to those treated with placebo (79). On the other hand, in the AMPLITUDE-O study, which included 4,076 patients, was shown that efpeglenatide significantly reduced the composite renal outcomes by 32% (a decrease in renal function or the occurrence of macroalbuminuria according to criteria defined in the study) (0.68; 95% CI, 0.57-0.79). This significant difference between the GLP-1 and placebo groups was mainly driven by a marked reduction in the incidence of macroalbuminuria (59). The REWIND trial also provided results consistent with previous studies. This study showed that the dulaglutide treated group had a lower risk of a composite renal outcome, (which includes the occurrence of macroalbuminuria, a 30% decrease in estimated glomerular filtration rate (eGFR) or the need for renal replacement therapy, (0.85, 95% CI 0 77–0.93), and the strongest statistically significant outcome was the reduction in the occurrence of macroalbuminuria (97).

The FLOW trial enrolled 3533 patients with T2DM and chronic kidney disease at high risk for kidney failure, cardiovascular events, and death. Participants were randomly assigned to receive subcutaneous semaglutide 1.0 mg weekly or placebo. The primary outcome was major kidney disease events. The semaglutide group experienced a 24% lower risk of the primary outcome compared to the placebo group (p<0.001). Additionally, the semaglutide group had an 18% lower risk of MACE (98). However, the SOUL trial, evaluating oral semaglutide, did not demonstrate a statistically significant reduction in major kidney disease events (90).

SGLT2 inhibitors have demonstrated significant renoprotective effects in patients with type 2 diabetes and CKD, reducing the risk of renal disease progression, the need for dialysis or kidney transplantation, and renal or cardiovascular mortality. GLP-1 RAs also confer renal benefits, particularly by reducing macroalbuminuria and slowing the progression of nephropathy. Together, these findings underscore the important role both drug classes play in renal protection for patients with type 2 diabetes.

4.6 Sex differences in cardiovascular outcomes

Subgroup analyses from the DAPA-HF trial revealed that women with heart failure experienced a reduction in the primary composite outcome with dapagliflozin (RR 0.79; 95% CI, 0.59–1.06), comparable to men (RR 0.73; 95% CI, 0.63–0.85), with no significant interaction by sex (62). Similar findings were reported in the CANVAS and EMPA-REG OUTCOME trials, where no significant sex-based differences were observed (34, 56). In contrast, a meta-analysis by Rivera et al. (2023) demonstrated a significant reduction in the primary composite outcome for both men (RR 0.77; 95% CI, 0.72–0.84; $p < 0.00001$) and women (RR 0.75; 95% CI, 0.67–0.84; $p < 0.00001$) receiving SGLT-2 inhibitors compared to placebo (99). Another meta-analysis evaluating three CVOTs with SGLT-2 inhibitors (N = 34,322) showed a reduction in MACE in men (RR 0.90; 95% CI, 0.83–0.97; $p = 0.006$), whereas in women, the risk reduction did not reach statistical significance (RR 0.88; 95% CI, 0.77–1.00; $p = 0.06$) (100).

Regarding safety, women experienced a higher incidence of genital infections while on SGLT-2 inhibitors, likely due to anatomical predisposition, which may impact treatment adherence (31).

For GLP-1 receptor agonists, the REWIND trial demonstrated a reduction in cardiovascular events with dulaglutide, with a trend toward greater benefit in women, although statistical significance was not achieved (RR 0.85; 95% CI, 0.71–1.02) vs. men (RR 0.90; 95% CI, 0.79–1.04; $p = 0.60$) (82). In the SUSTAIN-6 trial, no sex-based differences in cardiovascular outcomes were observed, indicating similar efficacy across genders (79). A meta-analysis including seven GLP-1 RA trials demonstrated significant MACE reduction in both men (RR 0.88; 95% CI, 0.82–0.93; $p < 0.0001$) and women (RR 0.88; 95% CI, 0.79–0.99; $p = 0.03$) (100).

In terms of safety, gastrointestinal adverse effects—particularly nausea—were common across both sexes, but women reported higher rates of intolerance, which may lead to treatment discontinuation (46). These observations underscore the importance of incorporating sex-specific factors when selecting GLP-1 RAs, favoring their use in women at elevated stroke risk, with potential dose adjustments to optimize adherence (8, 91).

The reduction in MACE with SGLT-2 inhibitors appears to be less consistent in women with type 2 diabetes than in men, while GLP-1 receptor agonists provide similar cardiovascular benefits across sexes.

4.7 Combined use of SGLT2i and GLP-1 RAs

Several studies have explored the combination of GLP-1 RAs and SGLT-2 inhibitors in patients with T2DM. Randomized clinical trials, such as DURATION-8, SUSTAIN-9, and AWARD-10, have documented the use of GLP-1 RAs in patients already receiving SGLT-2 inhibitors, demonstrating efficacy without adverse effects on the studied population (96, 97). Similarly, sub analyses of studies like EXSCEL, AMPLITUDE-O, HARMONY, CANVAS, DECLARE-TIMI 58, and VERTIS-CV have shown a positive impact with the concomitant use of GLP-1 RAs and SGLT-2 inhibitors, irrespective of whether the initial intervention involved GLP-1 RAs or SGLT-2 inhibitors (34, 57, 59, 80, 85, 101–105).

Among the studies evaluating GLP-1 RAs and SGLT-2 inhibitors, the study conducted by Riley et al. through the TriNetX network stands out. This study included approximately 2.2 million participants and compared cardiovascular outcomes among patients treated without GLP-1 RAs or SGLT-2 inhibitors, with one of these drug classes, or with a combination of both. After five years of follow-up in patients with T2DM, the GLP-1 RAs and SGLT-2 inhibitors groups demonstrated significant reductions in mortality, CHD, HF, AF, stroke, peripheral vascular disease, and CKD, regardless which one of the drugs or its combination were used. Notably, the simultaneous use of both pharmacological classes provided a significantly greater benefit in outcomes such as mortality, hospitalizations, heart failure, and CKD (106).

Building on the findings of the aforementioned trials, several meta-analyses have been conducted since 2019 to evaluate the safety and efficacy of combining GLP-1 RAs and SGLT-2 inhibitors. In 2019, Castellana et al. performed a meta-analysis focusing on patients with T2DM who required rescue medication for hyperglycemia and had a follow-up period of at least 24 weeks. This study demonstrated significant improvements in parameters such as HbA1c, body weight, and lipid profiles, along with a reduced need for rescue medications to control hyperglycemia (107), an effect that has been demonstrated again in other meta-analyses carried out subsequently (108). Additionally, to date it has been demonstrated to have an adequate safety profile by not increasing adverse effects with the combination of these pharmacological groups (108–111).

Among the prospective studies on this pharmacological combination, real-world evidence also plays a significant role. For instance, García-Vega et al. conducted a prospective study involving patients treated in Galicia between 2018 and 2022. The study included 15,549 patients who received either the combination therapy of GLP-1 RAs and SGLT-2 inhibitors or monotherapy with one of these drug classes. After an average follow-up of 19 months, the combination therapy did not demonstrate a reduction in coronary heart disease or ischemic stroke events compared to monotherapy. However, notable benefits were observed in other outcomes, including a 31% reduction in hospital admissions for heart failure and a 32% decrease in all-cause mortality (112).

Other high-profile studies on the use of GLP-1 RAs and SGLT-2 inhibitors combination therapy were conducted by Marfellas et al. (84, 96),. Marfellas et al. recruited patients with T2DM who had experienced acute myocardial infarction (AMI) and had been treated with one of these drug groups within the three months preceding the acute event. Patients with HbA1c >7% were initiated on the complementary drug to complete the GLP-1 RA + SGLT-2i combination therapy. The primary endpoint was a composite of cardiovascular death, recurrent acute coronary syndrome, and heart failure related to AMI after two years of follow-up. Among the 443 patients who completed the study, the combination therapy group demonstrated an ≈84% reduction in the primary endpoint (113).

Simms-Williams et al. conducted a population-based cohort study involving 15,638 patients receiving the combination therapy. Their findings revealed a ≈30% reduction in MACE compared to

10.3389/fendo.2025.1605746

TABLE 3 Summary of the main studies with combined use of GLP1-AR and SGLT2 inhibitors.

Study	Methodology	Number of patients	Duration (months)	Primary outcomes	Results	All-cause mortality (Reduction)	Heart failure consulting (Reduction)	CKD progression (Reduction)
Marfellas et al.	Prospective Cohort	443	24	Composite of the incidence of all-cause mortality, hospitalization for heart failure, acute coronary syndrome	Reduced incidence (≈84%) of cardiovascular events in patients with T2DM and AMI	N/A	N/A	N/A
Simms-Williams et al.	Population based cohort study	15,638	60	Cardio renal vascular disease with impatient consulting or mortality	GLP-1 RAs + SGLT-2 inhibitor combination was associated with a lower risk of MACE and serious renal events compared with either drug class alone.	29%	43%	57%
Riley et al.	Retrospective Cohort	108,507	60	All-cause mortality, hospitalization, Acute myocardial infarction	SGLT2i + GLP-1RAs combination therapy was associated with the greatest risk reduction in all-cause mortality.	75%	40%	28%
García-Vega et al.	Non-Concurrent prospective study	15,549	19	All-cause mortality, hospitalization or mortality by: coronary artery disease, heart failure, stroke	SGLT2i + GLP1ra reduces heart failure risk and all-cause mortality	32%	31%	Not evaluated
Castellana et al.	Meta Analysis	1,610	≈6	Efficacy and safety	The addition of GLP1 RAs to SGLT2i proved to be effective	Not evaluated	Not evaluated	Not evaluated
Ahmad and Sabbour	Meta Analysis of observational studies	≈110,000	3 to 60	Effectiveness and safety	Lower all-cause mortality and favorable improvements in cardiovascular, renal, and glycemic measurements.	51%	Not evaluated	Not evaluated

N/A, Not Available.

monotherapy. Regarding renal outcomes, the combination therapy showed a reduction in events that did not reach statistical significance when compared to SGLT-2i monotherapy. In contrast, when analyzing stroke outcomes, the effect was more pronounced with GLP-1 RAs, which provided the greatest contribution to the reduction of stroke events. However, a 57% reduction in renal events was observed compared to those receiving only GLP-1 RAs (114).

In 2024, Ahmad and Sabbour conducted a meta-analysis encompassing data from over 110,000 patients, encompassing 13 investigations that evaluated the combined use of GLP-1 RAs and SGLT-2 inhibitors. The findings demonstrated a significant

reduction in all-cause mortality, with an odds ratio of 0.49 (95% CI [0.41–0.60]; $p < 0.00001$). Additional benefits included reductions in body mass index (BMI), blood pressure levels, HbA1c, and fasting blood glucose, observed after a minimum of six months of clinical follow-up (111).

Notably, the study by Marfellas et al. focused on a cohort of patients following a coronary event, providing insights into the cardiovascular benefits of the therapeutic combination in this high-risk population. In contrast, Simms-Williams et al. analyzed patients initially treated with GLP-1 RAs or SGLT2i, subsequently adding the second agent to evaluate the effects of combination therapy compared to monotherapy and differencing across groups (113, 114). The study by Riley et al., despite its retrospective design, represents the largest dataset to date, offering robust evidence on cardiovascular and renal outcomes associated with this therapeutic strategy (106). Lastly, the analysis by García-Vega et al. incorporated stroke outcomes, broadening the scope of evidence for this combination therapy in real-world settings (112). The meta-analyses reviewed highlight the favorable safety profile of the pharmacological therapy, alongside its efficacy in optimizing clinical parameters, particularly glycemic control and lipid profiles (Table 3).

With respect to the SOUL trial, oral semaglutide demonstrated a 14% reduction in MACE outcomes, independent of concurrent SGLT2 inhibitor use. The combination therapy also exhibited a favorable safety profile in this trial (115).

To date, current evidence suggests that the combination of SGLT2 inhibitors and GLP-1 receptor agonists is generally well-tolerated. The adverse events observed align with the known safety profiles of each class used individually, with no indication of synergistic toxicity. This combination represents a promising therapeutic strategy for improving cardiovascular, renal, and metabolic outcomes in patients with T2DM.

5 Conclusions

The use of SGLT-2 inhibitors and GLP-1 RAs in patients with cardiovascular risk has been well-established over the past decade. When considering the initiation of these therapies, it is important to consider patient-specific factors. Patients with existing heart or kidney disease may benefit from starting SGLT-2 inhibitors therapy, while those with a higher risk of developing these conditions, such as obese patients and those with no cardiogenic stroke, may benefit more from GLP-1 RAs. However, it is essential to note that when additional pharmacological intervention is required to control diabetes mellitus, the choice between SGLT-2 inhibitors and GLP-1 RAs should be based on the patient's individual needs and the specific medications already being used. The combination of SGLT-2 inhibitors and GLP-1 RAs offer additive benefits in reducing cardiovascular and renal risk in patients with diabetes and should be considered.

Author contributions

DA: Resources, Funding acquisition, Formal analysis, Software, Conceptualization, Methodology, Writing – original draft, Investigation, Data curation. DC: Conceptualization, Data curation, Methodology, Writing – original draft, Investigation, Software, Resources, Formal analysis. SS: Investigation, Methodology, Writing – original draft, Software, Formal analysis, Data curation, Resources. CL: Formal analysis, Investigation, Resources, Writing – original draft, Data curation, Methodology, Software. DV: Validation, Resources, Data curation, Methodology, Software, Writing – original draft, Investigation. DW: Investigation, Writing – original draft, Supervision, Methodology, Software, Resources, Formal analysis. JI: Methodology, Visualization, Validation, Investigation, Supervision, Resources, Writing – review & editing, Funding acquisition, Software, Project administration. EO: Validation, Investigation, Writing – review & editing, Supervision, Methodology, Software, Funding acquisition, Resources, Project administration. JR: Methodology, Visualization, Investigation, Validation, Funding acquisition, Supervision, Writing – review & editing. JG: Software, Investigation, Supervision, Visualization, Writing – review & editing, Validation. AA: Visualization, Methodology, Investigation, Software, Writing – review & editing, Validation. WR: Project administration, Visualization, Validation, Writing – review & editing, Supervision, Software, Investigation.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

JR-F declares that he has received honoraria for lectures for AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lilly, Sanofi, Novartis, Abbvie, Merck, and Bayer. He has participated in Advisory Board with AstraZeneca, Boehringer Ingelheim, Bayer, and Novo Nordisk. J-EG-M declares that he has received honoraria for lectures for AstraZeneca, Bayer, Boheringer Ingelheim, Merck, and Xinetixs Pharma. He has participated in Advisory Board with AstraZeneca, and Boheringer Ingelheim.

The remaining 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.

Correction note

A correction has been made to this article. Details can be found at: 10.3389/fendo.2025.1663787.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

2. Coronado F, Melvin SC, Bell RA, Zhao G. Global responses to prevent, manage, and control cardiovascular diseases. *Prev Chronic Dis*. (2022) 19:E84. doi: 10.5888/pcd19.220347

3. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. (2022) 183. doi: 10.1016/j.diabres.2021.109119

4. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. *Lancet Diabetes Endocrinol*. (2015) 3:105–13. doi: 10.1016/S2213-8587(14)70219-0

5. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol*. (2019) 26:25–32. doi: 10.1177/2047487319878371

6. Kaze AD, Santhanam P, Musani SK, Ahima R, Echouffo-Tcheugui JB. Metabolic dyslipidemia and cardiovascular outcomes in type 2 diabetes mellitus: findings from the look AHEAD study. *J Am Heart Assoc*. (2021) 10:e016947. doi: 10.1161/JAHA.120.016947

7. Azam M, Sakinah LF, Kartasurya MI, Fibriana AI, Minuljo TT, Aljunid SM. Prevalence and determinants of obesity among individuals with diabetes in Indonesia. *F1000Research*. (2022) 11:1063. doi: 10.12688/f1000research.125549.3

8. Haile TG, Mariye T, Tadesse DB, Gebremeskel GG, Asefa GG, Getachew T. Prevalence of hypertension among type 2 diabetes mellitus patients in Ethiopia: a systematic review and meta-analysis. *Int Health*. (2023) 15:235–41. doi: 10.1093/inthealth/ihac060

9. Rodríguez-Gutiérrez R, Montori VM. Glycemic control for patients with type 2 diabetes mellitus: our evolving faith in the face of evidence. *Circ Cardiovasc Qual Outcomes*. (2016) 9:504–12. doi: 10.1161/CIRCOUTCOMES.116.002901

10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. (1998) 352:837–53. doi: 10.1016/S0140-6736(98)07019-6

11. The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. *Diabetes Care*. (1987) 10:1–19. doi: 10.2337/diacare.10.1.1

12. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. (2011) 343:d6898. doi: 10.1136/bmj.d6898

13. Monami M, Candido R, Pintaudi B, Targher G, Mannucci E, of the SID-AMD joint panel for Italian Guidelines on Treatment of Type 2 Diabetes. Improvement of glycemic control in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis NMCD*. (2021) 31:2539–46. doi: 10.1016/j.numecd.2021.05.010

14. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. (2008) 358:2545–59. doi: 10.1056/NEJMoa0802743

15. Crabtree T, Ogendo J-J, Vinogradova Y, Gordon J, Idris I. Intensive glycemic control and macrovascular, microvascular, hypoglycemia complications and mortality in older (age ≥60years) or frail adults with type 2 diabetes: a systematic review and meta-analysis from randomized controlled trial and observation studies. *Expert Rev Endocrinol Metab*. (2022) 17:255–67. doi: 10.1080/17446651.2022.2079495

16. Kilickap M, Kozluca V, Tan TS, Akbulut Koyuncu IM. GLP-1 receptor agonists and SGLT-2 inhibitors in patients with versus without cardiovascular disease: A systematic review, meta-analysis, and trial sequential analysis. *Angiology*. (2024) 75:820–30. doi: 10.1177/00033197231183229

17. Marilly E, Cottin J, Cabrera N, Cornu C, Boussageon R, Moulin P, et al. SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials balancing their risks and benefits. *Diabetologia*. (2022) 65:2000–10. doi: 10.1007/s00125-022-05773-8

18. Peronard R, Mayntz S. Comment on "SGLT2 inhibitors, and how they work beyond the glucosuric effect". *Am J Cardiovasc Drugs*. (2024) 25:129–30. doi: 10.1007/s40256-024-00706-9

19. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. (2023) 389:1069–84. doi: 10.1056/NEJMoa2306963

20. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). *Eur Heart J*. (2023) 44:ehad192. doi: 10.1093/eurheartj/ehad192

21. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. (2022) 45:2753–86. doi: 10.2337/dci22-0034

22. Rieg T, Vallon V. Development of SGLT1 and SGLT2 inhibitors. *Diabetologia*. (2018) 61:2079–86. doi: 10.1007/s00125-018-4654-7

23. Hsia DS, Grove O, Cefalu WT. An update on SGLT2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. (2017) 24:73–9. doi: 10.1097/MED.0000000000000311

24. Aristizábal-Colorado D, Ocampo-Posada M, Rivera-Martínez WA, Corredor-Rengifo D, Rico-Fontalvo J, Gómez-Mesa JE, et al. SGLT2 inhibitors and how they work beyond the glucosuric effect. State of the art. *Am J Cardiovasc Drugs*. (2024) 24:707–18. doi: 10.1007/s40256-024-00673-1

25. Fonseca-Correa JI, Correa-Rotter R. Sodium-glucose cotransporter 2 inhibitors mechanisms of action: A review. *Front Med*. (2021) 8:777861. doi: 10.3389/fmed.2021.777861

26. Pabel S, Hamdani N, Luedde M, Sossalla S. SGLT2 inhibitors and their mode of action in heart failure-has the mystery been unravelled? *Curr Heart Fail Rep*. (2021) 18:315–28. doi: 10.1007/s11897-021-00529-8

27. Hiraizumi M, Akashi T, Murasaki K, Kishida H, Kumanomidou T, Torimoto N, et al. Transport and inhibition mechanism of the human SGLT2-MAP17 glucose transporter. *Nat Struct Mol Biol*. (2024) 31:159–69. doi: 10.1038/s41594-023-01134-0

28. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. (2016) 134:752–72. doi: 10.1161/CIRCULATIONAHA.116.021887

29. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30-50% of filtered glucose load in humans. *Diabetes*. (2013) 62:3324–8. doi: 10.2337/db13-0604

30. Lam-Chung CE. Comprehensive review of SGLT2 inhibitors' efficacy through their diuretic mode of action in diabetic patients. *Front Endocrinol*. (2023) 14:1174692. doi: 10.3389/fendo.2023.1174692

31. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. (2017) 19:348–55. doi: 10.1111/dom.12825

32. Pittampalli S, Upadyayula S, Mekala HM, Lippmann S. Risks vs benefits for SGLT2 inhibitor medications. *Fed Pract*. (2018) 35:45–8.

33. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. (2016) 101:157–66. doi: 10.1210/jc.2015-3167

34. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. (2017) 377:2099. doi: 10.1056/NEJMc1712572

35. Aristizábal-Colorado D, Ocampo-Posada M, Rivera-Martínez WA, Corredor-Rengifo D, Rico-Fontalvo J, Gómez-Mesa JE, et al. Author's reply to Peronard and Mayntz: "SGLT2 inhibitors, and how they work beyond the glucosuric effect. " *Am J Cardiovasc Drugs*. (2025) 25:131–3. doi: 10.1007/s40256-024-00707-8

36. American Diabetes Association Professional Practice Committee. 13. Older adults: standards of care in diabetes-2025. *Diabetes Care*. (2025) 48:S266–82. doi: 10.2337/dc25-S013

37. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL, Kalyani RR, et al. 2020 Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: A report of the American College of Cardiology Solution set oversight committee. *J Am Coll Cardiol*. (2020) 76:1117–45. doi: 10.1016/j.jacc.2020.05.037

38. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. (2018) 41:2669–701. doi: 10.2337/dci18-0033

39. McGill JB, Subramanian S. Safety of sodium-glucose co-transporter 2 inhibitors. *Am J Cardiol*. (2019) 124 Suppl 1:S45–52. doi: 10.1016/j.amjcard.2019.10.029

40. Pandey S, Mangmool S, Parichatikanond W. Multifaceted roles of GLP-1 and its analogs: A review on molecular mechanisms with a cardiotherapeutic perspective. *Pharm Basel Switz*. (2023) 16:836. doi: 10.3390/ph16060836

41. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). *Mol Metab*. (2019) 30:72–130. doi: 10.1016/j.molmet.2019.09.010

42. Andrikou E, Tsioufis C, Andrikou I, Leontsinis I, Tousoulis D, Papanas N. GLP-1 receptor agonists and cardiovascular outcome trials: An update. *Hell J Cardiol HJC Hell Kardiologike Epitheorese*. (2019) 60:347–51. doi: 10.1016/j.hjc.2018.11.008

43. Rico-Fontalvo J, Reina M, Soler MJ, Unigarro-Palacios M, Castañeda-González JP, Quintero JJ, et al. Kidney effects of Glucagon-Like Peptide 1 (GLP1): from molecular foundations to a pharmacophysiological perspective. *J Bras Nefrol*. (2024) 46: e20240101. doi: 10.1590/2175-8239-JBN-2024-0101en

44. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab*. (2018) 27:740–56. doi: 10.1016/j.cmet.2018.03.001

45. Kayaniyil S, Lozano-Ortega G, Bennett HA, Johnsson K, Shaunik A, Grandy S, et al. A network meta-analysis comparing exenatide once weekly with other GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. *Diabetes Ther Res Treat Educ Diabetes Relat Disord*. (2016) 7:27–43. doi: 10.1007/s13300-016-0155-1

46. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectr Publ Am Diabetes Assoc*. (2017) 30:202–10. doi: 10.2337/ds16-0026

47. Pauza AG, Thakkar P, Tasic T, Felippe I, Bishop P, Greenwood MP, et al. GLP1R attenuates sympathetic response to high glucose via carotid body inhibition. *Circ Res*. (2022) 130:694–707. doi: 10.1161/CIRCRESAHA.121.319874

48. Maack C, Kartes T, Kilter H, Schäfers H-J, Nickenig G, Böhm M, et al. Oxygen free radical release in human failing myocardium is associated with increased activity of rac1-GTPase and represents a target for statin treatment. *Circulation*. (2003) 108:1567–74. doi: 10.1161/01.CIR.0000091084.46500.BB

49. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse effects of GLP-1 receptor agonists. *Rev Diabetes Stud RDS*. (2014) 11:202–30. doi: 10.1900/RDS.2014.11.202

50. Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet Lond Engl*. (2022) 400:1788–801. doi: 10.1016/S0140-6736(22)02074-8

51. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2025. *Diabetes Care*. (2025) 48:S181–206. doi: 10.2337/dc25-S009

52. Long B, Pelletier J, Koyfman A, Bridwell RE. GLP-1 agonists: A review for emergency clinicians. *Am J Emerg Med*. (2024) 78:89–94. doi: 10.1016/j.ajem.2024.01.010

53. Zhang J, Ma Y, Zu Q, Wang X, Zhang Y. GLP-1 receptor agonist–induced diabetic ketoacidosis: A case report. *Med (Baltimore)*. (2024) 103:e39799. doi: 10.1097/MD.0000000000039799

54. Akiyama H, Nishimura A, Morita N, Yajima T. Evolution of sodium-glucose co-transporter 2 inhibitors from a glucose-lowering drug to a pivotal therapeutic agent for cardio-renal-metabolic syndrome. *Front Endocrinol*. (2023) 14:1111984. doi: 10.3389/fendo.2023.1111984

55. Seidu S, Alabraba V, Davies S, Newland-Jones P, Fernando K, Bain SC, et al. SGLT2 inhibitors - the new standard of care for cardiovascular, renal and metabolic protection in type 2 diabetes: A narrative review. *Diabetes Ther Res Treat Educ Diabetes Relat Disord*. (2024) 15:1099–124. doi: 10.1007/s13300-024-01550-5

56. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. (2015) 373:2117–28. doi: 10.1056/NEJMoa1504720

57. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. (2019) 380:347–57. doi: 10.1056/NEJMoa1812389

58. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. (2019) 380:2295–306. doi: 10.1056/NEJMoa1811744

59. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. (2020) 383:1425–35. doi: 10.1056/NEJMoa2004967

60. Sridhar VS, Bhatt DL, Odutayo A, Szarek M, Davies MJ, Banks P, et al. Sotagliflozin and kidney outcomes, kidney function, and albuminuria in type 2 diabetes and CKD: A secondary analysis of the SCORED trial. *Clin J Am Soc Nephrol CJASN*. (2024) 19:557–64. doi: 10.2215/CJN.0000000000000414

61. Rolek B, Haber M, Gajewska M, Rogula S, Pietrasik A, Gąsecka A. SGLT2 inhibitors vs. GLP-1 agonists to treat the heart, the kidneys and the brain. *J Cardiovasc Dev Dis*. (2023) 10:322. doi: 10.3390/jcdd10080322

62. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. (2019) 381:1995–2008. doi: 10.1056/NEJMoa1911303

63. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. (2020) 383:1413–24. doi: 10.1056/NEJMoa2022190

64. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. *Eur J Heart Fail*. (2019) 21:1279–87. doi: 10.1002/ejhf.1596

65. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. (2022) 387:1089–98. doi: 10.1056/NEJMoa2206286

66. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. (2021) 384:117–28. doi: 10.1056/NEJMoa2030183

67. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. *JAMA Cardiol*. (2021) 6:148–58. doi: 10.1001/jamacardio.2020.4511

68. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet Lond Engl*. (2022) 400:757–67. doi: 10.1016/S0140-6736(22)01429-5

69. Vernaza-Trujillo DA, Bautista LYR, Espinosa CMR, Castillo S, Corredor-Rengifo D, Aristizabal-Colorado D, et al. Impact of SGLT2 inhibitors on preventing heart failure hospitalizations in Colombian patients with uncontrolled type 2 diabetes mellitus. *Cureus*. (2025) 17:1–13. doi: 10.7759/cureus.77725

70. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. (2022) 28:568–74. doi: 10.1038/s41591-021-01659-1

71. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE, et al. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J*. (2023) 44:41–50. doi: 10.1093/eurheartj/ehac530

72. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet Lond Engl*. (2022) 400:1938–52. doi: 10.1016/S0140-6736(22)02076-1

73. Rivera-Martínez W, Mejia-Cardona A, Salazar-Solarte A, Aristizabal-Colorado D, Garces-Villabon L, Pinillos-Senior O, et al. Impacto en desenlaces intrahospitalarios con el inició de un iSGLT2 en insuficiencia cardíaca aguda descompensada. *Rev Colomb Cardiol*. (2025) 32:78–89. doi: 10.24875/RCCAR.24000056

74. Cox ZL, Collins SP, Hernandez GA, McRae AT, Davidson BT, Adams K, et al. Efficacy and safety of dapagliflozin in patients with acute heart failure. *J Am Coll Cardiol*. (2024) 83:1295–306. doi: 10.1016/j.jacc.2024.02.009

75. Echeverría LE, Rojas LZ, Serrano-García AY, Botero DR, Cantillo-Reines M, Jurado AM, et al. Impact of early SGLT2 inhibitors prescription on acute decompensated heart failure outcomes: insights from a real-world setting. *Rev Esp Cardiol Engl Ed*. (2023) 93(2):160–72. doi: 10.1016/j.rec.2025.02.006

76. Rangaswami J, Bhalla V, de Boer IH, Staruschenko A, Sharp JA, Singh RR, et al. Cardiorenal protection with the newer antidiabetic agents in patients with diabetes and chronic kidney disease: A scientific statement from the American Heart Association. *Circulation*. (2020) 142:e265–86. doi: 10.1161/CIR.0000000000000920

77. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. (2015) 373:2247–57. doi: 10.1056/NEJMoa1509225

78. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. (2016) 375:311–22. doi: 10.1056/NEJMoa1603827

79. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. (2016) 375:1834–44. doi: 10.1056/NEJMoa1607141

80. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. (2017) 377:1228–39. doi: 10.1056/NEJMoa1612917

81. Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. *Nat Med*. (2022) 28:89–95. doi: 10.1038/s41591-021-01584-3

82. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet Lond Engl*. (2019) 394:121–30. doi: 10.1016/S0140-6736(19)31149-3

83. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. (2019) 381:841–51. doi: 10.1056/NEJMoa1901118

84. McGuire DK, Busui RP, Deanfield J, Inzucchi SE, Mann JFE, Marx N, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney

disease: Design and baseline characteristics of SOUL, a randomized trial. *Diabetes Obes Metab*. (2023) 25:1932–41. doi: 10.1111/dom.15058

85. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med*. (2021) 385:896–907. doi: 10.1056/NEJMoa2108269

86. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet Lond Engl*. (2018) 392:1519–29. doi: 10.1016/S0140-6736(18)32261-X

87. Giugliano D, Scappaticcio L, Longo M, Caruso P, Maiorino MI, Bellastella G, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol*. (2021) 20:189. doi: 10.1186/s12933-021-01366-8

88. Lee MMY, Kristensen SL, Gerstein HC, McMurray JJV, Sattar N. Cardiovascular and mortality outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A meta-analysis with the FREEDOM cardiovascular outcomes trial. *Diabetes Metab Syndr*. (2022) 16:102382. doi: 10.1016/j.dsx.2021.102382

89. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. (2019) 7:776–85. doi: 10.1016/S2213-8587(19)30249-9

90. McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. *N Engl J Med*. (2025) 392:2001–12. doi: 10.1056/NEJMoa2501006

91. Parab P, Chaudhary P, Mukhtar S, Moradi A, Kodali A, Okoye C, et al. Role of glucagon-like peptide-1 (GLP-1) receptor agonists in cardiovascular risk management in patients with type 2 diabetes mellitus: A systematic review. *Cureus*. (2023) 15:e45487. doi: 10.7759/cureus.45487

92. Vergès B, Aboyans V, Angoulvant D, Boutouyrie P, Cariou B, Hyafil F, et al. Protection against stroke with glucagon-like peptide-1 receptor agonists: a comprehensive review of potential mechanisms. *Cardiovasc Diabetol*. (2022) 21:242. doi: 10.1186/s12933-022-01686-3

93. Li J, Ji C, Zhang W, Lan L, Ge W. Effect of new glucose-lowering drugs on stroke in patients with type 2 diabetes: A systematic review and Meta-analysis. *J Diabetes Complications*. (2023) 37:108362. doi: 10.1016/j.jdiacomp.2022.108362

94. Nagahisa T, Saisho Y. Cardiorenal protection: potential of SGLT2 inhibitors and GLP-1 receptor agonists in the treatment of type 2 diabetes. *Diabetes Ther Res Treat Educ Diabetes Relat Disord*. (2019) 10:1733–52. doi: 10.1007/s13300-019-00680-5

95. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. (2020) 383:1436–46. doi: 10.1056/NEJMoa2024816

96. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. (2023) 388:117–27. doi: 10.1056/NEJMoa2204233

97. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet Lond Engl*. (2019) 394:131–8. doi: 10.1016/S0140-6736(19)31150-X

98. Pratley RE, Tuttle KR, Rossing P, Rasmussen S, Perkovic V, Nielsen OW, et al. Effects of semaglutide on heart failure outcomes in diabetes and chronic kidney disease in the FLOW trial. *J Am Coll Cardiol*. (2024) 84:1615–28. doi: 10.1016/j.jacc.2024.08.004

99. Rivera FB, Tang VAS, De Luna DV, Lerma EV, Vijayaraghavan K, Kazory A, et al. Sex differences in cardiovascular outcomes of SGLT-2 inhibitors in heart failure randomized controlled trials: A systematic review and meta-analysis. *Am Heart Hournal Plus Cardiol Res Pract*. (2023) 26:100261. doi: 10.1016/j.ahjo.2023.100261

100. Singh AK, Singh R. Gender difference in cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in type 2 diabetes: A systematic review and meta-analysis of cardio-vascular outcome trials. *Diabetes Metab Syndr*. (2020) 14:181–7. doi: 10.1016/j.dsx.2020.02.012

101. Clegg LE, Penland RC, BaChina S, Boulton DW, Thuresson M, Heerspink HJL, et al. Effects of exenatide and open-label SGLT2 inhibitor treatment, given in parallel or sequentially, on mortality and cardiovascular and renal outcomes in type 2 diabetes: insights from the EXSCEL trial. *Cardiovasc Diabetol*. (2019) 18:138. doi: 10.1186/s12933-019-0942-x

102. Lam CSP, Ramasundarahettige C, Branch KRH, Sattar N, Rosenstock J, Pratley R, et al. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. *Circulation*. (2022) 145:565–74. doi: 10.1161/CIRCULATIONAHA.121.057934

103. Neves JS, Borges-Canha M, Vasques-Nóvoa F, Green JB, Leiter LA, Granger CB, et al. GLP-1 receptor agonist therapy with and without SGLT2 inhibitors in patients with type 2 diabetes. *J Am Coll Cardiol*. (2023) 82:517–25. doi: 10.1016/j.jacc.2023.05.048

104. Arnott C, Neuen BL, Heerspink HJL, Figtree GA, Kosiborod M, Lam CS, et al. The effects of combination canagliflozin and glucagon-like peptide-1 receptor agonist therapy on intermediate markers of cardiovascular risk in the CANVAS program. *Int J Cardiol*. (2020) 318:126–9. doi: 10.1016/j.ijcard.2020.06.011

105. Cahn A, Wiviott SD, Mosenzon O, Murphy SA, Goodrich EL, Yanuv I, et al. Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: *Post hoc* analyses from DECLARE-TIMI 58. *Diabetes Obes Metab*. (2021) 23:29–38. doi: 10.1111/dom.14179

106. Riley DR, Essa H, Austin P, Preston F, Kargbo I, Ibarburu GH, et al. All-cause mortality and cardiovascular outcomes with sodium-glucose Co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and with combination therapy in people with type 2 diabetes. *Diabetes Obes Metab*. (2023) 25:2897–909. doi: 10.1111/dom.15185

107. Ma H, Lin Y-H, Dai L-Z, Lin C-S, Huang Y, Liu S-Y. Efficacy and safety of GLP-1 receptor agonists versus SGLT-2 inhibitors in overweight/obese patients with or without diabetes mellitus: a systematic review and network meta-analysis. *BMJ Open*. (2023) 13:e061807. doi: 10.1136/bmjopen-2022-061807

108. Li C, Luo J, Jiang M, Wang K. The efficacy and safety of the combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors in type 2 diabetes mellitus: A systematic review and meta-analysis. *Front Pharmacol*. (2022) 13. doi: 10.3389/fphar.2022.838277

109. Guo M, Gu J, Teng F, Chen J, Ma X, Chen Q, et al. The efficacy and safety of combinations of SGLT2 inhibitors and GLP-1 receptor agonists in the treatment of type 2 diabetes or obese adults: a systematic review and meta-analysis. *Endocrine*. (2020) 67:294–304. doi: 10.1007/s12020-019-02175-6

110. Patoulias D, Stavropoulos K, Imprialos K, Katsimardou A, Kalogirou M-S, Koutsampasopoulos K, et al. Glycemic efficacy and safety of glucagon-like peptide-1 receptor agonist on top of sodium-glucose co-transporter-2 inhibitor treatment compared to sodium-glucose co-transporter-2 inhibitor alone: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*. (2019) 158:107927. doi: 10.1016/j.diabres.2019.107927

111. Ahmad A, Sabbour H. Effectiveness and safety of the combination of sodium-glucose transport protein 2 inhibitors and glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of observational studies. *Cardiovasc Diabetol*. (2024) 23:99. doi: 10.1186/s12933-024-02192-4

112. García-Vega D, Cinza-Sanjurjo S, Eiras S, González-Juanatey JR. Combined sodium-glucose-transporters inhibitors and glucagon-like-peptide receptor agonist compared with monotherapy improves long-term survival: A real-world registry. *Am J Med*. (2024) 137:761–769.e1. doi: 10.1016/j.amjmed.2024.04.032

113. Marfella R, Prattichizzo F, Sardu C, Rambaldi PF, Fumagalli C, Marfella LV, et al. GLP-1 receptor agonists-SGLT-2 inhibitors combination therapy and cardiovascular events after acute myocardial infarction: an observational study in patients with type 2 diabetes. *Cardiovasc Diabetol*. (2024) 23:10. doi: 10.1186/s12933-023-02118-6

114. Simms-Williams N, Treves N, Yin H, Lu S, Yu O, Pradhan R, et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study. *BMJ*. (2024) 385:e078242. doi: 10.1136/bmj-2023-078242

115. Marx N, Deanfield JE, Mann JFE, Arechavaleta R, Bain SC, Bajaj HS, et al. Oral semaglutide and cardiovascular outcomes in people with type 2 diabetes, according to SGLT2i use: prespecified analyses of the SOUL randomized trial. *Circulation*. (2025) 151:1639–50. doi: 10.1161/CIRCULATIONAHA.125.074545

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 18 July 2025
DOI 10.3389/fendo.2025.1579836

Check for updates

OPEN ACCESS

EDITED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

REVIEWED BY
Luis Del Carpio-Orantes,
Mexican Social Security Institute, Mexico
Pietro Scicchitano,
ASLBari - Azienda Sanitaria Localedella provincia di Bari (ASL BA), Italy

*CORRESPONDENCE
Hongqiang Ren
rhq1980@163.com

†These authors have contributed equally to this work

RECEIVED 19 February 2025
ACCEPTED 26 June 2025
PUBLISHED 18 July 2025

CITATION
Tan Z, Liu Y, Liu L, Li S, Xue X, Li X and Ren H (2025) Association of estimated glucose disposal rate with atrial fibrillation, heart failure and cardiovascular mortality in patients with diabetes: a prospective cohort study from the UK Biobank. *Front. Endocrinol.* 16:1579836. doi: 10.3389/fendo.2025.1579836

COPYRIGHT
© 2025 Tan, Liu, Liu, Li, Xue, Li and Ren. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Association of estimated glucose disposal rate with atrial fibrillation, heart failure and cardiovascular mortality in patients with diabetes: a prospective cohort study from the UK Biobank

Zhen Tan[1†], Yijun Liu[1†], Lei Liu[1†], Shuang Li[1], Xinrui Xue[1], Xiaoping Li[2] and Hongqiang Ren[1*]

[1]Department of Cardiology, Suining Central Hospital, Suining, Sichuan, China, [2]Department of Cardiology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan, China

Background: Estimated glucose disposal rate (eGDR) was a novel non-insulin-based marker of insulin resistance (IR), which had been used in many studies to evaluate the clinical prognosis of diabetes. However, the association of eGDR with atrial fibrillation (AF), heart failure (HF) and cardiovascular mortality in patients with diabetes remains unclear.

Methods: The study utilized UK Biobank data from 31,733 participants. Kaplan-Meier curves and Log-rank tests assessed AF, HF, and cardiovascular mortality incidence. Multivariate Cox models and restricted cubic splines analyzed the associations of eGDR with these outcomes. Polygenic Risk Score (PRS) analysis evaluated the joint effects of eGDR and PRS. Boruta algorithm filtered key predictive variables. Subgroup analysis was performed using cardiovascular high-risk factors, and mediation analysis explored the relationships of eGDR with the outcomes.

Results: Subjects with higher eGDR were more likely to be female, younger, more physically active, non-smoker, and non-drinker. The cumulative incidence of AF, HF, and cardiovascular mortality in the higher quartiles of GDR were significantly lower than those in the lowest quartile (log-rank $P < 0.001$ for all). eGDR exhibited an independent negative linear correlation with the risk of AF (HR = 0.94, 95% CI: 0.91-0.96), HF (HR = 0.78, 95% CI: 0.74-0.82), and cardiovascular mortality (HR = 0.86, 95% CI: 0.83-0.88) risk. eGDR made the most significant contribution to the predicted outcomes. In diabetic patients with high genetic susceptibility, high eGDR could reduce the risk of AF (HR = 0.68, 95% CI: 0.51-0.90), HF (HR = 0.43, 95% CI: 0.29-0.62), and cardiovascular mortality (HR = 0.30, 95% CI: 0.22-0.42). Mediation analysis demonstrated that 10.7%, 7.9%, and 10.3% of the relationship between eGDR and AF, HF, and cardiovascular mortality among individuals with diabetes were mediated by eGFR, respectively.

Conclusions: This study demonstrated that higher eGDR levels were associated with a decreased risk of AF, HF, and cardiovascular mortality. Therefore, eGDR may serve as a valuable tool for predicting the risk of AF, HF, and cardiovascular mortality in patients with diabetes.

KEYWORDS

estimated glucose disposal rate, cardiovascular disease, atrial fibrillation, heart failure, cardiovascular mortality, patients with diabetes, UK Biobank

Introduction

Diabetes, a chronic metabolic disorder characterized by persistently elevated blood glucose levels, has emerged as a significant global health burden, ranking among the leading causes of death and disability worldwide (1). Individuals with diabetes exhibit a markedly increased risk of cardiovascular disease (CVD), which encompasses myocardial infarction (MI), heart failure (HF), atrial fibrillation (AF), and cardiovascular mortality (2, 3). Identifying risk factors for CVD in diabetic patients is critical, prompting extensive research into various biomarkers that can assess CVD risk in both diabetic and non-diabetic populations (4–7).

The estimated glucose disposal rate (eGDR) is an index derived from waist circumference, hypertension, and glycated hemoglobin (HbA1c), used to evaluate the body's capacity to process glucose (8). Notably, eGDR is closely linked to insulin resistance (IR), a key risk factor for CVD (9). IR not only underpins type 2 diabetes but also contributes to a cluster of metabolic abnormalities, including dyslipidemia, inflammation, and endothelial dysfunction, all of which drive the onset and progression of CVD (10). Consequently, eGDR has increasingly been utilized as a predictor of cardiovascular mortality risk (11–13). Traditional methods for assessing insulin sensitivity, such as the glucose clamp technique, are often complex, invasive, time-consuming, expensive, and require specialized equipment and trained personnel (14). In contrast, eGDR offers a simple, convenient, and cost-effective alternative, as it can be readily calculated using routinely available clinical parameters. This makes eGDR particularly suitable for routine clinical practice and large-scale epidemiological studies (15, 16).

Previous studies have demonstrated that eGDR is independently and negatively correlated with coronary artery disease severity, suggesting its potential utility in early identification and risk stratification of coronary heart disease patients, thereby improving prognosis (17). Similarly, eGDR has been shown to predict cardiovascular events and mortality in non-diabetic patients with chronic kidney disease (18). Additionally, eGDR has been associated with arterial stiffness and mortality in adults with non-alcoholic fatty liver disease (19). However, evidence regarding the association between eGDR and AF, HF, and cardiovascular mortality remains limited. Given that AF and HF represent two major cardiovascular complications of diabetes, elucidating their relationship with eGDR could provide novel insights into the pathophysiology of these conditions and inform more effective preventive and therapeutic strategies. Therefore, the aim of this study was to evaluate the association of eGDR with AF, HF, and cardiovascular mortality in patients with diabetes and to explore the underlying mechanisms.

Materials and methods

Study population

The UK Biobank (UKB) is a large-scale biomedical database and research resource and has collected an unprecedented amount of biological and medical data on 500,000 participants (229,041 males and 273,293 females) from UK. UKB has received approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. Therefore, researchers do not require separate ethical clearance and can operate under the RTB approval. Data from the UKB are accessible to researchers after receiving research approval from the UKB. This study was conducted under UKB licence (Application ID:106027).

This study sifted 36,126 participants who had evidence of diabetes at baseline, the inclusion criteria were as follows: (1) Hospital diagnosis records indicating diabetes. (2) HbA1c ≥ 6.5%. (3) Fasting glucose ≥ 7.0mmol/L. (4) Receipt of hypoglycemic treatment. Participants were excluded if they had missing data on waist circumference (WC), glycosylated hemoglobin (HbA1c), or a history of AF and HF. As a result, a total of 31,733 participants were included in the final analysis.

Data collection and definition

At recruitment, participants completed computerised questionnaires on lifestyle, baseline demographic, and medical history, including gender, age, race, education level, body mass index (BMI), WC, height, smoking status (never, former, and current), alcohol consumption status (never, former, and current),

frequency of moderate physical activity (Never, < 3 times per day, ≥ 3 times per day), household income. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, a hospital diagnosis record, use of blood pressure medication, specialist diagnosis, drug reimbursement records, or self-reported information. Additional data collected included the use of aspirin, insulin, blood pressure medication, and cholesterol-lowering medication. Laboratory assessments included measurements of glycated hemoglobin (HbA1c), glucose (Glu), albumin (ALB), serum creatinine (Scr), uric acid (Ua), blood urea nitrogen (BUN), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), and C-reactive protein (CRP).

The formula used to calculate the eGDR was as follows: eGDR=21.158 - [(0.09 × waist circumference (cm)] - [(3.407 × Hypertension (yes or no)] - [0.551 × HbA1c (%)] (15). Participants were categorized into four groups (Q1, Q2, Q3, Q4) based on eGDR level using the 25th, 50th, and 75th percentiles as cutoff points. The lowest quartile (Q1) served as the reference group.

Assessment of atrial fibrillation, heart failure and cardiovascular mortality

Hospital records linked to disease outcomes were obtained from the UK Biobank. The international statistical classification of diseases (ICD-10) was used to define the classification of diseases. The primary endpoints of this study were the diagnosis of AF (codes I48, I48.0-4, and I48.9), HF (codes I50, I13.0, I13.2, and I11.0) and cardiovascular death. Cardiovascular death was defined based on records as mortality caused by acute myocardial infarction (AMI), AF, HF, arrhythmia, cardiac surgery, or other cardiovascular-related causes. For this study, the hospital admission and death data were updated up to 19 December 2022, and thus the follow-up period was terminated on this date. The date of diagnosis was defined as the earliest day when the disease manifested. The follow-up duration was calculated as the time interval between the baseline survey date and the earliest occurrence among the disease diagnosis date, the death date, the loss-to-follow-up date, or the end of the follow-up period. During the follow-up period, cardiovascular mortality rates were computed for each quartile of eGDR.

Definition of polygenic risk score

Patients with missing Polygenic Risk Score (PRS) data were excluded from the analysis. Consequently, a total of 31,375 diabetic patients were included in the PRS analysis. Standard PRS for AF and CVD, available from the UK Biobank, has been previously published. The PRS was calculated as the weighted sum of the effect sizes of individual genetic variants multiplied by their allele dosages, using a Bayesian approach applied to meta-analyze summary statistics derived from genome-wide association study (GWAS) data (20). In this study, the PRS of AF and CVD were categorized into low genetic risk (quintile 1), intermediate genetic risk (quintile 2 to 4) and high genetic risk (quintile 5).

Statistical analysis

R software (version 4.3.0, Institute for Statistics and Mathematics, Vienna, Austria) was used for all analyses. Continuous variables were expressed as mean ± standard deviation, and if variables were normally distributed, analysis of variance (ANOVA) was performed to assess differences between groups. Otherwise, they were presented as Median or quartile *M* (P25, P75). Mann Whitney U test was used for comparison among quartiles. Categorical variables were expressed as frequency and percentage. Chi-square tests were conducted to compare proportions across groups. Missing values of covariates were handled using multiple imputation. The maximum proportion of missing values was 6.1%, with an average of 0.51%.

The cumulative incidence rate curves for AF, HF, and cardiovascular mortality were estimated using the Kaplan-Meier method and compared using the log-rank test across eGDR quartile groups. Three multivariate Cox proportional hazards regression models were constructed to evaluate the the association of eGDR with AF, HF and cardiovascular mortality in patients with diabetes. Model 1 was unadjusted; model 2 adjusted for age, gender, race, education level, BMI, smoking status, and alcohol consumption status. Model 3 included all variables from Model 2, and further adjusted for SBP, DBP, TG, TC, eGFR, UA, aspirin, cholesterol-lowering medication, blood pressure medication, and insulin use. Nonlinear correlations between eGDR and AF, HF and cardiovascular mortality were explored using a restricted cubic spline (RCS) curve based on Cox regression model.

To evaluate the joint effects of PRS on the association of eGDR with risk of AF, HF and cardiovascular mortality, analyses were stratified by genetic risk categories (low genetic risk, intermediate genetic risk and high genetic risk). Each genetic risk category was further divided into four groups (Q1, Q2, Q3, Q4) based on eGDR level using the 25th, 50th, and 75th percentiles as cutoff points individually. The association of eGDR with the risk of AF, HF, and cardiovascular mortality was analyzed using multivariate Cox proportional hazards regression Model 3.

Subgroup analyses were conducted for significant covariates (age, gender, BMI, education level, smoking status, and alcohol consumption status) to assess the effects of eGDR on the incidence of AF, HF, and cardiovascular mortality across several subgroups. We used the Random Forest-based Boruta`s algorithm for feature selection to filter out the variables that contribute most to prediction model by generating shadow features and comparing their importance. Mediation analysis was performed to investigate the mediating effects of eGDR on AF, HF, and cardiovascular mortality. Variables in Model 3 that exhibited substantial relationships with eGDR were selected as potential mediators. The percentage mediated was computed as indirect effect/(indirect+direct impact). A two-sided *P* values<0.05 indicated statistical significance.

Result

Demographic characteristics of the study participants

A total of 31,733 diabetes patients without AF and HF were included in this study from the UKB finally, and the patient selection process was shown in Figure 1. Demographic characteristics of the subjects according to the quartiles of eGDR were showed in Table 1. The average age of the subjects was 59.192 ± 7.295 years, with a majority being non-Hispanic White (88.56%). The mean value of eGDR was 5.934 ± 2.532. Subjects with higher eGDR were more likely to be female, younger, more physically active, non-smoker, and non-drinker. Additionally, subjects with atrial fibrillation, heart failure, or cardiovascular death exhibited lower eGDR levels. The group with the highest eGDR exhibited the lowest proportion of patients using blood pressure medication, cholesterol-lowering medication, aspirin, and insulin.

Analysis of the association of eGDR with AF, HF, and cardiovascular mortality

During a median follow-up of 12.8 years, 3,892 (12.26%) subjects developed atrial fibrillation (AF), 3,045 (9.60%) subjects developed heart failure (HF), and 1,911 (6.02%) subjects experienced cardiovascular mortality. The Kaplan-Meier survival curves and Log-rank test showed that the cumulative incidence of AF, HF and cardiovascular mortality was was significantly lower in the highest eGDR quartile compared to the lowest quartile (log-rank $P < 0.001$ for all) (Figure 2).

We conducted three Cox regression models to investigate the associations between eGDR with the risk of AF, HF and cardiovascular mortality. The results demonstrated that eGDR was significantly associated with both AF (HR=0.84, 95% CI: 0.83-0.85 in Model 1; HR = 0.90, 95% CI: 0.88-0.92 in Model 2; HR = 0.94, 95% CI: 0.91-0.96 in Model 3), HF (HR = 0.79, 95% CI: 0.78-0.80 in Model 1; HR = 0.82, 95% CI: 0.81-0.84 in Model 2; HR = 0.78, 95% CI: 0.74-0.82 in Model 3), and cardiovascular mortality (HR = 0.81, 95% CI: 0.80-0.83 in Model 1; HR = 0.84, 95% CI: 0.82-0.86 in Model 2; HR = 0.86, 95% CI: 0.83-0.88 in Model 3) (Table 2).

We performed restrictive cubic spline analysis based on the Cox proportional hazards regression model to investigate nonlinear correlations between eGDR and AF, HF and cardiovascular mortality. With eGDR as the x-axis and the hazard ratio as the y-axis, the smoothed curve fitting diagram after adjusting for confounding factors from Model 3 showed that eGDR presented a negative linear correlation with the AF (P for non-linear = 0.227) and HF (P for non-linearity = 0.067), and a non-linearity relationship with cardiovascular mortality (P for non-linearity = 0.012). Notably, despite the nonlinear pattern, an increasing level of eGDR was still associated with a decreasing trend in cardiovascular mortality (Figure 3).

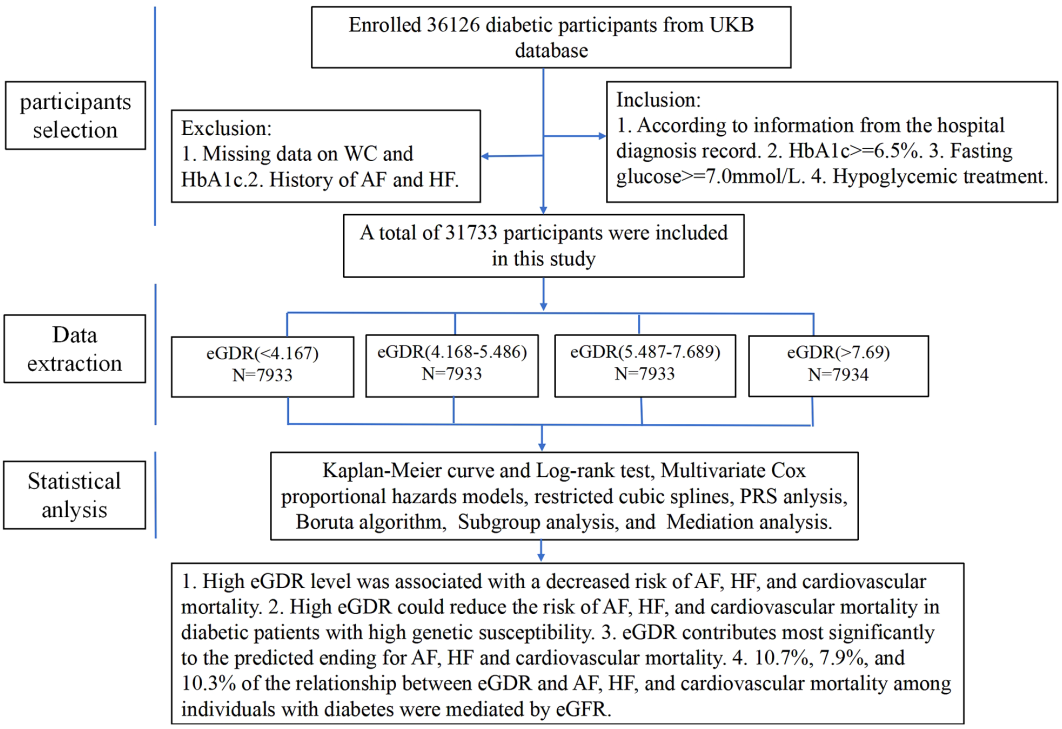


FIGURE 1
Flow chart of study selection.

TABLE 1 Demographic characteristics of the study participants.

Characteristic	Total	eGDR				P
		Q1 (<4.167)	Q2 (4.168 5.486)	Q3 (5.487-7.689)	Q4 (>7.690)	
Participants	n=31733	n=7933	n=7933	n=7933	n=7934	
Age, years	59.192±7.295	59.035±6.949	60.328±6.681	59.825±7.151	57.58±8.032	<0.001
Gender, male, n (%)	18178 (57.28)	5548 (69.94)	5135 (64.73)	4182 (52.72)	3313 (41.76)	<0.001
BMI, kg/m2	30.869±5.855	36.374±5.676	31.239±4.112	28.889±4.653	27.003±4.145	<0.001
Height, cm	2.5±1.54	2.234±1.468	2.422±1.516	2.559±1.551	2.785±1.573	<0.001
WC, cm	100.97±14.733	116.861±11.023	102.868±7.121	94.987±11.647	89.183±11.381	<0.001
SBP, mmHg	145.788±18.696	149.217±18.336	149.184±18.431	147.676±18.728	137.005±16.359	<0.001
DBP, mmHg	84.006±10.395	86.904±10.886	85.651±10.616	84.189±10.21	79.242±7.924	<0.001
HbA1c, (%)	6.812±1.357	7.704±1.66	6.767±0.995	6.51±1.193	6.268±1.007	<0.001
Hypertention, n (%)	22195 (69.94)	22195 (69.94)	22195 (69.94)	22195 (69.94)	22195 (69.94)	<0.001
eGDR	5.934±2.532	3.007±1.029	4.839±0.375	6.387±0.624	9.501±1.167	<0.001
Education level, n (%)						<0.001
College or above	7798 (25.05)	1681 (21.62)	1720 (22.08)	1922 (24.77)	2475 (31.72)	
others	23330 (74.95)	6093 (78.38)	6071 (77.92)	5838 (75.23)	5328 (68.28)	
Race						<0.001
White	27892 (88.56)	7204 (91.42)	6895 (87.44)	6862 (87.30)	6931 (88.06)	
Latin	202 (0.64)	48 (0.61)	48 (0.61)	60 (0.76)	46 (0.58)	
Black	2512 (7.98)	425 (5.39)	667 (8.46)	716 (9.11)	704 (8.94)	
Asian	890 (2.83)	203 (2.58)	275 (3.49)	222 (2.82)	190 (2.41)	
Smoking status, n (%))						<0.001
Never	14978 (47.67)	3309 (42.09)	3536 (45.04)	3916 (49.89)	4217 (53.69)	
Former	12918 (41.12)	3676 (46.76)	3518 (44.81)	3048 (38.83)	2676 (34.07)	
Now	3521 (11.21)	877 (11.15)	797 (10.15)	886 (11.29)	961 (12.24)	
Alcohol consumption status, n (%)						<0.001
Never	2631 (8.33)	619 (7.84)	646 (8.18)	671 (8.51)	695 (8.82)	
Former	2084 (6.60)	675 (8.55)	514 (6.51)	457 (5.79)	438 (5.56)	
Now	26854 (85.06)	6604 (83.62)	6741 (85.32)	6760 (85.70)	6749 (85.63)	
Frequency of moderated physical activity, n (%)						<0.001
Never	5278 (18.29)	1771 (24.85)	1294 (18.02)	1190 (16.43)	1023 (14.00)	
<3 times per day	10239 (35.48)	2494 (34.99)	2585 (35.99)	2525 (34.87)	2635 (36.06)	
≥3 times per day	13342 (46.23)	2862 (40.16)	3303 (45.99)	3527 (48.70)	3650 (49.95)	
Medications						
Cholesterol-lowering medication, n (%)	18997 (60.17)	5673 (71.78)	5614 (71.04)	4720 (59.85)	2990 (37.94)	<0.001
Blood pressure medication, n (%)	17029 (53.93)	6280 (79.46)	6050 (76.55)	4454 (56.47)	245 (3.11)	<0.001
Aspirin, n (%)	12773 (40.47)	4036 (51.13)	3864 (48.92)	3094 (39.22)	1779 (22.59)	<0.001

(Continued)

TABLE 1 Continued

Characteristic	Total	eGDR				P
		Q1 (<4.167)	Q2 (4.168 5.486)	Q3 (5.487-7.689)	Q4 (>7.690)	
Insulin, n (%)	18997 (60.17)	5673 (71.78)	5614 (71.04)	4720 (59.85)	2990 (37.94)	<0.001
Laboratory assessments						
Scr, umol/L	74.125±27.087	77.247±32.252	76.797±30.257	73.315±26.105	69.236±16.291	<0.001
eGFR, ml/min	87.96 (76.785-98.247)	85.306 (72.443-96.657)	85.961 (74.577-96.143)	87.907 (77.351-97.683)	92.149 (82.153-101.297)	<0.001
Ua, umol/L	329.089±84.511	349.869±89.019	345.259±81.717	324.739±80.827	297.131±75.625	<0.001
BUN, umol/L	5.732±1.813	5.954±2.161	5.871±1.91	5.695±1.68	5.415±1.369	<0.001
TC, mmol/L	4.858±1.215	4.608±1.143	4.68±1.146	4.92±1.235	5.215±1.239	<0.001
TG, mmol/L	1.870 (1.294-2.69)	2.175 (1.561-3.05)	1.968 (1.407-2.77)	1.772 (1.233-2.545)	1.568 (1.071-2.312)	<0.001
LDL-C, mmol/L	1.414 (1.153-1.728)	1.34 (1.097-1.625)	1.375 (1.132-1.656)	1.423 (1.161-1.756)	1.532 (1.242-1.856)	<0.001
HDL-C, mmol/L	1.184 (1.001-1.422)	1.069 (0.919-1.241)	1.144 (0.981-1.339)	1.234 (1.05-1.472)	1.338 (1.105-1.62)	<0.001
Cys-C, mmol/L	0.927 (0.832-1.048)	0.984 (0.872-1.125)	0.951 (0.854-1.071)	0.919 (0.827-1.031)	0.873 (0.791-0.97)	<0.001
GLU, mmol/L	7.044 (5.466-8.56)	7.678 (5.933-10.648)	6.616 (5.366-8.206)	6.678 (5.307-8.016)	7.104 (5.411-8.045)	<0.001
ALB, g/L	44.9±2.85	44.331±2.884	45.181±2.82	45.169±2.835	44.918±2.779	<0.001
CRP, g/L	1.93 (0.92-4.02)	2.98 (1.5-6.06)	1.98 (0.97-3.9)	1.66 (0.8-3.49)	1.38 (0.66-2.91)	<0.001
Primary endpoints						
Atrial fibrillation, n (%)	3892 (12.26)	1489 (18.77)	1075 (13.55)	863 (10.88)	465 (5.86)	<0.001
Heart failure, n (%)	3045 (9.60)	1346 (16.97)	790 (9.96)	627 (7.90)	282 (3.55)	<0.001
Cardiovascular mortality, n (%)	1911 (6.02)	770 (9.71)	532 (6.71)	395 (4.98)	214 (2.70)	<0.001
All-cause mortality, n (%)	5788 (18.24)	2048 (25.82)	1543 (19.45)	1311 (16.53)	886 (11.17)	<0.001

The chi-square test was used for the comparison of categorical variables; the t-test was employed to compare variates with normal distribution, and the rank-sum test was conducted for variates with skewed distribution. eGDR, estimated glucose disposal rate; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Ua, uric acid ; BUN, blood urea nitrogen; TC, total cholesterol; TG, HDL-C, high-density lipoprotein cholesterol; LDL-C,low-density lipoprotein cholesterol; GLU, glucose; Scr, serum creatinine; Cys-C,Cystatin C; ALB, Albumin; CRP, C-reactive protein.

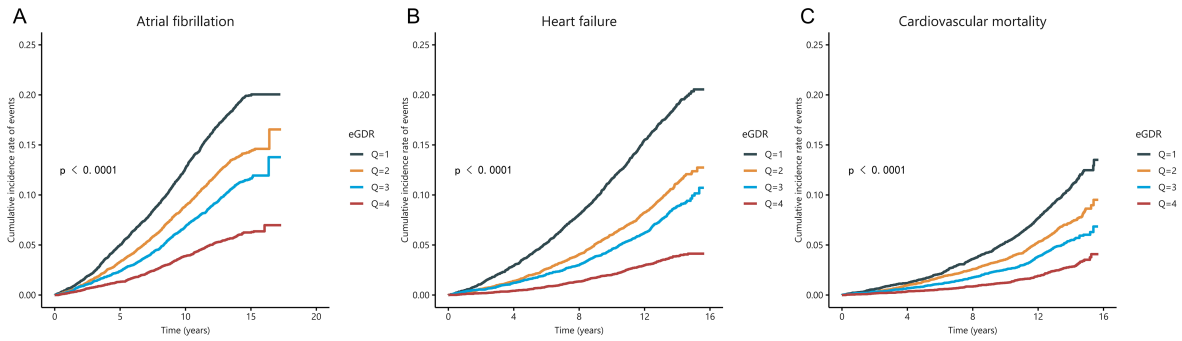


FIGURE 2
The Kaplan-Meier curve for cumulative incidence of AF **(A)**, HF **(B)**, and cardiovascular mortality **(C)** was based on eGDR quartiles for diabetic participants.

TABLE 2 HRs (95% CIs) for AF, HF, and cardiovascular mortality according to the eGDR quartiles.

Variables	Overall	Quartiles of eGDR				
		Q1 (<4.167)	Q2 (4.168-5.486)	Q3 (5.487-7.689)	Q4 (>7.690)	*P for trend*
AF						
Number of incidence	N=3892	N=1489	N=1075	N=863	N=465	
Model 1 HR (95%CI) P-value	0.84 (0.83, 0.85) <0.001	Reference	0.70 (0.65,0.76) <0.001	0.55 (0.51, 0.60) <0.001	0.29 (0.26, 0.32) <0.001	<0.001
Model 2 HR (95%CI) P-value	0.90 (0.88, 0.92) <0.001	Reference	0.83 (0.76, 0.90) <0.001	0.78 (0.70, 0.86) <0.001	0.53 (0.47, 0.60) <0.001	<0.001
Model 3 HR (95%CI) P-value	0.94 (0.91, 0.96) <0.001	Reference	0.86 (0.79, 0.94) 0.001	0.86 (0.78, 0.96) 0.007	0.70 (0.60, 0.82) <0.001	<0.001
HF						
Number of incidence	N=3045	N=1346	N=790	N=627	N=282	
Model 1 HR (95%CI) P-value	0.79 (0.788, 0.80) <0.001	Ref (1.0)	0.55 (0.50, 0.60) <0.001	0.43 (0.39, 0.47) <0.001	0.19 (0.16, 0.21) <0.001	<0.001
Model 2 HR (95%CI) P-value	0.82 (0.81, 0.83) <0.001	Ref (1.0)	0.60 (0.54, 0.66) <0.001	0.54 (0.48, 0.61) <0.001	0.30 (0.26, 0.35) 0.001	<0.001
Model 3 HR (95%CI) P-value	0.7 8 (0.74, 0.82) <0.001	Ref (1.0)	0.66 (0.59, 0.72) <0.001	0.65 (0.57, 0.73) <0.001	0.43 (0.35, 0.51) <0.001	<0.001
Cardiovascular mortality						
Number of incidence	N=1911	N=770	N=532	N=395	N=214	
Model 1 HR (95%CI) P-value	0.81 (0.80, 0.83) <0.001	Ref (1.0)	0.67 (0.60, 0.75) <0.001	0.49 (0.43, 0.55) <0.001	0.26 (0.22, 0.30) <0.001	<0.001
Model 2 HR (95%CI) P-value	0.84 (0.82, 0.86) <0.001	Ref (1.0)	0.69 (0.61, 0.78) <0.001	0.59 (0.51, 0.68) <0.001	0.39 (0.33, 0.47) 0.001	<0.001
Model 3 HR (95%CI) P-value	0.86 (0.83, 0.88) <0.001	Ref (1.0)	0.76 (0.67, 0.86) <0.001	0.69 (0.59, 0.80) <0.001	0.55 (0.42, 0.65) <0.001	<0.001

Model 1: Unadjusted.
Model 2: Adjusted for age, gender, race, education level, BMI, smoking status, and alcohol consumption status.
Model 3: Included all variables from Model 2, and further adjusted for SBP, DBP, TG, TC, eGFR, UA, aspirin, cholesterol-lowering medication, blood pressure medication, and insulin use.
Ref: reference; eGDR, estimated glucose disposal rate; AF, atrial fibrillation; HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; Ua, uric acid.

Joint association of eGDR and PRS with AF, HF and cardiovascular mortality

Compared to low genetic risk, high genetic risk was associated with increased risk of AF (HR = 2.84, 95% CI:2.54-3.17), HF (HR = 1.55, 95% CI:1.38-1.74), and cardiovascular mortality (HR = 1.65, 95% CI:1.43-1.91), respectively (Supplementary Table S1). Behavioral and genetic factors jointly contributed to the risk of AF, HF and cardiovascular mortality. Therefore, we further investigated whether appropriate eGDR levels could mitigate the risks of AF, HF, and cardiovascular mortality in individuals with genetic susceptibility. Figure 4A1 showed that no statistically significant difference between low genetic risk and eGDR for AF risk (P =0.335). However, high eGDR was associated with a 27% and 32% reduced risk of AF among intermediate (HR = 0.73, 95% CI: 0.60-0.89) and high genetic risk groups (HR = 0.68, 95% CI: 0.51-0.90), respectively. Figure 4B1 showed that high eGDR was associated with a 63%, 55% and 53% reduced risk of HF among low (HR = 0.37, 95% CI: 0.23-0.59), intermediate (HR = 0.45, 95% CI: 0.36-0.57) and high genetic risk groups (HR = 0.47, 95% CI: 0.29-0.62), respectively. Figure 4C1 showed that high eGDR was associated with a 77%, 75% and 70% reduced risk of cardiovascular mortality among low (HR = 0.23, 95% CI: 0.26-0.33), intermediate (HR = 0.25, 95% CI: 0.21-0.31) and high genetic

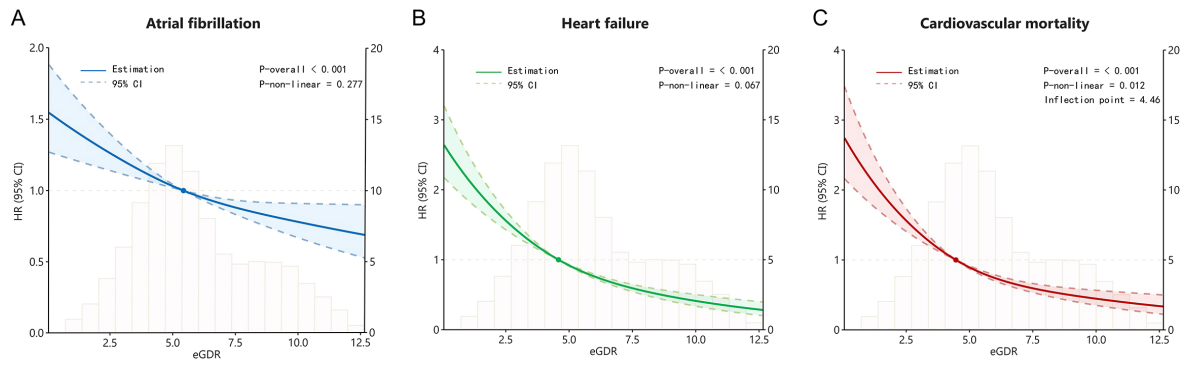


FIGURE 3
The restricted cubic spline curves for atrial fibrillation **(A)**, heart failure **(B)**, and cardiovascular mortality **(C)** based on eGDR for diabetic participants.

risk groups (HR = 0.30, 95% CI: 0.22-0.42), respectively. Individuals with low eGDR and high genetic risk exhibited a increased risk of AF, HF, and cardiovascular mortality compared with those with high eGDR and low genetic risk (Figures 4A2, B2, C2; Supplementary Table S2).

The variables that contribute most to model predictions

The feature screening results based on Boruta`s algorithm were showed in Figure 5; Supplementary Figure S1. After 500 iterations it was determined that the 20 variables most closely associated with AF were age, eGDR, BMI, WC, eGFR, DBP, SBP, HbAc1, UA, TC, AF-PRS, TG, gender, cholesterol-lowering medication, hypertension, blood pressure medication, asprin, insulin, race, alcohol consumption status, and smoking status. The 19 variables most closely associated with HF were eGDR, BMI, WC, eGFR, HbA1C, age, DSP, SBP, UA, TC, TG, blood pressure medication, insulin, hypertension, cholesterol-lowering medication, gender, asprin, CVD-PRS, and race. And the 20 variables most closely associated with cardiovascular mortality were eGDR, BMI, WC, eGFR, HbA1C, SBP, age, DSP, TC, UA, TG, gender, insulin, hypertension, cholesterol-lowering medication, blood pressure medication, race, asprin, smoking status, CVD-PRS, and education level. The analysis demonstrated that eGDR contributes most significantly to the the prediction of HF and cardiovascular mortality outcomes. While age contributes most significantly to the prediction of AF outcomes, eGDR ranks second in importance after age.

Subgroup analysis

To further evaluate the effect of eGDR on outcome indicators, subgroup analyses was performed according to ages, gender, BMI, education level, smoking status, and alcohol consumption status. The subgroup analysis of AF (Figure 6) revealed that there was no significant interaction between most subgroups (gender, education level, smoking status, and alcohol consumption status) (P for interaction > 0.05). However, significant interactions were observed between eGDR and age as well as BMI subgroups. we found eGDR was strongly associated with AF incidence in the age subgroup (P for interaction = 0.002). Compared with the lowest eGDR, high eGDR was associated with a 53% reduced risk of AF incidence in subjects < 65 years (HR = 0.47, 95% CI: 0.35–0.65) and a 24% reduced risk in subjects ≥ 65 years (HR = 0.76, 95% CI: 0.64–0.92). In the BMI subgroup, an interaction was also observed between eGDR and AF incidence (P for interaction = 0.009). High eGDR was associated with a 29% reduced risk of AF incidence in subjects with BMI < 30 kg/m^2 (HR = 0.71, 95% CI: 0.54-0.93) and a 43% reduced risk in subjects with BMI ≥ 30 kg/m^2 (HR = 0.57, 95% CI: 0.46-0.71).

The subgroup analysis of heart failure (HF) (Figure 6) showed that there was no significant interaction between eGDR and most subgroups (gender, BMI, smoking status, and alcohol consumption status) (P for interaction > 0.05). However, a significant interaction was observed between eGDR and age (P for interaction < 0.001). High eGDR was associated with a 78% reduced risk of HF incidence in subjects < 65 years (HR = 0.22, 95% CI: 0.15-0.32) and a 47% reduced risk in subjects ≥ 65 years (HR = 0.53, 95% CI: 0.43-0.66).

The subgroup analysis of cardiovascular mortality (Figure 6) demonstrated that there was no significant interaction between eGDR and any subgroups (P for interaction > 0.05), except for the age subgroup (P for interaction = 0.017). High eGDR was associated with a 64% reduced risk of cardiovascular mortality in subjects < 65 years (HR = 0.36, 95% CI: 0.24-0.55) and a 42% reduced risk in subjects ≥ 65 years (HR = 0.58, 95% CI: 0.45-0.75).

Mediation analysis

Insulin resistance was associated with renal function, particularly in individuals with diabetes. Mediation analysis revealed that 10.7%, 7.9%, and 10.3% of the associations between eGDR and AF, HF, and cardiovascular mortality, respectively, among individuals with

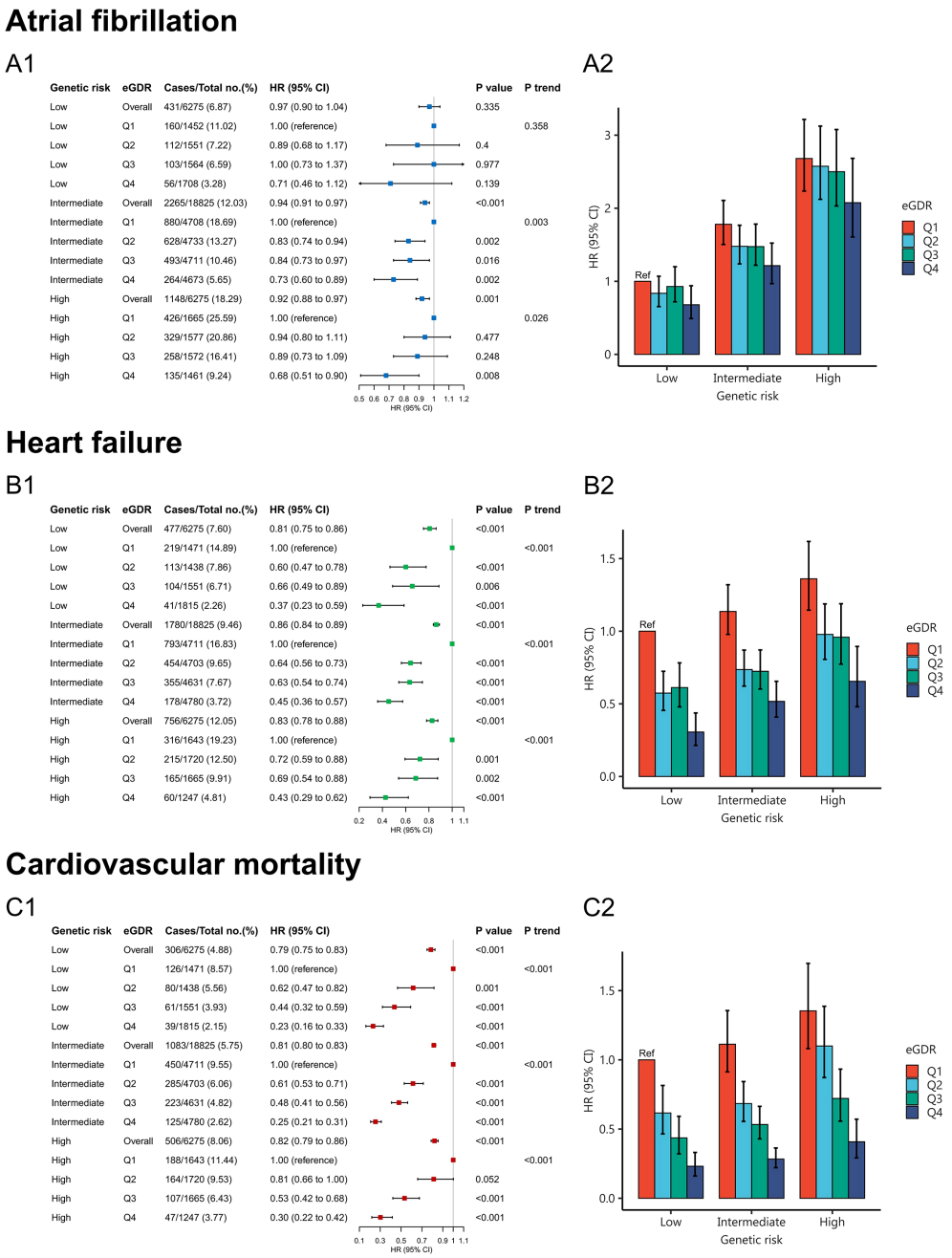


FIGURE 4
Joint association of eGDR and PRS with atrial fibrillation **(A1, A2)**, heart failure **(B1, B2)**, and cardiovascular mortality **(C1, C2)**.

diabetes were mediated by eGFR. eGFR was positively correlated with a reduced risk of AF (Estimate ± SE = 0.006 ± 0.001, $P < 0.001$), HF (Estimate ± SE = 0.009 ± 0.001, $P < 0.001$), and cardiovascular mortality (Estimate ± SE = -0.010 ± 0.001, $P < 0.001$). Additionally, eGDR was positively correlated with eGFR (Estimate ± SE = 0.897 ± 0.047, $P < 0.001$) and a reduced risk of AF (Estimate ± SE = 0.043 ± 0.009, $P < 0.001$), HF (Estimate ± SE = 0.097 ± 0.007, $P < 0.001$), and cardiovascular mortality (Estimate ± SE = 0.081 ± 0.008, $P < 0.001$) (Figure 7).

Discussion

This study clearly reveals a strong correlation between eGDR and atrial AF, HF, and cardiovascular mortality, providing important insights for a deeper understanding of the pathophysiology and clinical management of CVD. The following key findings were obtained: (1) Compared with the lowest eGDR group, the highest eGDR group exhibited a 30.1%, 57.2%, and 47.8% reduction in the risk of AF, HF, and cardiovascular mortality,

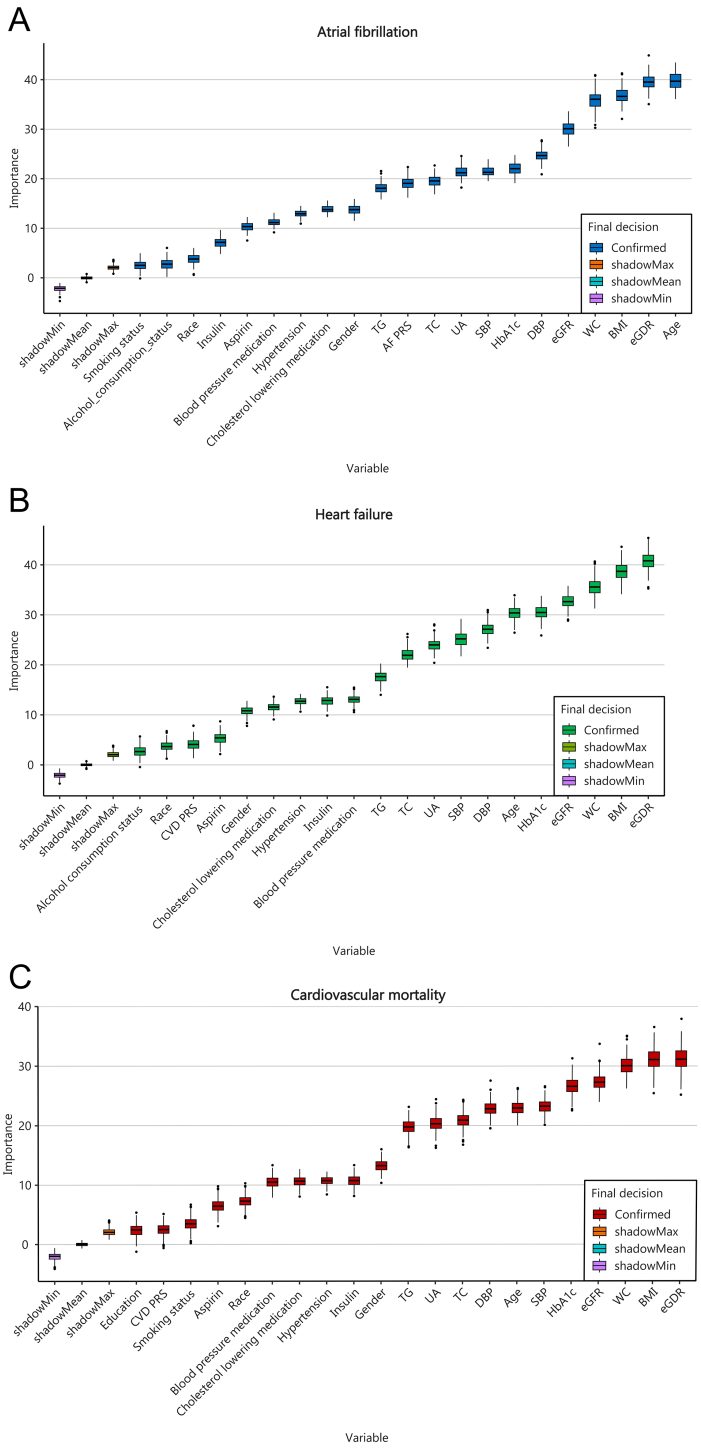


FIGURE 5
Feature selection based on the Boruta`s algorithm for AF **(A)**, HF **(B)**, and cardiovascular mortality **(C)**.

respectively. eGDR demonstrated a linear relationship with AF and HF; as eGDR increased, the risks of AF and HF progressively decreased. Although eGDR was non-linearly associated with cardiovascular mortality, it exhibited a negative correlation. When eGDR was ≥ 4.46, it showed a protective effect on cardiovascular mortality in diabetic patients. (2) High eGDR was associated with a 27% and 32% reduced risk of AF in intermediate and high genetic risk groups, respectively, a 63%, 55%, and 57% reduced risk of HF in low, intermediate, and high genetic risk groups, respectively, and a 77%, 75%, and 70% reduced risk of cardiovascular mortality in low, intermediate, and high genetic risk groups, respectively. High eGDR could reduce the risk of AF, HF, and cardiovascular mortality in

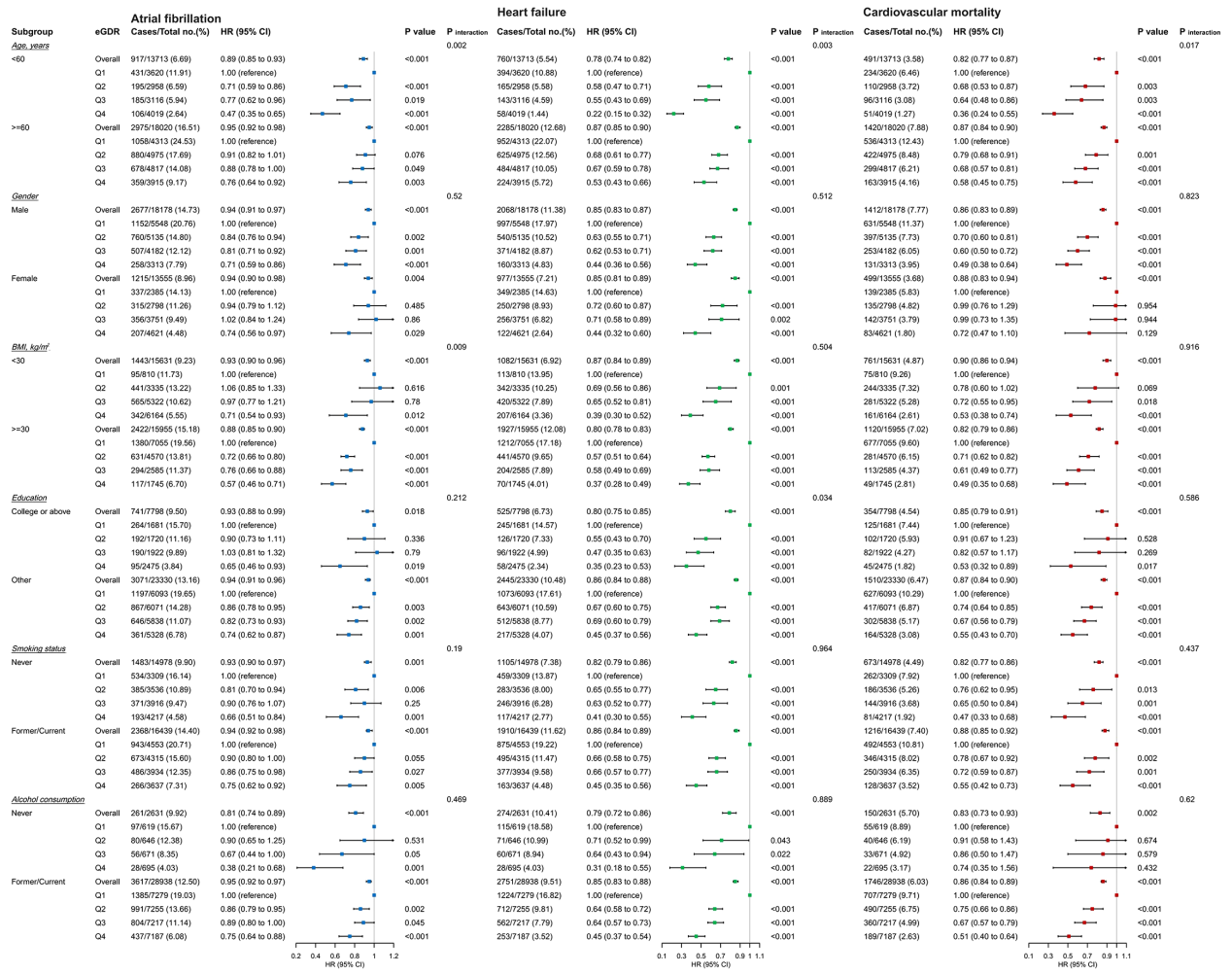


FIGURE 6
Subgroup and interaction analyses among the quartile Q1-Q4 and AF, HF, and cardiovascular mortality across various subgroups.

diabetic patients with high genetic susceptibility. (3) Boruta's algorithm demonstrated that eGDR contributes most significantly to the prediction of AF, HF, and cardiovascular mortality outcomes. (4) Mediation analysis revealed that 10.7%, 7.9%, and 10.3% of the relationships between eGDR and AF, HF, and cardiovascular mortality, respectively, among individuals with diabetes were mediated by eGFR.

The impact of IR on the cardiovascular system is multidimensional. IR reduces cellular sensitivity to insulin, rendering glucose ineffective for cellular use, and prolongs hyperglycaemic states, which may cause a range of vascular lesions. This leads to lipid deposition on vascular walls and accelerates the progression of atherosclerosis. Some reports indicate that IR represents a chronic inflammatory state (21, 22). In the pathology of IR, adipose tissue secretes various inflammatory factors such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) (23, 24). These inflammatory factors activate inflammatory cells such as monocytes and T-lymphocytes, which adhere to vascular endothelial cells and migrate to the subendothelium, where they phagocytose lipids to form foam cells, an early event in atherosclerotic plaque formation (25). Additionally, inflammatory factors inhibit the synthesis of nitric oxide, an important vasodilator, and a decrease in its synthesis leads to vascular endothelial dysfunction, promoting vasoconstriction and platelet aggregation, further increasing the risk of CVD (26).

A clear correlation between IR and hypertension has been demonstrated (27). On the one hand, insulin can directly act on renal tubules to increase sodium reabsorption; on the other hand, IR activates the sympathetic nervous system, increases catecholamine secretion, stimulates the renin-angiotensin-aldosterone system (RAAS), and contributes to increased aldosterone secretion (28, 29). These changes lead to sodium and water retention, resulting in high blood pressure. Chronic high blood pressure increases cardiac afterload, leading to myocardial hypertrophy, ventricular remodelling, and an increased risk of AF, HF, and cardiovascular mortality (30, 31). In addition, IR and insulin secretion are closely associated with the pancreas and gastrointestinal system (32, 33). Previous study had demonstrated a significant link between

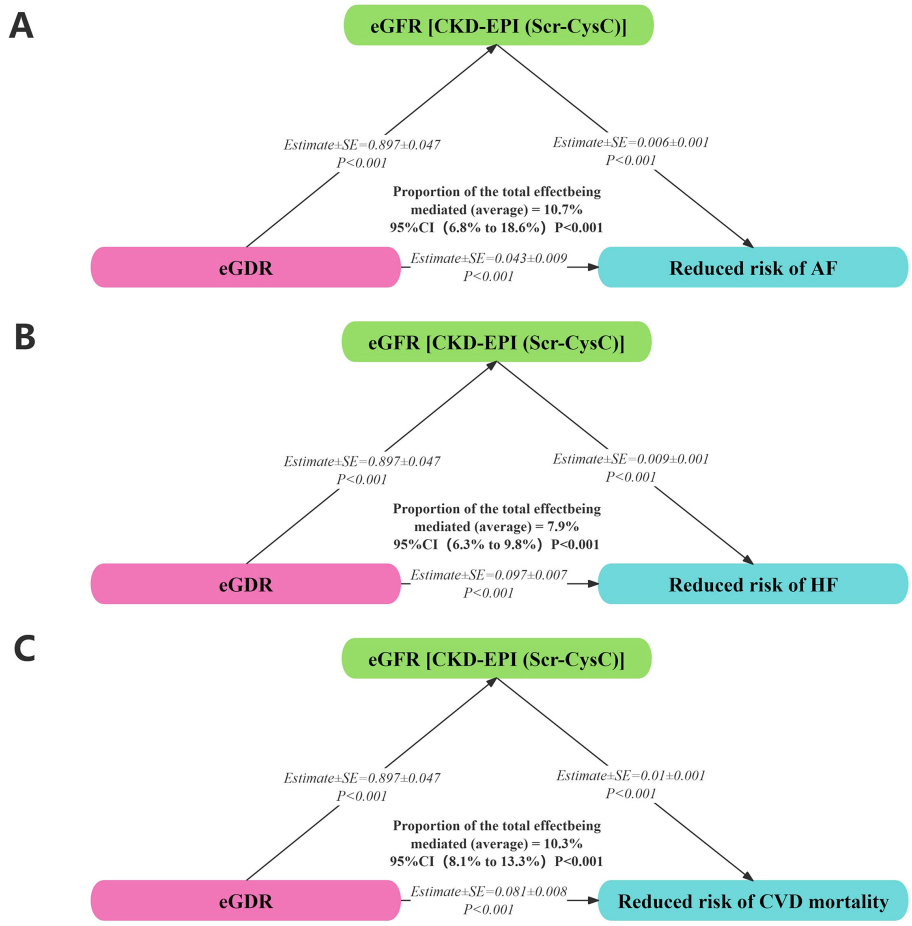


FIGURE 7
Mediation analysis on associations between eGDR with AF **(A)**, HF **(B)**, and cardiovascular mortality **(C)**.

gastrointestinal disorders and CVD, particularly AF. Despite their apparent differences as distinct pathological phenomena, they in fact share common pathogenic mechanisms, thereby establishing interconnections (34). We found that, among diabetic patients with a BMI ≥ 30 kg/m^2, an increase in eGDR was associated with a decreased risk of AF. Previous studies have demonstrated that obesity, IR, and excise are associated with the occurrence of AF, and however, the interrelationship among these three factors requires further investigation (35–37).

In past clinical practice, fasting plasma glucose (FPG), triglyceride-glucose index (TyG index), metabolic score for insulin resistance (METS-IR), and homeostasis model assessment of insulin resistance (HOMA-IR) were commonly used to evaluate IR (38–41). The TyG index was positively correlated with the incidence of CVD, all-cause mortality, and cardiovascular mortality in the general population (42). Previous studies have shown that METS-IR has important predictive value for coronary heart disease, hypertension, coronary artery calcification, diabetes, and non-alcoholic fatty liver disease, and higher levels of METS-IR indicate a higher degree of IR, placing individuals at higher risk of metabolic disorders (38, 43). HOMA-IR is calculated as (fasting plasma glucose × fasting plasma insulin)/22.5, serving as a quantifiable measure of IR (44). However, the complicated calculation formula and inconvenient detection method hindered its widespread use, and risk assessment for CVD in patients with diabetes was mainly based on traditional risk factors such as age, blood pressure, lipids, and blood glucose, which often do not comprehensively reflect the patient's cardiovascular risk status. Several previous findings indicate that eGDR impacts the prognosis of CVD (45–47). Therefore, the potential application value of eGDR deserves in-depth exploration. Xing et al. (48) found that eGDR serves as a potential biomarker for CVD risk assessment as a comprehensive indicator of glucose metabolic status. A nationwide prospective cohort study in China indicated that sustained low eGDR was associated with an increased risk of new-onset CVD (HR = 2.51, 95% CI: 2.04-3.09) in middle-aged and elderly populations (49). Besides, recent studies suggested that low eGDR was associated with an increased risk of stroke (HR = 0.77, 95% CI: 0.69-0.87) and cardiovascular mortality (HR = 0.82, 95% CI: 0.70-0.95) in individuals with type 2 diabetes (50). Li et al. (51) found that eGDR could be a potential biomarker for predicting AF recurrence after ablation, and participants with an eGDR ≥ 8

mg/kg/min had a lower risk of AF recurrence than those with an eGDR < 4 mg/kg/min (HR = 0.28, 95% CI: 0.18-0.42).

Peng et al. proved that eGDR could be a promising tool for predicting cardiovascular comorbidities and mortality, and non-diabetic chronic kidney disease (CKD) patients with high eGDR levels had lower risks of CVD events (HR = 0.641, 95% CI: 0.559-0.734) (18). Therefore, we further investigated the association of eGDR with AF, HF, and cardiovascular mortality using mediation analysis and found that eGDR influences AF, HF, and cardiovascular mortality through eGFR (10.7%, 7.9%, and 10.3%, respectively) in patients with diabetes. However, how eGDR interacts with eGFR to influence the prognosis of cardiovascular disease remains unclear. The kidney plays a critical role in maintaining water-electrolyte balance and excreting metabolic wastes from the body. Sodium and water retention increases cardiac preload, places cardiomyocytes under long-term stress, and promotes myocardial remodelling (52, 53). Electrolyte disturbances, such as abnormalities in potassium and magnesium ion concentrations, affect the electrophysiological stability of cardiomyocytes and predispose individuals to atrial fibrillation (54). Activation of the RAAS is a key component of renal dysfunction affecting the cardiovascular system (55). After RAAS activation, angiotensin II production increases, causing vasoconstriction and elevated blood pressure, which further aggravates cardiac afterload and stimulates cardiomyocytes to become hypertrophic and fibrotic, accelerating the progression of CVD (56).

The latest research has shown that eGDR is inversely associated with the incidence of myocardial infarction (MI), HF, AF, and ischemic stroke in the general population, and it is believed that eGDR serves as a more valuable predictive indicator than TyG, TyG-WC, TyG-BMI, TyG-WHtR, TG/HDL-C, and METS-IR for CVD events in clinical practice (57). Zhang et al. found (58) that eGDR may have a linear and robust association with prevalent HF (P for non-linearity = 0.313) and a potential value in reflecting the prevalence of HF in the general population (AUC = 0.873, P = 0.008). Our conclusions are consistent with those of the previous study. However, we extended our analysis to examine the relationship between eGDR and AF, HF, and cardiovascular mortality using polygenic risk scores (PRS), Boruta's algorithm, and mediation analysis, conducting a precise and systematic evaluation of the predictive value of eGDR for these diseases. We found that high eGDR could reduce the risk of AF, HF, and cardiovascular mortality in individuals with higher genetic risk among diabetic patients. However, these associations were not significant for AF in individuals with low genetic risk. This may result from a synergistic interaction between genes and the metabolic environment, and the causal relationship between eGDR and AF requires further in-depth studies. Integration of eGDR and PRS may optimize cardiovascular risk stratification. In individuals with high PRS, early monitoring of eGDR and intervention of IR may hold significant value in the prevention of CVD. The PRS data originated from the UK Biobank (UKB), and 31,375 cases were included. Therefore, we believe that the application of eGDR in predicting the risk of AF, HF, and cardiovascular mortality in patients with diabetes has high credibility.

Strengths and limitations

There were some limitations to this study. First, although the sample size reflects the research question to some extent, it was still relatively limited and may not cover all possible clinical situations and population characteristics, potentially introducing bias into the study results. Larger multi-centre studies are needed in the future to further validate and refine our findings, improving the reliability and universality of the findings. Second, this study was a observational prospective cohort study, and although we attempted to control for confounding factors, there may still be unmeasured or incompletely corrected factors that could affect the relationship between eGDR and CVD outcomes. Additionally, the calculation of eGDR in this study was based on specific formulas and laboratory indices, and different testing methods may have certain effects on eGDR values. Finally, the participants were predominantly from European populations, limiting the consistency and comparability with other populations. Nevertheless, it retains a certain degree of reference value.

Conclusions

In conclusion, despite certain limitations in this study, the identification of the negative correlation between eGDR and the risks of AF, HF, and cardiovascular mortality among diabetic participants in the UKB holds great significance. eGDR has shown remarkable potential in predicting these critical cardiovascular outcomes in diabetic patients. In the future, it will be necessary to further investigate its underlying molecular mechanisms and conduct large-scale, multi-centre, prospective clinical studies to comprehensively explore the value of eGDR in the diagnosis, treatment, and prognosis of CVD. This will provide stronger evidence for the precise prevention and management of CVD in patients with diabetes.

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: https://www.ukbiobank.ac.uk/, 106027.

Ethics statement

The studies involving humans were approved by UKB has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. Therefore, researchers do not require separate ethical clearance and can operate under the RTB approval. The studies were conducted in accordance with the local legislation and

institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ZT: Data curation, Formal Analysis, Writing – original draft. YL: Investigation, Methodology, Supervision, Writing – review & editing. LL: Data curation, Formal Analysis, Writing – original draft. SL: Investigation, Supervision, Validation, Writing – review & editing. XX: Investigation, Supervision, Validation, Writing – review & editing. XL: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. HR: Conceptualization, Project administration, Supervision, Writing – review & editing, Resources.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

The authors express their gratitude to the participants and staff of the UK Biobank for their invaluable contributions to this study. This research has been conducted using the UK Biobank Resource under Application Number 106027.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1579836/full#supplementary-material

References

1. Global regional, national burden of diabetes. From 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of Disease Study 2021. *Lancet*. (2023) 402:203–34. doi: 10.1016/S0140-6736(23)01301-6

2. Gyldenkerne C, Mortensen MB, Kahlert J, Thrane PG, Warnakula Olesen KK, Sørensen HT, et al. 10-year cardiovascular risk in patients with newly diagnosed type 2 diabetes mellitus. *J Am Coll Cardiol*. (2023) 82:1583–94. doi: 10.1016/j.jacc.2023.08.015

3. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. *Nat Rev Cardiol*. (2023) 20:685–95. doi: 10.1038/s41569-023-00877-z

4. Azarpazhooh MR, Najafi F, Darbandi M, Kiarasi S, Oduyemi T, Spence JD. Triglyceride/high-density lipoprotein cholesterol ratio: A clue to metabolic syndrome, insulin resistance, and severe atherosclerosis. *Lipids*. (2021) 56:405–12. doi: 10.1002/lipd.12302

5. Khalili D, Khayamzadeh M, Kohansal K, Ahanchi NS, Hasheminia M, Hadaegh F, et al. Are HOMA-IR and HOMA-B good predictors for diabetes and pre-diabetes subtypes? *BMC Endocr Disord*. (2023) 23:39. doi: 10.1186/s12902-023-01291-9

6. Flood D, Brant LCC, Sussman JB. The triglyceride glucose index and cardiovascular disease outcomes. *Lancet Healthy Longev*. (2023) 4:e2–3. doi: 10.1016/S2666-7568(22)00269-0

7. Zhou Y, Xie Y, Du L, Dong J, He K. Metabolic score for insulin resistance as a predictor of mortality in heart failure with preserved ejection fraction: results from a multicenter cohort study. *Diabetol Metab Syndr*. (2024) 16:220. doi: 10.1186/s13098-024-01463-0

8. Karamanakos G, Barmpagianni A, Kapelios CJ, Kountouri A, Bonou M, Makrilakis K, et al. The association of insulin resistance measured through the estimated glucose disposal rate with predictors of micro-and macrovascular complications in patients with type 1 diabetes. *Prim Care Diabetes*. (2022) 16:837–43. doi: 10.1016/j.pcd.2022.10.003

9. Liao J, Wang L, Duan L, Gong F, Zhu H, Pan H, et al. Association between estimated glucose disposal rate and cardiovascular diseases in patients with diabetes or prediabetes: a cross-sectional study. *Cardiovasc Diabetol*. (2025) 24:13. doi: 10.1186/s12933-024-02570-y

10. Zhang Q, Xiao S, Jiao X, Shen Y. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001-2018. *Cardiovasc Diabetol*. (2023) 22:279. doi: 10.1186/s12933-023-02030-z

11. Lam-Chung CE, Martínez Zavala N, Ibarra-Salce R, Pozos Varela FJ, Mena Ureta TS, Berumen Hermosillo F, et al. Association of estimated glucose disposal rate and chronic diabetic complications in patients with type 1 diabetes. *Endocrinol Diabetes Metab*. (2021) 4:e00288. doi: 10.1002/edm2.288

12. Nyström T, Holzmann MJ, Eliasson B, Svensson AM, Sartipy U. Estimated glucose disposal rate predicts mortality in adults with type 1 diabetes. *Diabetes Obes Metab*. (2018) 20:556–63. doi: 10.1111/dom.13110

13. Zhang Z, Zhao L, Lu Y, Xiao Y, Zhou X. Insulin resistance assessed by estimated glucose disposal rate and risk of incident cardiovascular diseases among individuals without diabetes: findings from a nationwide, population based, prospective cohort study. *Cardiovasc Diabetol*. (2024) 23:194. doi: 10.1186/s12933-024-02256-5

14. Domingues-Hajj PMS, Gomes PM, Magalhães PKR, Maciel LMZ. Assessment of cardiometabolic risk factors and insulin sensitivity by hyperinsulinemic-euglycemic clamp in resistance to thyroid hormone β Syndrome. *Thyroid*. (2024) 34:1038–46. doi: 10.1089/thy.2024.0132

15. Chen X, Li A, Ma Q. Association of estimated glucose disposal rate with metabolic syndrome prevalence and mortality risks: a population-based study. *Cardiovasc Diabetol*. (2025) 24:38. doi: 10.1186/s12933-025-02599-7

16. Antuna-Puente B, Disse E, Rabasa-Lhoret R, Laville M, Capeau J, Bastard JP. How can we measure insulin sensitivity/resistance? *Diabetes Metab*. (2011) 37:179–88. doi: 10.1016/j.diabet.2011.01.002

17. Feng X, Liu Y, Yang J, Zhou Z, Yang S, Zhou Y, et al. Evaluation of estimated glucose disposal rate with neutrophil-to-lymphocyte ratio integrated for prognosticating adverse cardiovascular and cerebrovascular events and risk stratification among acute coronary syndrome with type 2 diabetes mellitus

following percutaneous coronary intervention. *J Inflammation Res*. (2024) 17:9193–214. doi: 10.2147/JIR.S490790

18. Peng J, Zhang Y, Zhu Y, Chen W, Chen L, Ma F, et al. Estimated glucose disposal rate for predicting cardiovascular events and mortality in patients with non-diabetic chronic kidney disease: a prospective cohort study. *BMC Med*. (2024) 22:411. doi: 10.1186/s12916-024-03582-x

19. Song J, Ma R, Yin L. Associations between estimated glucose disposal rate and arterial stiffness and mortality among US adults with non-alcoholic fatty liver disease. *Front Endocrinol (Lausanne)*. (2024) 15:1398265. doi: 10.3389/fendo.2024.1398265

20. Albiñana C, Grove J, McGrath JJ, Agerbo E, Wray NR, Nordentoft M, et al. Leveraging both individual-level genetic data and GWAS summary statistics increases polygenic prediction. *Am J Hum Genet*. (2021) 108:1001–11. doi: 10.1016/j.ajhg.2021.04.014

21. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol*. (2010) 72:219–46. doi: 10.1146/annurev-physiol-021909-135846

22. Wu H. Ballantyne cardiovascular mortality. Metabolic Inflammation and Insulin Resistance in Obesity. *Circ Res*. (2020) 126:1549–64. doi: 10.1161/CIRCRESAHA.119.315896

23. Rosen ED, Kajimura S. Is it time to rethink the relationship between adipose inflammation and insulin resistance? *J Clin Invest*. (2024) 134:e184663. doi: 10.1172/JCI184663

24. Lee BC, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. *Biochim Biophys Acta*. (2014) 1842:446–62. doi: 10.1016/j.bbadis.2013.05.017

25. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res*. (2019) 124:315–27. doi: 10.1161/CIRCRESAHA.118.313591

26. Cyr AR, Huckaby LV, Shiva SS, Zuckerbraun BS. Nitric oxide and endothelial dysfunction. *Crit Care Clin*. (2020) 36:307–21. doi: 10.1016/j.ccc.2019.12.009

27. Hu X, Han P, Liu Y. Metabolic status and hypertension: the impact of insulin resistance-related indices on blood pressure regulation and hypertension risk. *J Am Nutr Assoc*. (2025) 10:1–11. doi: 10.1080/27697061.2025.2450711

28. Usui I. Hypertension and insulin resistance in adipose tissue. *Hypertens Res*. (2023) 46:1478–81. doi: 10.1038/s41440-023-01263-5

29. Das UN. Renin-angiotensin-aldosterone system in insulin resistance and metabolic syndrome. *J Transl Int Med*. (2016) 4:66–72. doi: 10.1515/jtim-2016-0022

30. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. *Metabolism*. (2021) 119:154766. doi: 10.1016/j.metabol.2021.154766

31. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol*. (2018) 17:122. doi: 10.1186/s12933-018-0762-4

32. Takeuchi T, Kubota T, Nakanishi Y, Tsugawa H, Suda W, Kwon AT, et al. Gut microbial carbohydrate metabolism contributes to insulin resistance. *Nature*. (2023) 621:389–95. doi: 10.1038/s41586-023-06466-x

33. Honzawa N, Fujimoto K, Kitamura T. Cell autonomous dysfunction and insulin resistance in pancreatic α Cells. *Int J Mol Sci*. (2019) 20:3699. doi: 10.3390/ijms20153699

34. Gesualdo M, Scicchitano P, Carbonara S, Ricci G, Principi M, Ierardi E, et al. The association between cardiac and gastrointestinal disorders: causal or casual link? *J Cardiovasc Med (Hagerstown)*. (2016) 17:330–8. doi: 10.2459/JCM.0000000000000351

35. D'Ascenzi F, Cameli M, Ciccone MM, Maiello M, Modesti PA, Mondillo S, et al. The controversial relationship between exercise and atrial fibrillation: clinical studies and pathophysiological mechanisms. *J Cardiovasc Med (Hagerstown)*. (2015) 16 (12):802–10. doi: 10.2459/JCM.0000000000000211

36. Aymond JD, Sanchez AM, Castine MR, Bernard ML, Khatib S, Hiltbold AE, et al. Dual vs single cardioversion of atrial fibrillation in patients with obesity: A randomized clinical trial. *JAMA Cardiol*. (2024) 9:641–8. doi: 10.1001/jamacardio

37. Lee Y, Cha SJ, Park JH, Shin JH, Lim YH, Park HC, et al. Association between insulin resistance and risk of atrial fibrillation in non-diabetics. *Eur J Prev Cardiol*. (2020) 27:1934–41. doi: 10.1177/2047487320908706

38. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A, et al. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. *Eur J Endocrinol*. (2018) 178:533–44. doi: 10.1530/EJE-17-0883

39. Khan S, Ahmad S, Khan M, Aqil F, Khan MY, Khan MS. Artificial intelligence derived categorizations significantly improve HOMA IR/β indicators: Combating diabetes through cross-interacting drugs. *Comput Biol Med*. (2024) :179:108848. doi: 10.1016/j.compbiomed.2024.108848

40. Lee YC, Lee JW, Kwon YJ. Comparison of the triglyceride glucose (TyG) index, triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio, and metabolic score for insulin resistance (METS-IR) associated with periodontitis in Korean adults. *Ther Adv Chronic Dis*. (2022) 13:20406223221122671. doi: 10.1177/20406223221122671

41. Tohidi M, Baghbani-Oskouei A, Ahanchi NS, Azizi F, Hadaegh F. Fasting plasma glucose is a stronger predictor of diabetes than triglyceride-glucose index, triglycerides/high-density lipoprotein cholesterol, and homeostasis model assessment of insulin resistance: Tehran Lipid and Glucose Study. *Acta Diabetol*. (2018) 55:1067–74. doi: 10.1007/s00592-018-1195-y

42. He HM, Xie YY, Chen Q, Li YK, Li XX, Mu YK, et al. The additive effect of the triglyceride-glucose index and estimated glucose disposal rate on long-term mortality among individuals with and without diabetes: a population-based study. *Cardiovasc Diabetol*. (2024) 23:307. doi: 10.1186/s12933-024-02396-8

43. Duan M, Zhao X, Li S, Miao G, Bai L, Zhang Q, et al. Metabolic score for insulin resistance (METS-IR) predicts all-cause and cardiovascular mortality in the general population: evidence from NHANES 2001-2018. *Cardiovasc Diabetol*. (2024) 23:243. doi: 10.1186/s12933-024-02334-8

44. Tahapary DL, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index. *Diabetes Metab Syndr*. (2022) 16(8):102581. doi: 10.1016/j.dsx.2022.102581

45. Zhu B, Cao C, Liu W, Liu Y, Luo Y, Peng D. The predictive value of estimated glucose disposal rate for all-cause and cardiovascular mortality in the US non-diabetic population aged ≥60 years: A population-based cohort study. *Diabetes Metab Syndr*. (2024) 19:103182. doi: 10.1016/j.dsx.2024.103182

46. Wang H, Zhou Z, Liu X, Chen Y. Gender differences in the association between insulin resistance assessed by estimated glucose disposal rate and the risk of all-cause and cardiovascular deaths in adults without diabetes. *Diabetes Res Clin Pract*. (2025) 219:111966. doi: 10.1016/j.diabres.2024.111966

47. Kim MJ, Cho YK, Kim EH, Lee MJ, Lee WJ, Kim HK, et al. Association between estimated glucose disposal rate and subclinical coronary atherosclerosis. *Nutr Metab Cardiovasc Dis*. (2025) 35:103686. doi: 10.1016/j.numecd.2024.07.004

48. Xing D, Xu J, Weng X, Weng X. Correlation between estimated glucose disposal rate, insulin resistance, and cardiovascular mortality among individuals with metabolic syndrome: a population-based analysis, evidence from NHANES 1999-2018. *DiabetolMetab Syndr*. (2025) 17:11. doi: 10.1186/s13098-024-01574-8

49. Yan L, Zhou Z, Wu X, Qiu Y, Liu Z, Luo L, et al. Association between the changes in the estimated glucose disposal rate and new-onset cardiovascular disease in middle-aged and elderly individuals: A nationwide prospective cohort study in China. *Diabetes Obes Metab*. (2025) 27(4):1859–67. doi: 10.1111/dom.16179

50. Zabala A, Darsalia V, Lind M, Svensson AM, Franzen S, Eliasson B, et al. Estimated glucose disposal rate and risk of stroke and mortality in type 2 diabetes: a nationwide cohort study. *Cardiovasc Diabetol*. (2021) 20:202. doi: 10.1186/s12933-021-01394-4

51. Li X, Zhou Z, Xia Z, Dong Y, Chen S, Zhan F, et al. Association between estimated glucose disposal rate and atrial fibrillation recurrence in patients undergoing radiofrequency catheter ablation: a retrospective study. *Eur J Med Res*. (2024) 29:325. doi: 10.1186/s40001-024-01911-7

52. Rossing P, Hansen TW, Kümler T. Cardiovascular and non-renal complications of chronic kidney disease: Managing risk. *Diabetes Obes Metab*. (2024) 26 Suppl 6:13–21. doi: 10.1111/dom.15747

53. Kotwal SS, Perkovic V. Kidney disease as a cardiovascular disease priority. *Circulation*. (2024) 150:975–7. doi: 10.1161/CIRCULATIONAHA.124.068242

54. Bansal N, Xie D, Tao K, Chen J, Deo R, Horwitz E, et al. Atrial fibrillation and risk of ESRD in adults with CKD. *Clin J Am Soc Nephrol*. (2016) 11:1189–96. doi: 10.2215/CJN.10921015

55. Lytvyn Y, Burns KD, Testani JM, Lytvyn A, Ambinathan JPN, Osuntokun O, et al. Renal hemodynamics and renin-angiotensin-aldosterone system profiles in patients with heart failure. *J Card Fail*. (2022) 28:385–93. doi: 10.1016/j.cardfail.2021.08.015

56. Maryam, Varghese TP, B T. Unraveling the complex pathophysiology of heart failure: insights into the role of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). *Curr Probl Cardiol*. (2024) 49:102411. doi: 10.1016/j.cpcardiol.2024.102411

57. Huang H, Xiong Y, Zhou J, Tang Y, Chen F, Li G, et al. The predictive value of estimated glucose disposal rate and its association with myocardial infarction, heart failure, atrial fibrillation and ischemic stroke. *Diabetes Obes Metab*. (2025) 27(3):1359–68. doi: 10.1111/dom.16132

58. Zhang D, Shi W, An T, Li C, Ding Z, Zhang J. Usefulness of estimated glucose disposal rate in detecting heart failure: results from national health and nutrition examination survey 1999-2018. *Diabetol Metab Syndr*. (2024) 16:189. doi: 10.1186/s13098-024-01402-z

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 15 September 2025
DOI 10.3389/fendo.2025.1637035

Check for updates

OPEN ACCESS

EDITED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

REVIEWED BY
Qazi Zeeshan,
University of Pittsburgh Medical Center,
United States
Guannan Zhou,
Karolinska Institutet (KI), Sweden
Loredana Bucciarelli,
University of Milan, Italy

*CORRESPONDENCE
Yu-Hao Lin
tzlinyuhao@163.com
Jian-Qing Tian
449256119@qq.com

RECEIVED 28 May 2025
ACCEPTED 26 August 2025
PUBLISHED 15 September 2025

CITATION
Tian J-Q, Zhang Z-J, Peng Y-T, Ye J-W, Wang Z-Y and Lin Y-H (2025) Effectiveness and use of evidence-based cardiovascular preventive therapies in type 2 diabetes patients with established or high risk of atherosclerotic cardiovascular disease. *Front. Endocrinol.* 16:1637035. doi: 10.3389/fendo.2025.1637035

COPYRIGHT
© 2025 Tian, Zhang, Peng, Ye, Wang and Lin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Effectiveness and use of evidence-based cardiovascular preventive therapies in type 2 diabetes patients with established or high risk of atherosclerotic cardiovascular disease

Jian-Qing Tian[1*], Zhi-Jun Zhang[1], Yi-Ting Peng[2], Jia-Wen Ye[1], Zhi-Yi Wang[1] and Yu-Hao Lin[1*]

[1]Department of Endocrinology, Xiamen Humanity Hospital, Fujian Medical University, Xiamen, Fujian, China, [2]Department of Endocrinology, Zhongshan Hospital Xiamen University, Xiamen, Fujian, China

Aim: To explore the association of evidence-based cardiovascular preventive therapies with cardiovascular and renal outcomes in type 2 diabetes (T2DM) patients with established or high risk of atherosclerotic cardiovascular disease (ASCVD).

Methods: In this cohort study, we identified T2DM patients with established or high risk of ASCVD using diagnostic codes from the institutional data of Xiamen Humanity Hospital between 2018 and 2023. Cohort 1 includes participants who were visited between 2018 and 2020, with follow-up until occurrence of an endpoint or December 31, 2020. Participants who were visited between 2018 and 2023 were included in cohort 2. A total of 5,335 patients were included in cohort 1, and 17,320 patients were included in cohort 2. Primary outcomes were hazard ratios (HRs) for the composite of 3-point major adverse cardiovascular event (3-P MACE), hospitalization for heart failure (HHF), and end-stage kidney disease or doubling of serum creatinine level.

Results: Relative to patients' non-use of evidence-based cardiovascular preventive therapies, the use of at least one evidence-based cardiovascular preventive therapy was associated with a lower risk of the 3-P MACE (HR, 0.82; 95% confidence interval [CI], 0.67 to 0.98), HHF (HR, 0.66; 95% CI, 0.47 to 0.92) and end-stage kidney disease or doubling of the serum creatinine level (HR, 0.73; 95% CI, 0.60 to 0.89) after adjustment for potential confounders. From 2018 to 2023, the use of glucagon-like peptide 1 receptor agonists increased from 2.7% to 13.7%; sodium–glucose cotransporter 2 inhibitors increased from 3.9% to 16.5%; angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers increased from 28.1% to 43.0%; moderate-intensity statins increased from 61.6% to 70.5%; and aspirin increased from 23.7% to 32.9%.

Conclusions: This study demonstrated that T2DM patients with established or high risk of ASCVD might benefit from the use of evidence-based cardiovascular preventive medications with respect to the risk of 3-P MACE, HHF, and end-stage kidney disease or doubling of the serum creatinine level. Despite a modest annual increase in the use of evidence-based cardiovascular preventive medications in T2DM individuals with established or high risk of ASCVD, multiple strategies are needed to overcome barriers to the implementation of evidence-based therapies.

KEYWORDS

type 2 diabetes, atherosclerotic, cardiovascular preventive therapies, cardiovascular and renal outcomes, cohort study

1 Introduction

Type 2 diabetes (T2DM) is a major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD), which is the leading cause of death and long-term complications in T2DM (1). A systematic review demonstrated that the prevalence of ASCVD in patients with T2DM was nearly 30%, and up to two-thirds of patients with T2DM will develop ASCVD during their lifetimes (2, 3). Therefore, there is an urgent need to initiate and intensify secondary prevention strategies to mitigate the risk of recurrent cardiovascular events and cardiovascular mortality in patients with T2DM and ASCVD.

Although, the US Food and Drug Administration (FDA) conducted randomized cardiovascular outcome trials (CVOTs) for all glucose–lowering medications in 2008, the cardiovascular benefit of these medications was controversial until 2015. The glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) are beneficial for the secondary prevention of ASCVD (4, 5). Most importantly, large CVOTs of GLP-1 RA and SGLT2i have demonstrated that these drug classes substantially decrease the risk of cardiovascular and renal outcomes (6–12). What's more, numerous studies have proved the beneficial effects of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs), statins, and aspirin therapy on cardiovascular and renal outcomes (13–15). Given this accumulating evidences, the American Diabetes Association (ADA) and the Chinese Diabetes Society recommend the cardio-protective glucose-lowering drug classes (GLP-1 RA and SGLT2i), ACEI/ARB, statins, and aspirin for comprehensive cardiovascular risk reduction in adults patients with T2DM and established or high risk of ASCVD (16, 17). However, limited evidence is available for the direct comparison of those using versus not using evidence-based cardiovascular preventive therapies (including: GLP-1 RA, SGLT2i, ACEI/ARB, statins, and aspirin) in terms of cardiovascular, hospitalization for heart failure and renal outcomes. We therefore conducted a large-scale trial to compare the cardiovascular and renal benefits of use to non-use evidence-based cardiovascular preventive therapies in adults with T2DM and established or high risk of ASCVD.

Despite several guidelines recommend the GLP-1 RA, SGLT2i, ACEI/ARB, statins, and aspirin for their cardioprotective effects, a degree of therapeutic inertia in clinical practice may be observed for many reasons. Previous observational studies on patients with T2DM and ASCVD demonstrate that the administration rates of GLP-1 RA and/or SGLT2i ranged from 6.7% to 23.2%, ACEI or ARB was from 53.1% to 72.0%, and high-intensity statins were from 24.7% to 45.4% (18–21). Accurately determining the gaps in evidence-based therapy is essential for disseminating and promoting the clinical application of guidelines. Thus, we also examine the administration of GLP-1 RA and/or SGLT2i, ACEI/ARB, moderate-intensity statins, and aspirin in T2DM patients with established or high risk of ASCVD from 2018 to 2023.

2 Materials and methods

2.1 Study design and data source

This study was a population-based cohort study. The source population comprised all outpatients who visited the Xiamen Humanity Hospital, Fujian Medical University, between January 1, 2018, and December 31, 2023. Informed consent was waived because the study used anonymized patient data. The study protocol was approved by the Xiamen Humanity Hospital Ethics Committee (no. HAXM-MEC-20240 820-048-01). The study was conducted according to the ethical principles of the Declaration of Helsinki. The trial is registered with Chinese Clinical Trial Registry (ChiCTR) (registration no. ChiCTR2500101328).

2.2 Study population

The study population included adults (age ≥ 18 years) between January 1, 2018, and December 31, 2023. Data analysis was performed

from January 1, 2024, to December 31, 2024. Disease information was obtained using the International Statistical Classification of Diseases, Tenth Revision (ICD-10) (Supplementary Table 1). ICD-10 diagnosis codes were utilized to identify T2DM patients at high cardiovascular risk, which include patients with concomitant ASCVD or high risk of ASCVD. Briefly, ASCVD was defined as having a history of coronary artery disease (previous prior myocardial infarction, unstable angina), peripheral arterial disease (amputation due to poor circulation), cerebrovascular disease (stroke, or transient ischemic attack), or any revascularization intervention. Patients at high risk of ASCVD were defined as those aged ≥ 55 years with two or more risk factors. Risk factors included obesity (body mass index [BMI] ≥ 28 kg/m2), hypertension, smoking, dyslipidemia, and albuminuria (22). In addition, age, height, weight, and history of smoking were obtained from an electronic medical record. History of hypertension and dyslipidemia were identified by the presence of ICD-10 diagnosis codes. Albuminuria was defined as urine albumin-to-creatinine ratio ≥ 30 mg/g. Patients < 30 years old at the time of initial insulin prescription, with end-stage kidney disease, or limited life expectancy were excluded.

This study population was divided into two cohorts. Participants who were visited between January 1, 2018, and December 31, 2020, were included in cohort 1 (Figure 1). To reduce the effects of prior treatment, we excluded those who had received medication adjustments in the three months preceding enrollment. Participants were followed from 1 day after cohort entry until occurrence of an endpoint or December 31, 2020. Participants were excluded if they discontinued the index drug, died of other causes, or were lost to follow-up. Cohort 1 was divided into group A (non-use of evidence-based cardiovascular preventive therapies) and group B (use at least one evidence-based cardiovascular preventive therapy). Participants who were visited between January 1, 2018, and December 31, 2023, were included in cohort 2 (Figure 2). Patients with longitudinal follow-up may be included in multiple years but only once annually. Within a given year, only patients with at least 1 glucose-lowering medication record were included. If a patient had multiple visits within a specific year, only the last visit was included in the analysis.

2.3 Study outcomes

We ascertained that the primary outcome was a composite of 3-point major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), hospitalization for heart failure and end-stage kidney disease or doubling of serum creatinine level in cohort 1. Secondary outcomes that were planned in cohort 1 and cohort 2 were specified in the following order: the difference in clinical characteristics between the use and non-use of evidence-based cardiovascular preventive therapies; the use of evidence-based cardiovascular preventive therapies in T2DM patients with established or high risk of ASCVD. The use of these medications was assessed through the day of the last dispensed prescription within a given year. The prescribed cardioprotective glucose-lowering pharmacotherapy included GLP-1 RA (e.g., semaglutide, dulaglutide, liraglutide, and lixisenatide) and SGLT2i (e.g., empagliflozin, dapagliflozin, and canagliflozin). Prescribed blood pressure-lowering pharmacotherapy included ACEI (e.g., captopril, benazepril, and so on), ARB (e.g., valsartan, irbesartan, and so on), and statins (atorvastatin, rosuvastatin, pitavastatin, simvastatin, and pravastatin).

2.4 Covariates

We examined demographic characteristics, including age and sex. Clinical characteristics included glycosylated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), and BMI. For patients with multiple measurements within a given year, only the last one was used. The comorbidities (heart failure, atrial fibrillation, hypertension, dyslipidemia, and nonalcoholic fatty liver disease) and diabetes chronic complications (retinopathy, neuropathy, and nephropathy) were identified using the ICD-10 code. Concomitant use of oral anti-diabetic, antihypertensive, and lipid-lowering medications was assessed.

2.5 Composite score for evidence-based therapy

Evidence-based therapy was defined as the use of either a GLP-1 RA and/or SGLT2i, either an ACEI or ARB, a moderate-intensity statins, and an aspirin. Although high-dose statins are important to prevent cardiovascular events, they are largely intolerable for most Chinese populations. Therefore, moderate-intensity statins are recommended as the first choice lipid-lowering drugs by the Endocrinology and Metabolism Physician Branch of the Chinese Medical Doctor Association (23). Patients in this cohort met the criteria for all four components and were assigned a composite score ranging from 0 to 4, indicating the number of evidence-based therapies prescribed.

2.6 Statistical analysis

Demographic and clinical characteristics, co-morbidities, and concomitant medications are presented as with means ± standard deviations (SDs) for continuous variables and frequency/percentages for categorical variables. The number and percentage of patients with T2DM and established or high risk of ASCVD who received GLP-1 RA and/or SGLT2i, ACEI/ARB, moderate-intensity statins, and aspirin were evaluated annually. Treatment effect was estimated using hazard ratios (HRs) from a Cox regression model. Subgroup analyses were performed by sex, the presence of ASCVD or high risk of ASCVD, the presence of heart failure, and the presence of chronic kidney disease. All data where necessary were

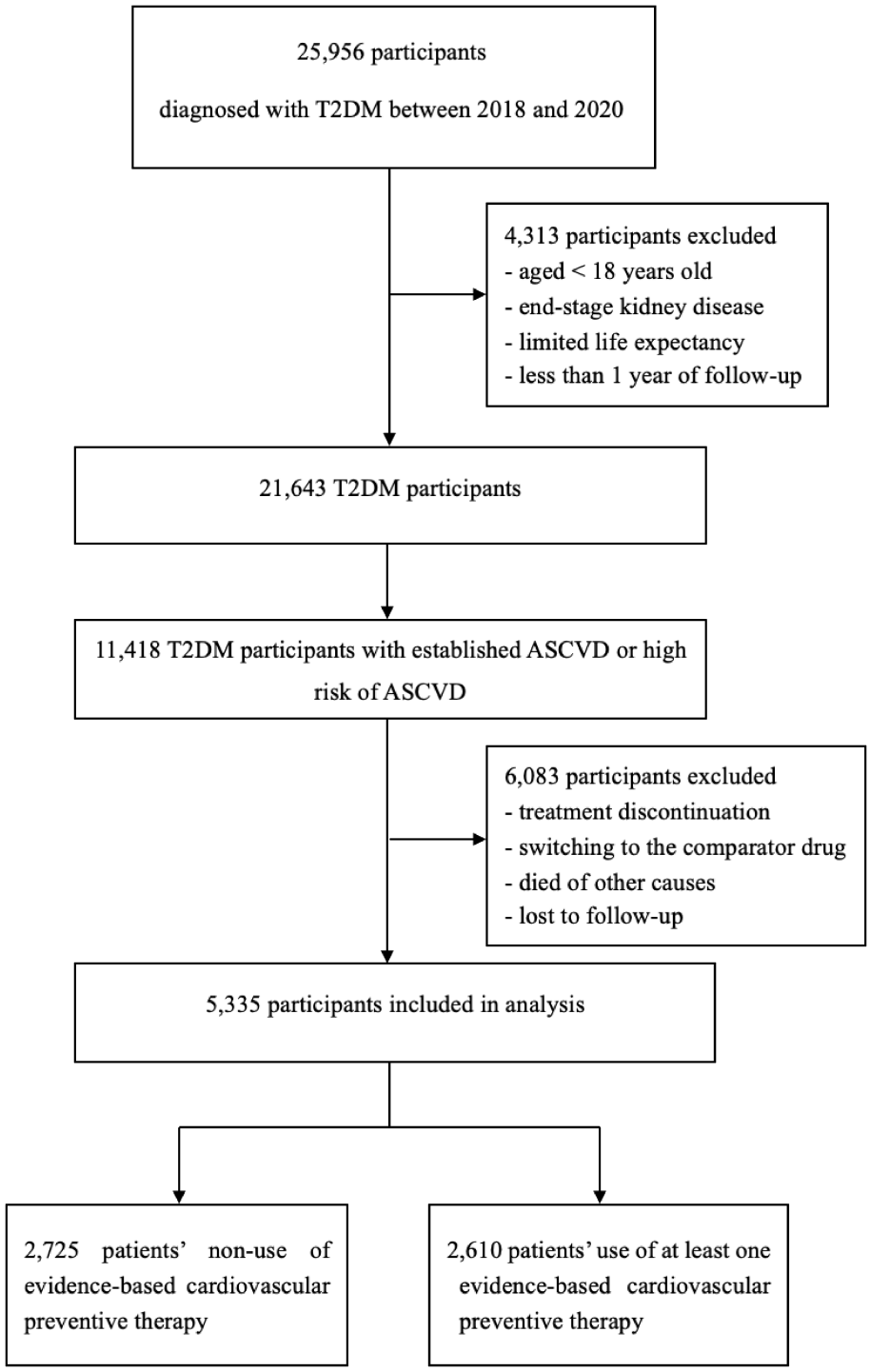


FIGURE 1
Flow diagram for cohort 1. T2DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease.

conducted to calculate 95% confidence interval (CI). Statistical comparisons baseline characteristics between the different groups were using the independent-sample t test for continuous variables and $\chi 2$ test or Fisher's exact test for categorical variables. Two-sided P values < 0.05 were considered statistically significant. All analyses were performed using R version 4.4.2 (R Foundation).

3 Results

3.1 Study participants

We identified 5,335 patients in cohort 1 (2,793 patients with a dual diagnosis of T2DM and ASCVD and 2,524 patients with

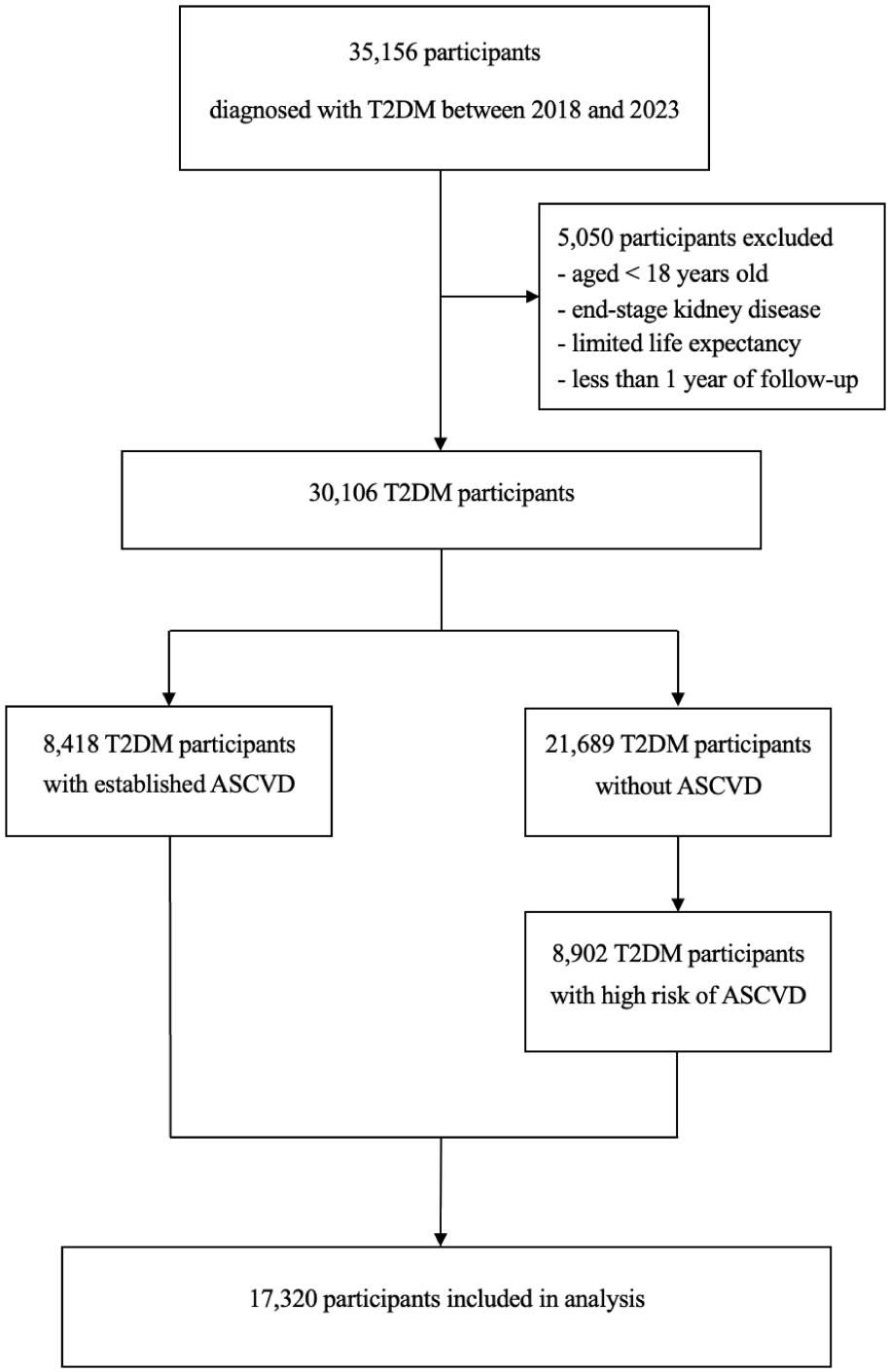


FIGURE 2
Flow diagram for cohort 2. T2DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease.

T2DM and high risk of ASCVD) and 17,320 patients in cohort 2 (8,418 patients with a dual diagnosis of T2DM and ASCVD and 8,902 patients with T2DM and high risk of ASCVD).

Among 5,335 patients in cohort 1, a total of 2,275 patients were assigned to the group A and 2,610 were assigned to the group B. Compared with the group A, patients in the group B were younger (mean [SD]: 65.4 [10.1] years vs 66.8 [10.1] years), more likely to be male (57.5% vs 55.2%), with a lower proportion of second-generation sulfonylurea use (22.4% vs 30.3%) and more common with Urban employee medical insurance (25.8% vs 24.7%). There were differences between group A and group B in clinical characteristics (e.g., 2,275 patients in group A vs 2,610 patients in group B: initiation of SGLT-2i or GLP-1 RAs, 1.6% vs 3.1%; coronary artery disease, 71.2% vs 74.6%; cerebrovascular disease, 20.1% vs 23.3%; heart failure, 30.6% vs 35.8%; hypertension, 88.8% vs 81.3%; hyperlipidemia, 86.7% vs 75.8%; CKD stage 3, 18.7% vs

21.5%; mean [SD] Charlson Comorbidity Index score, 4.0 [2.7] vs 4.4 [2.9]) (Table 1).

3.2 Primary outcomes

A 3-point major adverse cardiovascular event occurred in 228 of 2,610 patients (8.7%) in the group B (use of at least one evidence-based cardiovascular preventive therapy) and in 237 of 2725 patients (8.7%) in the group A (non-use of evidence-based cardiovascular preventive therapies) (hazard ratio, 0.96; 95% confidence interval [CI], 0.80 to 1.16; P = 0.69). Hospitalization for heart failure occurred in 79 of 2,610 patients (3.0%) in the group B and in 103 of 2,725 patients (3.8%) in the group A (hazard ratio, 0.84; 95% CI, 0.62 to 1.12; P = 0.23). With respect to the end-stage kidney disease or doubling of the serum creatinine level, the hazard ratio (group B vs group A) was 0.90 (95% CI, 0.75 to 1.09) (Table 2). After adjustment for potential confounders, patients in the group B showed a significant decreased risk of 3-P MACE (hazard ratio, 0.82; 95% CI, 0.67 to 0.98; P = 0.036), HHF (hazard ratio, 0.66; 95% CI, 0.47 to 0.92; P<0.01), and end-stage kidney disease or doubling of the serum creatinine level (hazard ratio, 0.73; 95% CI, 0.60 to 0.89; P<0.01) compared with the group A (Table 2). Subgroup analyses did not show a difference in the risk of 3-point MACE, HHF and end-stage kidney disease or doubling of serum creatinine level between the two groups (Supplementary Table 2).

3.3 Use ratios

Overall, the utilization of glucose-lowering drugs with documented cardiovascular benefits was low; however, the rate increased annually from 2018 to 2023 (GLP-1 RA: from 2.7% [73 of 2,720] to 13.7% [439 of 3,200]; SGLT2i: from 3.9% [107 of 2720] to 16.5% [529 of 3200]). Collectively, the percentage of patients with T2DM and established or high risk of ASCVD taking either agent increased from 5.7% (156 of 2,720) in 2018 to 21.0% (671 of 3200) in 2023 (Figure 3). Metformin use was essentially unchanged over this time (61.3% [1667 of 2,720] in 2018 vs 60.8% [1,945 of 3,200] in 2023). Use of noncardiovascular glucose-lowering agents exhibited a variable decline, including alpha-glucosidase inhibitors (30.1% [818 of 2,720] to 22.2% [709 of 3,200]) and dipeptidyl peptidase-4 inhibitors (DPP-4i) (25.5% [694 of 2,720] to 20.8% [665 of 3,200]), although these medications remained more commonly used than SGLT2i or GLP-1 RAs through 2023 (Supplementary Figure 1). Of the antihypertensive medications, the use of ACEI/ARB was increased from 28.1% [764 of 2,720] to 43.0% [1,377 of 3,200], while the use of calcium channel blockers was decreased (44.2% [1,202 of 2,720] to 41.8% [1,336 of 3,200]) from 2018 to 2023 (Supplementary Figure 2). The use of moderate-intensity statins (61.6% [1,676 of 2,720] to 70.5% [2,255 of 3,200]) and aspirin (23.7% [645 of 2,720] to 32.9% [1,053 of 3,200]) pharmacotherapy variably increased (Supplementary Figure 3, Figure 3). In patients with high risk of ASCVD, GLP-1 RA, SGLT2i, ACEI/ARB, moderate-intensity statins, and aspirin showed lower usage rates than patients with ASCVD (Supplementary Figure 4).

3.4 Evidence-based therapy

Compared with the overall cohort, patients prescribed GLP-1RA or SGLT2i were younger (mean age: GLP-1 RA: 61.1 years; SGLT2i: 63.0 years; overall: 66.3 years), had lower prevalence of heart failure (GLP-1 RA: 26.4%; SGLT2i: 21.4%; overall: 32.3%), had higher prevalence of dyslipidemia (GLP-1 RA: 87.2%; SGLT2i: 86.8%; overall: 81.5%), had fewer medical comorbidities (mean Charlson comorbidity index score: GLP-1 RA: 3.8; SGLT2i: 3.7; overall: 4.0) and had a lower percentage of patients with HbA1c < 7% (GLP-1 RA: 33.5%; SGLT2i: 36.6%; overall: 41.1%). Patients who prescribed a GLP-1 RA had higher prevalence of diabetes chronic complications (retinopathy: 16.1% vs 9.9%; neuropathy: 40.9% vs 27.6%) compared with the overall cohort (Table 3). The demographics and clinical characteristic of patients prescribed an ACEI or ARB, moderate-intensity statin and aspirin were displayed in Table 3.

4 Discussion

In our cohort of patients with T2DM and established or high risk of ASCVD, we demonstrated that the use of evidence-based cardiovascular preventive therapies was associated with a 18% lower risk of 3-point MACE, 34% lower risk of HHF and 17% lower risk of end-stage kidney disease or doubling of serum creatinine level relative to non-use.

Our study shows, in accordance with previous studies, that age, smoking, obesity, hypertension, hyperlipidemia, elevated levels of glycated hemoglobin and LDL-C are major risk factors for CVDs (24, 25). The baseline of clinical characteristics was different between those using and not using evidence-based cardiovascular preventive therapies, this might account for the failure to observe a difference in cardiovascular and renal outcomes between the two groups. The outcome of 3-point MACE, HHF and end-stage kidney disease or doubling of serum creatinine level showed significant differences between the two groups after adjustment for several potential confounders.

To our knowledge, this study was one of the few to date to compare the cardiovascular and renal effectiveness of using or not-using evidence-based cardiovascular preventive therapies. Consistent with a meta-analysis of cardiovascular outcome trials, we found that benefits of GLP-1 RA, SGLT2i, ACEI/ARB, statins, and aspirin were observed for the outcomes of 3-point MACE, HHF and end-stage kidney disease or doubling of serum creatinine level (26–30). Recently, a meta-analysis demonstrated that combination of GLP-1 RA and SGLT2i resulted in a 27% reduction in the risk of MACE and a 57% reduction in the risk of HHF compared to usual treatment in people with T2DM (31). The discrepancy of results between our study may be explained by the low use of either a GLP-

10.3389/fendo.2025.1637035

TABLE 1 Patient characteristics by overall evidence-based composite score (cohort 1).

Patient characteristics	Evidence-based therapy score, % (95% CI)	
	0 (n=2725)	1-4 (n=2610)
Age, mean (SD) [95% CI], y	66.8 (10.1) [66.7-66.9]	65.4 (10.1) [65.3-65.5]
Sex		
Male	55.2 (53.3-57.1)	57.5 (55.6-59.5)
Female	44.8 (42.9-46.8)	42.5 (40.6-44.5)
Lifestyle factors		
Obesity	46.2 (44.2-48.1)	48.0 (46.1-49.9)
Smoking	22.9 (21.2-24.5)	23.9 (22.3-25.6)
Diabetes-related conditions		
Retinopathy	7.2 (6.2-8.2)	11.4 (10.2-12.6)
Neuropathy	22.6 (21.0-24.2)	28.6 (26.9-30.4)
Nephropathy	27.5 (25.7-29.2)	31.9 (30.1-34.8)
Diabetes treatment		
Initiation of SGLT-2i or GLP-1 RAs	1.6 (1.1-2.1)	3.1 (2.4-3.8)
Concurrent metformin	63.1 (61.3-64.9)	62.3 (60.5-64.2)
Concurrent second-generation sulfonylurea	30.3 (28.6-32.0)	22.4 (20.8-24.0)
ASCVD (n=2793)		
Coronary artery disease	71.2 (69.5-72.9)	74.6 (72.9-76.3)
Cerebrovascular disease	20.1 (18.6-21.6)	23.3 (21.7-24.9)
Peripheral arterial disease	45.4 (43.5-47.3)	48.7 (46.8-50.6)
Comorbidities		
Heart failure	30.6 (28.9-32.4)	35.8 (34.0-37.7)
Atrial fibrillation	20.4 (18.9-21.9)	19.7 (18.2-21.2)
Hypertension	81.3 (79.8-82.8)	88.8 (87.6-90.0)
Hyperlipidemia	75.8 (74.2-77.4)	86.7 (85.4-88.0)
CKD stage 3	18.7 (17.2-20.2)	21.5 (19.9-23.1)
Nonalcoholic fatty liver disease	16.7 (15.3-18.1)	17.1 (15.6-18.6)
Charlson Comorbidity Index score, mean (SD) [95% CI]	4.0 (2.7) [3.9-4.1]	4.4 (2.9) [4.3-4.5]
Laboratory values, mean (SD)		
HbA1c, %	7.8 (1.9) [7.7-7.8]	7.8 (2.1) [7.7-7.9]
LDL-C, mmol/L	2.8 (1.0) [2.8-2.8]	2.9 (0.9) [2.9-2.9]
HbA1c < 7%	40.1 (38.3-42.0)	39.7 (37.8-41.6)
LDL-C < 1.8	14.4 (13.1-15.7)	13.9 (12.6-15.2)
LDL-C < 1.4	4.0 (3.3-4.7)	4.1 (3.3-4.9)
Insurance coverage		
Urban Employee	24.7 (23.1-26.3)	25.8 (24.1-27.5)
Urban Resident	56.1 (54.2-58.0)	51.4 (49.5-53.3)

(Continued)

TABLE 1 Continued

Patient characteristics	Evidence-based therapy score, %	(95% CI)
	0 (n=2725)	1-4 (n=2610)
Insurance coverage		
Self-pay	5.1 (4.3-5.9)	6.2 (5.3-7.1)
Missing	14.1 (12.8-15.4)	16.6 (15.2-18.0)

SGLT-2i, sodium-glucose cotransporter-2 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

1 RA or an SGLT2i. In our study, the use of either a GLP-1 RA or an SGLT2i was only 14%, which may weaken the effects of GLP-1 RA or SGLT2 on cardiovascular and kidney outcomes.

Although both GLP-1 RA, SGLT-2i, ACEI/ARB, statins and aspirin have demonstrated cardiovascular benefits, the overall utilization of evidence-based cardiovascular preventive therapies was lower than expected, particularly for GLP-1 RA and SGLT2i (32, 33). Our finding suggested that 14.0% of patients in our study were prescribed either a GLP-1 RA or SGLT2i (GLP-1 RA: 7.6%, SGLT2i: 10.5%),which is consistent with those of recent studies conducted in the US and Belgian (34–36). Fortunately, our study found that the use of both GLP-1 RA and SGLT2i increased gradually from 2018 to 2023. However, as recently as 2023, two glucose-lowering therapies without proven cardiovascular benefit, namely alpha-glucosidase inhibitors and DPP-4i, continue to be used more frequently than either GLP-1 RA or SGLT2i.

Likewise, the utilization rates of ACEI/ARB, moderate-intensity statins, and aspirin have been dismal. Our study suggested that only 35.5% of patients were prescribed ACEI/ARB, 66.3% were prescribed moderate-intensity statins, and 28.7% were prescribed aspirin between

TABLE 2 Treatment effect estimates for evidence-based therapies.

Outcome	Total No. of events (%)		Unadjusted		Model 1	
			Group B vs Group A			
	Group B (n=2610)	Group A (n=2725)	HR (95% CI)	*p*	HR (95% CI)	*p*
3-P MACE	228 (8.7)	237 (8.7)	0.96 (0.80-1.16)	0.69	0.82 (0.67-0.98)	0.036
HHF	79 (3.0)	103 (3.8)	0.84 (0.62-1.12)	0.23	0.66 (0.47-0.92)	<0.01
End-stage kidney disease, doubling of serum creatinine level	198 (7.6)	226 (8.3)	0.90 (0.75-1.09)	0.29	0.73 (0.60-0.89)	<0.01

3-P MACE, 3-point major adverse cardiovascular event; HHF, hospitalization for heart failure; HR, hazard ratio.
Model 1: Adjusted for sex, age, smoke, BMI, HbA1c, LDL-C, history of diseases including diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, hypertension, and hyperlipidemia.

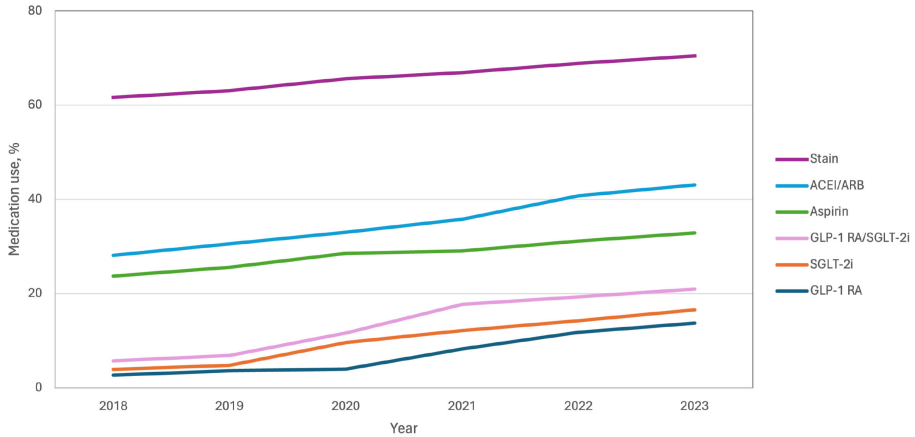


FIGURE 3
Trends in evidence-based therapy use among T2DM patients with established or high risk of ASCVD. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

TABLE 3 Patient characteristics at baseline by individual evident-based therapies (cohort 2).

Patient characteristics	Patients, % (95% CI)					
	Overall (N = 17320)	Therapy prescription				
		GLP-1 RA (N = 1321)	SGLT-2i (N = 1814)	ACEI/ARB (N = 6157)	moderate-intensity statin (N = 11476)	Aspirin (N = 4965)
Age, mean (SD) [95% CI], y	66.3 (10.8) [66.2-66.3]	61.1 (11.2) [60.5-61.7]	63.0 (8.4) [62.6-63.4]	67.0 (10.1) [66.7-67.3]	66.2 (10.2) [66.0-66.4]	65.4 (10.0) [65.1-65.7]
Sex						
Male	56.1 (55.4-56.8)	58.9 (56.2-61.6)	53.8 (51.5-56.1)	56.8 (55.6-58.0)	56.9 (56.0-57.8)	63.3 (62.0-64.6)
Female	43.9 (43.2-44.6)	41.1 (38.4-43.8)	46.2 (43.9-48.5)	43.2 (42.0-44.4)	43.1 (42.2-44.0)	36.7 (35.4-38.0)
Lifestyle factors						
Obesity	47.9 (47.2-48.6)	51.6 (48.9-54.3)	49.9 (47.6-52.2)	45.8 (44.6-47.1)	48.3 (47.4-49.2)	48.5 (47.1-49.9)
Smoking	23.0 (22.4-23.6)	22.4 (20.2-24.6)	20.2 (18.4-22.1)	23.8 (22.7-24.9)	25.9 (25.1-26.7)	24.3 (23.1-25.5)
Diabetes-related conditions						
Retinopathy	9.9 (9.5-10.3)	16.1 (14.1-79.2)	11.7 (10.2-13.2)	11.2 (10.4-12.1)	12.8 (12.2-13.4)	13.4 (12.5-14.3)
Neuropathy	27.6 (26.9-28.3)	40.9 (38.2-43.6)	29.9 (27.8-32.0)	29.3 (28.2-30.4)	29.7 (28.9-30.5)	31.7 (30.4-33.0)
Nephropathy	21.8 (21.1-22.5)	24.4 (21.7-27.1)	20.9 (28.6-23.2)	23.4 (22.2-24.6)	24.3 (23.4-25.2)	25.6 (24.2-27.0)
ASCVD (n=8418)						
Coronary artery disease	72.0 (71.3-72.7)	68.5 (66.0-71.0)	71.6 (69.5-73.7)	72.2 (71.1-73.3)	78.3 (77.5-79.1)	73.8 (72.6-75.0)
Cerebrovascular disease	21.7 (21.1-22.3)	17.8 (15.7-19.9)	18.1 (16.3-19.9)	20.1 (19.1-21.1)	25.1 (24.3-25.9)	24.4 (23.2-25.6)
Peripheral arterial disease	47.9 (47.1-48.6)	51.5 (48.4-54.2)	49.9 (47.6-52.2)	50.2 (49.0-51.4)	49.0 (48.1-49.9)	50.3 (48.9-51.7)

(Continued)

10.3389/fendo.2025.1637035

TABLE 3 Continued

Patient characteristics	Patients, % (95% CI)					
	Overall (N = 17320)	Therapy prescription				
		GLP-1 RA (N = 1321)	SGLT-2i (N = 1814)	ACEI/ARB (N = 6157)	moderate-intensity statin (N = 11476)	Aspirin (N = 4965)
Comorbidities						
Heart failure	32.3 (31.6-33.0)	26.4 (11.6-15.2)	21.4 (7.1-9.7)	31.2 (10.4-12.0)	39.6 (9.1-10.1)	38.7 (7.9-9.5)
Atrial fibrillation	19.8 (19.2-20.4)	15.6 (42.9-48.3)	16.0 (24.0-28.0)	20.9 (21.9-23.9)	20.7 (22.9-24.5)	21.7 (22.5-24.9)
Hypertension	84.4 (83.9-85.0)	85.6 (83.7-87.5)	84.2 (82.5-85.9)	88.1 (87.3-88.9)	86.1 (85.5-86.7)	87.3 (86.4-88.2)
Hyperlipidemia	81.5 (80.9-82.0)	87.2 (85.4-89.0)	86.8 (85.2-88.4)	84.2 (83.3-85.1)	90.2 (89.7-90.7)	89.5 (88.6-90.4)
CKD stage 3	19.2 (18.6-19.8)	21.4 (19.2-23.6)	18.7 (16.9-20.5)	21.6 (20.6-22.6)	22.1 (21.3-22.9)	23.2 (22.0-24.4)
Nonalcoholic fatty liver disease	17.4 (16.9-18.0)	25.6 (23.2-28.0)	23.2 (21.3-25.1)	19.2 (18.2-20.2)	21.3 (20.6-22.0)	18.5 (17.4-19.6)
Charlson Comorbidity Index score, mean (SD) [95% CI]	4.0 (2.6) [3.9-4.0]	3.9 (2.5) [3.8-4.0]	3.7 (2.4) (3.6-3.8)	4.2 (2.7) (4.1-4.3)	4.4 (2.9) (4.3-4.5)	4.5 (2.8) (4.4-4.6)
Laboratory values, mean (SD)						
HbA1c, %	7.7 (1.8) [7.7-7.7]	8.2 (2.0) [8.1-8.3]	8.1 (1.8) [8.0-8.2]	7.7 (1.8) [7.7-7.7]	7.8 (1.8) [7.8-7.8]	8.0 (1.9) [7.9-8.1]
LDL-C, mmol/L	2.8 (1.0) [2.8-2.8]	2.6 (0.9) [2.6-2.6]	2.7 (0.9) [2.7-2.7]	2.7 (1.0) [2.7-2.7]	2.7 (1.0) [2.7-2.7]	2.7 (1.0) [2.7-2.7]
HbA1c < 7%	41.1 (40.4-41.8)	39.5 (36.9-42.1)	40.2 (37.9-42.5)	41.7 (40.5-42.9)	40.3 (39.4-41.2)	40.8 (39.4-42.2)
LDL-C < 1.8	14.6 (14.1-15.1)	16.0 (14.0-18.0)	15.9 (14.2-17.6)	15.8 (14.9-16.7)	16.4 (15.7-17.1)	15.7 (14.7-16.7)
LDL-C < 1.4	4.3 (4.0-4.6)	4.8 (3.6-6.0)	4.6 (3.6-5.6)	4.7 (4.2-5.2)	5.3 (4.9-5.7)	4.7 (4.1-5.3)

(Continued)

10.3389/fendo.2025.1637035

TABLE 3 Continued

Patient characteristics	Patients, % (95% CI)						
	Overall (N = 17320)	Therapy prescription					
		GLP-1 RA (N = 1321)	SGLT-2i (N = 1814)	ACEI/ARB (N = 6157)	moderate-intensity statin (N = 11476)	Aspirin (N = 4965)
Insurance coverage						
Urban Employee	26.6 (26.0-27.3)	31.6 (29.1-34.1)	31.2 (29.1-33.3)	29.7 (28.6-30.8)	27.2 (26.4-28.0)	27.4 (26.2-28.6)
Urban Resident	51.2 (50.4-51.9)	45.4 (42.7-48.1)	47.2 (44.9-49.5)	49.3 (48.1-50.5)	49.8 (48.9-50.7)	50.1 (48.7-51.5)
Self-pay	5.9 (5.5-6.2)	4.1 (3.0-5.2)	4.4 (3.5-5.3)	4.6 (4.1-5.1)	4.5 (4.1-4.9)	5.1 (4.5-5.7)
Missing	16.4 (15.8-16.9)	18.9 (16.8-21.0)	17.2 (15.5-18.9)	16.4 (15.5-17.3)	18.5 (17.8-19.2)	17.4 (16.3-18.5)

GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

2018 and 2023. Further, approximately half of patients received no evidence-based cardiovascular benefit medication.

Addressing these gaps in optimal pharmacotherapy is pivotal to improve patient outcomes. Reasons for continued underuse of these evidence-based therapies are likely multifactorial, and include the guidelines update, the relatively higher cost and out-of-pocket cost of new therapies, as well as clinical inertia. As we known, GLP-1 RA and SGLT2i both have demonstrated substantial benefits on major adverse cardiovascular events in those with T2DM and ASCVD (27, 37, 38). Based on these data, the ADA has recommended GLP-1 RA and SGLT2i as first-line agents for patients with T2DM and ASCVD after metformin since 2019 (39). In 2023, the ADA recommended that clinicians consider prescribing GLP-1 RA and SGLT2i prior to metformin for patients with T2DM and established or high risk of ASCVD (40). In the wake of these updates, the use of GLP-1 RA and SGLT2i both slightly increased from 2018 through 2019, followed by a more than 3-fold from 2019 to 2023.

Despite the room for improvement, our findings support cautious optimism around the uptake of these agents in clinical practice. The use of GLP-1 RA rates doubled from 2020 through 2021, when the semaglutide was covered by health insurance in China. A similar trend was observed for SGLT2i, when the empagliflozin and dapagliflozin was covered by health insurance in 2020, the usage rates of these drugs doubled from 2019 to 2020. The rate of urban employee medical insurance was higher among those using evidence-based cardiovascular preventive therapies compared with those not using.

Therapeutic inertia within the realm of CVD prevention is a well-established barrier to widespread and consistent implementation of novel pharmacotherapeutic advances (41). Herein, we observed slightly higher HbA1c levels and had a lower percentage of patients achieved HbA1c < 7% among those treated with GLP-1 RA and SGLT2i. These agents remained to be used less frequently than metformin or alpha-glucosidase inhibitors. This could imply that GLP-1 RA and SGLT2i were not considered as first-line therapeutic in T2DM individuals with high cardiovascular risk by clinicians.

There are several strengths and limitations to this study. The primary strength of this study is that it was the first to compare the cardiovascular and renal effectiveness of using or not-using evidence-based cardiovascular preventive therapies. And we further confirmed the benefits of GLP-1 RA, SGLT-2i, ACEI/ARB, statins, and aspirin on the cardiovascular and renal outcomes for patients with T2DM and established or high risk of ASCVD. Second, we identified the rates of use of the evidence-based cardiovascular preventive therapies among T2DM patients with established or high risk of ASCVD. Additionally, we explored the possible reasons for the underuse of these evidence-based therapies. However, there are some limitations in this study. Firstly, given the nature of our study, it cannot prove causality or completely rule out residual confounding. We do our utmost to adjust for any possible confounding factors that may affect the primary outcomes. Secondly, our study sample consisting almost entirely of participants of Asian ethnicity, and whether the results can be extrapolated to non-Asian populations remains uncertain. Thirdly, this is a retrospective analysis, although it was based on a large study population. A well-designed and randomized trial is needed to identify

confounding factors and study a causal relationship. Finally, our findings suggest that treatment discontinuation is common. However, the reason for patients switching from cardiovascular evidence-based therapies to other noncardiovascular agents was not illuminated in this study.

5 Conclusion

In conclusion, it is particularly concerning that relative to cardiovascular evidence-based therapies (GLP-1 RA, SGLT-2i, ACEI/ARB, statins, and aspirin), was associated with a lower risk of the 3-point MACE, HHF and end-stage kidney disease or doubling of serum creatinine level outcome in T2DM patients with ASCVD or high risk of ASCVD after adjusting for covariates. Despite estimates of evidence-based therapy prescription are considerably lower than expected, the rates of cardiovascular evidence-based therapies increased annually from 2018 to 2023. To continue this momentum, creative implementation science approaches will be necessary to further increase the use of these safe and effective medications in T2DM individuals with established or high risk of ASCVD.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The administrative and clinical research databases used in this study are accessible to other researchers by contacting the corresponding author. The research data and data derivatives cannot be shared outside of the terms of these agreements. Requests to access these datasets should be directed to J-QT, 449256119@qq.com.

Ethics statement

The studies involving humans were approved by Xiamen Humanity Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin. Informed consent was waived because the study used anonymized patient data.

Author contributions

JT: Conceptualization, Writing – review & editing, Funding acquisition, Writing – original draft. YL: Software, Writing – review & editing, Writing – original draft, Data curation, Methodology. ZZ: Writing – review & editing, Supervision, Validation, Project administration. YP: Investigation, Visualization, Writing – review & editing, Formal Analysis. JY: Writing – review & editing, Methodology, Software. ZW: Writing – review & editing, Resources, Visualization.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This work was supported by the Medical and Health Guidance Projects of Xiamen, China (Grant No.3502Z20224ZD1106) and Natural Science Foundation of Xiamen Province, China.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1637035/full#supplementary-material

References

1. Yun JS, Ko SH. Current trends in epidemiology of cardiovascular disease and cardiovascular risk management in type 2 diabetes. *Metabolism*. (2021) 123:154838. doi: 10.1016/j.metabol.2021.154838

2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. (2018) 17:83. doi: 10.1186/s12933-018-0728-6

3. Bancks MP, Ning H, Allen NB, Bertoni AG, Carnethon MR, Correa A, et al. Long-term absolute risk for cardiovascular disease stratified by fasting glucose level. *Diabetes Care*. (2019) 42:457–65. doi: 10.2337/dc18-1773

4. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet*. (2021) 398:262–76. doi: 10.1016/s0140-6736(21)00536-5

5. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Prato SD, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. (2021) 9:653–62. doi: 10.1016/s2213-8587(21)00203-5

6. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. (2019) 394:121–30. doi: 10.1016/s0140-6736(19)31149-3

7. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. (2019) 381:841–51. doi: 10.1056/NEJMoa1901118

8. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. (2016) 375:1834–44. doi: 10.1056/NEJMoa1607141

9. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. (2016) 375:311–22. doi: 10.1056/NEJMoa1603827

10. Neal B, Perkovic V, Mahaffey KW, Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. (2017) 377:644–57. doi: 10.1056/NEJMoa1611925

11. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. (2019) 380:347–57. doi: 10.1056/NEJMoa1812389

12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. (2015) 373:2117–28. doi: 10.1056/NEJMoa1504720

13. Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, et al. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: A scientific statement from the American Heart Association. *Circulation*. (2022) 145:e722–59. doi: 10.1161/cir.0000000000001040

14. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. (2021) 42:3227–337. doi: 10.1093/eurheartj/ehab484

15. Peikert A, Vaduganathan M, Mc Causland F, Claggett BL, Chatur S, Packer M, et al. Effects of sacubitril/valsartan versus valsartan on renal function in patients with and without diabetes and heart failure with preserved ejection fraction: insights from PARAGON-HF. *Eur J Heart Fail*. (2022) 24:794–803. doi: 10.1002/ejhf.2450

16. Cardiovascular disease and risk management: standards of care in diabetes-2025. *Diabetes Care*. (2025) 48:S207–s238. doi: 10.2337/dc25-S010

17. Society. CD. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). *Chin J Diabetes Mellitus*. (2021) 13:315–409.

18. Arnold SV, Lemos JA, Rosenson RS, Ballantyne CM, Liu YY, Mues KE, et al. Use of guideline-recommended risk reduction strategies among patients with diabetes and atherosclerotic cardiovascular disease. *Circulation*. (2019) 140:618–20. doi: 10.1161/circulationaha.119.041730

19. Nelson AJ, O'Brien EC, Kaltenbach LA, Green JB, Lopes RD, Morse CG, et al. Use of lipid-, blood pressure-, and glucose-lowering pharmacotherapy in patients with type 2 diabetes and atherosclerotic cardiovascular disease. *JAMA Netw Open*. (2022) 5:e2148030. doi: 10.1001/jamanetworkopen.2021.48030

20. Berra C, Manfrini R, Mirani M, Bucciarelli L, Zakaria AS, Piccini S, et al. AWARE A novel web application to rapidly assess cardiovascular risk in type 2 diabetes mellitus. *Acta Diabetol*. (2023) 60:1257–66. doi: 10.1007/s00592-023-02115-x

21. Berra C, Manfrini R, Bifari F, Cipponeri E, Ghelardi R, Centofanti L, et al. Improved glycemic and weight control with Dulaglutide addition in SGLT2 inhibitor treated obese type 2 diabetic patients at high cardiovascular risk in a real-world setting. The AWARE-2 study. *Pharmacol Res*. (2024) 210:107517. doi: 10.1016/j.phrs.2024.107517

22. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2025. *Diabetes Care*. (2025) 48:S181–s206. doi: 10.2337/dc25-S009

23. Xiao Y, Yu B, Chao C, Wang S, Hu D, Wu C, et al. Chinese expert consensus on blood lipid management in patients with diabetes (2024 edition). *J Transl Int Med*. (2024) 12:325–43. doi: 10.2478/jtim-2024-0014

24. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. (2018) 379:633–44. doi: 10.1056/NEJMoa1800256

25. Khan AW, Jandeleit-Dahm KAM. Atherosclerosis in diabetes mellitus: novel mechanisms and mechanism-based therapeutic approaches. *Nat Rev Cardiol*. (2025) 22:482–96. doi: 10.1038/s41569-024-01115-w

26. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. (2019) 7:776–85. doi: 10.1016/s2213-8587(19)30249-9

27. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. (2019) 393:31–9. doi: 10.1016/s0140-6736(18)32590-x

28. Nazarzadeh M, Bidel Z, Canoy D, Copland E, Bennett DA, Dehghan A, et al. Blood pressure-lowering treatment for prevention of major cardiovascular diseases in people with and without type 2 diabetes: an individual participant-level data meta-analysis. *Lancet Diabetes Endocrinol*. (2022) 10:645–54. doi: 10.1016/s2213-8587(22)00172-3

29. Soroush N, Shahraki MN, Jouabadi SM, Amiri M, Aribas E, Stricker BH, et al. Statin therapy and cardiovascular protection in type 2 diabetes: The role of baseline LDL-Cholesterol levels. A systematic review and meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis*. (2024) 34:2021–33. doi: 10.1016/j.numecd.2024.04.015

30. Seidu S, Kunutsor SK, Sesso HD, Gaziano JM, Buring JE, Roncaglioni MC, et al. Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials. *Cardiovasc Diabetol*. (2019) 18:70. doi: 10.1186/s12933-019-0875-4

31. Mousavi A, Shojaei S, Soleimani H, Semirani-Nezhad D, Ebrahimi P, Zafari A, et al. Safety, efficacy, and cardiovascular benefits of combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists in patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabetol Metab Syndr*. (2025) 17:68. doi: 10.1186/s13098-025-01635-6

32. Arnold SV, Bhatt DL, Barsness GW, Beatty AL, Deedwania PC, Inzucchi SE, et al. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: A scientific statement from the American Heart Association. *Circulation*. (2020) 141:e779–806. doi: 10.1161/cir.0000000000000766

33. Leino AD, Dorsch MP, Lester CA. Changes in statin use among U.S. Adults with diabetes: A population-based analysis of NHANES 2011-2018. *Diabetes Care*. (2020) 43:3110–2. doi: 10.2337/dc20-1481

34. King A, Tan X, Dhopeshwarkar N, Bohn R, Dea K, Leonard CE, et al. Recent trends in GLP-1 RA and SGLT2i use among people with type 2 diabetes and atherosclerotic cardiovascular disease in the USA. *BMJ Open Diabetes Res Care*. (2024) 12(5):e004431. doi: 10.1136/bmjdrc-2024-004431

35. Raat W, Mamouris P, Mathieu C, Goderis G, Vaes B. Trends in type 2 diabetes medication use and guideline adherence in Belgian primary care (2019-2023). *Prim Care Diabetes*. (2024) 19(1):29–34. doi: 10.1016/j.pcd.2024.10.007

36. Shin JI, Xu Y, Chang AR, Carrero JJ, Flaherty CM, Mukhopadhyay A, et al. Prescription patterns for sodium-glucose cotransporter 2 inhibitors in U.S. Health systems. *J Am Coll Cardiol*. (2024) 84:683–93. doi: 10.1016/j.jacc.2024.05.057

37. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation*. (2019) 139:2022–31. doi: 10.1161/circulationaha.118.038868

38. Bucciarelli L, Andreini D, Stefanini G, Fiorina RM, Francone M, Catapano F, et al. Pharmacological regression of atherosclerotic plaque in patients with type 2 diabetes. *Pharmacol Res*. (2025) 213:107635. doi: 10.1016/j.phrs.2025.107635

39. Cardiovascular disease and risk management: standards of medical care in diabetes-2019. *Diabetes Care*. (2019) 42:S103–s123. doi: 10.2337/dc19-S010

40. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care*. (2023) 46:S140–s157. doi: 10.2337/dc23-S009

41. Dixon DL, Sharma G, Sandesara PB, Yang E, Braun LT, Mensah GA, et al. Therapeutic inertia in cardiovascular disease prevention: time to move the bar. *J Am Coll Cardiol*. (2019) 74:1728–31. doi: 10.1016/j.jacc.2019.08.014

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 02 October 2025
DOI 10.3389/fendo.2025.1637543

Check for updates

OPEN ACCESS

EDITED BY
Caterina Pipino,
University of Studies G. d'Annunzio Chieti and Pescara, Italy

REVIEWED BY
Mostafa Waly,
Sultan Qaboos University, Oman
Xintian Cai,
Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, China

*CORRESPONDENCE
Leiqun Lu
llqlzy1@163.com

†These authors have contributed equally to this work

RECEIVED 29 May 2025
ACCEPTED 22 September 2025
PUBLISHED 02 October 2025

CITATION
Tang D, Gu X, Xuan Y, Zhu F, Shen Y and Lu L (2025) Association between the triglyceride-glucose index and hyperuricemia: potential role of obesity in patients with Type 2 diabetes mellitus.
Front. Endocrinol. 16:1637543.
doi: 10.3389/fendo.2025.1637543

COPYRIGHT
© 2025 Tang, Gu, Xuan, Zhu, Shen and Lu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Association between the triglyceride-glucose index and hyperuricemia: potential role of obesity in patients with Type 2 diabetes mellitus

Dou Tang†, Xi Gu†, Yan Xuan†, Fanfan Zhu, Ying Shen and Leiqun Lu*

Department of Endocrinology, RuiJin Hospital Lu Wan Branch, Shanghai Jiaotong University School of Medicine, Shanghai, China

Background: The triglyceride-glucose (TyG) index has recently emerged as a simple surrogate marker of insulin resistance. However, the relationships among the TyG index, obesity, and hyperuricemia in individuals with T2DM remain unclear. This study investigates the associations of the TyG index and obesity with hyperuricemia in T2DM, and the possible role of obesity in these associations.

Methods: In this cross-sectional study, 1,159 adults with T2DM were enrolled. The TyG index was calculated as ln [fasting triglyceride (mg/dl) × fasting plasma glucose (mg/dl)/2]. Participants were stratified into hyperuricemia and non-hyperuricemia groups based on serum uric acid levels. Multivariable logistic regression and subgroup analyses were performed to assess the association between the TyG index and hyperuricemia. Mediation analysis quantified BMI's contribution to this relationship.

Results: The prevalence of hyperuricemia was 30.7%. After adjustment for age, gender, HbA1c, diabetes duration, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption, each unit increase in the TyG index was independently associated with a 36% elevated risk of hyperuricemia (OR = 1.36, 95% CI: 1.10-1.68). Subgroup analyses showed consistent associations across different patient subgroups. Mediation analysis indicated that BMI accounted for 20.0% of the relationship.

Conclusions: The TyG index and BMI were both associated with hyperuricemia in Chinese patients with T2DM, with BMI potentially representing an indirect link.

KEYWORDS

the TyG index, hyperuricemia, BMI, mediation analysis, type 2 diabetes mellitus

1 Introduction

Hyperuricemia has emerged as a crucial public health challenge globally. Hyperuricemia is defined by elevated serum uric acid levels, primarily due to excessive production, impaired urinary excretion, or a combination of both (1). Recent meta-analyses have demonstrated a consistent rise in hyperuricemia prevalence across China over recent decades (2). A national survey conducted in 2018–19 found that about 14.0% of adults in China have hyperuricemia (3). Similarly, in the general U.S. population, approximately 20% had hyperuricemia according to the National Health and Nutrition Examination Survey from 1999 to 2018 (4). Numerous epidemiologic studies have shown that hyperuricemia correlates with type 2 diabetes mellitus (T2DM), insulin resistance, metabolic syndrome, renal disease, cardiovascular disease, and all-cause mortality (5–8). Notably, individuals with T2DM exhibit a significantly higher prevalence of hyperuricemia compared to the general population (9–11). Therefore, identifying modifiable risk factors for hyperuricemia is critical to enable targeted prevention and management approaches.

The TyG index is a simple, cost-effective, and reliable surrogate marker of insulin resistance (IR), avoiding the technical and financial constraints linked to the hyperinsulinemic-euglycemic clamp (HEC) or HOMA-IR in regular practice (12). Accumulating evidence underscores its strong predictive value for IR-related metabolic disturbances, with studies demonstrating significant correlations between elevated TyG index and incident T2DM, cardiovascular events, chronic kidney disease, and non-alcoholic fatty liver disease (13, 14). The TyG index, derived from fasting triglyceride and glucose levels, indicates lipid and glucose metabolism dysregulation, which is mechanistically linked to hyperuricemia pathogenesis (15, 16).

Some studies have consistently demonstrated a significant association between IR and hyperuricemia (12). In the Chinese general population, a linear positive association between the TyG index and hyperuricemia has been observed (17). In contrast, a cross-sectional study from the general population in the United States revealed a non-linear, reverse U-shaped relationship between the TyG index and hyperuricemia (4). Among hypertensive individuals, this relationship remains positively correlated (18, 19). Although insulin resistance is recognized as a central pathophysiological mechanism in T2DM, evidence investigating the specific interplay between the TyG index and hyperuricemia in diabetic populations remains limited.

BMI, an indicator of obesity, is strongly associated with hyperuricemia (20–22). Existing research also shows a positive correlation between the TyG index and BMI (23). However, the complex relationship among these three factors has not been thoroughly explored, particularly in individuals with type 2 diabetes, who represent a population characterized by high insulin resistance, high incidence of hyperuricemia, and a strong association with obesity. Therefore, this study aims to examine the association between the TyG index and hyperuricemia in individuals with T2DM and to assess the potential mediating role of obesity, measured by BMI, in this relationship.

2 Methods

2.1 Study participants

A total of 1,193 consecutive T2DM inpatients at the Department of Endocrinology, RuiJin Hospital Lu Wan Branch, from March 2020 to December 2024, were retrospectively selected as the research subjects. T2DM diagnosis was established according to the 2020 American Diabetes Association (ADA) criteria [23]. Participants were excluded based on the following criteria: missing data of uric acid (n=12), missing data of TyG index (n=32), or age < 18 years (n=1). In total, 34 individuals (2.9%) were excluded, leaving 1,159 participants in the final analysis. According to the Helsinki Declaration, the study protocol was approved by the Ethics Committee of RuiJin Hospital Lu Wan Branch, Shanghai Jiaotong University School of Medicine. All participants gave their written informed consent.

2.2 Clinical and biochemical analysis

All participants completed structured interviews by trained research staff, including sex, age, duration of diabetes mellitus, smoking status (never, former, or current), smoking (never or current), and medical history. BMI was calculated as body weight (kg)/height (m^2). An electronic sphygmomanometer measured SBP and DBP after a 5-minute rest period. Blood samples were collected from subjects after an overnight fast of at least eight hours, typically in the morning, ensuring standardized fasting conditions. Fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), and renal function tests were measured using standard methods. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula (24).

2.3 Definitions of the exposure and outcome variables

The TyG index was calculated using the formula: TyG = ln [TG (mg/dL) × FBG (mg/dL) / 2] (25). Hyperuricemia was defined as a serum uric acid level ≥ 420 μmol/L in males or ≥ 360 μmol/L in females (26).

2.4 Statistical analysis

Continuous variables with normal distributions (assessed by Kolmogorov-Smirnov tests and Q-Q plots) were expressed as mean ± standard deviation, while non-normally distributed variables were reported as median (interquartile range). Categorical variables were presented as frequencies (percentages). Differences between the hyperuricemia and non-hyperuricemia groups were assessed

10.3389/fendo.2025.1637543

using the Student's t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the chi-square test for categorical variables. P-values for baseline comparisons are presented for descriptive purposes only and were not adjusted for multiple comparisons.

The associations between the TyG index and hyperuricemia were assessed using univariate and multivariable logistic regression models across three different models. The results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Model 1 was unadjusted. Model 2 was adjusted for age and gender. Model 3 was additionally adjusted for HbA1c, diabetes duration, estimated glomerular filtration rate (eGFR), HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption. Covariate selection was based on clinical relevance, existing literature, or a ≥ 10% change in the effect estimate when added to the model (6). In addition, restricted cubic spline (RCS) regression was performed with 3 knots at the 10th, 50th, 90th percentiles to assess potential nonlinear relationship between the TyG index and hyperuricemia after adjusting variables in Model 3.

Stratified analyses were performed to investigate the relationship between the TyG index and hyperuricemia and their interaction in different subgroups, with adjustments for corresponding confounding factors. Mediation analysis was used to evaluate whether BMI is associated with the link between the TyG index and hyperuricemia. Three distinct statistical models were employed to evaluate the adjusted mediation effect. Mediation analysis was performed using the bootstrap method with 1,000 resamples to estimate total, direct, and indirect effects and to calculate the proportion mediated (PM). A mediation effect was considered statistically significant if the 95% CI of the β coefficient did not include zero (27). Given the cross-sectional design of this study, causal relationships inferred from the mediation analysis should be interpreted with caution. Statistical significance was defined as a two-tailed P-value <0.05. All analyses were performed using SPSS software (Version 25.0), EmpowerStats, and statistical package R (Version 4.2.0). Mediation analysis was conducted in R using the mediation package (28).

3 Results

3.1 Participants' characteristics by hyperuricemia

The characteristics of the participants are presented in Table 1. A total of 1159 patients with T2DM (701 males and 458 females) were enrolled in the final study, among whom 356 patients (30.7%) were diagnosed with hyperuricemia. Compared to patients without hyperuricemia, those with hyperuricemia were more likely to be younger (P = 0.003). However, no significant gender difference was observed (P = 0.062). Patients with hyperuricemia exhibited higher weight, BMI, elevated triglyceride, total cholesterol levels, along with reduced high-density lipoprotein cholesterol (all P<0.001).

TABLE 1 Clinical characteristics of participants by hyperuricemia.

Variables	Non-hyperuricemia (N = 803)	Hyperuricemia (N = 356)	*P* value
Age, years	59.74 ± 10.25	57.63 ± 12.31	0.003
Male, n (%)	500 (62.27%)	201 (56.46%)	0.062
Height, cm	166.42 ± 8.54	166.80 ± 8.49	0.479
Weight, kg	70.47 ± 12.88	75.64 ± 15.64	<0.001
BMI, kg/m^2	25.34 ± 3.52	27.03 ± 4.19	<0.001
SBP, mmHg	127.63 ± 19.43	128.20 ± 19.23	0.645
DBP, mmHg	74.47 ± 10.88	75.21 ± 11.28	0.298
FBG, mmol/L	7.34 ± 2.44	7.15 ± 2.29	0.209
HbA1C, (%)	8.58 ± 2.12	8.37 ± 2.07	0.133
Triglyceride, mmol/L	1.45 (1.04-2.12)	1.94 (1.43-2.82)	<0.001
Total Cholesterol, mmol/L	4.93 ± 1.30	5.28 ± 1.53	<0.001
HDL-C, mmol/L	1.17 ± 0.30	1.10 ± 0.25	<0.001
LDL-C, mmol/L	3.16 ± 0.94	3.38 ± 0.99	<0.001
eGFR, mL/min/ 1.73m^2	109.58 ± 27.90	99.94 ± 27.60	<0.001
Creatinine, umol/L	65.82 ± 17.38	71.29 ± 19.10	<0.001
Uric acid, umol/L	309.47 ± 57.86	457.76 ± 65.90	<0.001
The TyG index	9.06 ± 0.75	9.37 ± 0.77	<0.001
Hypertension, n (%)	426 (53.05%)	215 (60.39%)	0.02
Hyperlipidemia, n (%)	271 (33.75%)	156 (43.94%)	<0.001
Coronary Heart Disease, n (%)	93 (11.58%)	47 (13.20%)	0.435
Diabetic duration, years	9.73 ± 8.59	8.45 ± 8.36	0.018
Smoking status, n (%)			0.075
Never smoker	426 (53.25%)	215 (60.39%)	
Ex-smoker	96 (12.00%)	38 (10.67%)	
Current smoker	278 (34.75%)	103 (28.93%)	
Alcohol consumption, n (%)	78 (9.75%)	36 (10.11%)	0.849

Data are presented as mean ± SD, median (interquartile range), or number (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin; HDL-C, high-density lipoprotein-C; LDL-C, low-density lipoprotein-C; eGFR, estimated glomerular; the TyG index, the triglyceride-glucose index.

Additionally, they had lower estimated glomerular filtration rates (eGFR), markedly elevated serum uric acid (457.76 ± 65.90 vs. 309.47 ± 57.86 μmol/L; $P < 0.001$), higher prevalence of hypertension and hyperlipidemia, and longer diabetes duration (all $P < 0.05$). The TyG index was also significantly higher in patients with hyperuricemia than in those without (9.37 ± 0.77 vs. 9.06 ± 0.75, P<0.001). However, no significant differences were

found in height, systolic blood pressure, diastolic blood pressure, fasting blood glucose, HbA1c, LDL-C, coronary heart disease status, smoking status, or alcohol consumption between groups.

3.2 Association between TyG and BMI with hyperuricemia

The univariate and multivariable regression models are shown in Table 2. In the unadjusted model (Model 1), each unit increase in the TyG index was associated with a 1.67-fold increase of hyperuricemia (95% CI: 1.42-1.97; P < 0.001). When the TyG index was categorized into tertiles, the odds of hyperuricemia were significantly higher in the second (OR = 2.21, 95% CI: 1.59–3.08, P < 0.001) and third tertiles (OR = 2.67, 95% CI: 1.93–3.70, P < 0.001) compared with the first tertile. The association remained significant in multivariable logistic regression models after adjusting for potential confounders. After adjusting for age, gender, HbA1c, diabetes duration, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption in model 3, each one-unit increase in the TyG index was associated with an OR of 1.36 (95% CI: 1.10-1.68; P = 0.005) for hyperuricemia. Similarly, the adjusted ORs were 1.64 (95% CI: 1.15–2.35; P = 0.006) for the second TyG tertile and 1.75 (95% CI: 1.19–2.56; P = 0.004) for the third tertile, compared with the first tertile (P for trend <0.01).Accordingly, the relationship between the TyG index and hyperuricemia appeared to be approximately linear in RCS (P for nonlinearity = 0.123, Supplementary Figure S1).

The correlation between BMI and hyperuricemia was also rigorously analyzed (Table 2). In the crude model (Model 1), each one-unit increase in BMI was associated with a 12% increased risk of hyperuricemia (OR = 1.12, 95% CI: 1.09–1.16, P<0.001). After adjusting for age and gender, Model 2 confirmed similar findings (OR = 1.12, 95% CI: 1.08–1.16, P<0.001). With further adjustment for potential confounders in Model 3, the risk slightly declined but remained significant (OR = 1.08, 95% CI: 1.04–1.12, P<0.001).

3.3 Association between TyG and BMI

Table 3 presents the results of the multivariable linear regression analysis examining the association between the TyG index and BMI. In the unadjusted model (Model 1), the TyG index showed a positive association with BMI (β=1.62, 95% CI: 1.35–1.89, P < 0.001). After adjustment for age and sex in Model 2, the association remained significant (β=1.31, 95% CI: 1.03–1.58, P < 0.001). Further adjustment in model 3 for additional covariates, including HbA1c, diabetes duration, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption attenuated the strength of the association, but it remained statistically significant (β=0.95, 95% CI: 0.63–1.26, P < 0.001).

To ensure the robustness of the results, we further categorized the TyG index into tertiles. Compared with the lowest tertile, the highest tertile of the TyG index was associated with a higher BMI (β=1.47, 95% CI: 0.91–2.02, P < 0.001). Moreover, a significant dose-response relationship was observed (P for trend <0.001).

3.4 Subgroup analyses

Stratified analyses were performed to explore the robustness of the association between the TyG index and hyperuricemia, as shown in Figure 1. We found a positive association between the TyG index and hyperuricemia across subgroups defined by age, gender, hypertension status, hyperlipidemia, smoking status and alcohol consumption.

Notably, we observed no significant interaction effects among these subgroups (all P for interaction > 0.05). These results support the independent and robust correlation between TyG and hyperuricemia across all subgroups.

TABLE 2 Association between the triglyceride-glucose index and BMI with hyperuricemia.

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
TyG (continuous)	1.67 (1.42, 1.97)	<0.001	1.65 (1.39, 1.96)	<0.001	1.36 (1.10, 1.68)	0.005
TyG (tertile)						
T1:6.91-8.81	Reference		Reference		Reference	
T2:8.82-9.37	2.21 (1.59, 3.08)	<0.001	2.20 (1.58, 3.06)	<0.001	1.64 (1.15, 2.35)	0.006
T3:9.38-12.28	2.67 (1.93, 3.70)	<0.001	2.53 (1.81, 3.53)	<0.001	1.75 (1.19, 2.56)	0.004
P for trend	<0.001		<0.001		0.006	
BMI	1.12 (1.09, 1.16)	<0.001	1.12 (1.08, 1.16)	<0.001	1.08 (1.04, 1.12)	<0.001

OR, odds ratio; CI, confidence interval; TyG, triglyceride-glucose; BMI, body mass index.
Model 1: unadjusted.
Model 2: adjusted for age and gender.
Model 3: adjusted for the variables in Model 2 plus HbA1c, the duration of diabetes, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption.

TABLE 3 The association between the triglyceride-glucose index and BMI.

Variables	Model 1		Model 2		Model 3	
	β (95%CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
TyG (continuous)	1.62 (1.35, 1.89)	<0.001	1.31 (1.03, 1.58)	<0.001	0.95 (0.63, 1.26)	<0.001
TyG (tertile)						
T1:6.91-8.81	Reference		Reference		Reference	
T2:8.82-9.37	1.68 (1.17, 2.20)	<0.001	1.59 (1.09, 2.09)	<0.001	1.05 (0.54, 1.55)	<0.001
T3:9.38-12.28	2.71 (2.19, 3.22)	<0.001	2.19 (1.68, 2.70)	<0.001	1.47 (0.91, 2.02)	<0.001
P for trend	<0.001		<0.001		<0.001	

β, regression coefficient; CI, confidence interval. TyG, triglyceride-glucose.
Model 1: unadjusted.
Model 2: adjusted for age and gender.
Model 3: adjusted for the variables in Model 2 plus HbA1c, the duration of diabetes, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption.

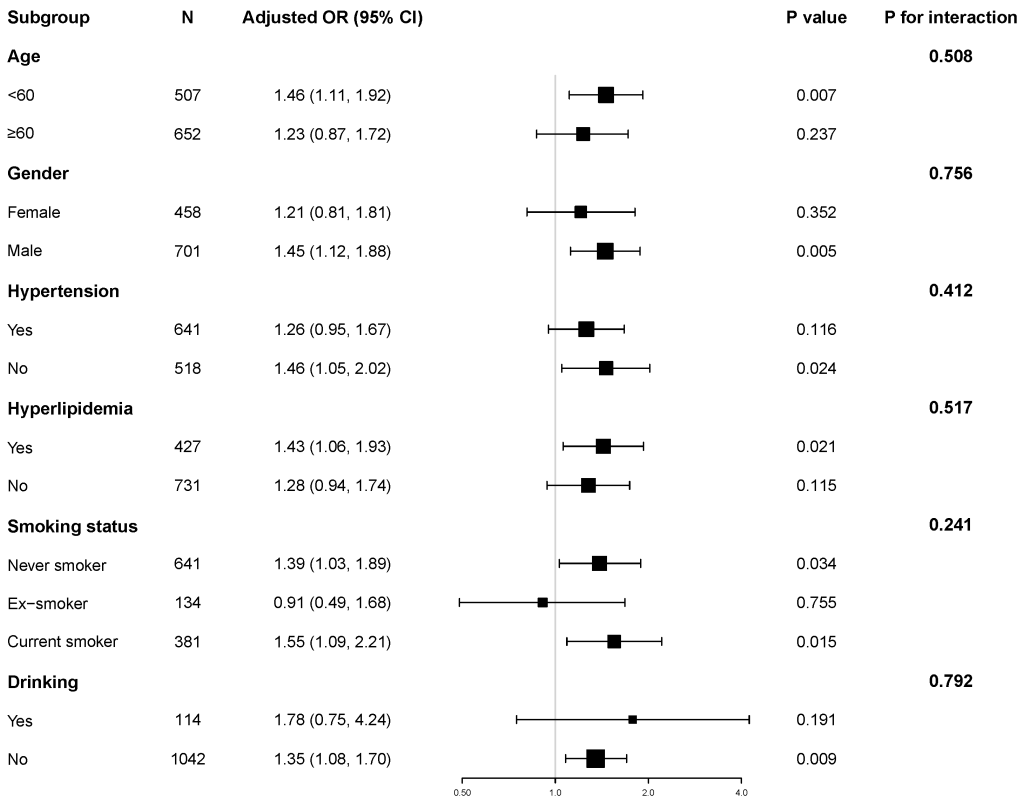


FIGURE 1
Subgroup and interaction analyses of the TyG index and hyperuricemia. Adjusted for age, gender, HbA1c, the duration of diabetes, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption.

3.5 Mediation analyses

Mediation analysis was conducted to assess the relationship of BMI with the TyG index and hyperuricemia (Table 4, Figure 2). The total effect of the TyG index on hyperuricemia was statistically significant across all three models. The indirect effect through BMI was also significant, accounting for approximately 20.0% to 27.9% of the total effect, indicating a meaningful mediation role of BMI. Even after adjusting for multiple potential confounders, including age, gender, HbA1c, diabetes duration, eGFR, HDL-C, LDL-C,

TABLE 4 Mediation analysis of the association between the triglyceride-glucose index and hyperuricemia mediated by BMI.

	Model 1		Model 2		Model 3	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Total effect	0.101 (0.072, 0.130)	<0.001	0.099 (0.068, 0.129)	<0.001	0.058 (0.024, 0.097)	0.002
Indirect effect	0.028 (0.018, 0.041)	<0.001	0.023 (0.014, 0.034)	<0.001	0.012 (0.005, 0.019)	<0.001
Direct effect	0.073 (0.042, 0.104)	<0.001	0.075 (0.043, 0.107)	<0.001	0.046 (0.013, 0.086)	0.006
PM, %	27.9%		23.6%		20.0%	
P value	<0.001		<0.001		0.002	

OR, odds ratio; CI, confidence interval; PM, proportion mediated.
Model 1: unadjusted.
Model 2: adjusted for age and gender.
Model 3: adjusted for the variables in Model 2 plus HbA1c, the duration of diabetes, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption.

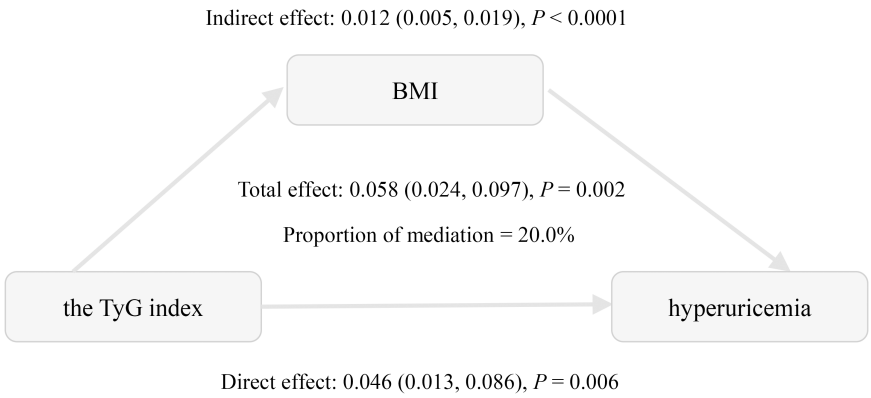


FIGURE 2
Mediation effect of BMI in the association between the triglyceride-glucose index and hyperuricemia. Adjusted for age, gender, HbA1c, the duration of diabetes, eGFR, HDL-C, LDL-C, hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption.

hypertension, hyperlipidemia, coronary heart disease, smoking status, and alcohol consumption, both the direct and indirect effects remained statistically significant. These findings are consistent with a potential role of BMI in the relationship between the TyG index and hyperuricemia.

4 Discussion

This study explored the relationships between insulin resistance, obesity, and hyperuricemia in the context of T2DM. We demonstrated significant positive associations between the TyG index, BMI, and hyperuricemia in Chinese patients with T2DM. These associations remained significant after adjusting for confounding factors. Subgroup analyses further confirmed the consistent relationship between the TyG index and hyperuricemia. Notably, mediation analysis reveals that BMI accounts for 20.0% of this association, suggesting that obesity may be involved in this relationship.

A recent systematic review and meta-analysis reported a pooled hyperuricemia prevalence of 27.28% among African individuals with T2DM, with regional variations ranging from 24.72% in North Africa to 33.72% in Central Africa (10). Similar regional differences exist in China. A previous study in Southwest China revealed a prevalence rate of 21.24% in diabetic patients (11), whereas another research in Urumqi reported a notably lower prevalence of 12.6% (29). In our research, 30.7% of individuals with type 2 diabetes were found to have hyperuricemia. These variations may reflect differences in genetic profiles, dietary habits, lifestyle choices, and environmental exposures across regions. While most epidemiological studies report higher hyperuricemia prevalence in males, our findings showed no significant sex difference. This contradicts established phenomenon where premenopausal women typically exhibit lower uric acid levels due to estrogen's protective effect. Notably, in our study, the female participants had a median age of 63 years (interquartile range [IQR]: 57-67), suggesting that the majority were likely postmenopausal and had lost the protective effect of estrogen. Consequently, their serum uric

acid levels progressively elevated, approximating those observed in males (30–32).

Accumulating evidence establishes a significant association between the TyG index and hyperuricemia. Shi et al. revealed a linear relationship between TyG and hyperuricemia in the general Chinese population, with each SD increase in TyG corresponding to a 54.1% higher risk of hyperuricemia (17). Recently, Qiu et al. further demonstrated a positive, reverse U-shaped association in U.S. adults, suggesting a complex relationship that may be influenced by geographic and ethnic factors (4). Moreover, several studies have confirmed this association in hypertensive populations (18, 19). However, evidence specific to diabetic populations remains limited (12). Consistent with prior studies, our research confirmed a positive and linear association in the Chinese diabetic population. Subgroup analyses and interaction tests further demonstrated its consistency across diverse patient subgroups. So far, the role of obesity as a mediator between the TyG index and hyperuricemia has not been thoroughly investigated. A cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) revealed that BMI mediated 46.8% of this association in the general U.S. population (33). In contrast, a study conducted among middle-aged and elderly hypertensive individuals in China found that BMI mediated only 8.9% of this association (34). Notably, our study revealed a mediation proportion of 20.0% for the association between the TyG index and hyperuricemia in patients with T2DM, a proportion intermediate between the 46.8% reported in the general U.S. population and the 8.9% observed in middle-aged and elderly Chinese hypertensive patients. These discrepancies may arise from metabolic characteristics in a specific population. Ethnic differences in susceptibility to insulin resistance may also contribute to the heterogeneity in the mediation effect of BMI across populations (35). Additionally, unmeasured confounders and methodological differences may also contribute to the observed heterogeneity. To the best of our knowledge, this is the first study to investigate the mediating effect of BMI on the association between the TyG index and hyperuricemia in a diabetic population.

The mechanisms behind this observation are not yet clearly established, but several potential biological mechanisms may account for this observation. The TyG index, derived from triglycerides and fasting blood glucose levels, reflects dysregulated lipid and glucose metabolism, both implicated in hyperuricemia pathogenesis (15, 16). Animal studies suggest IR exacerbates hyperuricemia primarily through enhancing urate reabsorption via increased expression of urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9), elevating serum uric acid levels (36, 37). Obesity, as a key component of metabolic syndrome, promotes free fatty acid (FFA) release, further enhancing insulin resistance and urate transporters expression (33, 37, 38). Adipocytes secrete inflammatory factors such as TNF-α and IL-6, as well as adipokines like leptin, adiponectin, and resistin. These substances contribute to insulin resistance and induce a chronic low-grade inflammatory state, thereby damaging the kidneys (39, 40). This may ultimately impair uric acid excretion and elevate uric acid levels.

The study has several limitations. Firstly, because TyG, BMI, and SUA were measured simultaneously, temporality cannot be established and causal inference is not possible. Our mediation analysis revealed indirect associations consistent with a potential pathway from TyG through BMI to hyperuricemia, but alternative or reverse pathways, such as hyperuricemia leading to insulin resistance (41), are biologically plausible. These findings are exploratory and hypothesis-generating, and require confirmation in future longitudinal or interventional studies. Secondly, residual and unmeasured confounding may exist, including dietary intake, certain medications, and renal factors beyond eGFR, and potential bias from self-reported variables such as smoking, alcohol consumption, and medical history. Additionally, both TyG and hyperuricemia were measured from the same blood sample, introducing a shared-source bias that may inflate the observed association. Results should be interpreted with caution. Thirdly, consecutive inpatients may represent a population with more severe or poorly controlled diabetes, and as a single-center study of Chinese patients, caution is needed when generalizing these findings.

5 Conclusions

In this cross-sectional study of Chinese patients with T2DM, both the TyG index and BMI were independently associated with hyperuricemia. The observed associations were consistent with a possible indirect link through BMI, but causal mediation cannot be established due to the study design. These findings suggest that obesity may partly explain the relationship between insulin resistance reflected by the TyG index and hyperuricemia. Weight management and lifestyle interventions targeting both insulin resistance and obesity may therefore have potential clinical value in reducing hyperuricemia risk in this population. Future longitudinal studies with prospective follow-up and external validation are needed to clarify whether integrating insulin resistance and obesity into multivariable models can improve risk stratification for hyperuricemia in patients with type 2 diabetes.

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 humans were approved by the Ethics Committee of RuiJin Hospital Lu Wan Branch, Shanghai Jiaotong

University School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DT: Writing – original draft, Methodology, Project administration, Conceptualization, Funding acquisition. XG: Methodology, Software, Writing – review & editing, Conceptualization, Funding acquisition. YX: Data curation, Supervision, Investigation, Methodology, Writing – review & editing. FZ: Formal Analysis, Software, Data curation, Writing – review & editing, Methodology. YS: Supervision, Conceptualization, Writing – review & editing, Project administration. LL: Conceptualization, Resources, Writing – review & editing, Supervision.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This work was supported by grants from the Shanghai Huangpu District Health Commission (Grant No. HLM202206, HLM202401, HLQ202205).

Acknowledgments

The authors thank all colleagues in the Department of Endocrinology of RuiJin Hospital Lu Wan Branch, Shanghai Jiaotong University School of Medicine for their contributions to this work.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1637543/full#supplementary-material

References

1. Crawley WT, Jungels CG, Stenmark KR, Fini MA. U-shaped association of uric acid to overall-cause mortality and its impact on clinical management of hyperuricemia. *Redox Biol.* (2022) 51:102271. doi: 10.1016/j.redox.2022.102271

2. Li Y, Shen Z, Zhu B, Zhang H, Zhang X, Ding X. Demographic, regional and temporal trends of hyperuricemia epidemics in mainland China from 2000 to 2019: a systematic review and meta-analysis. *Glob Health Action*. (2021) 14:1874652. doi: 10.1080/16549716.2021.1874652

3. Zhang M, Zhu X, Wu J, Huang Z, Zhao Z, Zhang X, et al. Prevalence of hyperuricemia among chinese adults: findings from two nationally representative cross-sectional surveys in 2015–16 and 2018–19. *Front Immunol.* (2022) 12:791983. doi: 10.3389/fimmu.2021.791983

4. Qiu L, Ren Y, Li J, Li M, Li W, Qin L, et al. Nonlinear association of triglyceride-glucose index with hyperuricemia in US adults: a cross-sectional study. *Lipids Health Dis.* (2024) 23:145. doi: 10.1186/s12944-024-02146-5

5. Chang J-B, Chen Y-L, Hung Y-J, Hsieh C-H, Lee C-H, Pei D, et al. The role of uric acid for predicting future metabolic syndrome and type 2 diabetes in older people. *J Nutr Health Aging*. (2017) 21:329–35. doi: 10.1007/s12603-016-0749-3

6. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med.* (2000) 343:1826–32. doi: 10.1056/NEJM200012213432501

7. Du L, Zong Y, Li H, Wang Q, Xie L, Yang B, et al. Hyperuricemia and its related diseases: mechanisms and advances in therapy. *Signal Transduct Target Ther*. (2024) 9:212. doi: 10.1038/s41392-024-01916-y

8. Song S, Cai X, Hu J, Zhu Q, Shen D, Ma H, et al. Plasma aldosterone concentrations elevation in hypertensive patients: the dual impact on hyperuricemia and gout. *Front Endocrinol.* (2024) 15:1424207. doi: 10.3389/fendo.2024.1424207

9. Abujbara M, Al Hourani HM, Al-Raoush RI, Khader YS, Ajlouni K. Prevalence of hyperuricemia and associated factors among type 2 diabetic patients in Jordan. *Int J Gen Med.* (2022) 15:6611–9. doi: 10.2147/IJGM.S376857

10. Alemayehu E, Fiseha T, Bambo GM, Sahile Kebede S, Bisetegn H, Tilahun M, et al. Prevalence of hyperuricemia among type 2 diabetes mellitus patients in Africa: a systematic review and meta-analysis. *BMC Endocr Disord.* (2023) 23:153. doi: 10.1186/s12902-023-01408-0

11. Sun S, Chen L, Chen D, Li Y, Liu G, Ma L, et al. Prevalence and associated factors of hyperuricemia among Chinese patients with diabetes: a cross-sectional study. *Ther Adv Endocrinol Metab.* (2023) 14:20420188231198620. doi: 10.1177/20420188231198620

12. Han R, Zhang Y, Jiang X. Relationship between four non-insulin-based indexes of insulin resistance and serum uric acid in patients with type 2 diabetes: a cross-sectional study. *Diabetes Metab Syndr Obes.* (2022) 15:1461–71. doi: 10.2147/DMSO.S362248

13. Lee D-H, Park JE, Kim SY, Jeon HJ, Park J-H. Association between the triglyceride-glucose (TyG) index and increased blood pressure in normotensive subjects: a population-based study. *Diabetol Metab Syndrome*. (2022) 14:161. doi: 10.1186/s13098-022-00927-5

14. Sun Y, Ji H, Sun W, An X, Lian F. Triglyceride glucose (TyG) index: A promising biomarker for diagnosis and treatment of different diseases. *Eur J Internal Med.* (2025) 131:3–14. doi: 10.1016/j.ejim.2024.08.026

15. Cui N, Cui J, Sun J, Xu X, Aslam B, Bai L, et al. Triglycerides and total cholesterol concentrations in association with hyperuricemia in chinese adults in qingdao, China. *Risk Manag Healthc Policy*. (2020) 13:165–73. doi: 10.2147/RMHP.S243381

16. Li H, Zha X, Zhu Y, Liu M, Guo R, Wen Y. An invert U-shaped curve: relationship between fasting plasma glucose and serum uric acid concentration in a large health check-up population in China. *Med (Baltimore)*. (2016) 95:e3456. doi: 10.1097/MD.0000000000003456

17. Shi W, Xing L, Jing L, Tian Y, Liu S. Usefulness of triglyceride-glucose index for estimating hyperuricemia risk: insights from a general population. *Postgrad Med*. (2019) 131:348–56. doi: 10.1080/00325481.2019.1624581

18. Yu C, Wang T, Zhou W, Zhu L, Huang X, Bao H, et al. Positive association between the triglyceride-glucose index and hyperuricemia in chinese adults with hypertension: an insight from the China H-type hypertension registry study. *Int J Endocrinol*. (2022) 2022:4272715. doi: 10.1155/2022/4272715

19. Liu S, Zhou Z, Wu M, Zhang H, Xiao Y. Association between the triglyceride glucose index and hyperuricemia in patients with primary hypertension: a cross-sectional study. *Int J Endocrinol*. (2023) 2023:5582306. doi: 10.1155/2023/5582306

20. Bae J, Park K-Y, Son S, Huh Y, Nam GE. Associations between obesity parameters and hyperuricemia by sex, age, and diabetes mellitus: A nationwide study in Korea. *Obes Res Clin Pract*. (2023) 17:405–10. doi: 10.1016/j.orcp.2023.09.007

21. Choi HK, McCormick N, Lu N, Rai SK, Yokose C, Zhang Y. Population impact attributable to modifiable risk factors for hyperuricemia. *Arthritis Rheumatol*. (2020) 72:157–65. doi: 10.1002/art.41067

22. Mao T, He Q, Yang J, Jia L, Xu G. Relationship between gout, hyperuricemia, and obesity-does central obesity play a significant role?-a study based on the NHANES database. *Diabetol Metab Syndr*. (2024) 16:24. doi: 10.1186/s13098-024-01268-1

23. Sergi D, Spaggiari R, Dalla Nora E, Angelini S, Castaldo F, Omenetto A, et al. HOMA-IR and TyG index differ for their relationship with dietary, anthropometric, inflammatory factors and capacity to predict cardiovascular risk. *Diabetes Res Clin Pract*. (2025) 222:112103. doi: 10.1016/j.diabres.2025.112103

24. Moazzeni SS, Arani RH, Hasheminia M, Tohidi M, Azizi F, Hadaegh F. High incidence of chronic kidney disease among Iranian diabetic adults: using CKD-EPI and MDRD equations for estimated glomerular filtration rate. *Diabetes Metab J*. (2021) 45:684–97. doi: 10.4093/dmj.2020.0109

25. Huo R, Liao Q, Zhai L, You X, Zuo Y. Interacting and joint effects of triglyceride-glucose index (TyG) and body mass index on stroke risk and the mediating role of TyG in middle-aged and older Chinese adults: a nationwide prospective cohort study. *Cardiovasc Diabetol*. (2024) 23:30. doi: 10.1186/s12933-024-02122-4

26. Zhang Y, Zhang M, Yu X, Wei F, Chen C, Zhang K, et al. Association of hypertension and hypertriglyceridemia on incident hyperuricemia: an 8-year prospective cohort study. *J Transl Med*. (2020) 18:409. doi: 10.1186/s12967-020-02590-8

27. Wang Y, Li Y, Liu K, Han X, Dong Y, Wang X, et al. Nonalcoholic fatty liver disease, serum cytokines, and dementia among rural-dwelling older adults in China: A population-based study. *Eur J Neurol*. (2022) 29:2612–21. doi: 10.1111/ene.15416

28. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *psychol Methods*. (2010) 15:309–34. doi: 10.1037/a0020761

29. Abudureyimu P, Pang Y, Huang L, Luo Q, Zhang X, Xu Y, et al. A predictive model for hyperuricemia among type 2 diabetes mellitus patients in Urumqi, China. *BMC Public Health*. (2023) 23:1740. doi: 10.1186/s12889-023-16669-6

30. Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women – The Third National Health and Nutrition Examination Survey. *Arthritis Res Ther*. (2008) 10:R116. doi: 10.1186/ar2519

31. Cho SK, Winkler CA, Lee S-J, Chang Y, Ryu S. The prevalence of hyperuricemia sharply increases from the late menopausal transition stage in middle-aged women. *J Clin Med*. (2019) 8:296. doi: 10.3390/jcm8030296

32. Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol*. (2015) 11:649–62. doi: 10.1038/nrrheum.2015.91

33. Mazidi M, Katsiki N, Mikhailidis DP, Banach M. The link between insulin resistance parameters and serum uric acid is mediated by adiposity. *Atherosclerosis*. (2018) 270:180–6. doi: 10.1016/j.atherosclerosis.2017.12.033

34. Sun J, Sun M, Su Y, Li M, Ma S, Zhang Y, et al. Mediation effect of obesity on the association between triglyceride-glucose index and hyperuricemia in Chinese hypertension adults. *J Clin Hypertens (Greenwich)*. (2022) 24:47–57. doi: 10.1111/jch.14405

35. Tay J, Goss AM, Garvey WT, Lockhart ME, Bush NC, Quon MJ, et al. Race affects the association of obesity measures with insulin sensitivity. *Am J Clin Nutr*. (2020) 111:515–25. doi: 10.1093/ajcn/nqz309

36. Miao Z, Yan S, Wang J, Wang B, Li Y, Xing X, et al. Insulin resistance acts as an independent risk factor exacerbating high-purine diet induced renal injury and knee joint gouty lesions. *Inflammation Res*. (2009) 58:659–68. doi: 10.1007/s00011-009-0031-9

37. Yanai H, Adachi H, Hakoshima M, Katsuyama H. Molecular biological and clinical understanding of the pathophysiology and treatments of hyperuricemia and its association with metabolic syndrome, cardiovascular diseases and chronic kidney disease. *Int J Mol Sci*. (2021) 22:9221. doi: 10.3390/ijms22179221

38. Boden G. Obesity, insulin resistance and free fatty acids. *Curr Opin Endocrinol Diabetes Obes*. (2011) 18:139–43. doi: 10.1097/MED.0b013e3283444b09

39. Lubawy M, Formanowicz D. Insulin resistance and urolithiasis as a challenge for a dietitian. *Int J Environ Res Public Health*. (2022) 19:7160. doi: 10.3390/ijerph19127160

40. Arabi T, Shafqat A, Sabbah BN, Fawzy NA, Shah H, Abdulkader H, et al. Obesity-related kidney disease: beyond hypertension and insulin-resistance. *Front Endocrinol*. (2023) 13:1095211. doi: 10.3389/fendo.2022.1095211

41. Han T, Lan L, Qu R, Xu Q, Jiang R, Na L, et al. Temporal relationship between hyperuricemia and insulin resistance and its impact on future risk of hypertension. *Hypertension*. (2017) 70:703–11. doi: 10.1161/HYPERTENSIONAHA.117.09508

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 08 October 2025
DOI 10.3389/fendo.2025.1663831

Check for updates

OPEN ACCESS

EDITED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

REVIEWED BY
Zeshan Ali,
Bohai University, China
Kusum Devi,
The University of Iowa, United States
Varun Kashyap,
Indian Council of Medical Research (ICMR), India

*CORRESPONDENCE
Jie Shen
sjiesy@smu.edu.cn

RECEIVED 11 July 2025
ACCEPTED 25 September 2025
PUBLISHED 08 October 2025

CITATION
He S, Meng W, Huang M, Fu Q and Shen J (2025) Association of blood urea nitrogen to serum albumin ratio with arterial stiffness in type 2 diabetes patients: a Chinese cross-sectional study.
Front. Endocrinol. 16:1663831.
doi: 10.3389/fendo.2025.1663831

COPYRIGHT
© 2025 He, Meng, Huang, Fu and Shen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Association of blood urea nitrogen to serum albumin ratio with arterial stiffness in type 2 diabetes patients: a Chinese cross-sectional study

Shengqing He[1,2,3], Wanrui Meng[3], Miaoling Huang[3], Qingsong Fu[4] and Jie Shen[1,2*]

[1]Department of Endocrinology and Metabolism, The Eighth Affiliated Hospital, Southern Medical University (The First People's Hospital of Shunde), Foshan, Guangdong, China, [2]GuangDong Engineering Technology Research Center of Metabolic Disorders Interdisciplinary Precision Prevention and Digital Healthcare, The Eighth Affiliated Hospital of Southern Medical University (The First People's Hospital of Shunde), Foshan, Guangdong, China, [3]Department of Endocrinology, Longgang Central Hospital, Shenzhen, Guangdong, China, [4]Department of Laboratory, Longgang Central Hospital, Shenzhen, Guangdong, China

Background: Arterial stiffness is an early indicator of atherosclerosis. The blood urea nitrogen to serum albumin ratio(BAR) is associated with poor prognosis in several chronic diseases. However, the relationship between BAR and arterial stiffness in type 2 diabetes mellitus (T2DM) patients has not been extensively studied. This study aimed to examine the relationship between BAR and brachial-ankle pulse wave velocity (baPWV), an indicator of arterial stiffness in patients newly diagnosed with T2DM.

Methods: A total of 510 adult patients newly diagnosed with T2DM were enrolled between January 2021 and December 2023. BAR was calculated by blood urea nitrogen/albumin ratio. A baPWV ≥1400 cm/s was defined as arterial stiffness. A linear regression model and logistic regression model were used to assess the relationship between BAR and baPWV after adjusting for potential confounders.

Results: The average age of the patients in this study was 45.66 ± 10.18 years, and 78.8% were male. The mean baPWV was 1469.15 ± 295.82 cm/s, and 50.8% of patients exhibited arterial stiffness. The prevalence of arterial stiffness increased significantly across ascending BAR tertiles (T1: 39.3%, T2: 51.7%, T3: 61.4%; p = 0.002). Linear correlation analysis revealed a positive correlation between BAR and baPWV. According to the fully adjusted logistic regression model, each unit increase in the lnBAR was associated with a 3.452-fold greater risk of arterial stiffness[95% CI(1.586, 7.513), p = 0.002]. Compared to the lowest tertile (T1), participants in the middle (T2) and highest (T3) BAR tertiles had a significantly greater risk of arterial stiffness [T2: OR = 1.915, 95% CI (1.016, 3.609), p = 0.044; T3: OR = 2.064, 95% CI (1.051, 4.054), p = 0.035]. Stratified analyses

demonstrated consistent positive correlations between BAR and baPWV across sex and BMI subgroups, as well as in individuals aged < 50 years.
Conclusion: BAR levels were independently and positively correlated with baPWV in Chinese patients with newly diagnosed T2DM.

KEYWORDS

type 2 diabetes mellitus, arterial stiffness, blood urea nitrogen to serum albumin ratio, brachial-ankle pulse wave velocity, cardiovascular disease

1 Introduction

The global diabetes epidemic poses a significant challenge to public health systems worldwide, imposing considerable economic and social burdens. According to the International Diabetes Federation (IDF) (1), 589 million adults aged 20–79 years are living with diabetes globally. This number is expected to rise to 853 million by 2050, with over 90% of cases attributed to type 2 diabetes mellitus (T2DM). China has the highest diabetes burden, affecting 12.8% of the adult population (2). Crucially, diabetes-related complications, particularly macrovascular diseases such as atherosclerosis, ischemic heart disease, and stroke, have emerged as the leading causes of mortality and disability among patients with diabetes. Importantly, these complications are increasingly prevalent among younger populations (3), underscoring the urgent need for early screening of high-risk individuals and implementation of targeted vascular protection strategies.

Arterial stiffness, characterized by diminished arterial elasticity due to structural and functional abnormalities of the arterial wall, represents an early indicator of atherosclerosis (4). Substantial evidence indicates that increased arterial stiffness is independently correlated with cardiovascular disease (CVD) and renal impairment, serving as a predictor of cardiovascular morbidity and mortality (4–6). Diabetes exacerbates arterial stiffening through various pathophysiological mechanisms, including insulin resistance, endothelial dysfunction, non-enzymatic glycation, platelet dysfunction, chronic inflammation, and increased oxidative stress (7). In patients with T2DM, early detection of arterial stiffness, in conjunction with biomarker identification, is crucial for mitigating the progression of atherosclerosis. Brachial-ankle pulse wave velocity (baPWV), a noninvasive and cost-effective clinical tool, has a strong ability to predict for cardiovascular risk and all-cause mortality in diabetic patients (8, 9). Notably, assessing baPWV in newly diagnosed with T2DM is of significant clinical importance. Many of these patients have already experienced prolonged hyperglycemia, which initiates the progression of vascular stiffness. Early detection of arterial stiffness in this population provides a critical opportunity for intervention, potentially altering the progression of CVD.

Blood urea nitrogen (BUN), a metabolic byproduct of protein catabolism, serves as a biomarker of renal function, nutritional status, and volume status. It has also been independently associated with CVD mortality risk, establishing its utility in the assessment of CVD prognosis (10, 11). Serum albumin(ALB), a key nutritional indicator, critically mediates substance transport, ligand binding, and maintenance of plasma colloid osmotic pressure. Additionally, it has antioxidant, anti-inflammatory, and endothelial stabilizing functions (12, 13). The blood urea nitrogen to serum albumin ratio (BAR) is an innovative biomarker that combines indicators of BUN and ALB, reflecting both nutritional and inflammatory factors. Studies have demonstrated that it has significant predictive value in assessing the prognosis of various diseases, including pneumonia, chronic heart failure, sepsis, and renal insufficiency (14–17). However, its association with arterial stiffness in patients with T2DM remains unknown. Therefore, this study aimed to investigate the correlation between BAR and arterial stiffness, as determined by baPWV, in individuals newly diagnosed with T2DM.

2 Methods

2.1 Data source and study population

This was a cross-sectional study. A total of 510 adults with newly diagnosed (< 3 months) with T2DM who were drug-naïve—defined as individuals who had not previously received any treatment with oral hypoglycemic agents or insulin—were enrolled. These patients were under follow-up care at the National Metabolic Management Center (MMC) of Longgang Central Hospital in Shenzhen between January 2021 and December 2023. The MMC is a platform for the standardized diagnosis, management, and follow-up of patients with metabolic diseases. All individuals who met the 1999 WHO diagnostic criteria for T2DM were included in the study. The main exclusion criteria were autoimmune diabetes, secondary diabetes, pregnancy, malignancy, chronic kidney disease (eGFR <60 ml/min), chronic liver disease, coronary artery disease, heart failure, and stroke. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, and the research protocol received approval from the Ethics Committee of Longgang Central Hospital. Informed consent was obtained from all participants.

2.2 Clinical and laboratory data

Face-to-face interviews were conducted with all patients to obtain relevant information, including age, sex, occupation, medical history,

and personal habits such as smoking and drinking. The duration of T2DM was calculated from the time of the first diagnosis. Blood pressure was measured via an automated blood pressure cuff with the participant in a seated position on the upper arm. The average value was derived from three consecutive measurements. The subjects' height and weight were measured in a fasted state on the morning of the study, and the body mass index(BMI) of each individual was calculated via the following formula: weight (kg)/height $(m)^2$. Waist circumference was measured at the midpoint between the lower edge of the lowest rib and the upper edge of the hipbone using a non-elastic flexible ruler. The average of the two measurements was calculated. Plasma was collected from the patients in a fasted state eight hours after their overnight stay, and the following indicators were measured via a fully automated biochemical analyzer: fasting blood glucose, fasting C-peptide, glycosylated hemoglobin(HbA_1c), alanine aminotransferase(ALT), aspartate aminotransferase(AST), gamma-glutamyltransferase(GGT), serum albumin(ALB), serum uric acid, creatinine, blood urea nitrogen (BUN), triglyceride(TG), total cholesterol(TC), HDL cholesterol(HDL-C) and LDL cholesterol(LDL-C). The eGFR was calculated from serum creatinine using by abbreviated MDRD study equation [eGFR (mL/min/1.73 m^2) = 186 × (Scr)^-1.154 × (Age)^-0.203 × (0.742 if female)] and included as a continuous variable. BAR(mmol/g) was calculated by the ratio of BUN (mmol/L) to albumin(g/L). The patients were divided into three equal groups according to their BAR level:T1, BAR <0.0874; T2, BAR between 0.0874 and 0.1161; and T3, BAR >0.1161.

2.3 Brachial-ankle pulse wave velocity measurement

BaPWV was measured via an automated atherosclerosis testing device (VP-1000; Omron Corporation, Kyoto, Japan). The participants were placed in the supine position and allowed to rest for at least five minutes. Blood pressure cuffs were then attached to the upper arms (brachial arteries) and ankles (posterior tibial arteries) bilaterally. Cardiac leads were also connected to synchronize the pulse waveforms in the cuff arteries. The conduction distance between the arm and ankle was measured, and the conduction time was defined as the interval between the initial rise in the waveforms of the brachial and posterior tibial arteries. The baPWV was calculated by the following formula: baPWV (cm/s) = conduction distance (cm)/conduction time (s). The average baPWV was calculated by averaging the baPWV readings from both sides, and baPWV ≥1400 cm/s was defined as arterial stiffness, as previously reported (18, 19). All operations were performed by technicians who had received uniform technical training, and measurements with poor waveforms were excluded.

2.4 Statistical analyses

Data that followed a normal distribution are presented as the means ± standard deviations, while data that did not follow a normal distribution are presented as medians with quartile ranges. Count data are presented as frequencies and percentages (n, %). BaPWV was analyzed as a continuous variable using its raw values (cm/s). In the binary logistic regression analysis, BAR was treated as a continuous variable and was transformed and analyzed in the form of natural logarithm because the raw data was skewed. Patients were grouped into tertiles on the basis of BAR. To evaluate trends, linear regression was applied to continuous variables, whereas chi-square trend tests were used for categorical variables. The assumption of linearity in the logit for these continuous variables in the logistic regression model was confirmed using Box-Tidwell test, while for continuous predictors in linear regression, it was confirmed using the Residuals *vs*. Fitted plot. Pearson or Spearman correlation coefficients were used to examine the relationships between baPWV and other indicators. The assessment of multicollinearity among the relative variables was conducted by calculating the Variance Inflation Factor (VIF), and none were found. A multivariable binary logistic regression model was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) for assessing the independent effects of BAR on baPWV. The Receiver Operating Characteristic (ROC) curve analysis was employed to ascertain the optimal cut-off for the BAR in predicting increased arterial stiffness in individuals newly diagnosed with T2DM. Statistical analyses were performed using SPSS 27.0, and a bilateral p-value <0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics

The demographic and clinical characteristics of the enrolled patients are shown in Table 1. A total of 510 patients with newly diagnosed T2DM were included in this study. The average age of the patients was 45.66 ± 10.18 years. Among these patients, 402 (78.8%) were male and 98 (21.2%) were female. The mean baPWV was 1469.15 ± 295.82 cm/s, and 50.8% of patients exhibited arterial stiffness. The enrolled patients were categorized into three groups according to BAR level: T1, BAR <0.0874; T2, BAR between 0.0874 and 0.1161; and T3, BAR >0.1161. A higher BAR was associated with older age, higher blood creatinine and BUN, and lower BMI, eGFR and ALB. However, no significant differences were observed in sex, SBP, DBP, waist circumference, fasting blood glucose, HbA1c, fasting C-peptide, ALT, AST, GGT, serum uric acid, UACR, TG, TC, LDL-C or HDL-C levels. There were no statistically significant differences in smoking or alcohol consumption among the three groups. The higher BAR group had a greater baPWV. The percentage of patients with arterial stiffness in the T1, T2, and T3 subgroups were 40.6%, 52.4%, and 59.4%, respectively (p = 0.002), indicating an increase in the prevalence of arterial stiffness according to BAR subgroup.

3.2 Relationships between BAR and clinical indicators in patients with newly diagnosed with T2DM

As shown in Table 2, linear correlation analysis revealed that BAR was positively correlated with age (r = 0.222, p = 0.001), fasting

TABLE 1 Baseline characteristics of participants according to different BAR level groups.

Variables	ALL	T1 (n=170)	T2 (n=170)	T3 (n=170)	*p-value*
Sex (men) (case, %)	402, 78.8%	131, 77.1%	132, 77.6%	139, 81.1%	0.512
Age (years)	45.66 ± 10.18	44.07 ± 10.24	45.44 ± 9.91	47.49 ± 10.17	0.008
SBP (mmHg)	123.50 ± 10.89	123.28 ± 10.36	123.36 ± 9.53	123.87 ± 12.60	0.865
DBP (mmHg)	79.11 ± 7.48	79.48 ± 7.15	79.21 ± 6.03	78.66 ± 8.98	0.597
BMI (kg/m^2)	25.82 ± 4.41	26.60 ± 4.84	25.47 ± 4.21	25.38 ± 4.04	0.018
Waist circumference (cm)	91.83 ± 11.07	92.80 ± 11.64	91.25 ± 10.94	91.43 ± 10.59	0.382
Fasting glucose (mmol/L)	10.20 ± 3.93	9.92 ± 3.45	10.12 ± 4.27	10.57 ± 4.04	0.296
HbA_1c (%)	11.90 ± 2.49	12.09 ± 2.50	11.74 ± 2.37	11.86 ± 2.58	0.434
Fasting C-peptide (ng/ml)	1.68 ± 1.24	1.67 ± 1.07	1.52 ± 0.93	1.84 ± 1.60	0.060
ALT (U/L) (median (IQR))	20.00 (14.00-35.00)	21.00 (14.00-39.00)	21.00 (14.00-38.00)	18.00 (13.00-31.00)	0.080
AST (U/L) (median (IQR))	17.00 (13.00-27.00)	18.00 (14.00-31.00)	18.00 (13.00-28.00)	16.00 (13.00-23.25)	0.089
GGT (U/L) (median (IQR))	30.00 (19.00-54.60)	32.50 (19.00-57.50)	33.00 (19.25-62.00)	29.00 (13.70-49.25)	0.431
ALB (g/L)	39.98 ± 4.47	40.34 ± 5.14	40.51 ± 3.86	39.09 ± 4.20	0.006
Uric acid (μmol/L)	334.62 ± 113.50	337.90 ± 120.08	325.17 ± 100.01	340.88 ± 119.43	0.401
Creatinine (μmol/L) (median (IQR))	64.90 (55.15-73.70)	61.90 (53.55-69.30)	65.35 (54.95-72.93)	70.75 (57.76-81.10)	<0.001
eGFR ($ml/min/1.73m^2$) (median (IQR))	118.47 (103.08-137.48)	125.12 (110.96-142.81)	119.43 (103.23-138.72)	109.62 (93.28-130.21)	<0.001
BUN (mmol/L)	4.27 ± 1.85	2.74 ± 0.64	4.07 ± 0.54	5.99 ± 2.08	<0.001
UACR (median (IQR))	4.84 (2.64-10.92)	4.92 (2.48-10.91)	4.94 (2.87-10.25)	4.58 (2.72-12.15)	0.855
TG (mmol/L) (median (IQR))	1.60 (1.08-2.58)	1.66 (1.08-2.99)	1.58 (1.08-2.55)	1.59 (1.06-2.49)	0.694
TC (mmol/L)	4.82 ± 1.62	4.93 ± 1.43	4.64 ± 1.01	4.89 ± 2.20	0.215
LDL-C (mmol/L)	3.13 ± 0.93	3.17 ± 0.93	3.13 ± 0.95	3.07 ± 0.93	0.629
HDL-C (mmol/L)	1.00 ± 0.28	0.99 ± 0.29	0.98 ± 0.27	1.02 ± 0.28	0.477
BAR	0.11 ± 0.05	0.07 ± 0.01	0.10 ± 0.01	0.16 ± 0.07	<0.001
History of drinking					0.447
Never (case, %)	341, 66.9%	108, 63.5%	114, 67.1%	119, 70.0%	
Current or ever (case, %)	169, 33.1%	62, 36.5%	56, 32.9%	51, 30.0%	
History of smoking					0.662
Never (case, %)	322, 63.1%	108, 63.5%	103, 60.6%	111, 65.3%	
Current or ever (case, %)	188, 36.9%	62, 33.0%	67, 35.6%	59, 31.4%	
baPWV (cm/s)	1469.15 ± 295.82	1406.42 ± 255.04	1462.12 ± 285.45	1538.92 ± 328.85	<0.001
Arterial stiffness, (case, %)	259, 50.8%	69, 40.6%	89, 52.4%	101, 59.4%	0.002

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALB, albumin; BUN, blood urea nitrogen; UACR, urine albumin-to-creatinine ratio; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BAR, blood urea nitrogen to serum albumin ratio; baPWV, brachial-ankle pulse wave velocity

C-peptide ($r = 0.206$, $p < 0.001$), creatinine ($r = 0.615$, $p < 0.001$), BUN ($r = 0.950$, $p < 0.001$), UACR ($r = 0.362$, $p < 0.001$) and baPWV ($r = 0.226$, $p < 0.001$) and negatively correlated with BMI ($r = -0.089$, $p = 0.045$), ALT ($r = -0.091$, $p = 0.039$), AST ($r = -0.090$, $p = 0.042$), ALB ($r = -0.253$, $p < 0.001$) and eGFR($r = -0.305$, $p < 0.001$) in the total population. Among male patients, BAR was positively associated with age ($r = 0.199$, $p < 0.001$), fasting C-peptide ($r = 0.189$, $p < 0.001$), creatinine ($r = 0.701$, $p = 0.006$), BUN ($r = 0.947$, $p < 0.001$), UACR ($r = 0.376$, $p < 0.001$), HDL-C ($r = 0.122$, $p = 0.016$) and baPWV ($r = 0.210$, $p < 0.001$). However, it was negatively correlated with ALT ($r = -0.110$, $p = 0.027$), AST ($r = -0.113$, $p = 0.023$) and eGFR($r = -0.319$, $p < 0.001$). In female patients, BAR was positively correlated with age ($r = 0.371$, $p < 0.001$),

10.3389/fendo.2025.1663831

TABLE 2 Correlation analysis of relationship between lnBAR and characteristics in patients with type 2 diabetes.

Variables	*Whole*		*Male*		*Female*	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Age	0.222	0.001	0.199	<0.001	0.371	<0.001
SBP	-0.009	0.884	-0.019	0.712	0.018	0.857
DBP	-0.049	0.275	-0.010	0.849	-0.180	0.062
BMI	-0.089	0.045	-0.083	0.097	-0.122	0.211
Waist circumference	-0.029	0.524	-0.088	0.086	0.047	0.633
Fasting glucose	0.072	0.108	0.076	0.130	0.023	0.812
HbA_1c	-0.046	0.316	-0.063	0.224	0.018	0.854
Fasting C-peptide	0.206	<0.001	0.189	<0.001	0.286	0.003
ALT	-0.091	0.039	-0.110	0.027	-0.072	0.459
AST	-0.090	0.042	-0.113	0.023	-0.048	0.619
GGT	-0.041	0.361	-0.093	0.065	0.052	0.597
ALB	-0.253	<0.001	-0.283	<0.001	-0.165	0.088
Uric acid	0.036	0.423	0.083	0.096	-0.190	0.049
Creatinine	0.615	<0.001	0.701	<0.001	0.280	0.004
eGFR	-0.305	<0.001	-0.319	<0.001	-0.230	0.017
BUN	0.950	<0.001	0.947	<0.001	0.973	<0.001
UACR	0.362	<0.001	0.376	<0.001	0.153	0.199
TG	-0.031	0.489	-0.080	0.112	0.093	0.342
TC	-0.073	0.103	-0.075	0.136	-0.047	0.632
LDL-C	-0.059	0.189	-0.037	0.462	-0.136	0.166
HDL-C	0.085	0.059	0.122	0.016	0.071	0.469
baPWV	0.226	<0.001	0.210	<0.001	0.334	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALB, albumin; BUN, blood urea nitrogen; UACR, urine albumin-to-creatinine ratio; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BAR, blood urea nitrogen to serum albumin ratio; baPWV, brachial-ankle pulse wave velocity.

fasting C-peptide ($r = 0.286$, $p = 0.003$), creatinine ($r = 0.280$, $p = 0.004$), BUN ($r = 0.937$, $p < 0.001$) and baPWV ($r = 0.334$, $p < 0.001$), and negatively correlated with uric acid ($r = 0.190$, $p = -0.049$) and eGFR($r = -0.230$, $p = 0.017$). Multifactorial stepwise linear regression analysis revealed a significant positive correlation between BAR and baPWV($\beta = 0.187$, $p < 0.001$) after adjusting for relevant confounders (Table 3).

3.3 Association of BAR with arterial stiffness in patients with newly diagnosed with T2DM

Arterial stiffness (baPWV ≥1400 cm/s) was assessed in relation to BAR using multivariable binary logistic regression analysis (Table 4). Three models were constructed to evaluate this association. As a continuous variable, each unit increase in the lnBAR was significantly associated with a greater risk of arterial stiffness (OR = 2.845, 95% CI: 1.745- 4.639, $p < 0.001$) in Model 1, with no adjustment for covariates. After adjusting for age and sex in Model 2, the lnBAR remained significantly associated with arterial stiffness (OR = 2.483, 95% CI: 1.484- 4.153, $p = 0.001$). After adjusting for age, sex, systolic blood pressure, diastolic blood pressure, BMI, WC, fasting glucose, fasting C-peptide, HbA1c, ALT, AST, GGT, creatinine, uric acid, TG, TC, HDL-C, and LDL-C, the associations between lnBAR and arterial stiffness remained significant (OR = 3.452, 95% CI: 1.586- 7.513, $p = 0.002$). When analyzed categorically, the T2 and T3 BAR groups presented a significantly greater risk of arterial stiffness than the T1 subgroup (T2: OR = 1.608, 95% CI: 1.047- 2.471, $p = 0.030$, T3: OR = 2.143, 95% CI: 1.390- 3.303, $p = 0.001$). In Model 2, the T3 subgroup had a greater risk than the T1 subgroup (OR = 1.914, 95% CI: 1.209- 3.029, $p = 0.006$). Following full adjustment, both the T2 (OR = 1.915, 95% CI: 1.106- 3.609, $p = 0.044$)) and T3 (OR = 2.064, 95% CI: 1.051- 4.054, $p = 0.035$) groups presented persistently elevated risks compared with the T1 group.

TABLE 3 Relationships between baPWV and various covariates including BAR, according to multiple stepwise linear regression analyses.

Variables	Unstandardized coefficients (95% CI)	Standardized coefficients	*p*-value
Age	10.525 (8.109, 12.941)	0.374	<0.001
SBP	8.687 (6.498, 10.875)	0.337	<0.001
HbA1c	-18.788 (-28.691, -8.884)	-0.163	<0.001
ALT	-0.835 (-1.552,-0.119)	-0.101	0.022
BAR	958.651 (518.429, 1398.874)	0.187	<0.001

SBP, systolic blood pressure; HbA1c, hemoglobin A1c; UACR, urine albumin-to-creatinine ratio; BAR, blood urea nitrogen to serum albumin ratio.

3.4 Stratified analysis of BAR and arterial stiffness

The association between BAR and arterial stiffness was assessed by stratifying the covariates including age, sex, and BMI. The positive association between BAR and baPWV remained consistent when the data were divided into subgroups according to sex (male and female) and BMI (<25 kg/m^2 and ≥25 kg/m^2)(*p* for interaction >0.05). An interaction effect for the association between BAR and baPWV was present between age groups, and the positive association between BAR and baPWV was found to be more significant in the <50 years subgroup than in the ≥50 years subgroup (Table 5).

3.5 The cut-off BAR value to indicate arterial stiffness analyzed by ROC

The optimal cut-off value of BAR to predict increased arterial stiffness (defined as baPWV≥1400cm m/s) in newly diagnosed with T2DM was determined through ROC curve analysis. The value that maximized the Youden Index was selected as the optimal threshold. From our analysis of 510 patients, the optimal BAR cut-off was 0.1089, with an area under the curve (AUC) of 0.699(95% CI:0.654-0.744), with a sensitivity of 70.3% and a specificity of 62.2% (Figure 1).

4 Discussion

In this study, we investigated the relationship between arterial stiffness, as quantified by baPWV and BAR, in patients newly diagnosed with T2DM. To our knowledge, this study is the first to identify a positive association between BAR and arterial stiffness in T2DM patients, even after adjusting for relevant potential confounders. In each subgroup, the positive association between BAR and baPWV was consistently maintained, as shown by further stratified analyses. Thus, these findings suggest that BAR may be useful in assessing early arterial stiffness in people with T2DM.

Research has consistently shown that there is a significant connection between arterial stiffness and atherosclerotic diseases, including myocardial infarction, heart failure, peripheral vascular disease, and stroke (20–22). Additionally, widespread cardiovascular risk factors such as diabetes, aging, hypertension, obesity, and chronic kidney disease can increase arterial stiffness and decrease elasticity (23). Pulse wave velocity (PWV) is an important index for assessing arterial stiffness and can be characterized by carotid-femoral PWV (cfPWV), brachial-ankle PWV (baPWV), aortic PWV (aPWV), femoral-ankle PWV (faPWV), and carotid-radial PWV (crPWV) according to the pulse wave recording area. Compared with other parameters of arterial stiffness, such as the CAI, CAVI, and CAP, PWV is the most reliable indicator of CVD and is strongly correlated with CVD events and their risk factors, such as hypertension, obesity, and diabetes (9, 24). An increase in arterial stiffness is positively correlated with an increased risk of cardiovascular events and all-cause mortality among T2DM patients (25). The baPWV is a clinically validated, simple, and cost-effective measure for evaluating arterial stiffness. Prospective clinical studies have demonstrated that arterial stiffness, quantified by baPWV, is a predictor of all-cause and cause-specific mortality in individuals with T2DM (8, 26). Research has indicated that an elevated baPWV

TABLE 4 Multivariable binary logistic regression for the association between BAR with arterial stiffness.

Variables	Model 1 OR (95%CI), *p*-value	Model 2 OR (95%CI), *p*-value	Model 3 OR (95%CI), *p*-value
baPWV (cm/s)			
lnBAR	2.845 (1.745, 4.639), <0.001	2.483 (1.484, 4.153), 0.001	3.452 (1.586, 7.513), 0.002
BAR			
T1	Ref	Ref	Ref
T2	1.608 (1.047, 2.471), 0.030	1.553 (0.987, 2.443), 0.057	1.915 (1.016, 3.609), 0.044
T3	2.143 (1.390, 3.303), 0.001	1.914 (1.209, 3.029), 0.006	2.064 (1.051, 4.054), 0.035
p for trend	0.015	<0.001	<0.001

lnBAR, BAR levels were analyzed as naturally logarithmically transformed values.
BAR, blood urea nitrogen to serum albumin ratio; baPWV, brachial-ankle pulse wave velocity.
Model 1: unadjusted model.
Model 2: adjusted for age, sex.
Model 3: additionally adjusted for SBP, DBP, BMI, waist circumference, history of drinking, history of smoking, fasting glucose, fasting C-peptide, HbA1c, ALT, AST, GGT, Uric acid, UACR, eGFR, TG, TC, HDL-C, LDL-C.

TABLE 5 Stratified analysis of the association between BAR and arterial stiffness.

Variables	Adjusted II OR(95%CI)	*p*-value	*p* for interaction
Stratified by Gender			0.362
Female	20.007(1.421, 281.780)	0.026	
Male	3.002(1.386, 6.503)	0.005	
Stratified by Age			0.011
<50 years	3.402(1.378, 8.397)	0.008	
≥50 years	2.532(0.746, 8.598)	0.136	
Stratified by BMI			0.495
<25kg/m^2	3.729(1.177, 11.810)	0.025	
≥25kg/m^2	3.212(1.218, 8.471)	0.018	

Adjusted for age, sex, SBP, DBP, BMI, waist circumference, history of drinking, history of smoking, fasting glucose, fasting C-peptide, HbA1c, ALT, AST, GGT, Uric acid, UACR, eGFR, TG, TC, HDL-C, LDL-C.

acts as an independent predictor of adverse prognosis in individuals with ASCVD (27). A 1-SD increase in baPWV raises the likelihood of cardiovascular events by 1.41 times (27). An improvement in arterial stiffness was related to a 43% decrease in the risk of primary composite events, which included stroke, myocardial infarction, and all-cause mortality (28). Research has further indicated that arterial stiffness is an independent risk factor for heart failure. Notably, for every 359 cm/s increase in baPWV, the risk of heart failure increases by 10% over an average period of 5.53 years (20). Recent research has indicated a potential bidirectional connection between the onset of diabetes and arterial stiffness. The Chinese Kailuan Study cohort demonstrated that an increased baPWV significantly elevates the risk of developing diabetes, suggesting that arterial stiffness may act as an early pathological contributor to the development of the disease (29). Further study suggested that aortic stiffness may impair glucose metabolic homeostasis through microvascular damage to the pancreas, liver, and skeletal muscle, potentially serving as an early predictive marker of diabetes (30). Therefore, early assessment of arterial stiffness could be beneficial for predicting T2DM and diabetes-related macrovascular diseases. The identification of simple biomarkers to predict arterial stiffness in clinical settings remains a focal point of research in the field of metabolic diseases.

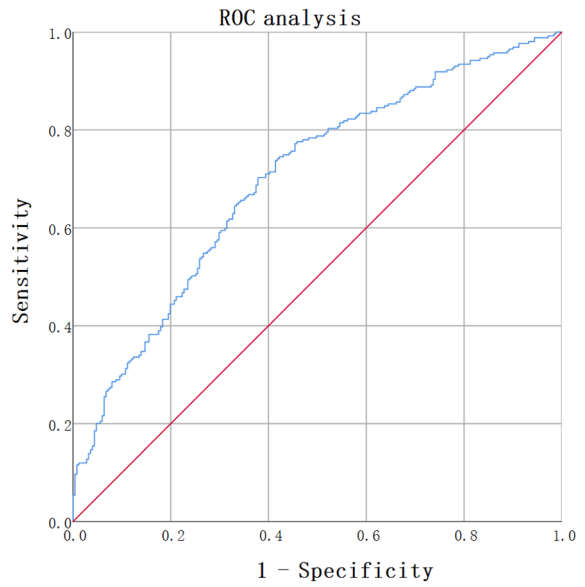


FIGURE 1
ROC analysis of BAR for predicting arterial atiffness in newly diagnosed T2DM. ROC analysis was used to identify the optimal cut-off value of BAR to predict increased arterial stiffness in T2DM. The AUC was 0.699(95% CI: 0.654-0.744). The optimal BAR cut-off was 0.1089. Youden index was 0.325, with a sensitivity of 70.3%, and a specificity of 62.2%.

BUN and ALB are widely used biochemical markers that are easily accessible in routine clinical practice and offer a cost-effective means of assessment. Elevated BUN levels have been shown to be associated with a heightened risk of developing diabetes and its microvascular complications (31, 32), along with a positive, non-linear relationship with the risk of all-cause and cardiovascular mortality in individuals with T2DM (11). Elderly patients with low ALB levels are more likely to have cardiovascular disease, and even those within low-normal ALB level may also be at higher risk of CVD and mortality (33). BAR acts as an indicator of variations in BUN and ALB levels, offering insights into nutritional health, protein metabolism, and the function of the liver and kidney. It serves as an independent predictor of adverse prognosis and short-term mortality in various critical illnesses including pneumonia, sepsis, renal insufficiency, and CVD (14–17, 34–36). Recent studies have identified BAR as a significant prognostic marker of chronic diseases. In a cohort of healthy individuals undergoing physical examinations, a significant positive correlation was identified between BAR and cerebral small vessel disease, including all its subtypes, in a dose-response relationship (37). Moreover, a recent study has identified a significant positive correlation between elevated BAR and increased risks of CVD (OR 1.09), cardiovascular mortality (OR 1.13), and all-cause mortality (OR 1.12) in patients with diabetes (38). In our study, 510 patients with newly diagnosed T2DM were stratified according to BAR tertiles. The group in the highest BAR group presented increased age, blood creatinine and BUN levels. Additionally, the highest BAR group had

a greater proportion of patients with arterial stiffness than the other groups. Regardless of whether it was treated as a continuous or categorical variable, BAR was positively correlated with elevated baPWV after adjusting for relevant factors. These findings are consistent with the hypothesis that BAR may interact with various metabolic factors influencing cardiovascular disease and could be a useful marker for the early differentiation of patients with newly diagnosed T2DM with or without arterial stiffness. The stratified analyses indicated that the independent association between the BAR and elevated baPWV in different groups divided by sex and BMI remained consistent. Nevertheless, the limited sample size of the female group may result in imprecise estimated values. These results should be validated in larger, adequately powered studies. Stratified analysis also revealed that the association between BAR and baPWV was more significant in younger patients newly diagnosed with T2DM who were <50 years old. This finding suggests that BAR may be a more prominent correlation factor of arterial stiffness in younger patients with T2DM. Previous studies has been demonstrated that arterial stiffness is more readily improved in young individuals when a healthy lifestyle is adopted (28). In contrast, arterial stiffness in older patients may be influenced by aging, multiple concurrent diseases, and other factors beyond liver and kidney function, thereby potentially explaining the observed attenuation of the association between BAR and baPWV in this subgroup.

The pathophysiological mechanisms connecting BAR and arterial stiffness in individuals with T2DM remain incompletely understood. Previous research has demonstrated a significant association between BAR and type 2 diabetic retinopathy, nephropathy, and macrovascular diseases (17, 38, 39). It was hypothesized that this association was attributable to the effects of the two principal components that constitute BAR. In the hyperglycemic state of T2DM, the body experiences hemodynamic abnormalities, renal function impairment, inflammation, oxidative stress, and endothelial dysfunction. These conditions lead to changes in BUN and ALB levels, promote arterial stiffness, and increase cardiovascular risk and adverse prognosis in patients with diabetes. First, BUN is a critical parameter for evaluating renal function. Elevated BUN levels signify increased protein catabolism and impaired renal function (40). Arterial stiffness and chronic kidney disease may share common pathological pathways that facilitate their co-occurrence and progression (23). The Framingham study established a significant correlation between PWV and the onset of proteinuria (41). Early vascular dysfunction, indicated by a baPWV exceeding the 90th percentile, was significantly associated with proteinuria alone, impaired renal function alone, and the combined risk of proteinuria and renal dysfunction (42). Second, existing research has demonstrated that inflammation is an important factor in the development of diabetes and its related complications (39). Elevated BUN levels have been linked to inflammation, oxidative stress, and compromised endothelial function (43, 44). Urea can induce endoplasmic reticulum stress by inactivating the anti-atherogenic enzyme PGI2 synthase, thereby impairing endothelial function by inhibiting of cell proliferation and inducing endothelial-mesenchymal transition (45, 46). Additionally, urea induces the production of oxygen free radicals from endothelial progenitor cells (EPCs), leading to impaired EPCs function and the development of cardiovascular disease (47). Plasma ALB fulfills several physiological functions, including reducing inflammation, preventing oxidative stress, preservation of vascular endothelial integrity. Research indicates that ALB can attenuate the expression of VCAM-1 induced by TNF-α, thereby inhibiting the onset of vascular inflammation (48). Furthermore, ALB acts as a scavenger of oxygen-free radicals, inhibits the activity of angiotensin-converting enzymes, reduces the sensitivity of blood vessels to nitric oxide, and reduces apoptosis in endothelial cells (49, 50). Finally, elevated BUN levels may serve as indirect markers of a hypercoagulable state, thereby facilitating the onset of diabetic complications. Serum albumin also contributes to the stability of the circulatory system through its anticoagulant, antithrombotic, and antiplatelet aggregation properties (51).

This study encountered various limitations. Firstly, the cross-sectional design of the study precludes the establishment of causal relationships between BAR and baPWV, and the possibility of reverse causality cannot be dismissed. Secondly, despite adjustments for multiple confounding variables, residual confounding, such as that related to lifestyle factors or unmeasured inflammatory markers, may persist. Thirdly, the single-center design and the homogeneous Chinese cohort limit the generalizability of the findings to other populations. Fourthly, the inclusion of only newly diagnosed T2DM patients may restrict the applicability of the results to individuals with a longer disease duration or those undergoing treatment. Finally, the absence of longitudinal data precludes the assessment of BAR's predictive value for the progression of arterial stiffness. Consequently, it is essential to conduct more prospective randomized controlled trials to substantiate the conclusions of this study.

5 Conclusions

In conclusion, our findings indicate that BAR is positively and independently associated with arterial stiffness, as determined by baPWV, in Chinese patients with newly diagnosed T2DM. These results imply that BAR levels could play a role in improving the management of cardiovascular complications in patients with newly diagnosed T2DM, particularly those younger than 50 years.

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 humans were approved by Ethics Committee of Longgang Central Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SH: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. WM: Conceptualization, Data curation, Writing – review & editing. MH: Data curation, Writing – review & editing, Investigation. QF: Methodology, Writing – review & editing, Investigation, Resources. JS: Writing – review & editing, Supervision.

Funding

The author(s) declare that no financial support was received for the research, and/or publication of this article.

Acknowledgments

We thank all of study participants involved in this study.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1663831/full#supplementary-material

References

1. IDF global clinical practice recommendations for managing type 2 diabetes 2025. *Diabetes Res Clin Pract.* (2025) 224:112238. doi: 10.1016/j.diabres.2025.112238

2. Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. *BMJ.* (2020) 369:m997. doi: 10.1136/bmj.m997

3. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol.* (2019) 26:25–32. doi: 10.1177/2047487319878371

4. Chen CM, Lu CF, Liu WS, Gong ZH, Wang XQ, Xu F, et al. Association between fibrinogen/albumin ratio and arterial stiffness in patients with type 2 diabetes: A cross-sectional study. *Front Pharmacol.* (2022) 13:1120043. doi: 10.3389/fphar.2022.1120043

5. Tąpolska M, Spałek M, Szybowicz U, Domin R, Owsik K, Sochacka K, et al. Arterial stiffness parameters correlate with estimated cardiovascular risk in humans: A clinical study. *Int J Environ Res Public Health.* (2019) 16:2547. doi: 10.3390/ijerph16142547

6. Xuereb RA, Magri CJ, Xuereb RG. Arterial stiffness and its impact on cardiovascular health. *Curr Cardiol Rep.* (2023) 25:1337–49. doi: 10.1007/s11886-023-01951-1

7. Giraldo-Grueso M, Echeverri D. From endothelial dysfunction to arterial stiffness in diabetes mellitus. *Curr Diabetes Rev.* (2020) 16:230–7. doi: 10.2174/1573399814666181017120415

8. Maeda Y, Inoguchi T, Etoh E, Kodama Y, Sasaki S, Sonoda N, et al. Brachial-ankle pulse wave velocity predicts all-cause mortality and cardiovascular events in patients with diabetes: the Kyushu Prevention Study of Atherosclerosis. *Diabetes Care.* (2014) 37:2383–90. doi: 10.2337/dc13-1886

9. Kim HL, Jeon WK, Joh HS, Lim WH, Seo JB, Kim SH, et al. Brachial-ankle pulse wave velocity as a predictor of long-term cardiovascular events in 2174 subjects with type 2 diabetes mellitus: A retrospective cohort study. *Med (Baltimore).* (2022) 101:e31758. doi: 10.1097/MD.0000000000031758

10. Shen J, Wang Z, Liu Y, Wang T, Wang XY, Qu XH, et al. Association of blood urea nitrogen with all-cause and cardiovascular mortality in hyperlipidemia: NHANES 1999-2018. *Lipids Health Dis.* (2024) 23:164. doi: 10.1186/s12944-024-02158-1

11. Liu H, Xin X, Gan J, Huang J. The long-term effects of blood urea nitrogen levels on cardiovascular disease and all-cause mortality in diabetes: a prospective cohort study. *BMC Cardiovasc Disord.* (2024) 24:256. doi: 10.1186/s12872-024-03928-6

12. Sun L, Yin H, Liu M, Xu G, Zhou X, Ge P, et al. Impaired albumin function: a novel potential indicator for liver function damage. *Ann Med.* (2019) 51:333–44. doi: 10.1080/07853890.2019.1693056

13. Taverna M, Marie AL, Mira JP, Guidet B. Specific antioxidant properties of human serum albumin. *Ann Intensive Care.* (2013) 3:4. doi: 10.1186/2110-5820-3-4

14. Agarwal M, Joshi M, Gupta M, Bharti N, Chakraborti A, Sonigra M. Role of blood urea nitrogen and serum albumin ratio in predicting severity of community acquired pneumonia (CAP). *Monaldi Arch Chest Dis.* (2021) 92:3. doi: 10.4081/monaldi.2021.2091

15. Zhao L, Liu Y, Tan Z, Zhang M, Li S, Luo G, et al. The prognostic value of blood urea nitrogen to albumin ratio on patients with heart failure. *Int Heart J.* (2023) 64:1010–7. doi: 10.1536/ihj.23-383

16. Min J, Lu J, Zhong L, Yuan M, Xu Y. The correlation study between blood urea nitrogen to serum albumin ratio and prognosis of patients with sepsis during hospitalization. *BMC Anesthesiol.* (2022) 22:404. doi: 10.1186/s12871-022-01947-4

17. Liu S, Qiu C, Li W, Li X, Liu F, Hu G. Blood urea nitrogen to serum albumin ratio as a new prognostic indicator in type 2 diabetes mellitus patients with chronic kidney disease. *Sci Rep.* (2024) 14:8002. doi: 10.1038/s41598-024-58678-4

18. Gu X, Zhao L, Zhu J, Gu H, Li H, Wang L, et al. Serum mimecan is associated with arterial stiffness in hypertensive patients. *J Am Heart Assoc.* (2015) 4:e002010. doi: 10.1161/JAHA.115.002010

19. Zhao L, Zhou X, Chen Y, Dong Q, Zheng Q, Wang Y, et al. Association of visceral fat area or BMI with arterial stiffness in ideal cardiovascular health metrics among T2DM patients. *J Diabetes.* (2024) 16:e13463. doi: 10.1111/1753-0407.13463

20. Zheng H, Wu S, Liu X, Qiu G, Chen S, Wu Y, et al. Association between arterial stiffness and new-onset heart failure: the kailuan study. *Arterioscler Thromb Vasc Biol.* (2023) 43:e104–104e111. doi: 10.1161/ATVBAHA.122.317715

21. Miyagi T, Ishida A, Shinzato T, Ohya Y. Arterial stiffness is associated with small vessel disease irrespective of blood pressure in stroke-free individuals. *Stroke.* (2023) 54:2814–21. doi: 10.1161/STROKEAHA.123.042512

22. Ecobici M, Voiculescu M. Importance of arterial stiffness in predicting cardiovascular events. *Rom J Intern Med*. (2017) 55:8–13. doi: 10.1515/rjim-2016-0043

23. Inserra F, Forcada P, Castellaro A, Castellaro C. Chronic kidney disease and arterial stiffness: A two-way path. *Front Med (Lausanne)*. (2021) 8:765924. doi: 10.3389/fmed.2021.765924

24. Darroudi S, Eslamiyeh M, Mansoori A, Nazar E, Alinezhad-Namaghi M, Rezvani R, et al. Multivariate linear regression to predict association of non-invasive arterial stiffness with cardiovascular events. *ESC Heart Fail*. (2025) 12:1141–50. doi: 10.1002/ehf2.15077

25. Sharif S, Visseren F, Spiering W, de Jong PA, Bots ML, Westerink J, et al. Arterial stiffness as a risk factor for cardiovascular events and all-cause mortality in people with Type 2 diabetes. *Diabetes Med*. (2019) 36:1125–32. doi: 10.1111/dme.13954

26. Kim JM, Kim SS, Kim IJ, Kim JH, Kim BH, Kim MK, et al. Arterial stiffness is an independent predictor for risk of mortality in patients with type 2 diabetes mellitus: the REBOUND study. *Cardiovasc Diabetol*. (2020) 19:143. doi: 10.1186/s12933-020-01120-6

27. Sang T, Lv N, Dang A, Cheng N, Zhang W. Brachial-ankle pulse wave velocity and prognosis in patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Hypertens Res*. (2021) 44:1175–85. doi: 10.1038/s41440-021-00678-2

28. Zuo Y, Chen S, Tian X, Wu S, Wang A. Changes in baPWV and the risk of clinical outcomes: a cohort study of Chinese community-based population. *J Hum Hypertens*. (2024) 38:460–6. doi: 10.1038/s41371-024-00902-9

29. Zheng M, Zhang X, Chen S, Song Y, Zhao Q, Gao X, et al. Arterial stiffness preceding diabetes: A longitudinal study. *Circ Res*. (2020) 127:1491–8. doi: 10.1161/CIRCRESAHA.120.317950

30. Cohen JB, Mitchell GF, Gill D, Burgess S, Rahman M, Hanff TC, et al. Arterial stiffness and diabetes risk in framingham heart study and UK biobank. *Circ Res*. (2022) 131:545–54. doi: 10.1161/CIRCRESAHA.122.320796

31. Li SN, Cui YF, Luo ZY, Lou YM, Liao MQ, Chen HE, et al. Association between blood urea nitrogen and incidence of type 2 diabetes mellitus in a Chinese population: a cohort study. *Endocr J*. (2021) 68:1057–65. doi: 10.1507/endocrj.EJ20-0794

32. Wang R, Xu YX, Xu F, Wang CH, Zhao LH, Wang LH, et al. Increased blood urea nitrogen levels and compromised peripheral nerve function in patients with type 2 diabetes. *World J Diabetes*. (2025) 16:101966. doi: 10.4239/wjd.v16.i4.101966

33. Schalk BW, Visser M, Bremmer MA, Penninx BW, Bouter LM, Deeg DJ. Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam. *Am J Epidemiol*. (2006) 164:969–77. doi: 10.1093/aje/kwj312

34. Wang Y, Qin LH, Zhang K, Zhang DW, Wang WJ, Xu AM, et al. Blood urea nitrogen to albumin ratio is a novel predictor of fatal outcome for patients with severe fever with thrombocytopenia syndrome. *J Med Virol*. (2024) 96:e29731. doi: 10.1002/jmv.29731

35. Wu Q, Zheng J, Lin J, Xie L, Tang M, Ke M, et al. Preoperative blood urea nitrogen-to-serum albumin ratio for prediction of in-hospital mortality in patients who underwent emergency surgery for acute type A aortic dissection. *Hypertens Res*. (2024) 47:1934–42. doi: 10.1038/s41440-024-01673-z

36. Zeng Z, Ke X, Gong S, Huang X, Liu Q, Huang X, et al. Blood urea nitrogen to serum albumin ratio: a good predictor of in-hospital and 90-day all-cause mortality in patients with acute exacerbations of chronic obstructive pulmonary disease. *BMC Pulm Med*. (2022) 22:476. doi: 10.1186/s12890-022-02258-7

37. Nam KW, Kwon HM, Jeong HY, Park JH, Min K. Blood urea nitrogen to albumin ratio is associated with cerebral small vessel diseases. *Sci Rep*. (2024) 14:4455. doi: 10.1038/s41598-024-54919-8

38. Zhu H, Xie W, Wang P, Jiang S, Hua Y, Shao G, et al. The relationship between blood urea nitrogen to serum albumin ratio and cardiovascular diseases, cardiovascular mortality, and all-cause mortality in patients with diabetes mellitus. *Front Endocrinol (Lausanne)*. (2025) 16:1456731. doi: 10.3389/fendo.2025.1456731

39. Dai FF, Pan JD, He XJ. Association between blood urea nitrogen to albumin ratio and diabetic retinopathy: insights from the US National Health and Nutrition Examination Survey. *Int J Ophthalmol*. (2025) 18:1097–104. doi: 10.18240/ijo.2025.06.17

40. Macedo E. Blood urea nitrogen beyond estimation of renal function. *Crit Care Med*. (2011) 39:405–6. doi: 10.1097/CCM.0b013e318205c33a

41. Upadhyay A, Hwang SJ, Mitchell GF, Vasan RS, Vita JA, Stantchev PI, et al. Arterial stiffness in mild-to-moderate CKD. *J Am Soc Nephrol*. (2009) 20:2044–53. doi: 10.1681/ASN.2009010074

42. Li J, Gao J, Zhang X, Cui L, Hou J, Gao B, et al. The relationship between vascular aging phenotypes and renal damage among individuals with type 2 diabetes. *Cardiorenal Med*. (2023) 13:91–100. doi: 10.1159/000526345

43. Guo C, Cai Q, Li Y, Li F, Liu K. A cross-sectional National Health and Nutrition Examination survey-based study of the association between systemic immune-inflammation index and blood urea nitrogen levels in United States adolescents. *Sci Rep*. (2024) 14:13248. doi: 10.1038/s41598-024-64073-w

44. Bosevski M, Soedamah-Muthu SS. Blood urea level and diabetes duration are independently associated with ankle-brachial index in type 2 diabetic patients. *Diabetes Metab Syndr*. (2012) 6:32–5. doi: 10.1016/j.dsx.2012.05.006

45. D'Apolito M, Du X, Pisanelli D, Pettoello-Mantovani M, Campanozzi A, Giacco F, et al. Urea-induced ROS cause endothelial dysfunction in chronic renal failure. *Atherosclerosis*. (2015) 239:393–400. doi: 10.1016/j.atherosclerosis.2015.01.034

46. Colombo G, Altomare A, Astori E, Landoni L, Garavaglia ML, Rossi R, et al. Effects of physiological and pathological urea concentrations on human microvascular endothelial cells. *Int J Mol Sci*. (2022) 24:691. doi: 10.3390/ijms24010691

47. D'Apolito M, Colia AL, Lasalvia M, Capozzi V, Falcone MP, Pettoello-Mantovani M, et al. Urea-induced ROS accelerate senescence in endothelial progenitor cells. *Atherosclerosis*. (2017) 263:127–36. doi: 10.1016/j.atherosclerosis.2017.06.028

48. Zhang WJ, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. *Cardiovasc Res*. (2002) 55:820–9. doi: 10.1016/s0008-6363(02)00492-3

49. Bihari S, Bannard-Smith J, Bellomo R. Albumin as a drug: its biological effects beyond volume expansion. *Crit Care Resusc*. (2020) 22:257–65. doi: 10.1016/S1441-2772(23)00394-0

50. Bevers LM, van Faassen EE, Vuong TD, Ni Z, Boer P, Koomans HA, et al. Low albumin levels increase endothelial NO production and decrease vascular NO sensitivity. *Nephrol Dial Transplant*. (2006) 21:3443–9. doi: 10.1093/ndt/gfl443

51. Manolis AA, Manolis TA, Melita H, Mikhailidis DP, Manolis AS. Low serum albumin: A neglected predictor in patients with cardiovascular disease. *Eur J Intern Med*. (2022) 102:24–39. doi: 10.1016/j.ejim.2022.05.004

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 14 October 2025
DOI 10.3389/fendo.2025.1671932

Check for updates

OPEN ACCESS

EDITED BY
Mariela Mercedes Gironacci,
University of Buenos Aires, Argentina

REVIEWED BY
Ilaria Campesi,
University of Sassari, Italy
Desh Deepak Singh,
Amity University Jaipur, India
Germán González,
National Scientific and Technical Research Council (CONICET), Argentina

*CORRESPONDENCE
Caterina Pipino
caterina.pipino@unich.it

†These authors have contributed equally to this work

RECEIVED 23 July 2025
ACCEPTED 26 September 2025
PUBLISHED 14 October 2025

CITATION
Cappellacci I, Di Pietrantonio N, Viola D, Formoso G, Zujko ME, Martín-García B, Gomez-Caravaca AM, Verardo V, Pandolfi A and Pipino C (2025) Unveiling the anti-inflammatory potential of olive leaf phenolic extracts in diabetes-related endothelial dysfunction.
Front. Endocrinol. 16:1671932.
doi: 10.3389/fendo.2025.1671932

COPYRIGHT
© 2025 Cappellacci, Di Pietrantonio, Viola, Formoso, Zujko, Martín-García, Gomez-Caravaca, Verardo, Pandolfi and Pipino. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Unveiling the anti-inflammatory potential of olive leaf phenolic extracts in diabetes-related endothelial dysfunction

Ilaria Cappellacci[1†], Nadia Di Pietrantonio[1†], Davide Viola[1], Gloria Formoso[2], Małgorzata Elżbieta Zujko[3], Beatriz Martín-García[4,5], Ana M. Gomez-Caravaca[4,5], Vito Verardo[5,6], Assunta Pandolfi[1] and Caterina Pipino[1*]

[1]Department of Medical, Oral and Biotechnological Sciences, Center for Advanced Studies and Technology (CAST), University G. d'Annunzio Chieti-Pescara, Chieti, Italy, [2]Department of Medicine and Aging Sciences, Center for Advanced Studies and Technology (CAST), University G. d'Annunzio Chieti-Pescara, Chieti, Italy, [3]Department of Food Biotechnology, Faculty of Health Science, Medical University of Białystok, Białystok, Poland, [4]Department of Analytical Chemistry, University of Granada, Granada, Spain, [5]Institute of Nutrition and Food Technology 'José Mataix', Biomedical Research Centre, University of Granada, Granada, Spain, [6]Department of Nutrition and Food Science, University of Granada, Granada, Spain

Introduction: Diabetes mellitus is a severe metabolic disorder strongly linked to vascular complications driven by endothelial dysfunction, chronic inflammation, and oxidative stress. Novel strategies to mitigate endothelial activation are urgently needed. In this context, phenolic compounds derived from olive leaves, a byproduct of olive oil production, have shown promising potential in counteracting diabetes- associated endothelial inflammation. This study investigates the potential anti-inflammatory effect of polyphenol-rich extracts derived from two olive leaves Spanish monocultivars, Picual and Changlot Real, in human umbilical vein endothelial cells from healthy pregnancies (C-HUVEC) and gestational diabetes (GD-HUVEC), which serve as a relevant in vitro model of hyperglycemia-induced endothelial dysfunction.

Methods: Olive leaf extracts were characterized by HPLC-ESI-TOF-MS. C-HUVEC and GD-HUVEC were treated with the extracts, and pro-inflammatory markers expression (NF-kB p65, MCP-1, and VCAM-1), NF-kB p65 phosphorylation, and monocyte adhesion were assessed under basal and TNFα-stimulated conditions using RT-PCR, flow cytometry, and adhesion assays.

Results: Both Picual and Changlot Real extracts showed no cytotoxicity at concentrations up to 50 mg/mL. Treatment with 10 mg/mL of both extracts significantly reduced NF-kB p65 and MCP-1 gene expression, as well as NF-kB p65 phosphorylation, particularly in GD-HUVEC. VCAM-1 protein expression and TNFα-induced monocyte adhesion were also significantly decreased following extract treatment. Notably, Changlot Real exhibited a broader anti-inflammatory effect across both cell types, while Picual exerted a more selective effect in GD-HUVEC.

Discussion: These findings support the anti-inflammatory activity of olive leaf polyphenols and highlight the potential of Changlot Real and Picual extracts in

mitigating endothelial dysfunction associated with diabetes. By modulating the NF-kB–VCAM-1 axis, these compounds may attenuate endothelial activation, warranting further investigation into their possible role in the prevention or mitigation of diabetes-related vascular complications.

KEYWORDS

endothelial inflammation, olive leaf polyphenols, diabetes mellitus, NF-κB signaling pathway, VCAM-1 expression, monocyte adhesion

Introduction

Diabetes Mellitus is a major global health challenge primarily characterized by chronic hyperglycemia and associated with a significantly increased risk of cardiovascular disease (CVD). Individuals with diabetes face a significantly higher probability of vascular complications, categorized as either microvascular, such as diabetic nephropathy and retinopathy, or macrovascular, including coronary artery disease, stroke, and peripheral artery disease (1–4).

A fundamental contributing factor to these complications is endothelial dysfunction which represents an early and critical step in diabetes-associated vascular disease progression. The dysregulation of endothelial function arises from an intricated interplay of metabolic disturbances including hyperglycemia, dyslipidemia and insulin resistance, all of which foster vascular inflammation, oxidative stress, arterial stiffness, and impaired blood flow regulation (5, 6).

Chronic inflammation and oxidative stress play a key role in this pathological process by activating the transcription factor nuclear factor kappa B (NF-κB), which in turn promotes the expression of pro-inflammatory cytokines and adhesion molecules, such as Vascular Cell Adhesion Molecule-1 (VCAM-1), Intercellular Adhesion Molecule-1 (ICAM-1), E-selectin, Interleukin-6 (IL-6), and Monocyte Chemoattractant Protein-1 (MCP-1). These mediators enhance monocyte adhesion to the endothelium, thereby contributing to atherosclerosis development (7, 8).

Despite significant progress in diabetes control, lifestyle modifications, including diet and exercise, remain the first-line interventions for type 2 diabetes (4). However, while such interventions have proven advantages in managing blood glucose levels, the strategies available at the moment to prevent and manage diabetes-related vascular complications remain insufficient. This highlights the need for additional complementary therapeutic approaches that could help reduce the vascular burden of diabetes. In this context, bioactive polyphenols derived from natural sources, especially from olive tree (*Olea europaea L.*), have gained substantial attention due to their potent anti-inflammatory, antioxidant, and cardioprotective effects. Olive tree-derived compounds have shown promise in modulating the inflammatory and oxidative processes that drive endothelial dysfunction, suggesting their potential important role in diabetes management (9–11).

The olive tree (*Olea europaea L.*), a cornerstone of the Mediterranean diet, is rich in polyphenolic compounds that are well-documented for their beneficial effects on human health (12). While much research on olive products has focused on the health benefits of extra virgin olive oil (EVOO), olive leaves, typically discarded as agricultural byproducts, represent an untapped resource of powerful bioactive compounds (13–15). Olive leaf extract (OLE), rich in polyphenols such as oleuropein, hydroxytyrosol, luteolin, and apigenin, has demonstrated strong antioxidant, anti-inflammatory, cardioprotective, and neuroprotective properties. Among these compounds, oleuropein stands out for its ability to modulate oxidative stress, inhibit platelet aggregation, and improve glucose homeostasis by enhancing insulin sensitivity and glycemic control (16–20).

Preclinical studies have demonstrated that OLE supplementation may counteract oxidative damage induced by diabetes by ameliorating antioxidant enzyme activity and reducing levels of inflammatory markers. In diabetic animal models, OLE has been shown to improve glycemic control, preserve pancreatic islet integrity, and mitigate metabolic disturbances (11, 21–23). Furthermore, OLE's neuroprotective effects may help alleviate cognitive impairment associated with diabetes reducing oxidative stress in brain tissue (24). These findings underscore OLE potential as an adjunctive therapy in diabetes management offering new perspectives for addressing the disease's systemic complications.

This study investigates the potential of olive leaf polyphenols to mitigate endothelial inflammation associated with diabetes. It focuses on the effects of polyphenol-rich extracts from two Spanish olive tree monocultivars, Picual and Changlot Real, on human umbilical vein endothelial cells (HUVEC) derived from healthy pregnancies (C-HUVEC) and from pregnant women with gestational diabetes (GD-HUVEC). The GD-HUVEC model, characterized by a stable proinflammatory phenotype due to epigenetic alterations induced by hyperglycemia during pregnancy (25–27) offers a relevant *in vitro* system for studying diabetes-related vascular dysfunction. By examining how these specific phenolic extracts modulate endothelial activation and inflammatory pathways, the study aims to explore their possible

TABLE 1 Anthropometric and biochemical characteristics of control women, women with gestational diabetes and newborns.

Pregnant women	Control	GD	*p*
women (n)	4	4	
age (years)	35 ± 2	35 ± 6	0.9
OGTT (gestational week)	26 ± 2	26 ± 1	0.6
basal glycaemia (mmol/L)	4.4 ± 0.4	5.1 ± 0.2	0.01
1 h glycaemia (mmol/L)	5.8 ± 1	10.4 ± 0.9	0.001
2 h glycaemia (mmol/L)	4.4 ± 0.7	9 ± 1	0.001
height (cm)	162 ± 8	161 ± 6	0.8
pre-gestational weight (kg)	60 ± 7	67 ± 17	0.4
post-gestational weight (kg)	71 ± 8	76 ± 15	0.5
gestational weight gain (kg)	11 ± 3	9 ± 3	0.3
pre-gestational BMI (kg/m^2)	23 ± 1	26 ± 5	0.3
post-gestational BMI (kg/m^2)	27 ± 2	29 ± 4	0.4
SBP (mmHg)	112 ± 13	112 ± 5	1
DBP (mmHg)	72 ± 12	65 ± 4	0.3
GA at delivery	40 ± 0.5	38 ± 1	0.1
Newborns	**Control**	**GD**	***p***
Newborns (n)	4	4	
Sex (female/male)	3/1	2/2	
Birth Height (cm)	51 ± 1.5	50 ± 0.5	0.2
Birth Weight (kg)	3.4 ± 0.4	3 ± 0.2	0.2

Data are expressed as mean ± SD; GD, gestational diabetes; BMI, body mass index; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; DBP, diastolic blood pressure; GA, gestational age.

role as natural agents that might contribute to managing vascular complications in diabetes.

Methods

Olive leaf samples

Olive leaves samples from cultivar Changlot Real and Picual were provided by "IFAPA, Centro Alameda del Obispo" in Córdoba, Spain (37°51′36.5″ N 4°47′53.7″W). Both samples were grown under the same agronomic and environmental conditions in the same olive orchards, and the leaves were collected in July.

Extraction of phenolic compounds and their analysis by HPLC-ESI-TOF-MS

According to Talhaoui et al. (28), 0.5 g of dried leaf were extracted with methanol/water 80/20 v/v. The extracts were reconstituted with methanol/water 50/50 v/v and they were analyzed by HPLC-TOF-MS. The determination of targeted compounds was done using an Agilent 1200 HPLC system coupled to a QTOF Agilent 6520 B mass spectrometer using the column and chromatographic condition reported by Talhoui et al. (28).

Clinical characteristics of cords donors and newborns

Umbilical cords were obtained from randomly recruited healthy Caucasian mothers (Control, C) and women affected by Gestational Diabetes (GD) in the third trimester of pregnancy and followed by 'Diabetes and Pregnancy Clinic' until delivery at the Hospital Santo Spirito of Pescara (Italy).

GD women were treated with diet only and women with pre-gestational diabetes were excluded. All procedures agreed with the Declaration of Helsinki principles and with the ethical standards of the Institutional Committee on Human Experimentation. After approval of the protocol by the Institutional Review Board, signed informed consent was obtained from each participating subject. The characteristics of donors' Control (n = 4) and GD (n = 4) women together with the newborns are described in Table 1. Women matched by age and body mass index (BMI) were divided into two groups, one normoglycemic/healthy controls (basal glycaemia < 5.1 mmol/L, oral glucose tolerance test (OGTT) 1 h < 10 mmol/L and OGTT 2 h < 8.5 mmol/L, n = 4) and the other diagnosed with gestational diabetes (basal glycaemia ≥ 5.1 mmol/L, OGTT 1 h ≥ 10 mmol/L, and OGTT 2 h ≥ 8.5 mmol/L, GD, n = 4) according to the criteria of the American Diabetes Association (29).

HUVEC isolation and culture

Primary human umbilical vein endothelial cells (HUVEC) were isolated from umbilical cords of newborns delivered between the 37th and 40th gestational weeks at the hospitals of Chieti and Pescara (Italy). Donors were randomly selected Caucasian mothers, either diagnosed with gestational diabetes (GD) or serving as healthy controls (C), following previously established protocols (7, 8).

Briefly, umbilical cords were collected immediately after delivery, and the veins were cannulated and enzymatically digested with 1 mg/mL collagenase 1A at 37 °C. The resulting HUVEC were isolated and cultured in a basal medium consisting of DMEM/M199 (1:1), supplemented with 1% L-glutamine, 1% penicillin/streptomycin, and 20% fetal bovine serum (FBS) (ThermoFisher; Waltham, MA, USA). After centrifugation at 1,200 rpm for 10 minutes, the cell pellet was resuspended in the same medium and plated onto 1.5% gelatin-coated culture flasks (Sigma-Aldrich, Germany).

Phenotypic characterization of HUVEC was confirmed by expression of endothelial markers such as von Willebrand factor, CD31, and CD34, along with inducible expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and cytokines (IL-6

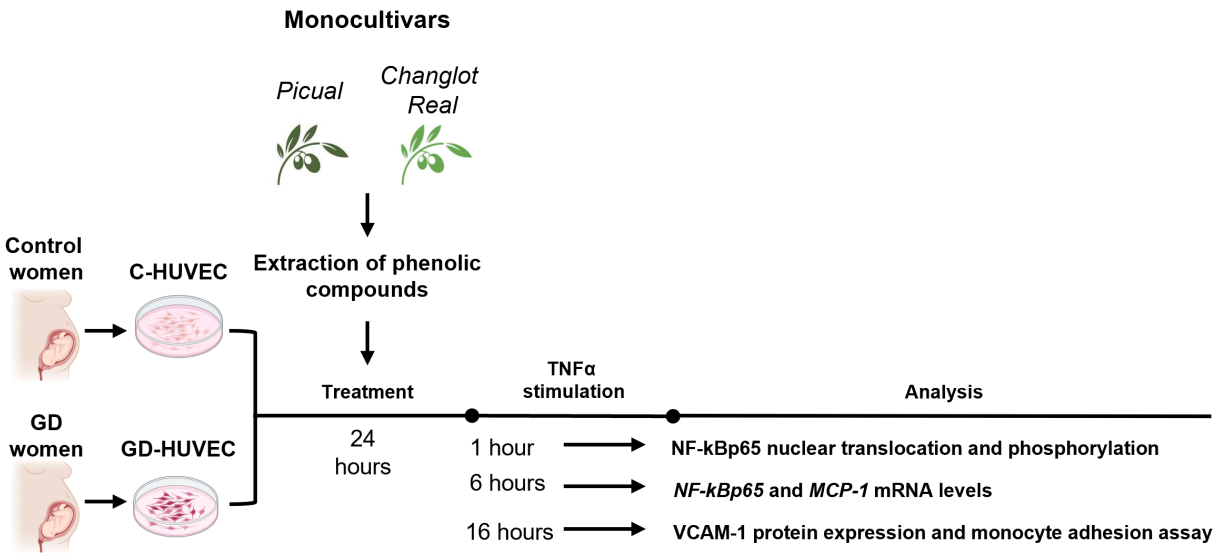


FIGURE 1
Experimental plan. Briefly, C- and GD-HUVEC were pre-treated with Changlot Real and Picual phenolic extracts for 24h (10 µg/mL) and then, cells were stimulated with TNFα (10 ng/mL) at different timing (1h, 6h and 24h) according to the experiment performed.

and IL-8) upon pro-inflammatory stimulation (7, 8, 15, 30). Functional validation showed their ability to form capillary-like structures on Matrigel. Notably, GD-HUVEC formed less interconnected tubes with fewer segments, meshes, junctions, and nodes compared to controls, confirming impaired angiogenic capacity (30, 31).

Furthermore, GD-HUVEC showed a stable pro-inflammatory phenotype caused by epigenetic modifications acquired during *in vivo* hyperglycemia exposure (26). Accordingly, in this study GD-HUVEC demonstrated a significant upregulation of *NF-kB p65* gene expression and VCAM-1 protein expression compared to control cells (Supplementary Figure 1). Cells used for experiments were cultured between passages 3 and 5, with passage 5 never exceeded. For assays, HUVEC were maintained on 1.5% gelatin-coated plates in complete endothelial growth medium composed of low-glucose (1 g/L) DMEM and M199 (1:1), supplemented with 10 mg/mL heparin, 50 mg/mL endothelial cell growth factor (ECGF), 20% FBS, 1% penicillin/streptomycin, and 1% L-glutamine (all from Sigma-Aldrich, Germany).

All experiments were performed in technical triplicates using HUVECs from at least three independent donors per group (control and GD, n = 3). TNFα exposure times were chosen to reflect the temporal dynamics of the NF-κB cascade: 1h to capture rapid p65 phosphorylation, 6h to monitor transcriptional activation, and 16h to assess late functional effects such as VCAM-1 surface expression and leukocyte adhesion (8, 26, 32) (Figure 1).

MTT assay

Experiments were conducted on HUVEC isolated from control women and those diagnosed with gestational diabetes, following a previously established protocol (26). To determine the effect of polyphenol extract Picual and Changlot Real on C- and GD-HUVEC viability, the 3-(4,5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) assay (cat # M2128, Sigma-Aldrich, Germany) was carried out. HUVEC were seeded in 96-well plates at a density of 5.600 cells/cm^2. After 24 hours treatment with increasing concentration of extracts (0.1-100 µg/mL), cells were incubated for 3 hours at 37 °C with 5 mg/mL of MTT dissolved in PBS. Thereafter, MTT crystals were dissolved by DMSO addition (200 µL per well) and gentle shaking for 30 minutes. Finally, the absorbance of each sample was recorded at 540 nm using a microplate spectrophotometer system (Multimode Microplate Reader, BioTek Synergy H1, Agilent).

RNA extraction and real-time quantitative PCR

The total RNA was isolated and extracted from HUVEC, treated with Picual and Changlot Real polyphenol extracts 10µg/mL, using the TRIzol reagent (Sigma-Aldrich, Germany) protocol. Quantification of recovered RNA was assessed using NanoDrop 2000 spectrophotometer (Thermo Scientific; Waltham, MA, USA). The High-Capacity cDNA Reverse Transcription Kit was employed to synthesize cDNA. The TaqMan Universal Master Mix II and TaqMan Gene Expression Assay probes for human NF-κB p65 (Hs01042014_m1), MCP-1 (Hs00234140_m1) and RPLP0 (Hs00420895_gH) were used according to the manufacturer's instructions. All samples were analyzed in technical duplicate. The relative expression of the target genes was calculated using the $2^{-\Delta Ct}$ method using RPLP0 as housekeeping (Applied Biosystems QuantStudio 7 Pro Real-Time PCR System, Thermo Fisher Scientific).

Immunofluorescence analysis

HUVEC were fixed with 3% formaldehyde for 20 min at RT. Formaldehyde was then removed and cells were washed with PBS for 5 min twice, and permeabilized with 0.1% Triton X-100 (Sigma-Aldrich, Germany) in PBS for 10 min. Cells were blocked with 1% bovine serum (cat # A4503, Sigma-Aldrich, Germany) in PBS for 1 h at RT. Subsequently, cells were incubated 1 hour with primary antibody NF-κB p65 (cat # C22B4, Cell Signaling Technology, 1:50). After washing with PBS, cells were incubated with Alexa Fluor 488-conjugated secondary antibody (cat #A-11034, Thermo Fisher Scientific, 1:50) and Phalloidin (cat #A12379, Thermo Fisher Scientific, Karlsruhe, Germany) at RT for 1 h. Nuclei were stained DAPI mounting medium (4′6′-diamidino-2-phenylindole; Thermo Fisher Scientific, Karlsruhe, Germany). Finally, cells were washed with PBS and mounted with Fluorescence Mounting Medium (cat # S3023, Agilent Dako, USA). For the acquisition of the immunofluorescence signals, slides were observed under a confocal microscope (Zeiss LSM-800; Carl Zeiss Meditec AG, Oberkochen, Germany).

Flow cytometry analysis

Flow cytometry analysis was performed using BD FACS Canto II flow cytometer. Specifically, 1×10^4 events for each sample were analyzed using FACSDiva v 6.1.3, IDEAS software (BD Biosciences). Cells were pretreated with polyphenolic extracts for 24 hours and, subsequently, incubated with or without TNFα (10 ng/mL) for 16 hours to assess VCAM-1 protein expression, and for 1 hour to evaluate NF-κB p65 and its phosphorylated form phospho-NF-κB p65 S536. To determine protein expression, cells were permeabilized using the Intrasure kit (cat # 641778, BD Biosciences, Sweden), processed, and incubated with primary antibodies: anti-VCAM-1 PE conjugate (cat # 12-1069-42, Invitrogen, 1:100), anti-NF-κB p65 (cat # C22B4, Cell Signaling Technology, 1:100), and anti-phospho-NF-κB p65 S536 (cat #3033, Cell Signaling Technology, 1:750) for 30 minutes at 4 °C. A subsequent incubation with Alexa Fluor 488-conjugated secondary antibody (cat #A-11034, Thermo Fisher Scientific, 1:100) was performed for 30 minutes at 4 °C to assess NF-κB p65 and phospho-NF-κB p65 expression. All results are expressed as the Mean Fluorescence Intensity (M.F.I.) Ratio, calculated by dividing the M.F.I. of positive events by the M.F.I. of negative events (M.F.I. of the secondary antibody).

Monocyte adhesion assay

Control- and GD-HUVEC were pretreated for 24 hours with polyphenol extracts Picual and Changlot Real at 10 μg/mL concentration in six-well tissue culture plates, starved for 2 hours with 0.1% FBS, and treated with or without TNFα (10ng/mL for 16 h) as inflammatory stimulus. Briefly, 1×10^6 U937 cells [European Collection of Authenticated Cell Cultures (ECACC)], grown in RPMI 1640, were co-cultured with HUVEC under rotating conditions at RT. After 20 min, non-adhering cells were removed with PBS, and monolayers were fixed with 1% paraformaldehyde. Images were obtained from high power fields taken at half-radius distance from the center of the wells using an inverted optical microscope PAULA cell imager (Leica, Wetzlar, Germany). The number of adherent cells in four individual experiments was determined with ImageJ software.

Statistical analysis

All experimental data are expressed as mean ± Standard Deviation (SD). Each experiment was conducted in technical triplicates using at least 3 independent donors of C- and GD-HUVEC. The normal distribution of quantitative data was assessed by the Shapiro–Wilk test. One-way ANOVA test followed by Tukey's test was used for multiple comparisons. Probability values were calculated considering a 95% compatibility interval. All analyses were performed with GraphPad Prism (version 9, GraphPad Software).

Results

Determination of phenolic compounds in olive leaf extracts

Phenolic content of the two studied samples is reported in Table 2. A total of 36 phenolic compounds from secoiridoids, flavonoids, simple phenols, oleosides and elenolic acids were identified and quantified by HPLC-ESI-TOF-MS in both olive leaf extracts. Changlot Real showed higher content of phenolic compounds than Picual. As expected, secoiridoids was the main phenolic class in both cultivar (65.7-79.5%), being oleuropein the first compounds accounting from more than 53.5% of the phenolic content. Flavonoids ranged from 6 to 12% of total phenolic compounds in Changlot Real and Picual, respectively. Simple phenols (tyrosol and hydroxytyrosol derivatives) represented less than 1.6% in both cultivars. Oleosides were from 10 to 15% and, finally, elenolic acids ranged from 3.5 to 6% of total phenolic compounds. These data are consistent with the previous ones of Talhoui et al. (28).

Effects of phenolic extracts Picual and Changlot Real on cell viability

To assess the possible cytotoxicity, polyphenol extracts derived from both Picual and Changlot Real olive leaves, two monocultivars widely spread throughout the Mediterranean basin, were tested using the MTT assay on both GD-HUVEC and C-HUVEC (Figures 2A, B). Cells were treated for 24 hours with four different concentrations of extracts (0.1, 1, 10, and 100 μg/mL) prepared in DMSO and added to the culture medium at a final DMSO concentration of 0.05%. Vehicle-matched controls were included in all experiments. The results showed no significant changes in cell viability at any concentration, indicating

10.3389/fendo.2025.1671932

TABLE 2 Phenolic compounds in Changlot Real and Picual extracts quantified by HPLC-ESI-TOF-MS presented as percentage (%) and as concentration (mg/g).

N.	Name	Changlot Real (%)	Changlot Real (mg/g)	Picual (%)	Picual (mg/g)
1	Hydroxytyrosol-hexose isomer a	0,01	0.001 ± 0.0002	0,01	0.001 ± 0.0001
2	Oleoside	1,16	0.17 ± 0.2	0,82	0.07 ± 0.1
3	Hydroxytyrosol-hexose isomer b	0,66	0.10 ± 0.1	1,03	0.09 ± 0.05
4	Hydroxytyrosol	0,11	0.02 ± 0.001	0,36	0.03 ± 0.001
5	Secologanoside isomer a	7,96	1.17 ± 0.2	7,55	0.66 ± 0.1
6	Tyrosol glucoside	0,35	0.05 ± 0.002	0,07	0.01 ± 0.002
7	Caffeoyl glucoside	0,26	0.04 ± 0.003	0,06	0.01 ± 0.001
8	Tyrosol	0,04	0.01 ± 0.001	0,06	0.01 ± 0.001
9	Elenolic acid glucoside isomer a	0,10	0.01 ± 0.001	0,22	0.02 ± 0.001
10	Secologanoside isomer b	1,16	0.17 ± 0.1	6,93	0.60 ± 0.005
11	Elenolic acid glucoside isomer b	1,31	0.19 ± 0.2	2,59	0.23 ± 0.1
12	Oleuropein aglycon	2,55	0.37 ± 0.1	4,00	0.35 ± 0.2
13	Elenolic acid glucoside isomer c	1,96	0.29 ± 0.2	2,82	0.25 ± 0.1
14	Luteolin diglucoside	0,05	0.01 ± 0.002	0,16	0.01 ± 0.002
15	Elenolic acid glucoside isomer d	0,15	0.02 ± 0.001	0,38	0.03 ± 0.001
16	Demethyloleuropein	0,37	0.05 ± 0.002	1,66	0.14 ± 0.1
17	Hydroxyoleuropein isomer a	0,36	0.05 ± 0.002	1,08	0.09 ± 0.001
18	Rutin	0,43	0.06 ± 0.002	0,58	0.05 ± 0.002
19	Luteolin rutinoside	0,05	0.01 ± 0.001	0,18	0.02 ± 0.001
20	Luteolin glucoside isomer a	2,84	0.42 ± 0.2	4,90	0.43 ± 0.1
21	Verbascoside	0,04	0.01 ± 0.001	0,03	0.003 ± 0.001
22	Hydroxyoleuropein isomer b	0,27	0.04 ± 0.001	0,27	0.02 ± 0.001
23	Apigenin rutinoside	0,08	0.01 ± 0.001	0,13	0.01 ± 0.001
24	Oleuropein diglucoside isomer a	0,07	0.01 ± 0.001	0,10	0.01 ± 0.001
25	Apigenin-7-glucoside	0,59	0.09 ± 0.002	0,40	0.03 ± 0.001
26	Oleuropein diglucoside isomer b	0,07	0.01 ± 0.001	0,12	0.01 ± 0.001
27	Luteolin glucoside isomer b	1,34	0.20 ± 0.01	3,17	0.28 ± 0.02
28	Oleuropein diglucoside isomer c	0,29	0.04 ± 0.003	0,17	0.01 ± 0.001
29	Chrysoeriol-7-O-glucoside	0,45	0.07 ± 0.002	1,00	0.09 ± 0.003
30	Luteolin glucoside isomer c	0,24	0.04 ± 0.001	0,90	0.08 ± 0.001
31	Oleuropein isomer a	67,35	9.90 ± 0.13	52,55	4.57 ± 0.19
32	Oleuropein isomer b	1,63	0.24 ± 0.03	1,10	0.10 ± 0.01
33	Oleuropein/Oleuroside2	4,29	0.63 ± 0.04	2,76	0.24 ± 0.01
34	Ligstroside aglycone	0,29	0.04 ± 0.003	1,21	0.11 ± 0.01
35	Ligstroside	1,96	0.29 ± 0.03	0,66	0.06 ± 0.003
36	Luteolin	0,02	0.003 ± 0.001	0,16	0.01 ± 0.001

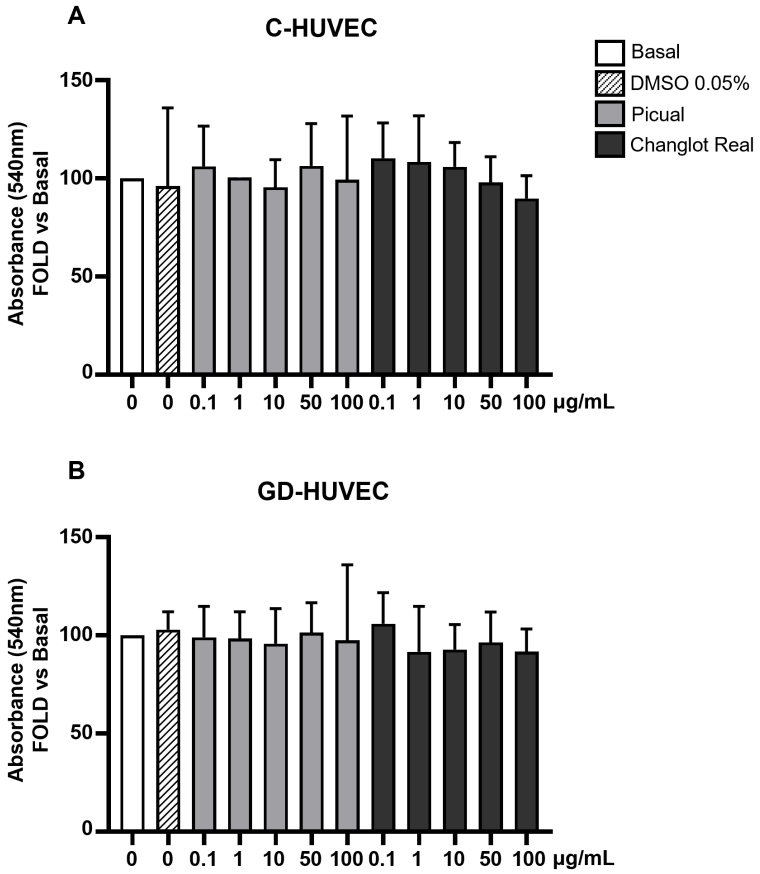


FIGURE 2
Changlot Real and Picual phenolic extracts treatment do not alter cell viability. Cell viability of C- **(A)** and GD-HUVEC **(B)** after 24 hours treatment with Changlot Real and Picual phenolic extracts at different concentrations (0.1–100 µg/mL) analyzed by MTT assay. Data are expressed as mean ± SD (n = 3).

that both extracts are well tolerated and non-cytotoxic under the tested conditions.

Effects of phenolic extracts Picual and Changlot Real on NF-κB p65 and MCP-1 mRNA Level

To evaluate and compare the possible anti-inflammatory effect of Picual and Changlot Real polyphenol extracts, the expression levels of the proinflammatory genes *NF-κB p65* and *MCP-1* were detected in HUVEC under different conditions (Figure 3). As expected, *NF-κB p65* and *MCP-1* basal expression was slightly higher in GD-HUVEC compared to controls. Following the selection of the optimal concentration by using a vehicle-matched controls (Supplementary Figure 2), cells were pre-treated with Picual and Changlot Real polyphenol extracts at 10 µg/mL. The results showed that both extracts led to a reduction in *NF-κB p65* and *MCP-1* gene expression, with a more pronounced effect in GD-HUVEC. In GD-HUVEC, a decrease, though not statistically significant, was also observed in the absence of a pro-inflammatory stimulus. (Figures 3B-D). Stimulation with TNFα (10 ng/mL) for 6 hours significantly upregulated *NF-κB p65* and *MCP-1* in both C-HUVEC and GD-HUVEC, indicating a robust inflammatory response. However, treatment with Changlot Real polyphenol extract effectively counteracted this effect, significantly reducing the expression of both genes in both cell types (Figures 3A-D). Similarly, Picual treatment also downregulated *NF-κB p65* and *MCP-1* expression; however, its effect was more pronounced and reached statistical significance in GD-HUVEC (Figures 3B, D). These findings indicate that both phenolic extracts may exert anti-inflammatory effects, with Changlot Real showing a broader impact across the tested cell conditions, whereas Picual appeared to have a marked effect primarily in GD-HUVEC.

Effects of phenolic extracts Picual and Changlot Real on NF-κB p65 phosphorylation

To further investigate the anti-inflammatory role of Picual and Changlot Real phenolic extracts, NF-κB p65 phosphorylation on Ser536 was evaluated in C- and GD-HUVEC (Figure 4). Under basal conditions, NF-κB p65 phosphorylation appeared modestly

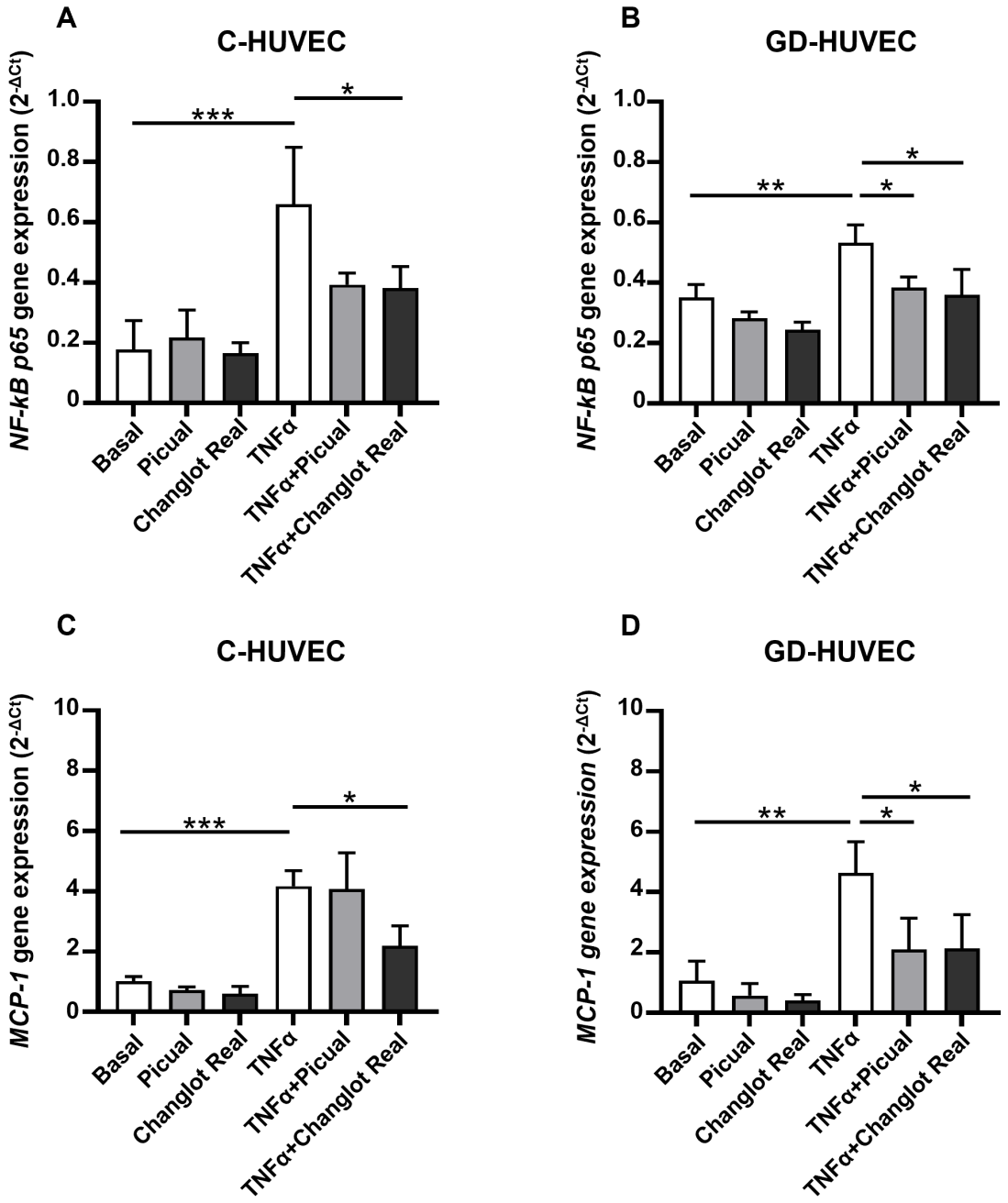


FIGURE 3
Changlot Real and Picual phenolic extracts treatment reduce *NF-κB p65* and *MCP-1* gene expression, with a more pronounced effect in GD-HUVEC. Relative mRNA expression of the inflammatory markers *NF-κB p65* **(A, B)** and *MCP-1* **(C, D)** in C- and GD-HUVEC following 24-hour treatment with Changlot Real and Picual phenolic extracts (10 μg/mL), with or without a 6-hour stimulation with TNFα (10 ng/mL) analyzed by RT-PCR. Data are expressed as mean ± SD (n = 3). Asterisks point out statistically significant differences between the selected conditions (*p<0.05; **p<0.01; ***p<0.001).

elevated in GD-HUVEC relative to control cells, though this difference was not statistically significant. Upon TNFα stimulation, a significant increase in NF-κB p65 phosphorylation was detected in both cell types. Pre-treatment with the Picual phenolic extract led to a marked reduction trend in NF-κB p65 phosphorylation in TNFα-stimulated C-HUVEC and GD-HUVEC. Similarly, pre-treatment with the Changlot Real polyphenol extract effectively counteracted TNFα-induced NF-κB p65 phosphorylation in both cell types, with a more pronounced and statistically significant effect in GD-HUVEC (Figures 4A, B). These findings align with NF-κB p65 nuclear translocation (Figure 4C) and previous data, suggesting that the anti-inflammatory effect of both phenolic extracts may be mediated through NF-κB pathway downregulation.

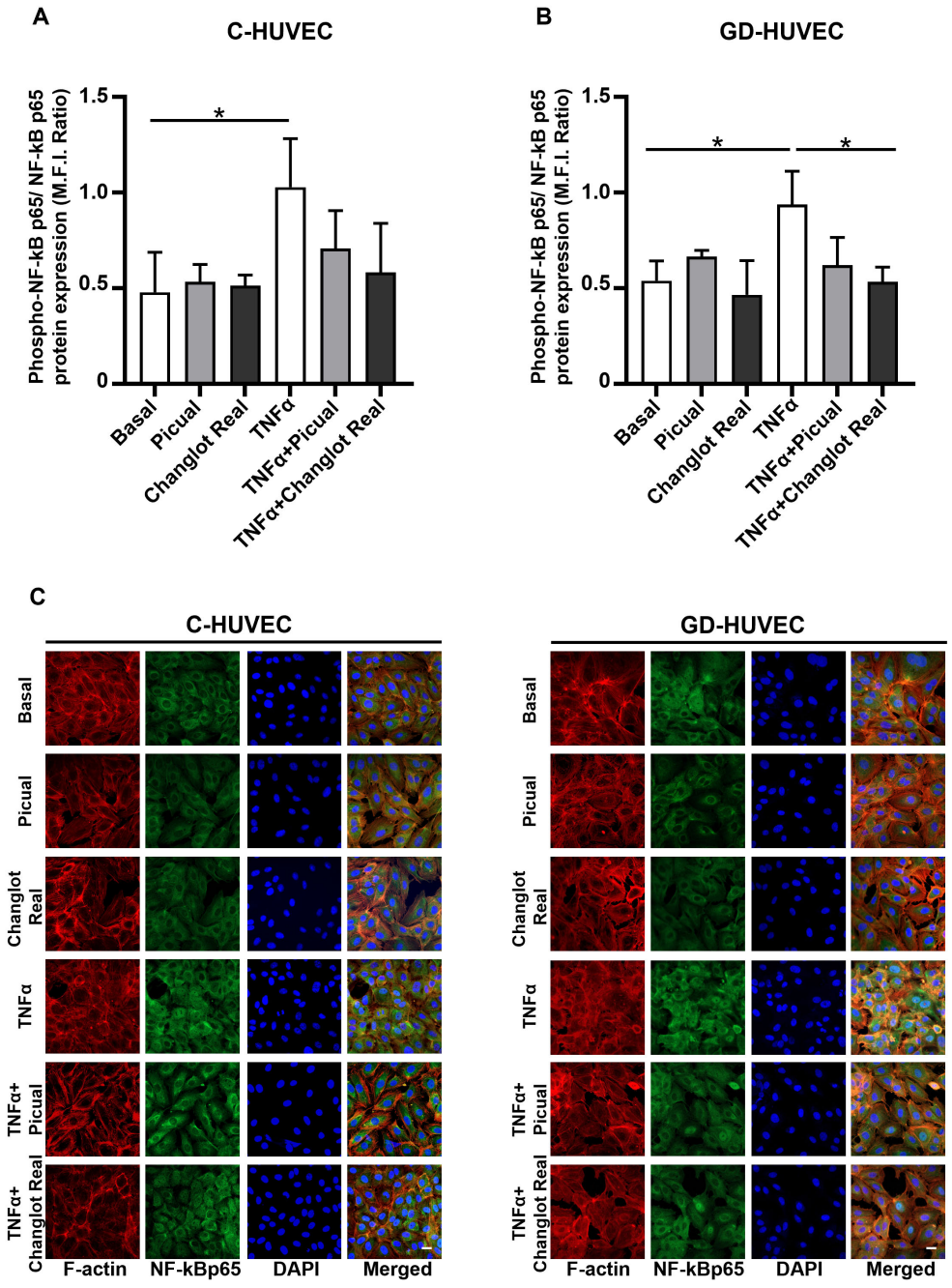


FIGURE 4
Changlot Real and Picual phenolic extract treatment reduces NF-κB p65 phosphorylation and nuclear translocation. Phosphorylated NF-κB p65 (Ser536) to total NF-κB p65 ratio in C- **(A)** and GD-HUVEC **(B)**. NF-κB p65 nuclear translocation representative figures in C- and GD-HUVEC **(C)**. Cells were treated for 24-hours with Changlot Real and Picual phenolic extracts (10 μg/mL), with or without 1-hour stimulation with TNFα (10 ng/mL). Histograms data are presented as mean ± SD (n = 3). Asterisks point out statistically significant differences between the selected conditions (*p<0.05). Scale bar 20 μm.

Effects of phenolic extracts Picual and Changlot Real on VCAM-1 protein expression

To further study the NF-κB p65 mediated pathway, VCAM-1 protein expression, a main downstream molecule that strongly modulates endothelial inflammation, was investigated in C- and GD-HUVEC treated with Picual and Changlot Real phenolic extracts with or without TNFα stimulation (Figure 5). GD-HUVEC exhibited a significantly increased basal VCAM-1 protein expression compared to control cells confirming their pro-inflammatory phenotype. Interestingly, treatment with Picual and Changlot Real extracts resulted in reduced VCAM-1 expression in GD-HUVEC; however, this reduction did not reach statistical

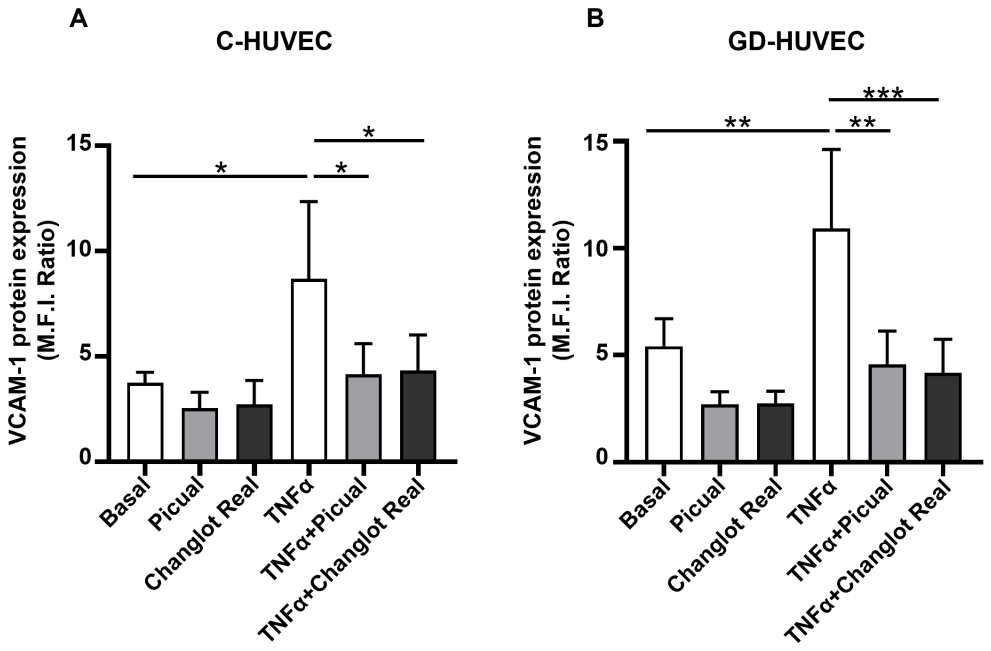


FIGURE 5
Changlot Real and Picual phenolic extracts treatment decreases VCAM-1 protein expression in TNFα-stimulated HUVEC. VCAM-1 protein expression in C- **(A)** and GD-HUVEC **(B)** following 24-hour treatment with Changlot Real and Picual phenolic extracts (10 µg/mL) with or without a 16-hour stimulation with TNFα (10ng/mL) analyzed by flow cytometry. Results are presented as mean ± SD (n=4). Asterisks point out statistically significant differences between the selected conditions (*p<0.05;**p<0.01;***p<0.001).

significance. As expected, TNFα stimulation significantly increased VCAM-1 expression in both cell types, with a more pronounced effect in GD-HUVEC. Furthermore, the pre-treatment with both Picual and Changlot Real phenolic extracts caused a significant decrease in VCAM-1 expression induced by TNFα in both C- and GD-HUVEC, mostly in the latter one. These findings provide additional evidence of the possible capacity of Picual and Changlot Real extracts in modulating endothelial inflammation.

Effects of phenolic extracts Picual and Changlot Real on U937 monocyte–HUVEC interaction

To assess the *in vitro* potential anti-inflammatory role of the phenolic extracts Picual and Changlot Real in a functionally relevant context, a monocyte adhesion assay was performed. This assay closely mimics the early stages of vascular inflammation observed in pathological conditions such as atherosclerosis. As shown in Figure 6, pre-treatment with the Changlot Real phenolic extract for 24 hours significantly reduced TNFα-stimulated monocyte adhesion to both C-HUVEC and GD-HUVEC, strongly supporting its anti-inflammatory effect on the endothelium. Pre-treatment with the Picual phenolic extract for 24 hours led to a decrease in TNFα-stimulated monocyte adhesion in C-HUVEC, although this reduction was only statistically significant in GD-HUVEC, supporting its selective effect in the diabetic-like endothelial model.

Discussion

This study demonstrates the anti-inflammatory potential of phenolic extracts derived from *Picual* and *Changlot Real* monocultivar olive leaves, focusing on their effects on an *in vitro* model of endothelial cells derived from umbilical cords of neonates born to mothers with gestational diabetes and therefore exposed to hyperglycemia *in vivo* (26). The extracts were thoroughly characterized by HPLC-ESI-TOF-MS, revealing a rich and various phenolic composition. In particular, Changlot Real exhibited a higher total phenolic content than Picual, particularly in secoiridoids, known for their strong bioactivity. These results are consistent with previous reports, such as Talhoui and collaborators, confirming the prevalence of oleuropein as the major constituent (28).

The gestational diabetes-derived endothelial cell (GD-HUVEC) model represents a valuable *in vitro* system for studying the effects of chronic hyperglycemia on endothelial function. Having developed in a hyperglycemic intrauterine environment, these cells exhibit molecular and functional alterations that mirror diabetes-associated vascular dysfunction, including changes driven by epigenetic modifications (7, 26, 33). This makes GD-HUVEC a relevant model to investigate mechanisms underlying endothelial impairment, such as inflammation resulting from prolonged high glucose exposure. Consistent with our previous findings (26), we confirmed baseline differences between GD-HUVECs and control endothelial cells (C-HUVEC) in both NF-κB p65

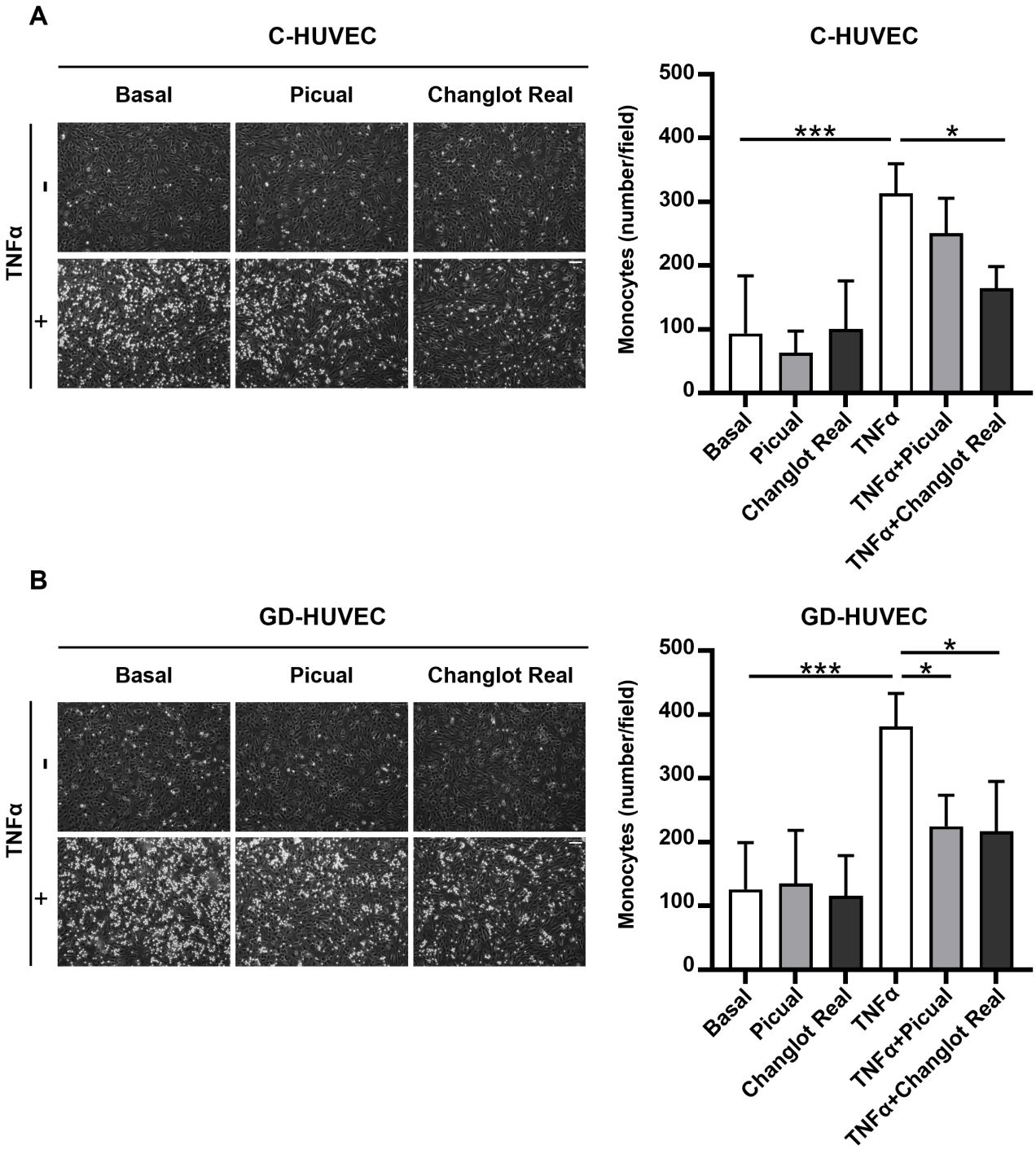


FIGURE 6
Changlot Real and Picual phenolic extracts treatment decreases monocytes adhesion in both cell types, with a more pronounced effect on Changlot Real pre-treated GD-HUVEC stimulated with TNFα. HUVEC–monocyte adhesion assay and relative quantification of adherent monocytes to C- **(A)** and GD-HUVEC **(B)** after 24-hour treatment with Changlot Real and Picual phenolic extracts (10 µg/mL), with or without 16-hour stimulation with TNFα (10 ng/mL). Data are expressed as mean ± SD (n = 4). Asterisks point out statistically significant differences between the selected conditions (*p<0.05; ***p<0.001). Scale bar 100 µm.

gene expression and VCAM-1 protein levels, key regulators of endothelial inflammatory pathways.

Our data indicate that both Picual and Changlot extracts are non-toxic to endothelial cells across a wide range of concentrations (0.1–50 µg/mL). The cell viability of both control (C-HUVEC) and gestational diabetes-derived endothelial cells (GD-HUVEC) remained stable upon treatment, demonstrating that these extracts do not compromise cell integrity. This finding is crucial for potential therapeutic applications, as it confirms that the tested polyphenols can be used at these concentrations without adverse effects on endothelial cell viability.

At the molecular level, olive leaf extracts anti-inflammatory effects were evidenced by a consistent downregulation of key inflammatory markers. Specifically, pre-treatment with both Picual and Changlot Real significantly reduced *NF-κB p65* and *MCP-1* gene expression in both basal and TNFα-stimulated conditions. Interestingly, while Changlot Real showed a broader inhibitory effect across both control and GD-HUVEC, Picual exerted a more pronounced action exclusively in GD-HUVEC, which we have previously shown to exhibit an inflammatory phenotype due to epigenetic alterations induced by the diabetic environment (26). This suggests potential differences in the bioactive compound profiles or bioavailability between the two monocultivars, possibly linked to the higher phenolic content in Changlot Real.

Interestingly, both extracts attenuated NF-κB p65 phosphorylation at Ser536, a key activation step in the NF-κB signaling cascade, especially under TNFα stimulation. This inhibitory effect was more significant in GD-HUVEC, reinforcing the notion that these cells are particularly responsive to polyphenol treatment and that the extracts may be especially effective in pathological conditions associated with endothelial dysfunction.

Downstream NF-κB, VCAM-1, a critical adhesion molecule involved in monocyte recruitment during vascular inflammation, was also downregulated following treatment with both extracts. Again, Changlot Real and Picual reduced VCAM-1 expression more effectively in GD-HUVEC, even under basal conditions, indicating a preventive anti-inflammatory effect beyond the response to external stimuli. Similar results have been recently reported using olive leaf extract and its phenolics, oleuropein and hydroxytyrosol, to suppress LPS-induced VCAM-1 expression and monocyte adhesion in human coronary and umbilical endothelial cells (34, 35).

Functionally, this molecular modulation translated into reduced monocyte adhesion to the endothelium, an early crucial step in atherogenesis. Changlot Real significantly decreased TNFα-induced monocyte adhesion in both control and GD-HUVEC, while Picual exerted a comparable effect exclusively in GD-HUVEC. Collectively, these results confirm the anti-inflammatory activity of both extracts and suggest a potential disease-modifying effect under diabetic-like conditions, characterized by sustained oxidative stress and low-grade inflammation.

Taking together, these data indicate that Picual and Changlot Real olive leaf extracts exert their anti-inflammatory effects via the NF-κB pathway, reducing both transcriptional and post-translational activation steps, and ultimately limiting monocyte recruitment. The stronger and broader effect observed with Changlot Real may be attributed to its higher content of phenolic compounds, particularly secoiridoids, which are known to modulate oxidative and inflammatory pathways. Supporting this, studies on extra virgin olive oil and related supplements consistently report dose-dependent reductions in inflammatory cytokines and soluble adhesion molecules in humans, reinforcing the relevance of our *in vitro* findings (36). Further corroborating these results, our recent work demonstrated that oleanolic acid, a bioactive triterpenoid abundant in olive leaves and oil, lowers expression of key inflammatory adhesion molecules (VCAM1, ICAM1, SELE), reduces monocyte adhesion, and restores angiogenic function and migration in endothelial cells derived from gestational diabetic pregnancies, highlighting its potential to counteract hyperglycemia-induced endothelial dysfunction via epigenetic mechanisms (15). In addition, our *in vitro* findings align with previous *in vivo* studies demonstrating the beneficial effects of olive leaf extract (OLE) in ameliorating systemic inflammation and vascular dysfunction. For instance, OLE supplementation in aged rats improved endothelial function and metabolic parameters, including reductions in pro-inflammatory markers such as TNF-α and IL-6, together with enhanced antioxidant gene expression, highlighting its protective role against age-related vascular decline (15, 37, 38). Moreover, in a model of high-fat diet-induced obesity, OLE not only improved glycemic control and lipid profiles but also reduced systemic and adipose tissue inflammation, restored gut microbiota composition, and reversed endothelial dysfunction, indicating its multifaceted therapeutic potential in cardiometabolic diseases (15, 37, 38). These *in vivo* data strongly support our current observations and further underscore the translational relevance of OLE, particularly in pathological settings characterized by chronic inflammation and endothelial impairment. In addition, recognizing the importance of pharmacokinetics, bioavailability, and safety for therapeutic applications, previous toxicological studies have confirmed the safety of Olea europaea leaf extracts (39). Investigations into the bioavailability and metabolism of key polyphenols such as oleuropein and hydroxytyrosol provide evidence of their systemic activity in humans (40–42). Clinical trials have also reported improved insulin sensitivity following OLE supplementation (43), and herb-drug interaction studies suggest its safe use alongside antihypertensive medications (44).

In summary, our pilot *in vitro* study indicates that Picual and Changlot Real olive leaf polyphenols may modulate the NF-κB–VCAM-1 axis and reduce endothelial inflammation and monocyte adhesion. The observed stronger effect of Changlot Real suggests that monocultivar extracts with higher phenolic content could have potential relevance for further investigation in the prevention or mitigation of diabetic vascular complications.

The results of this study align with previous findings and suggest that monocultivar olive leaf polyphenols, particularly those from Changlot Real, may offer a promising natural and non-toxic approach to reducing endothelial inflammation, especially in the context of diabetes-related vascular complications. Nonetheless, a notable limitation of our work is the inability to evaluate the potential influence of sex on offspring outcomes, since several studies have suggested that sex differences can affect metabolic responses and long-term health during gestational diabetes (45–47). This aspect warrants further investigation. It should also be considered that our evidence is currently limited to *in vitro* observations, and that detailed phytochemical profiling of the individual bioactive constituents was beyond the scope of this study. Future research will focus on comprehensive chemical characterization and dose–response analyses to better define the active constituents and elucidate their mechanisms of action. Additionally, further investigations involving larger sample

sizes, *in vivo* models, clinical trials, and appropriate positive pharmacological controls will be essential to confirm these preliminary findings and clarify the molecular pathways involved.

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

The studies involving humans were approved by COMITATO ETICO territoriale REGIONE ABRUZZO C.Et.R.A (reference number 123821/25). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IC: Methodology, Writing – original draft, Formal analysis, Investigation, Data curation. NP: Writing – original draft, Investigation, Formal analysis, Data curation, Methodology. DV: Data curation, Formal analysis, Methodology, Writing – original draft. GF: Data curation, Investigation, Writing – review & editing, Formal analysis. MZ: Investigation, Writing – review & editing, Formal analysis, Data curation. BM-G: Methodology, Data curation, Writing – original draft, Formal analysis. AG-C: Supervision, Formal analysis, Writing – original draft, Data curation, Investigation, Methodology. VV: Methodology, Supervision, Data curation, Investigation, Writing – original draft, Formal analysis. AP: Writing – review & editing, Visualization, Validation, Investigation, Data curation. CP: Project administration, Investigation, Validation, Writing – review & editing, Supervision, Formal analysis, Data curation, Visualization, Conceptualization, Writing – original draft.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. Project funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.3 -Call for tender No. 341 of 15 March 2022 of Italian Ministry of University and Research funded by the European Union -NextGenerationEU; Award Number: Project code PE00000003, Concession Decree No. 1550 of 11 October 2022 adopted by the Italian Ministry of University and Research, Project title "ON Foods -Research and innovation network on food and nutrition Sustainability, Safety and Security -Working ON Foods". DV was funded by the PhD program in Biomolecular and Pharmaceutical Sciences at the University G. d'Annunzio of Chieti Pescara, Cycle XXXIX, with the support of a scholarship co-financed by the Ministerial Decree no. 117 of 2nd March 2023, based on the NRRP -funded by the European Union -NextGenerationEU -Mission 4 "Education and Research", Component 2 "From Research to Business", Investment 3.3, and by the company Comecer S.p.A. CP was partially supported by Italian Ministry of Health Grant "Ricerca Finalizzata 2019" -GR-2019-12369702.This study was also funded by project RTI2018-099835-A-I00 financed by MCIN/AEI/10.13039/501100011033/FEDER "Una manera de hacer Europa".

Acknowledgments

We thank Dr. Pamela Di Tomo, Quality Manager of UdA-BIOBANK, for providing the biobanked HUVEC and for her support in ensuring the quality standards of the biological materials used in this study.

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1671932/full#supplementary-material

References

1. American Diabetes Association Professional Practice, C. 10. Cardiovascular disease and risk management: standards of care in diabetes-2025. *Diabetes Care*. (2025) 48:S207–38. doi: 10.2337/dc25-S010

2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. (2018) 17:83. doi: 10.1186/s12933-018-0728-6

3. Emerging Risk Factors C, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. (2010) 375:2215–22. doi: 10.1016/S0140-6736(10)60484-9

4. Marx N, Federici M, Schutt K, Muller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. (2023) 44:4043–140. doi: 10.1093/eurheartj/ehad192

5. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J*. (2013) 34:2436–43. doi: 10.1093/eurheartj/eht149

6. Paneni F, Costantino S, Cosentino F. Insulin resistance, diabetes, and cardiovascular risk. *Curr Atheroscler Rep*. (2014) 16:419. doi: 10.1007/s11883-014-0419-z

7. Di Fulvio P, Pandolfi A, Formoso G, Di Silvestre S, Di Tomo P, Giardinelli A, et al. Features of endothelial dysfunction in umbilical cord vessels of women with gestational diabetes. *Nutr Metab Cardiovasc Dis*. (2014) 24:1337–45. doi: 10.1016/j.numecd.2014.06.005

8. Ucci M, Di Tomo P, Tritschler F, Cordone VGP, Lanuti P, Bologna G, et al. Anti-inflammatory role of carotenoids in endothelial cells derived from umbilical cord of women affected by gestational diabetes mellitus. *Oxid Med Cell Longev*. (2019) 2019:8184656. doi: 10.1155/2019/8184656

9. Esquius L, Garcia-Retortillo S, Balague N, Hristovski R, Javierre C. Physiological- and performance-related effects of acute olive oil supplementation at moderate exercise intensity. *J Int Soc Sports Nutr*. (2019) 16:12. doi: 10.1186/s12970-019-0279-6

10. Hasler CM, Brown AC, American Dietetic A. Position of the American Dietetic Association: functional foods. *J Am Diet Assoc*. (2009) 109:735–46. doi: 10.1016/j.jada.2009.02.023

11. Menezes RCR, Peres KK, Costa-Valle MT, Faccioli LS, Dallegrave E, Garavaglia J, et al. Oral administration of oleuropein and olive leaf extract has cardioprotective effects in rodents: A systematic review. *Rev Port Cardiol*. (2022) 41:167–75. doi: 10.1016/j.repc.2021.05.011

12. Somova LI, Shode FO, Ramnanan P, Nadar A. Antihypertensive, antiatherosclerotic and antioxidant activity of triterpenoids isolated from Olea europaea, subspecies africana leaves. *J Ethnopharmacol*. (2003) 84:299–305. doi: 10.1016/S0378-8741(02)00332-X

13. Andreadou I, Sigala F, Iliodromitis EK, Papaefthimiou M, Sigalas C, Aligiannis N, et al. Acute doxorubicin cardiotoxicity is successfully treated with the phytochemical oleuropein through suppression of oxidative and nitrosative stress. *J Mol Cell Cardiol*. (2007) 42:549–58. doi: 10.1016/j.yjmcc.2006.11.016

14. Soni MG, Burdock GA, Christian MS, Bitler CM, Crea R. Safety assessment of aqueous olive pulp extract as an antioxidant or antimicrobial agent in foods. *Food Chem Toxicol*. (2006) 44:903–15. doi: 10.1016/j.fct.2006.01.008

15. Stelling-Ferez J, Cappellacci I, Pandolfi A, Gabaldon JA, Pipino C, Nicolas FJ. Oleanolic acid rescues critical features of umbilical vein endothelial cells permanently affected by hyperglycemia. *Front Endocrinol (Lausanne)*. (2023) 14:1308606. doi: 10.3389/fendo.2023.1308606

16. Al-Azzawie HF, Alhamdani MS. Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. *Life Sci*. (2006) 78:1371–7. doi: 10.1016/j.lfs.2005.07.029

17. Asghari AA, Hosseini M, Bafadam S, Rakhshandeh H, Farazandeh M, Mahmoudabady M, et al. (olive) leaf extract ameliorates learning and memory deficits in streptozotocin-induced diabetic rats. *Avicenna J Phytomed*. (2022) 12:163–74. doi: 10.22038/AJP.2021.18989

18. Jemai H, El Feki A, Sayadi S. Antidiabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats. *J Agric Food Chem*. (2009) 57:8798–804. doi: 10.1021/jf901280r

19. Jemai H, Fki I, Bouaziz M, Bouallagui Z, El Feki A, Isoda H, et al. Lipid-lowering and antioxidant effects of hydroxytyrosol and its triacetylated derivative recovered from olive tree leaves in cholesterol-fed rats. *J Agric Food Chem*. (2008) 56:2630–6. doi: 10.1021/jf072589s

20. Manna C, Migliardi V, Golino P, Scognamiglio A, Galletti P, Chiariello M, et al. Oleuropein prevents oxidative myocardial injury induced by ischemia and reperfusion. *J Nutr Biochem*. (2004) 15:461–6. doi: 10.1016/j.jnutbio.2003.12.010

21. Lins PG, Marina Piccoli Pugine S, Scatolini AM, de Melo MP. *In vitro* antioxidant activity of olive leaf extract (Olea europaea L.) and its protective effect on oxidative damage in human erythrocytes. *Heliyon*. (2018) 4:e00805. doi: 10.1016/j.heliyon.2018.e00805

22. Romani A, Ieri F, Urciuoli S, Noce A, Marrone G, Nediani C, et al. Health effects of phenolic compounds found in extra-virgin olive oil, by-products, and leaf of olea europaea L. *Nutrients*. (2019) 11:153. doi: 10.3390/nu11081776

23. Sahin S, Samli R, Tan ASB, Barba FJ, Chemat F, Cravotto G, et al. Solvent-free microwave-assisted extraction of polyphenols from olive tree leaves: antioxidant and antimicrobial properties. *Molecules*. (2017) 22:1056. doi: 10.3390/molecules22071056

24. Al-Hafidh SHA, Abdulwahid AA. Neurotoxic effects of type II-diabetes mellitus and the possible preventive effects of olive leaves supplement in male rats. *Open Vet J*. (2024) 14:2651–61. doi: 10.5455/OVJ.2024.v14.i10.15

25. Di Pietrantonio N, Cappellacci I, Mandatori D, Baldassarre MPA, Pandolfi A, Pipino C. Role of epigenetics and metabolomics in predicting endothelial dysfunction in type 2 diabetes. *Adv Biol (Weinh)*. (2023) 7:e2300172. doi: 10.1002/adbi.202300172

26. Di Pietrantonio N, Sanchez-Ceinos J, Shumliakivska M, Rakow A, Mandatori D, Di Tomo P, et al. The inflammatory and oxidative phenotype of gestational diabetes is epigenetically transmitted to the offspring: role of methyltransferase MLL1-induced H3K4me3. *Eur Heart J*. (2024) 45:5171–85. doi: 10.1093/eurheartj/ehae688

27. Schiavone V, Romasco T, Di Pietrantonio N, Garzoli S, Palmerini C, Di Tomo P, et al. Essential oils from mediterranean plants inhibit *in vitro* monocyte adhesion to endothelial cells from umbilical cords of females with gestational diabetes mellitus. *Int J Mol Sci*. (2023) 24:7225. doi: 10.3390/ijms24087225

28. Talhaoui N, Gomez-Caravaca AM, Roldan C, Leon L, de la Rosa R, Fernandez-Gutierrez A, et al. Chemometric analysis for the evaluation of phenolic patterns in olive leaves from six cultivars at different growth stages. *J Agric Food Chem*. (2015) 63:1722–9. doi: 10.1021/jf5058205

29. American Diabetes Association Professional Practice, C. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. *Diabetes Care*. (2022) 45:S17–38. doi: 10.2337/dc22-S002

30. Pipino C, Bernabe-Garcia A, Cappellacci I, Stelling-Ferez J, Di Tomo P, Santalucia M, et al. Effect of the human amniotic membrane on the umbilical vein endothelial cells of gestational diabetic mothers: new insight on inflammation and angiogenesis. *Front Bioeng Biotechnol*. (2022) 10:854845. doi: 10.3389/fbioe.2022.854845

31. Zheng L, Li M, Li H. High glucose promotes and aggravates the senescence and dysfunction of vascular endothelial cells in women with hyperglycemia in pregnancy. *Biomolecules*. (2024) 14:329. doi: 10.3390/biom14030329

32. Kim JH, Kim S, Piao S, Kim M, Kim DW, Jeon BH, et al. Non-thermal plasma attenuates TNF-alpha-induced endothelial inflammation via ROS modulation and NF-kappaB inhibition. *Int J Mol Sci*. (2025) 26:4449. doi: 10.3390/ijms26094449

33. Di Tomo P, Alessio N, Falone S, Pietrangelo L, Lanuti P, Cordone V, et al. Endothelial cells from umbilical cord of women affected by gestational diabetes: A suitable *in vitro* model to study mechanisms of early vascular senescence in diabetes. *FASEB J*. (2021) 35:e21662. doi: 10.1096/fj.202002072RR

34. Burja B, Kuret T, Janko T, Topalovic D, Zivkovic L, Mrak-Poljsak K, et al. Olive leaf extract attenuates inflammatory activation and DNA damage in human arterial endothelial cells. *Front Cardiovasc Med*. (2019) 6:56. doi: 10.3389/fcvm.2019.00056

35. Silvestrini A, Giordani C, Bonacci S, Giuliani A, Ramini D, Matacchione G, et al. Anti-inflammatory effects of olive leaf extract and its bioactive compounds oleacin and oleuropein-aglycone on senescent endothelial and small airway epithelial cells. *Antioxidants (Basel)*. (2023) 12:1509. doi: 10.3390/antiox12081509

36. Tehrani SD, Ahmadi AR, Sadeghi N, Keshani M. The effects of the mediterranean diet supplemented with olive oils on pro-inflammatory biomarkers and soluble adhesion molecules: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab (Lond)*. (2025) 22:52. doi: 10.1186/s12986-025-00947-8

37. Gonzalez-Hedstrom D, Garcia-Villalon AL, Amor S, de la Fuente-Fernandez M, Almodovar P, Prodanov M, et al. Olive leaf extract supplementation improves the vascular and metabolic alterations associated with aging in Wistar rats. *Sci Rep*. (2021) 11:8188. doi: 10.1038/s41598-021-87628-7

38. Vezza T, Rodriguez-Nogales A, Algieri F, Garrido-Mesa J, Romero M, Sanchez M, et al. The metabolic and vascular protective effects of olive (Olea europaea L.) leaf extract in diet-induced obesity in mice are related to the amelioration of gut microbiota dysbiosis and to its immunomodulatory properties. *Pharmacol Res*. (2019) 150:104487. doi: 10.1016/j.phrs.2019.104487

39. Clewell AE, Beres E, Vertesi A, Glavits R, Hirka G, Endres JR, et al. A comprehensive toxicological safety assessment of an extract of olea europaea L. Leaves (Bonolive). *Int J Toxicol*. (2016) 35:208–21. doi: 10.1177/1091581815619764

40. Nikou T, Sakavitsi ME, Kalampokis E, Halabalaki M. Metabolism and bioavailability of olive bioactive constituents based on *in vitro*, *in vivo* and human studies. *Nutrients*. (2022) 14:2079–85. doi: 10.3390/nu14183773

41. de Bock M, Thorstensen EB, Derraik JG, Henderson HV, Hofman PL, Cutfield WS. Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (Olea europaea L.) leaf extract. *Mol Nutr Food Res*. (2013) 57:2079–85. doi: 10.1002/mnfr.201200795

42. Bender C, Strassmann S, Golz C. Oral bioavailability and metabolism of hydroxytyrosol from food supplements. *Nutrients*. (2023) 15:325. doi: 10.3390/nu15020325

43. de Bock M, Derraik JG, Brennan CM, Biggs JB, Morgan PE, Hodgkinson SC, et al. Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial. *PloS One*. (2013) 8:e57622. doi: 10.1371/journal.pone.0057622

44. Mmopele K, Combrinck S, Hamman J, Willers C, Chen W, Viljoen A. Potential herb-drug pharmacokinetic interactions between african wild olive leaf extract and selected antihypertensive drugs. *Planta Med*. (2018) 84:886–94. doi: 10.1055/a-0583-0543

45. Retnakaran R, Shah BR. Fetal sex and the natural history of maternal risk of diabetes during and after pregnancy. *J Clin Endocrinol Metab*. (2015) 100:2574–80. doi: 10.1210/jc.2015-1763

46. Retnakaran R, Shah BR. Sex of the baby and future maternal risk of Type 2 diabetes in women who had gestational diabetes. *Diabetes Med*. (2016) 33:956–60. doi: 10.1111/dme.12989

47. Zhang S, Wang J, Xu F, Yang J, Qin Y, Leng J, et al. Sex-specific mediating effect of gestational weight gain between pre-pregnancy body mass index and gestational diabetes mellitus. *Nutr Diabetes*. (2022) 12:25. doi: 10.1038/s41387-022-00203-5

frontiers | Frontiers in Endocrinology

TYPE Systematic Review
PUBLISHED 06 November 2025
DOI 10.3389/fendo.2025.1698360

Check for updates

OPEN ACCESS

EDITED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

REVIEWED BY
Zhenwei Wang,
The First Affiliated Hospital of Zhengzhou University, China
Grzegorz K. Jakubiak,
Medical University of Silesia, Poland

*CORRESPONDENCE
Maoying Wei
weimaoying@bucm.edu.cn
Yanbing Gong
gyb_1226@163.com

†These authors have contributed equally to this work

RECEIVED 03 September 2025
ACCEPTED 22 October 2025
PUBLISHED 06 November 2025

CITATION
Wu C, Li A, Zhu Q, Guo J, Li Y, Gu X, Sun A, Wei M and Gong Y (2025) Glycemic variability of glycated hemoglobin in patients with type 2 diabetes mellitus and the risk of cardiovascular diseases: a latest systematic review and meta-analysis. *Front. Endocrinol.* 16:1698360. doi: 10.3389/fendo.2025.1698360

COPYRIGHT
© 2025 Wu, Li, Zhu, Guo, Li, Gu, Sun, Wei and Gong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Glycemic variability of glycated hemoglobin in patients with type 2 diabetes mellitus and the risk of cardiovascular diseases: a latest systematic review and meta-analysis

Chan Wu[1†], Aijing Li[1†], Qingyi Zhu[1†], Jingyi Guo[1], Yincheng Li[1], Xin Gu[1], Anning Sun[1], Maoying Wei[1*] and Yanbing Gong[1,2*]

[1]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [2]Beijing University of Chinese Medicine, Beijing, China

Objective: Glycated hemoglobin (HbA1c) variability is a crucial indicator for evaluating the stability of long-term glycemic control in patients with diabetes mellitus. This study aimed to clarify the association between HbA1c variability and the risk of incident cardiovascular disease (CVD) and mortality in patients with type 2 diabetes mellitus (T2DM) through a systematic review, thereby providing evidence-based support for the early prevention of adverse cardiovascular events in T2DM patients.

Methods: We systematically searched the PubMed, Web of Science, The Cochrane Library, and Embase databases for studies on the association between HbA1c variability and cardiovascular outcomes in patients with T2DM, published from the establishment of each database up to August 5, 2025. Cardiovascular outcomes included the incidence of CVD and CVD-related mortality. Two researchers independently conducted literature screening, data extraction, and risk of bias assessment. Meta-analysis was performed using Review Manager 5.3 software, with hazard ratio (HR) or odds ratio (OR) as the effect size.

Results: A total of 31 cohort studies were included, covering 545,956 participants from 13 countries and regions. The results of the meta-analysis showed that a higher coefficient of variation (CV) of HbA1c was significantly associated with an increased risk of cardiovascular events (HR = 1.32, 95% CI: 1.18–1.49, P < 0.00001; OR = 1.39, 95% CI: 1.22–1.57, P < 0.00001), and also significantly elevated the risk of mortality (HR = 1.35, 95% CI: 1.16–1.57, P < 0.00001). The standard deviation (SD) of HbA1c was also significantly correlated with a higher risk of cardiovascular events (HR = 1.27, 95% CI: 1.17–1.38, P < 0.00001; OR = 1.30, 95% CI: 1.07–1.57, P = 0.008) and a significant increase in mortality risk (HR = 1.27, 95% CI: 1.17–1.37, P<0.00001). The hemoglobin glycation index (HGI) was significantly associated with the risk of cardiovascular events in terms of HR (HR = 1.36, 95% CI: 1.14–1.62, P = 0.0006), but no statistical significance was observed in terms of OR (OR = 1.47, 95% CI: 0.98–2.20, P = 0.06). In contrast, the HbA1c variability score (HVS) showed no significant association with either the risk of cardiovascular events (HR = 1.31, 95% CI: 0.97–1.78, P = 0.08) or mortality risk (HR = 1.00, 95% CI: 0.76–1.31, P = 1.00).

Conclusions: HbA1c variability is positively associated with the risk of adverse cardiovascular events in patients with T2DM. Among the indicators of HbA1c variability, the coefficient of variation (CV), standard deviation (SD), and hemoglobin glycation index (HGI) can serve as significant predictors for the risk of cardiovascular disease (CVD) occurrence and mortality. However, the HbA1c variability score (HVS) did not show significant predictive value in this study.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier CRD420251132972.

KEYWORDS

HbA1c variability, type 2 diabetes mellitus, cardiovascular disease, meta-analysis, diabetes complications

1 Introduction

The global prevalence of diabetes is increasing. Statistics show that there are currently 537 million adults living with diabetes worldwide, with the majority residing in low- and middle-income countries (1). As the cost of disease treatment rises, the burden on healthcare systems will further escalate—this is particularly true when patients in the middle and late stages of diabetes develop diabetes-related complications (2). Cardiovascular disease (CVD) remains the leading cause of mortality and disability among patients with type 2 diabetes mellitus (T2DM), posing a significant public health challenge and imposing a heavy economic burden on countries across all levels of socioeconomic development (3).

There is a complex pathophysiological link between diabetes and cardiovascular complications, and this mechanism has driven extensive research focused on the development of risk prediction models and the optimization of early intervention strategies (4). Although a causal relationship between glycemic control and vascular complications has been clearly established, traditional biochemical markers such as glycated hemoglobin (HbA1c)—which serves as an indicator of peripheral insulin resistance and reflects the average blood glucose concentration over the past 2 to 3 months—are widely used biomarkers for diabetes monitoring and prognosis in clinical practice. However, HbA1c is prone to errors due to factors such as pregnancy and anemia; studies have reported that HbA1c levels are only associated with chronic hyperglycemia (5). In contrast, HbA1c is not correlated with glycemic variability parameters, and thus has certain limitations in reflecting the dynamic characteristics of blood glucose fluctuations and their impact on diabetes-related vascular outcomes.

Recent studies have shown that glycemic variability, especially indicators of HbA1c variability such as standard deviation (SD), coefficient of variation (CV), HbA1c variability score (HVS), and hemoglobin glycation index (HGI), can independently predict cardiovascular-related outcomes and serve as additional predictive indicators for diabetes complications (6). Among these, the standard deviation (SD) and coefficient of variation (CV) of HbA1c are the most commonly used measurement indicators. HVS can more comprehensively reflect the pathophysiological process of vascular complications through multiple mechanisms, including blood glucose dynamic fluctuations induced by it, hypoglycemia-related oxidative stress responses, and persistent chronic inflammatory states (7–9). Therefore, high HVS is closely associated with an increased risk of cardiovascular diseases in patients with diabetes. In addition, for critical adverse events in cardiovascular diseases—such as blood glucose fluctuations caused by acute stress responses during myocardial infarction—the prognostic value of HbA1c decreases significantly (10). In such cases, the hemoglobin glycation index (HGI), by quantifying the difference between measured HbA1c and predicted HbA1c, can more comprehensively assess blood glucose status and timely reflect individual blood glucose fluctuation (11). Although the SD and CV are widely used to assess HbA1c variability, the evidence for HVS and HGI remains fragmentary and inconsistent (12–14). For example, two cohort studies in East Asia reported opposite findings for HVS (15). A Korean study reported that higher HVS was significantly associated with increased Major Adverse Cardiovascular Events (MACE) risk, whereas a contemporary Scottish cohort found no significant link between HVS and CVD events. Similarly, the association between HGI and CVD differs

Abbreviations: Adj-SD, Adjusted Standard Deviation; CGM, Ccontinuous Glucose Monitoring; CI, Confidence Interval; CIs, Confidence Intervals; CV, Coefficient of Variation; CVD, Cardiovascular Disease; Embase, Excerpta Medica DataBASE; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; HFpEF, Heart Failure with Preserved Ejection Fraction; HGI, Hemoglobin Glycation Index; HR, Hazard Ratio; HRs, Hazard Ratios; HVS, HbA1c Variability Score; IHD, Ischemic Heart Disease; MACE, Major Adverse Cardiovascular Events; MeSH, Medical Subject Headings; NOS, Newcastle-Ottawa Scale; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; ORs, Odds Ratios; PubMed, Public Medicine; RRs, Relative Risks; SD, Standard Deviation; T2DM, Type 2 Diabetes Mellitus; Web of Science, Web of Science Core Collection.

between Western and Korean populations (16, 17). Large, multicenter cohorts in Europe and North America consistently show a linear, positive correlation between HGI and MACE. In contrast, Korean data reveal a U-shaped curve, indicating that both extremely high and extremely low HGI levels are associated with elevated MACE risk. Another source of inconsistency in existing studies lies in the variation of statistical measures used to quantify the association between HbA1c variability indicators and CVD outcomes. Some studies used relative risk (RR) as the measure of association (18, 19), which does not account for the time factor. In contrast, the hazard ratio (HR) incorporates time information and can handle censored data, making it more accurate for evaluating the long-term impact of HbA1c variability on cardiovascular outcomes. In addition, multicenter cohorts published after 2023 have not yet been included in any published synthesis. Therefore, an updated synthesis comparing the consistency and robustness of different indicators is urgently needed.

The relationship between HbA1c variability indicators and the risk of cardiovascular events in patients with T2DM remains not fully understood, especially in diverse populations with different diabetes durations and treatment regimens, which requires more in-depth research (20). Although the variability of glycated hemoglobin has potential clinical significance, current diabetes management guidelines mainly focus on average glycemic control rather than glycemic variability. This study systematically conducts literature search, quality assessment, and quantitative synthesize of prospective/retrospective cohort studies published up to August 2025. Using a random-effects meta-analysis approach, it aims to clarify the independent predictive value of four HbA1c variability indicators (SD, CV, HVS, HGI) for incident cardiovascular events and cardiovascular mortality in patients with type 2 diabetes mellitus.

2 Research design and methods

2.1 Protocol and registration

This study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD420251132972) in advance. This meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (21). Since the included studies were cohort studies (observational studies), the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (22) were also followed.

2.2 Search strategy

A comprehensive search was conducted using PubMed, Embase, Web of Science, and the Cochrane Library, with no language restrictions applied. The search covered the period from the inception of each database up to August 5, 2025. For the search strategy, we combined Medical Subject Headings (MeSH) terms (23) with text words related to HbA1c variability and cardiovascular disease progression, integrating both controlled terms and free-text terms. The search terms included: ① Glycated Hemoglobin, Glycated Hemoglobin A1c, HbA1c, HbA(1c) variability, HbA(1c) variation; ②Disease, Cardiovascular, Cardiac Events, Adverse Cardiac Event, Major Adverse Cardiac Events, Cardiovascular Diseases; ③ Diabetes Mellitus, Diabetes Insipidus, Diet, Diabetic, Prediabetic State, Scleredema Adultorum, Glucose Intolerance, Gastroparesis, Glycation End Products. Two reviewers (C.W. and A.J.L.) independently screened all titles and abstracts, and selected full texts of potentially relevant articles. Disagreements were resolved through debate, discussion, or consultation with a third investigator (Q.Y.Z.). Meanwhile, EndNote X20 was used for literature analysis and management.

2.3 Selection of studies (PICOS)

P: Inclusion Criteria:

1. Studies investigating HbA1c variability indicators (including SD, CV, HVS, and HGI).
2. Adult patients (aged ≥18 years) with a confirmed diagnosis of type 2 diabetes.
3. Studies that included patients without a history of cardiovascular-related events at baseline. To avoid reverse causation, where acute events drive HbA1c fluctuations through stress-induced hyperglycemia, we restricted the analysis to a primary prevention population, ensuring that any observed association reflects the prospective direction of interest.
4. Studies from which hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) could be extracted.

Full texts of potentially relevant studies were downloaded and reviewed for inclusion.

Exclusion Criteria:

1. Studies involving patients with type 1 diabetes, gestational diabetes, a history of major cardiovascular events (e.g., myocardial infarction, stroke) at baseline, an expected lifespan shorter than the follow-up period, or an insufficient number of HbA1c measurements during the follow-up period.
2. Reviews, case reports, practice guidelines, commentaries, *in vitro* or animal studies, *post-hoc* analyses of randomized controlled trials, or analyses unrelated to the topic of this study.
3. Non-English articles. Following the practice of previous systematic reviews (24, 25), this study extracted data only from full-text articles published in English to ensure consistency in data extraction and interpretation. To assess the potential impact of this limitation, we

sensitivity-checked the abstracts of non-English studies and found no directional change, which indicates the exclusion of these articles is unlikely to alter our conclusions.

4. Duplicate articles; if identical literature was identified, only one article was included.
5. Articles for which the full text was unavailable, relevant valid data could not be extracted, or there were obvious errors in the data.

I: High levels of glycated hemoglobin (HbA1c) variability: Standard Deviation (SD) and adjusted Standard Deviation (Adj-SD); Coefficient of Variation (CV = SD/Mean); HVS: HbA1c variability score; HGI: hemoglobin glycation index.

C: The control group consisted of a patient population with low HbA1c variability. Studies typically compared the risk differences between the highest quartile group and the lowest quartile group. Comparison condition: Logistic or Cox regression analysis was used for outcome risk prediction.

O: Cardiovascular events:

Primary outcomes: CVD (events of myocardial infarction, ischemic heart disease, heart failure, nonfatal ischemic stroke, or peripheral vascular disease).

Secondary outcomes: Cardiovascular mortality.

S: Prospective Cohort Study or Retrospective Cohort Study.

2.4 Quality assessment

The risk of bias was also independently assessed by C.W. and A.J.L. For cohort studies and *post-hoc* analyses, in accordance with the recommendations of the Cochrane Collaboration, the Newcastle-Ottawa Scale (NOS) (26) was selected to evaluate study quality, with details available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. In this context, a 9-star rating system (maximum score of 9 stars) was used, which is divided into three domains: selection of participants (0–4 stars), comparability of study groups (0–2 stars), and determination of outcomes (0–3 stars). Studies with a score of ≥ 8 stars were classified as low risk of bias, those with 6–7 stars as moderate risk, and those with 5 stars as high risk.

2.5 Data analysis and synthesis

The meta-analysis was conducted using Review Manager (RevMan) Version 5.3. Stratified analyses were performed based on the variations in data regarding HbA1c variability indicators and types of effect sizes among the included studies, with subgroup analysis results and pooled values presented separately. Given the methodological differences between HR and OR, independent analyses were conducted for each. A random-effects model was used for data pooling.

The results were visualized as a forest plot using the inverse variance method. Data were entered into RevMan 5.3 in the form of the natural logarithm of risk estimates (HR or OR) and their standard errors. When necessary, the standard error was derived from the confidence interval (CI) using the formula: (ln upper CI - ln lower CI)/(2×1.96). A random-effects model was used to calculate the I^2 statistic for assessing heterogeneity, with the following judgment criteria: 0%-25% indicates very low heterogeneity, 25%-50% indicates low heterogeneity, 50%-75% indicates moderate heterogeneity, and >75% indicates high heterogeneity (27). Subgroup analyses were performed based on dimensions such as HbA1c variability indicators, sample size, region, study design, follow-up duration of HbA1c variability, and comparison levels of HbA1c variability to identify the sources of heterogeneity. Sensitivity analyses were conducted to evaluate the robustness of the results by excluding low-quality studies, removing studies that only reported relative risk (RR), excluding studies with short or unclear average follow-up duration, and re-analyzing using a fixed-effects model instead. Publication bias was assessed using Egger's test and funnel plots. If publication bias existed, the trim-and-fill method was used to estimate the impact of missing studies. A P-value < 0.05 was set as the threshold for statistical significance in all analyses. Subgroup analyses, Egger's test, Trim-and-Fill adjustment results, and sensitivity analyses have been provided in Appendix A (Supplementary Tables S1–S6) to ensure transparency and reprehensibility of the findings.

2.6 Clinical definitions

SD was calculated as $\sqrt{\Sigma_{k=1}^{n}\frac{(x_i-\bar{x})^2}{n-1}}$ and adjusted SD was calculated as $SD/\sqrt{\frac{n}{n-1}}\cdot CV$ was calculated as $SD/\bar{X}$ and adjusted CV was calculated as $CV/\sqrt{\frac{n}{n-1}}$, where n = total number of HbA1c measurements, X_i = serially measured HbA1c, and $\bar{X}$ = mean of HbA1c (27). HVS was the number of HbA1c changes >0.5% over the total number of HbA1c measurements (17). HGI was calculated as measured HbA1c minus predicted HbA1c from fasting blood glucose (FBG) levels (28).

The diagnostic criteria for T2DM were as follows: (1) FBG ≥7.0 mmol/L; (2) 2-h oral glucose tolerance test or casual plasma glucose level ≥11.1 mmol/L; (3) HbA1c ≥ 6.5%; or (4) prior diagnosis of T2DM.

3 Results

3.1 Characteristics of included studies

Through the search method described above, a total of 5,369 articles were retrieved. After removing 891 duplicate articles, 4,386 articles that did not match the research topic were excluded after a preliminary review of titles and abstracts, resulting in 105 articles after initial screening. Subsequently, 65 articles were excluded after a detailed full-text review, including non-cohort studies, studies involving non-type 2 diabetes patients, studies without relevant results, conference abstracts, non-English studies, and systematic reviews, leaving 40 articles. Finally, articles that could not be

downloaded and had incomplete data were excluded, resulting in 31 articles. The search process is shown in Figure 1.

All 31 included articles were cohort studies, covering 545,956 participants from 13 countries and regions. The basic characteristics of the included articles are shown in Table 1. Six studies (29, 38, 45–47, 49) reported adjusted HRs or ORs for high SD versus low SD, involving a total of 140,260 participants, with the sample size ranging from 689 to 101,533. These studies were conducted in multiple countries including China, the United States, Brazil, Japan, and Thailand, with an average follow-up period ranging from 3 years to 15.9 years. Among the included studies, 20 reported (19, 29–33, 35–38, 41, 42, 45–49, 52–54) SD values, and 3 (30, 32, 47) provided adjusted SD values. The average glycated hemoglobin (HbA1c) level ranged from 6.8% to 8.69%. Sixteen studies (19, 29, 30, 32, 33, 35–37, 41, 42, 45, 47, 49, 52–54) explored the relationship between SD and the incidence of diabetes-related adverse cardiovascular events, while seven studies (31, 36, 38, 41, 46, 48, 54) investigated the relationship between SD and mortality from diabetes-related cardiovascular events; details can be found in Table 1.

Four studies (29, 31, 45, 47) reported HRs or ORs for the high versus low coefficient of variation (CV) groups, involving a total of 33,610 participants, with the sample size ranging from 689 to 29,260. These studies were conducted in Mainland China, the United States, Japan, and Iran, with a follow-up period ranging from 3.3 to 10.0 years. Among the included studies, fourteen (19, 29, 31, 32, 36, 37, 40, 43–45, 47, 51, 53, 54) reported CV values, and the average HbA1c level ranged from 6.7% to 8.69%. Twelve studies (19, 29, 32, 36, 37, 40, 43–45, 47, 53, 54) explored the relationship between CV and the incidence of diabetes-related adverse cardiovascular events, while four studies (31, 36, 51, 54) investigated the relationship between CV and mortality from diabetes-related adverse cardiovascular events.

Regarding the HVS, four studies (8, 15, 39, 50) reported adjusted HRs or ORs, involving a total of 72,425 participants, with the sample size ranging from 820 to 45,436. These studies were conducted in Mainland China, Taiwan (China), the Democratic People's Republic of Korea, and Scotland. The average follow-up period was 3 to 9 years, and the average HbA1c level ranged from 7.0% to 8.05%. Three of the studies (15, 39, 50) explored the relationship between HVS and the incidence of cardiovascular events, while one study (8) investigated the relationship between HVS and the mortality of cardiovascular events. Three studies (16, 17, 34) were included in the meta-analysis of the HGI, involving a total of 3,237 participants, with the studies conducted in South Korea and Brazil. The average HbA1c level ranged from 7.0% to 8.4%.

Meanwhile, the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of all included cohort studies. Among the 31 articles, 3 scored 6 points (19, 39, 51), 13 scored 7 points (8, 15, 16,

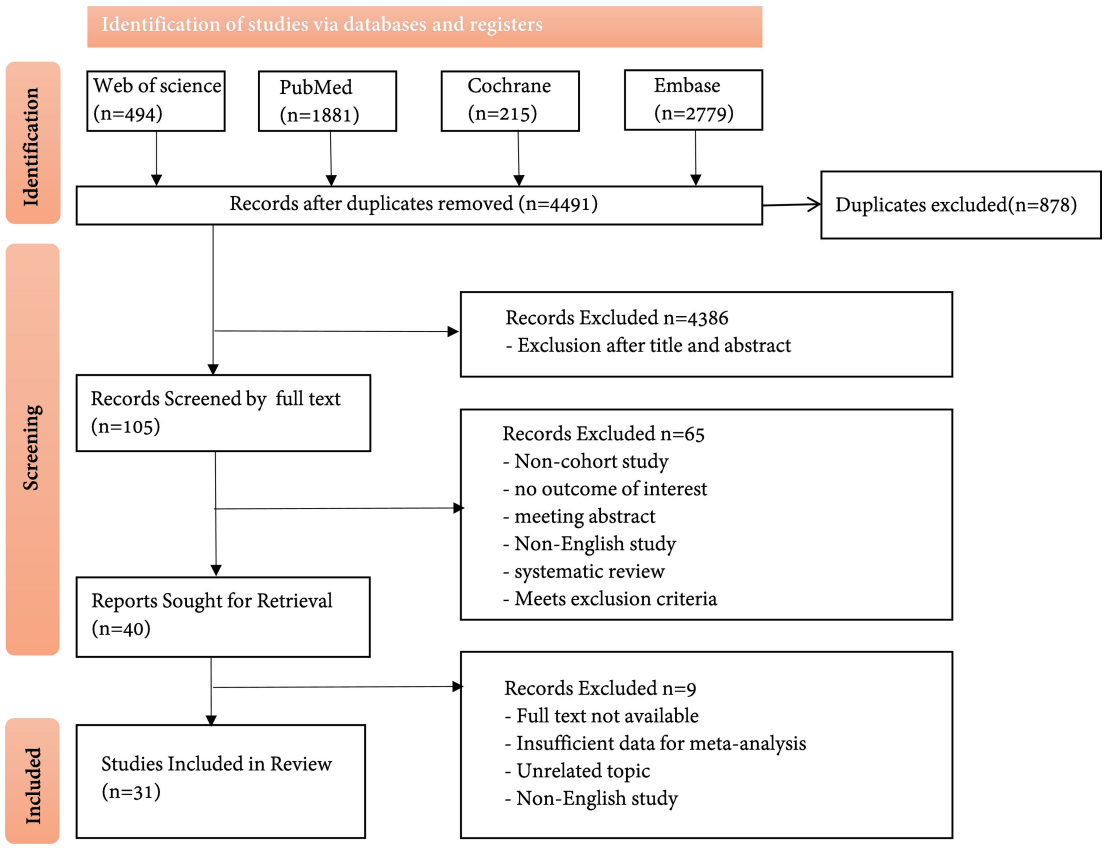


FIGURE 1
PRISMA flow diagram outlining the selection process that was undertaken for the systematic review and meta-analysis.

TABLE 1 Characteristics of the studies considered in the meta-analysis.

Study (Author, year)	Design (Type of study)	Number (male%)	Age at enrolment	Area (follow-up time, years)	Inclusion criteria	HbA1c variability and follow-up time	Mean HbA1c (%)	Outcome	Variable adjustment	NOS score
Bouchi R et al. (2012) (29)	observational cohort study	689 (57.18%)	65±11	Japan(3.3(1.0-6.3))	patients with T2DM without CVD	SD:0.6±0.42, CV:8.0±4.6, ≥12months	7.8±1.2	Incidence of CVD	Adjusted for age, sex, duration of diabetes, the presence of proliferative diabetic retinopathy, smoking status, the use of insulin, renin–angiotensin system inhibitors, antiplatelet agents, and statins, hemoglobin, uric acid, eGFR, urinary ACR at baseline, BMI, SBP and DBP, triglycerides, HDL-C and LDL-C levels	7
Luk AO et al. (2013) (30)	prospective cohort study	8439 (47.0%)	57.6±13.2	Hong Kong, CHINA (median follow-up period of 7.2 years)	patients with T2DM	Adjusted SD: NA, median number of HbA1c measurements was 10(IQR: 5–17)	NA	CVD (events of myocardial infarction , ischemic heart disease, heart failure, nonfatal ischemic stroke or peripheral vascular disease)	Adjusted for age, gender, smoking history, diabetes duration, BMI, waist circumference, SBP/DBP, LDL-C, HDL-C, log triglyceride, log urine ACR, eGFR, haemoglobin and baseline medication use including the use of ACE inhibitors/ARB, antihypertensive drugs, lipid-lowering drugs, oral hypoglycaemic drugs and insulin.	7
Takao T et al. (2014) (31)	observational cohort study	754 (81.83%)	54.4±10.0	Japan(15.9 (10.3-16.6))	patients with T2DM	SD:NA, CV:NA, ≥24months	8.0±1.7	Mortality of CVD	Adjusted for age, sex, mean HbA1c, the number of HbA1c measurements, duration of diabetes, mean BMI, mean SBP, mean TC/HDL-C, and current smoker.	8
Yang HK et al. (2015) (32)	observational cohort study	595 (58.32%)	64.88	Korea(9.63 ±9.04)	patients with T2DM without history of CVD	Adjusted-SD: 0.48(0.45, 0.51), CV:6.98 (6.64, 7.33), 973 days	8.69 ±2.30	Incidence of CACS	Adjusted for age, sex, duration of diabetes, HbA1c-MEAN, HbA1c-SD groups, total cholesterol level, use of insulin and statin.	9
Bonke FC et al. (2016) (33)	observational cohort study	13777 (54.70%)	67.4±11.1	Bavaria(9.0 ±6.7)	patients with T2DM without CVD	SD:NA, ≥5years	8.2±1.4	Incidence of CVD	Adjusted for age, sex, smoking status, absolute HbA1c value at baseline, diabetes history of more than 8 years (i.e. the median duration at baseline), peripheral artery disease, the presence of diabetic complications (retinopathy, neuropathy or nephropathy) and a record of previous myocardial infarction, stroke or diabetes-related emergency admission	8
Ahn CH et al. (2017) (34)	prospective cohort study	1248 (59.54%)	55.3±11.3	Korea(1.07 (1.05-1.09))	patients with T2DM	HGI:0.05± 0.98, NA	7.0±1.7	Incidence of CVD	Adjusted for age, sex,BMI, smoking, hypertension, dyslipidemia, family history of CVD, HDL-C, LDL-C, and hsCRP level.	8
Lee MY et al. (2017) (35)	longitudinal cohort study	8259(52%)	62.0±11.9	Taiwan, China (6.3±1.3)	patients with T2DM	SD:0.84±0.58, mean follow-up of 6.3 years	7.5±1.2	Incidence of CVD	Adjusted for age, gender, a history of hypertension, retinopathy and neuropathy, SD of HbA1C, mean HbA1C, triglyceride, HDL-cholesterol, eGFR, and medications use, including ACEI and/or ARB, aspirin, statin and/or fibrate, and insulin.	7

(Continued)

10.3389/fendo.2025.1698360

TABLE 1 Continued

Study (Author, year)	Design (Type of study)	Number (male%)	Age at enrolment	Area (follow-up time, years)	Inclusion criteria	HbA1c variability and follow-up time	Mean HbA1c (%)	Outcome	Variable adjustment	NOS score
Cardoso CRL et al. (2018) (36)	prospective cohort study	654(38.1%)	60.1(9.6)	Rio de Janeiro, Brazil(9.3(5.2-10.8))	patients with T2DM	SD:NA, CV:NA, NA	8.1(1.9)	Incidence and mortality of CVD	Adjusted for age, sex number of HbA1c or FG measurements, diabetes duration, BMI, smoking status, physical inactivity, arterial hypertension, number of anti-hypertensive drugs in use, ambulatory 24-h SBP, presence of micro- and macrovascular complications at baseline, serum mean HDL-C and LDL-C, use of insulin, statins and aspirin, mean fasting glycemia and HbA1c.	8
Gu J et al. (2018) (37)	retrospective cohort study	201(NA)	65.2±7.5	China(7.3±0.5)	patients with T2DM	SD:NA, CV:NA, median follow-up of 7.3 years	7.1±0.5	Incidence of CVD	Adjusted for age, gender, SBP, DBP, HbA1c-mean, HbA1c-SD, eGFR, BMI, duration of T2DM and hypertension, atrial fibrillation, medical treatment, LAD, LVMI, E/E′, and LVEF.	7
Kim MK et al. (2018) (17)	prospective cohort study	1302 (41.94%)	55.5±10.9	Korea(6.5±6.6)	patients with T2DM	HGI:−0.01 ± 1.34, median follow-up of 11.1 years	8.4 ± 1.8	Incidence and mortality of CVD	Adjusted for age, sex, duration of diabetes, presence of hypertension, BMI, eGFR, albuminuria, smoking, insulin treatment, and use of sulfonylurea and aspirin.	8
Kaze AD et al. (2020) (38)	prospective cohort study	3560 (37.9%)	58.4(6.7)	U.S.A.(median follow-up period of 6.8 years (IQR 6.0-7.4))	patients with T2DM	SD:NA, ≥36months	7.0(1.0)	Mortality of CVD	Adjusted for age, sex, race/ethnicity, randomization arm, BMI, current smoking, alcohol drinking, use of antihypertensive medications, TC/HDL-C, eGFR, duration of diabetes, average SBP and average HbA1c.	8
Li S et al. (2020)-1 (39)	retrospective cohort study	21352 (54.6%)	63.3±11.1	Scotland(6.8 (4.6-11.2))	patients with T2DM	HVS:NA, NA	7.7±2.0	Incidence of CVD	Adjusted for sex, index age, calendar year, Scottish Index of Multiple Deprivation quintiles, ever smoking, hypertension at baseline, BMI at baseline, HDL-C at baseline, eGFR at baseline, antiplatelet therapy at baseline, and CCI (≥1 vs. 0).	6
Li S et al. (2020)-2 (40)	prospective cohort study	396 (50.50%)	46.30±10.9	China(2.3(1.8-3.1))	patients with T2DM	CV:16.73 ±7.87, NA	6.7±1.4	Incidence of CVD (coronary artery plaque progression)	Adjusted for age, sex, BMI, diabetes duration, smoking, alcohol consumption, hypertension, hypoglycemia rate, triglyceride, LDL-C, HDL-C, FPG, 2h-FBG, HbA1c, eGFR, UA, HOMA-IR, UACR, and medications.	8
Wan EYF et al. (2020) (41)	prospective cohort study	147811 (46.0%)	64.2(10.0)	Hong Kong, China(median follow-up period of 7.4 years)	patients with T2DM without CVD	SD:0.8(0.7), ≥12months	7.5(0.9)	Incidence and mortality of CVD	Adjusted for gender, age, smoking status, duration of diabetes, BMI, SBP and DBP, LDL-C, eGFR, Charlson's comorbidity index, and use of anti-hypertensive drugs, oral antidiabetic drugs, including metformin, sulphonylureas and other oral diabetes drugs, insulin, and lipid-lowering agents.	9

(Continued)

10.3389/fendo.2025.1698360

TABLE 1 Continued

Study (Author, year)	Design (Type of study)	Number (male%)	Age at enrolment	Area (follow-up time, years)	Inclusion criteria	HbA1c variability and follow-up time	Mean HbA1c (%)	Outcome	Variable adjustment	NOS score
Akselrod D et al. (2021) (42)	retrospective cohort study	2866 (43.3%)	58.6	southern region of Israel (NA)	patients with T2DM and having a normal kidney function	SD:1.2, 11 years	7.8	Incidence of IHD	Adjusted for insulin use, gender, age, ischemic heart disease, BMI ≥ 30, smoking.	7
Moosaie F et al. (2021) (43)	cohort study	1500 (54.8%)	62.12(8.66) 61.21(9.18) 62.58(11.06) 58.16(10.06)	Iran(median follow-up period of 10 years)	patients with T2DM	CV:0.165 ±0.012, median follow-up of 10 years	7.834 (0.932) 7.862 (1.102) 7.903 (1.291) 7.817 (1.546)	Incidence of CVD	Adjusted for age, gender, duration of diabetes, lipid lowering drugs, antidiabetic drugs.	7
Sato M et al. (2021) (44)	prospective cohort study	4532 (47.51%)	65.1±9.5 64.5±10.0 63.5±10.0 61.9± 0.9 60.2±11.5	Japan(median follow-up period of 3.17 years)	patients with T2DM	CV:Q1:0.59–3.95, Q2:3.95–5.56, Q3:5.56–7.32, Q4:7.32–10.07, Q5:10.07–45.42, median follow-up of 38 months	7.0±0.8 7.3±0.9 7.5±0.9 7.7±1.1 8.1±1.2	Incidence of CVD	Adjusted for sex, age, smoking habits, duration of diabetes, BMI, group of statin therapy, hypertension, diabetic nephropathy, diabetic neuropathy, eGFR at baseline, the number of HbA1c measurements and mean-HbA1c.	8
Shen Y et al. (2021) (45)	retrospective cohort study	29,260 (45.9%)	66.0±11.6	Louisiana, U.S.A.(mean follow-up period of 4.18 years)	patients with T2DM	CV:NA, SD:NA, NA	6.3±0.7 6.7±0.8 7.5±1.1 8.6±1.5	Incidence of CVD	Adjusted for age, race, sex, smoking, BMI, SBP, non-HDL/HDL ratio, eGFR, insurance type, hypoglycaemic events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications, and antiplatelet and anticoagulant medications by category differences, as well as the updated mean value of HbA1c.	7
Ceriello A et al. (2022) (46)	retrospective cohort study	101,533 (55.63%)	64(52-72) 68.0(61.0–74.0) 66.0(58.0–72.0) 63.0(55.0–71.0) 60.0(52.0–68.0)	Swedish(mean follow-up period of 4.4 years)	patients with T2DM	SD:NA, NA	NA	Mortality of CVD	Adjusted for age, gender, duration of diabetes, body weight, smoking, values of HbA1c, SBP/DBP, TC, HDL, LDL, triglycerides, albuminuria, eGFR, retinopathy, treatment for diabetes, hypertension, dyslipidemia, and aspirin.	8
Ma C et al. (2022) (47)	prospective cohort study	2161 (38.45%)	NA	China(NA)	patients with T2DM	SD:NA, CV:NA, NA	NA	Cardiovascular events	Adjusted for gender, age, duration of type 2 diabetes, BMI, smoking, baseline concomitant disease, triglycerides, LDL-C, blood pressure, anti-hyperglycemic therapy, and ACEI or ARB treatment, average HbA1c.	7

(Continued)

10.3389/fendo.2025.1698360

TABLE 1 Continued

Study (Author, year)	Design (Type of study)	Number (male%)	Age at enrolment	Area (follow-up time, years)	Inclusion criteria	HbA1c variability and follow-up time	Mean HbA1c (%)	Outcome	Variable adjustment	NOS score
Wu TE et al. (2022) (48)	prospective cohort study	1869 (50.4%)	63.2±12.7	Taiwan, China (median follow-up period of 9.5 years)	patients with T2DM	SD:0.728 ±0.528%, 5 years(10-42)	8.0±1.77	Mortality due to CVD	Adjusted for HbA1c-mean or HbA1c-SD, age, sex, diabetes duration, blood pressure, BMI, TC, HDL-C, triglyceride, and smoking status.	7
Hsu JC et al. (2023) (8)	retrospective cohort study	45,436 (48.36%)	>50	Taiwan, China (median follow-up period of 5.38 years)	patients with T2DM	HVS:NA, NA	6.34 (0.74) 6.87 (0.99) 7.48 (1.38) 8.05 (1.78)	Mortality of CVD	Adjusted for age, sex, baseline BMI, hypertension, coronary artery disease, average of fasting glucose, average HbA1c, baseline eGFR, model 2 plus medications (metformin, SGLT2i, DDP4i , GLP-1 agonist).	7
Kim H et al. (2023) (15)	retrospective cohrot study	4817 (51.5%)	59.9±9.8	Korea(9)	patients with T2DM	HVS:31.2 ± 22.8, NA	7.2±1.4	Incidence of CVD	Adjusted by age, sex, BMI.	7
Manosroi W et al. (2023) (49)	prospective cohort study	3057 (45.67%)	64.7±9.2	Thailand (median follow-up period of 4.51 years)	patients with prediabetes and T2DM	SD:NA, NA	7.3±1.5	Incidence of CVD (MACE)	Adjusted for age, educational level, sex, BMI, established atherosclerotic cardiovascular disease status, SBP, smoking status, mean glycated hemoglobin, lipid profiles, creatinine level number of glycated hemoglobin measurements,plus antihypertensive medications, diabetes medications, lipid-lowering agents, and antiplatelet and/or anti-coagulant.	8
Zhang F et al. (2023) (50)	retrospective cohort study	820(51.7%)	56.9±14.6	China(median follow-up period of 3.67 (1-16.5) [IQR: 2.25,5.83] years)	peritoneal dialysis patients with T2DM and over 18 years old	HVS:NA, NA	7.0±2.3	Incidence of MACE	Adjusted for time-weighted average HbA1c, age, sex, cardiovascular disease history, BMI, hemoglobin, albumin and C-reactive protein.	8
Cardoso CRL et al. (2024) (16)	prospective cohort study	687(38.4%)	60.1±9.5	Rio de Janeiro, Brazil(10.6 (6.3,13.2))	patients with T2DM	HGI:0±1.6, NA	8.0±1.9	Incidence of CVD	Adjusted for age sex, BMI, physical activity, smoking status, diabetes duration, pre-existent macrovascular and microvascular complications, SBP, serum LDL-C, use of insulin, aspirin and statins, number of antihypertensive drugs in use, HGI and HbA1c parameters.	7
Lin CC et al,(2024) (51)	retrospective cohort study	3628 (53.25%)	66.23±10.94	China(≥0.25 years)	patients with T2DM	CV:8.89 ± 7.85, NA	7.70 ±1.56	Mortality of CVD	Adjusted for baseline sociodemographic factors, lifestyle behavior, diabetes-related variables, HbA1c, complications, medication, and glycemic variation.	6

(Continued)

10.3389/fendo.2025.1698360

TABLE 1 Continued

Study (Author, year)	Design (Type of study)	Number (male%)	Age at enrolment	Area (follow-up time, years)	Inclusion criteria	HbA1c variability and follow-up time	Mean HbA1c (%)	Outcome	Variable adjustment	NOS score
Liu X et al. (2024) (19)	retrospective cohort study	147 (58.86%)	62.07±8.86 63.80±9.95 66.49±12.22	China(NA)	patients with T2DM	SD:NA, CV:NA, NA	NA	Incidence of CVD	Adjusted for sex, age, duration, SBP, DBP, LDL, use of insulin using and HbA1c.	6
Maajani K et al. (2025) (52)	retrospective cohort study	2078 (44.8%)	64.7(10.6)	Iran(median follow-up period of 2.67 years)	patients with T2DM	SD:0.23±0.06, CV:3.5±0.9, NA	6.8±0.82	Incidence of CVD	Adjusted for BMI, SBP and DBP, HbA1c, FBS and TC, HDL-C, LDL-C and Triglyceride, SGL-2, other oral medications, GLP-1, insulin, antihypertensive drugs, lipid-lowering drugs, anti-platelet drugs, age, sex, duration of disease, the baseline and lagged value of time-varying covariates.	7
Teh XR et al. (2025) (53)	retrospective cohort study	40,662 (38.3%)	57.2(13.9)	Thailand(10)	patients with T2DM	SD:0.67(0.87), CV:0.07(0.08), 3–6 months	7.7(2.0)	Incidence of CVD	Adjusted for age, gender, insurance scheme, BMI, TC, LDL, HDL, triglyceride, haemoglobin, SBP/DBP, hypertension, dyslipidemia, presence of T2D complications (CVD, DR, or CKD) prior to the outcome of interest, medication use in terms of drug classes (biguanides, sulphonylurea, insulin, alpha- glucosidase inhibitors, DPP-4i, GLP1-RA, TZD, SGLT2i, meglitinides, statins) and the number of antihypertensive drugs.	8

Studies are presented in chronological order of publication.

HbA1c, glycated hemoglobin A1C; T2DM, Type 2 Diabetes Mellitus; NOS, Newcastle-Ottawa Scale; CVD, cardiovascular disease; BMI, mean body mass index; SD, standard deviation; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not available; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; TC, total cholesterol; CACS, Coronary Artery Calcium Score; HGI, hemoglobin glycation index; hsCRP, high-sensitivity C-reactive protein; FG, fasting glucose; LAD, left atrium diameter; LVMI, left ventricular mass index; E/E', E wave to e' wave ratio; LVEF, left ventricular ejection fraction, HVS, HbA1c variability score; CCI, Charlson Comorbidity Index; FPG, fasting plasma glucose; 2h-FBG, 2-hour fasting blood glucose; UA, uric acid; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; UACR, urine albumin-to-creatinine ratio; IHD, ischemic heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2i, sodium-glucose cotrans-porter-2 inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-Like Peptide-1 agonist; MACE, major adverse cardiovascular events; DR, diabetic retinopathy; CKD, chronic kidney disease; GLP1-RA, glucagon-like peptide-1 agonists; TZD, thiazolidinedione.

10.3389/fendo.2025.1698360

29, 30, 35, 37, 42, 43, 45, 47, 48, 52), 13 scored 8 points (17, 31, 33, 34, 36, 38, 40, 44, 46, 49, 50, 53, 54), and 2 scored 9 points (32, 41); all were articles with low to moderate risk of bias. The detailed NOS scores of the included articles are shown in Table 1.

3.2 HbA1c variability and incidence of CVD outcomes

3.2.1 HbA1c-SD and the incidence of cardiovascular disease

When the effect size was HR, 13 studies (29, 30, 33, 35–37, 41, 45, 47, 49, 52–54) with a total of 26 sub-studies explored the relationship between HbA1c-SD and the incidence of cardiovascular disease. There was heterogeneity among the studies (I^2=90%, P<0.00001), so a random-effects model was used for analysis. The meta-analysis results showed that compared with type 2 diabetes patients with lower HbA1c-SD, the incidence of cardiovascular disease in type 2 diabetes patients with higher HbA1c-SD increased by 27% (HR = 1.27, 95%CI 1.17-1.38, P<0.00001). When the effect size was OR, 3 studies (19, 32, 42) with a total of 4 sub-studies explored the relationship between HbA1c-SD and the incidence of cardiovascular disease. There was no heterogeneity among the studies (I^2=27%, P = 0.25), so a fixed-effects model was used for analysis. The meta-analysis results showed that higher HbA1c-CV was a risk factor for cardiovascular disease in type 2 diabetes patients (HR = 1.30, 95% CI 1.07-1.57, P = 0.008), as shown in Figure 2.

3.2.2 HbA1c-CV and the incidence of cardiovascular disease

When the effect size was HR, 8 studies (29, 36, 37, 43, 45, 47, 53, 54) with a total of 19 sub-studies explored the relationship between HbA1c-CV and the incidence of cardiovascular disease. There was heterogeneity among the studies (I^2=93%, P<0.00001), so a random-effects model was used for analysis. The meta-analysis

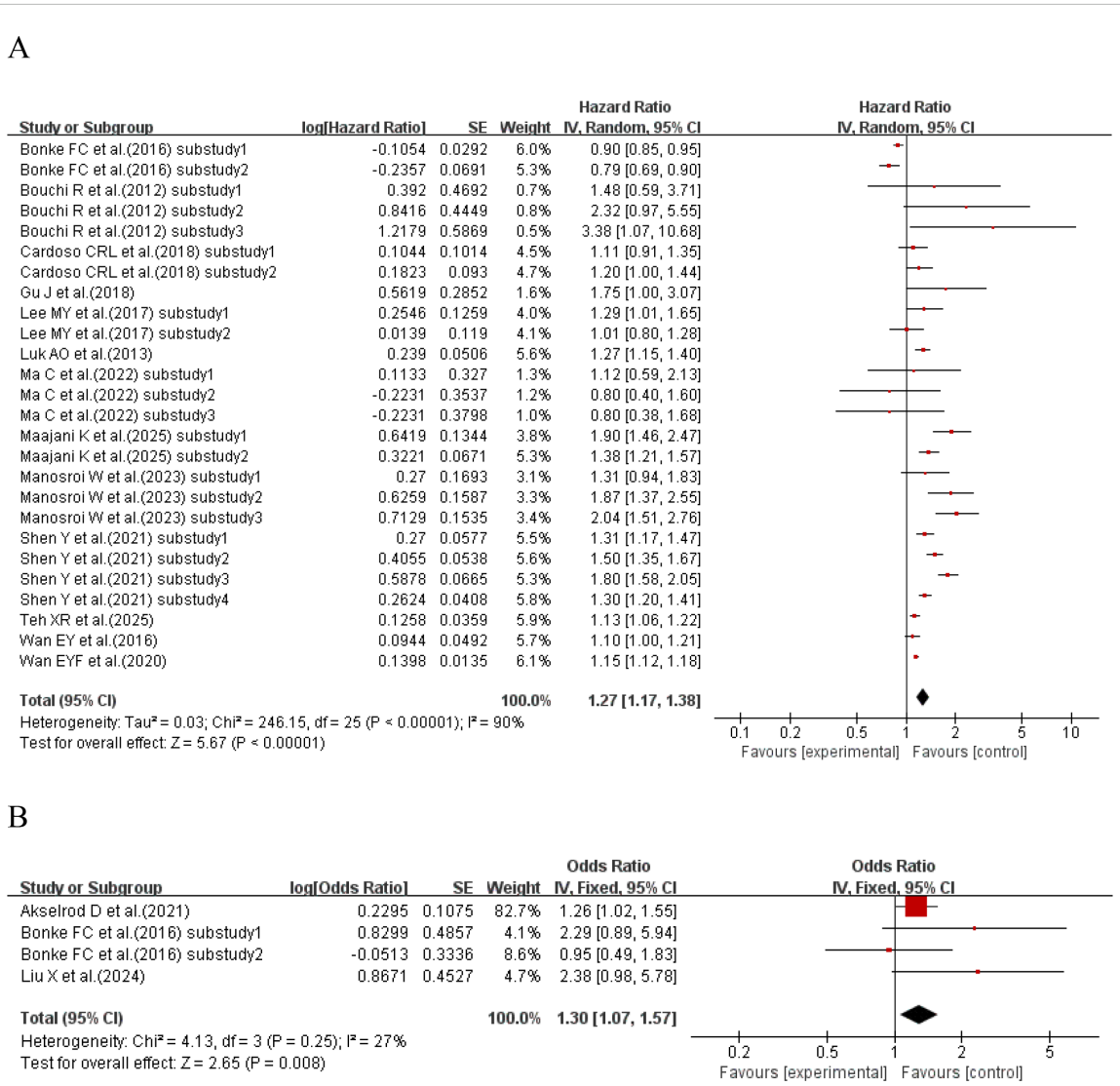


FIGURE 2
Forest plot showing the association between HbA1c variability (HbA1c-SD) and cardiovascular disease incidence in patients with T2DM, including **(A)** Hazard Ratio (HR) and **(B)** Odds Ratio (OR).

results showed that compared with type 2 diabetes patients with lower HbA1c-CV, the incidence of cardiovascular disease in type 2 diabetes patients with higher HbA1c-CV increased by 32% (HR = 1.32, 95%CI 1.18-1.49, P<0.00001). When the effect size was OR, 4 studies (19, 32, 40, 44) with a total of 8 sub-studies explored the relationship between HbA1c-CV and the incidence of cardiovascular disease. There was no heterogeneity among the studies (I^2=0%, P = 0.46), so a fixed-effects model was used for analysis. The meta-analysis results showed that higher HbA1c-CV was a risk factor for cardiovascular disease in type 2 diabetes patients (OR = 1.39, 95%CI 1.22-1.57, P<0.00001), as shown in Figure 3.

3.2.3 HbA1c-HGI and the incidence of cardiovascular disease

When the effect size was HR, one study (16) explored the relationship between HbA1c-HGI and the incidence of cardiovascular disease. The results showed that compared with type 2 diabetes patients with lower HbA1c-HGI, the incidence of cardiovascular disease in type 2 diabetes patients with higher HbA1c-HGI increased by 36% (HR = 1.36, 95%CI 1.14-1.62, P = 0.0006). When the effect size was OR, 2 studies (17, 34) with a total of 5 sub-studies explored the relationship between HbA1c-HGI and the incidence of cardiovascular disease. There was heterogeneity among the studies (I^2=69%, P = 0.01), so a random-effects model was used for analysis. The results showed a positive trend that higher HbA1c-HGI might increase the risk of cardiovascular disease (P = 0.06 > 0.05), with no statistically significant difference, as shown in Figure 4.

3.2.4 HbA1c-HVS and the incidence of cardiovascular disease

Three studies (15, 39, 50) with a total of 6 sub-studies used HR as the effect size to explore the relationship between HbA1c-HVS and the incidence of cardiovascular disease. There was heterogeneity among the studies (I^2=84%, P<0.00001), so a random-effects model was used for analysis. The results showed a positive trend that higher HbA1c-HVS might increase the risk of cardiovascular disease (P = 0.08 > 0.05), but there was no statistically significant difference. Details are shown in Figure 5.

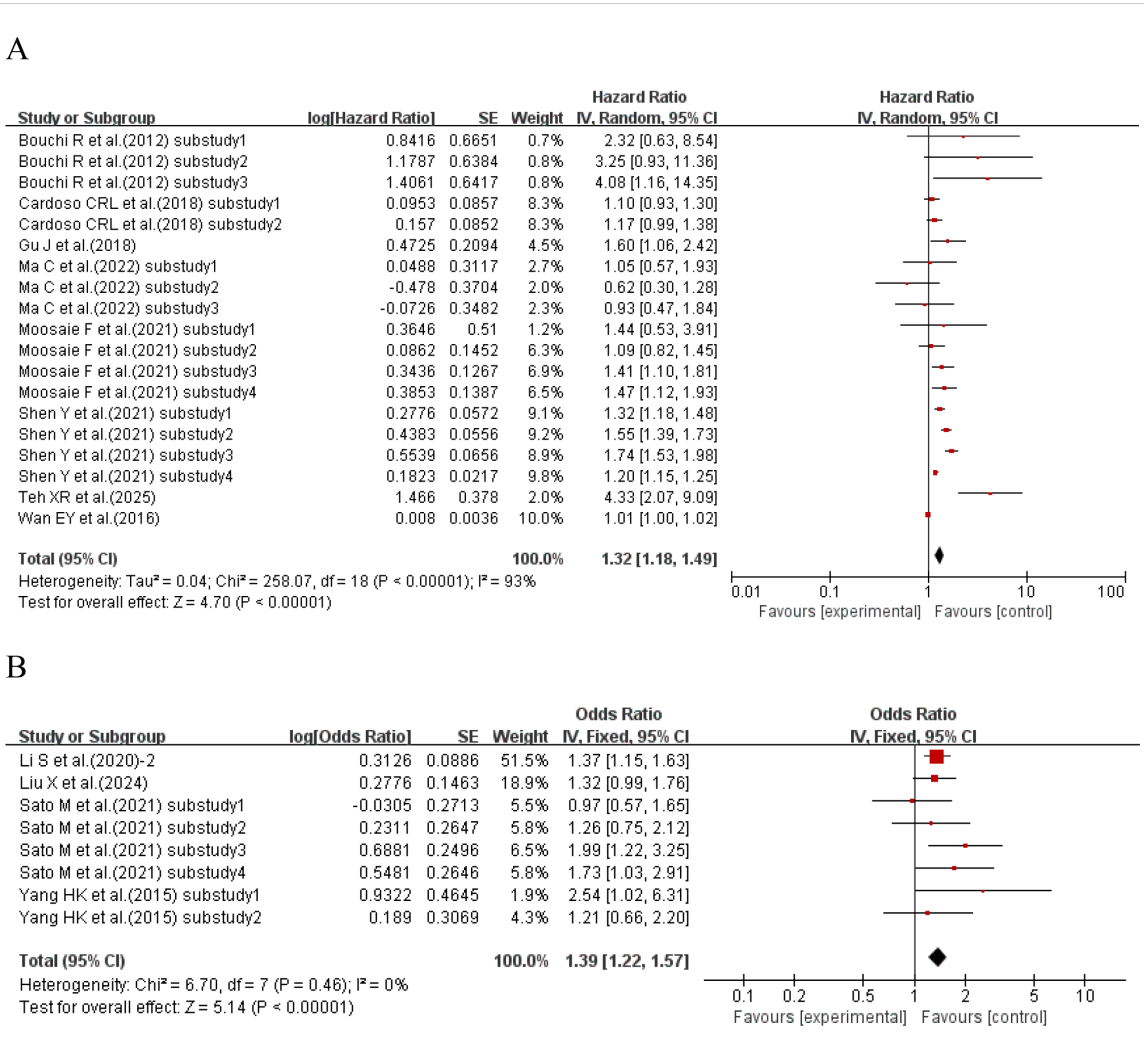


FIGURE 3
Forest plot showing the association between HbA1c variability (HbA1c-CV) and cardiovascular disease incidence in patients with T2DM, including **(A)** Hazard Ratio (HR) and **(B)** Odds Ratio (OR).

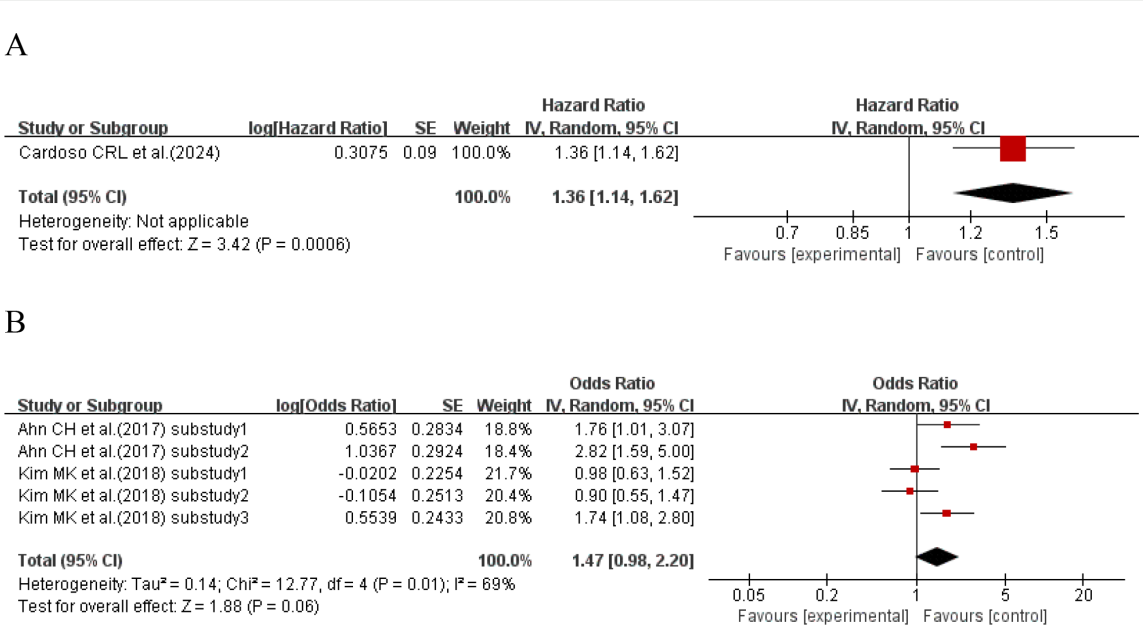


FIGURE 4
Forest plot showing the association between HbA1c variability (HbA1c-HGI) and cardiovascular disease incidence in patients with T2DM, including **(A)** Hazard Ratio (HR) and **(B)** Odds Ratio (OR).

3.3 HbA1c variability and mortality of CVD outcomes

3.3.1 HbA1c-SD and cardiovascular disease mortality

Seven studies (31, 36, 38, 41, 46, 48, 54) with a total of 14 sub-studies explored the relationship between HbA1c-SD and cardiovascular disease mortality. There was heterogeneity among the studies (I^2=78%, P<0.00001), so a random-effects model was used for analysis. The meta-analysis results showed that compared with type 2 diabetes patients with lower HbA1c-SD, the cardiovascular disease mortality of type 2 diabetes patients with higher HbA1c-SD increased by 27% (HR = 1.27, 95%CI 1.17-1.37, P<0.00001), as shown in Figure 6A.

3.3.2 HbA1c-CV and cardiovascular disease mortality

Four studies (31, 36, 51, 54) with a total of 9 sub-studies explored the relationship between HbA1c-CV and cardiovascular disease mortality. There was heterogeneity among the studies (I^2=90%, P<0.00001), so a random-effects model was used for analysis. The meta-analysis results showed that compared with type 2 diabetes patients with lower HbA1c-CV, the cardiovascular disease mortality of type 2 diabetes patients with higher HbA1c-CV increased by 35% (HR = 1.35, 95%CI 1.16-1.57, P<0.00001), as shown in Figure 6B.

3.3.3 HbA1c-HVS and cardiovascular disease mortality

One study (8) with a total of 3 sub-studies explored the relationship between HbA1c-HVS and cardiovascular disease mortality. There was heterogeneity among the studies (I^2=94%, P<0.00001), so a random-effects model was used for analysis. The meta-analysis results showed that HbA1c-HVS had no effect on cardiovascular disease mortality in patients with type 2 diabetes (HR = 1.00, 95%CI 0.76-1.31, P<0.00001), as shown in Figure 6C.

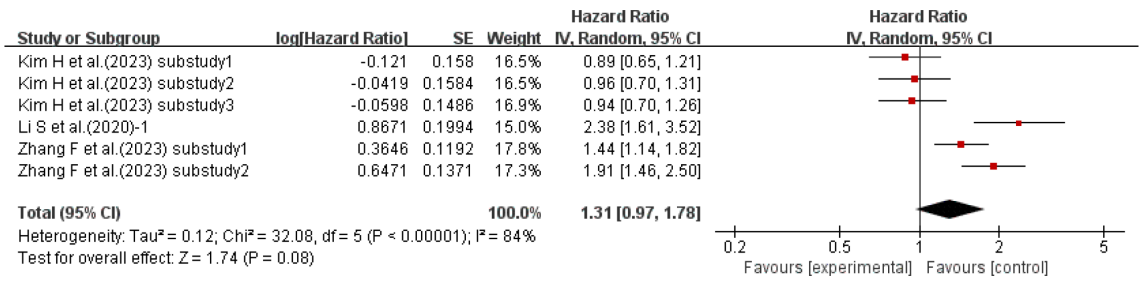


FIGURE 5
Forest plot of cardiovascular incidence data: HRs for HbA1c-HVS based on published reports of T2DM.

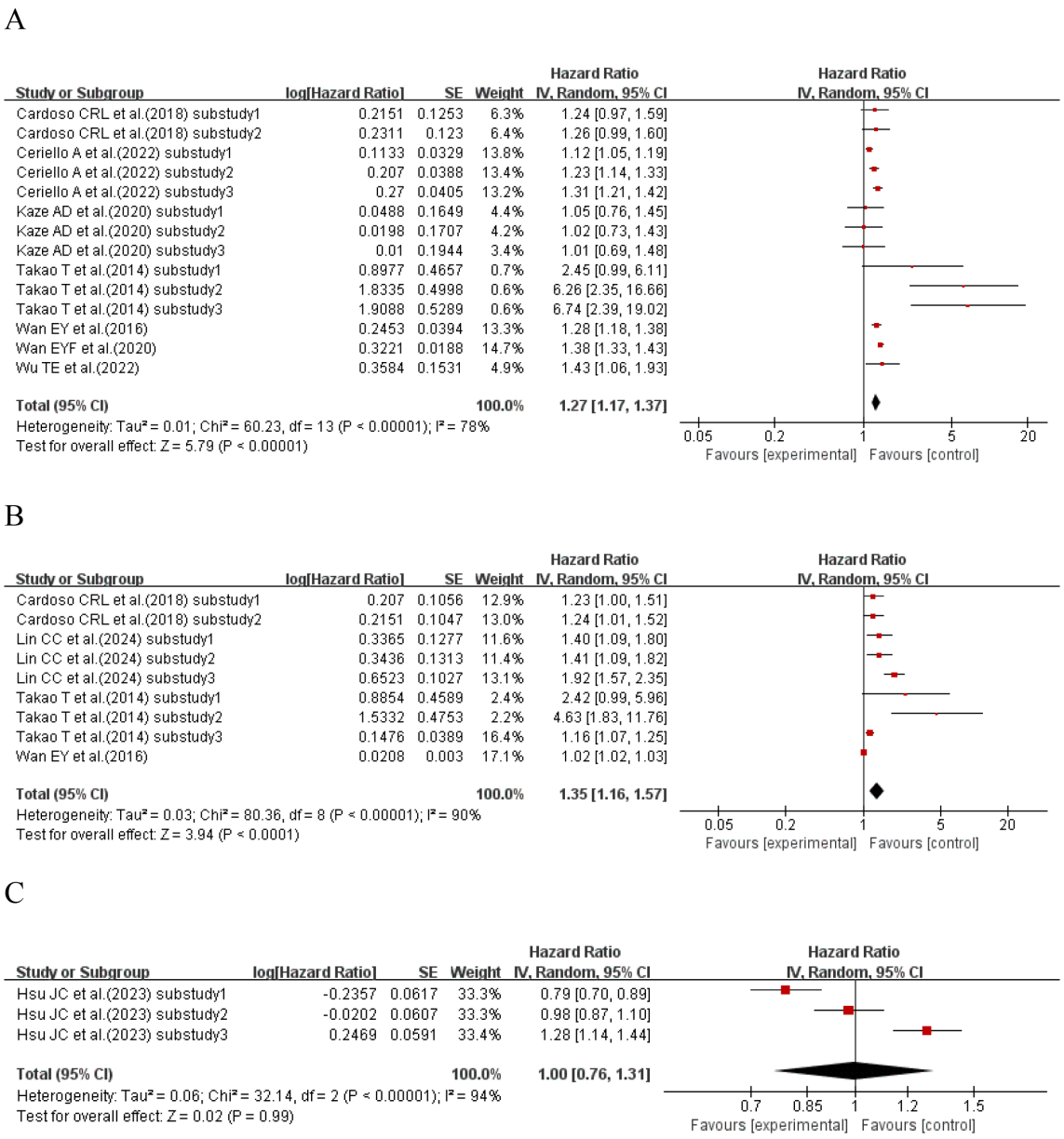


FIGURE 6
Forest plot of cardiovascular mortality in patients with type 2 diabetes mellitus from published reports, presenting Hazard Ratios (HRs) for **(A)** HbA1c-SD, **(B)** HbA1c-CV, and **(C)** HbA1c-HVS.

3.4 Subgroup analyses

Subgroup analyses consistently showed a positive association between HbA1c variability and CVD risk, but the robustness of the indices differed. As presented in Appendix Table S1, the pooled effects for SD-HR and CV-HR were highly consistent (1.27 and 1.32, respectively) and remained directionally stable across all subgroups. In contrast, HVS-HR (1.31, 95% CI 0.97–1.78) and HGI-OR (1.47, 95% CI 0.98–2.20) did not reach conventional statistical significance; nevertheless, their effect directions were consistent, suggesting a potential association rather than a "true null". Notably, in studies with < 1000 participants the ORs for both HVS and HGI were statistically significant, implying that insufficient statistical power may be the main reason for the lack of significance in the overall analysis. When stratified by sample size, the SD-HR was 1.16 (95%CI: 1.13-1.18) in studies with a sample size of ≥1000, compared with 1.31 (95%CI: 1.07-1.61) in studies with a sample size of <1000. Subgroup analysis by region revealed that the association was strongest in non-Chinese Asian regions (SD-HR=1.77, 95%CI: 1.49-2.10), followed by 1.15 (95%CI: 1.13-1.18) in China and 1.13 (95%CI: 1.09-1.17) in other countries. In terms of study design, the SD-HR was 1.38 (95%CI: 1.16-1.64) for prospective studies and 1.23 (95%CI: 1.11-1.35) for retrospective studies. Studies with a follow-up duration of ≥5 years showed a higher hazard ratio (SD-HR=1.10, 95%CI: 1.08-1.13). Additionally, subgroup analysis by glycemic variability quartiles indicated that

the risk of CVD in the highest quartile (Q4) was significantly higher compared with the lowest quartile (Q1) (SD-HR=1.52, 95%CI: 1.03-2.25). In summary, the associations for SD and CV are the most robust, whereas the "non-significance" observed for HVS and HGI is more likely attributable to insufficient statistical power rather than to a genuine biological null effect.

Subgroup analyses stratified by region (China vs. Other Asian vs. Other countries), study design (prospective vs. retrospective) and sample size (<1000 vs. ≥1000) reduced I^2 from the overall 90%–93% to 26%, 0% and 36%–52%, respectively, indicating that geographic setting and design features are the main sources of heterogeneity. Similarly, for HVS and HGI, restricting to follow-up<5 years or to small-sample studies lowered I^2 to 0%–25%, showing that time span and statistical power are also key moderators. For example, the pooled CV-HR had I^2 = 93%, yet every subgroup showed a consistent direction (HR > 1), and the pooled HR fluctuated only between 1.29 and 1.35 after sequential exclusion, implying that heterogeneity reflects magnitude rather than direction. Full details are given in Appendix A Table S1–S2.

3.5 Sensitivity analysis

The results of the sensitivity analysis showed that the association between glycemic variability (SD, CV) and cardiovascular disease risk was generally robust. After excluding specific studies or changing the statistical model, there was no substantial change in the direction or significance of the pooled effect size. After excluding studies with short follow-up durations, the effect sizes of SD-HR and CV-HR changed slightly; however, their 95% confidence intervals (CIs) did not include 1, still maintaining statistical significance, and the heterogeneity remained at a high level. When re-analyzed using a fixed-effects model, the pooled results of SD-HR and CV-HR were basically consistent with those of the random-effects model, which further confirmed the stability of the results.

Sensitivity analysis for different outcome indicators showed that after excluding studies reporting only specific endpoints such as heart failure with preserved ejection fraction (HFpEF) or ischemic heart disease (IHD), there was no significant deviation in the effect size. Similar patterns were observed in the analysis of HVS-HR and HGI-OR: excluding low-quality studies or studies of specific types did not alter the original conclusions. In summary, the sensitivity analysis supports the reliability of the conclusion regarding the association between glycemic variability and CVD risk. Details are shown in Appendix A Table S3-S4.

3.6 Publication bias

In this study, funnel plot analysis and Egger's test were used to assess the presence of publication bias, and the trim-and-fill method was applied to correct for publication bias. The analysis showed that there was publication bias in the CV-HR for CVD incidence (Egger's test, p=0.002). After imputing 2 potentially missing studies, the effect size decreased slightly from 0.280 to 0.246 (95% CI: 0.112-0.380). Although the effect was slightly weakened, it remained statistically significant. The p-value remained significant, and heterogeneity was not reported. These results indicate the presence of mild publication bias, which did not alter the statistical significance of the original conclusion. No significant publication bias was detected for other indicators. Details are shown in Appendix A Table S5-S6.

4 Discussion

Based on a systematic review and meta-analysis of 31 prospective/retrospective cohorts comprising >540000 patients with type 2 diabetes, we found that HbA1c variability (SD and CV) is independently associated with incident cardiovascular events and mortality, with pooled hazard ratios consistently between 1.27 and 1.35. In contrast, HVS and HGI showed the same directional trend but did not reach statistical significance, indicating that SD and CV are more robust predictors. SD/CV can be calculated easily without extra laboratory costs and can be integrated instantly into existing electronic medical-record systems to help identify "hidden high-risk" patients, whereas HVS/HGI require standardized algorithms and validation in larger samples before they can be considered as novel clinical predictors. Unlike most previous studies that primarily focused on mean HbA1c, this study provides the first population-level evidence that HbA1c fluctuations per se significantly increase cardiovascular risk even when average glycemic control has reached the target level, offering a new precision-glycaemia management target beyond conventional mean HbA1c.

Assessment of glucose homeostasis based solely on fasting blood glucose cannot capture post-prandial hyperglycemia, and short-term monitoring such as random blood glucose is insufficient to evaluate the progression risk of diabetic chronic complications. HbA1c, on the other hand, reflects overall exposure to both fasting and post-prandial glucose and therefore provides a more comprehensive picture of total glycemic control. Consequently, we selected HbA1c variability as the primary focus of this investigation.

Although methods for quantifying HbA1c variability are increasingly diverse, there is currently no unified "gold standard". The most commonly used and simplest methods are calculating the SD and its derived CV. Numerous studies have reported a significant association between SD/CV and the deterioration of cardiovascular outcomes in patients with T2DM. A meta-analysis including 23 studies found that HbA1c variability, as assessed by SD or CV, was significantly associated with the risk of macrovascular complications (13). Another meta-analysis, which included 40 studies and 4,102,589 participants, showed that each increase in a variability indicator (HbA1c SD or CV) was associated with a 20%-26% increase in cardiovascular risk (55). Similar conclusions have also been drawn from multiple large-scale multicenter observational studies both domestically and internationally (52, 56). Consistent with previous studies, the present study also found that both SD and

CV were positively correlated with the progression of cardiovascular disease.

HVS and HGI have also emerged as novel indicators, providing deeper insights into glucose metabolism. HVS is a specific indicator used to quantify long-term blood glucose fluctuations. Unlike the simple calculation of SD or CV, the calculation method of HVS is designed to reduce the impact of the number of measurements and measurement time intervals on results, and focuses more on evaluating fluctuations in HbA1c values that exceed specific thresholds. Hsu H et al. conducted a longitudinal cohort study, which retrospectively reviewed the incidence of MACE in patients with T2DM. The study concluded that early management of HbA1c using HVS is crucial for reducing the risk of adverse cardiovascular events in patients. HGI serves as an important individualized risk marker (57). Different from indicators such as SD, CV, and HVS that directly measure the magnitude of blood glucose fluctuations, HGI predicts the risk of diabetic cardiovascular complications from the perspective of an individual's glycation susceptibility to blood glucose. Previous studies have shown that HGI is closely associated with various cardiovascular events. A large-scale multicenter cohort study, which included 9,791 participants, found that there was a U-shaped association between HGI values and 5-year MACE risk—both low and high HGI values were associated with an increased risk of MACE (58). Even when the average blood glucose level was similar, patients with high HGI still had a significantly increased risk of complications.

This is the first study to integrate three observational cohorts evaluating HVS and four cohorts addressing HGI. It was found that there was no significant association between increased HVS and the progression of cardiovascular events. Although multiple previous studies have suggested that glycemic variability is a potential predictor of cardiovascular risk in patients with T2DM, this study did not confirm this association. The possible reasons for this include the following aspects: First, in the included observational studies, confounding factors such as smoking status, hypoxic environment, and inflammatory levels were fully adjusted for. To a certain extent, this may have weakened the apparent association between HVS and cardiovascular outcomes (59). Second, there may be a U-shaped curvilinear relationship between HVS and cardiovascular risk—meaning the risk increases significantly only at extreme levels of variability, while a general increase does not independently elevate the risk of events (60). Furthermore, although HVS, as an indicator for measuring glycemic variability, has advantages such as being unaffected by the number of measurements and time intervals, and having strong clinical interpretability (it can reflect the frequency characteristics of HbA1c variability), its neglect of the magnitude of variability may limit its ability to predict long-term cardiovascular risk. Meanwhile, at the genetic level, Mendelian randomization analyses based on the HGI strategy also found no significant association between hemoglobin-related genetic variations and cardiovascular risk (61). This result further supports the aforementioned conclusion. The possible reasons for this include insufficient power of instrumental variables, failure of hemoglobin changes driven by genetic variations to capture specific biological processes related to disease pathways, or the presence of pleiotropic effects that interfere with causal inference. Overall, the null findings for HVS and HGI are more plausibly attributed to technical factors (few studies, heterogeneous definitions, population-specific effect patterns) than to a true absence of association. Future individual-patient-data meta-analyses with harmonized algorithms are warranted.

Meanwhile, this study estimated the OR of HbA1c variability using datasets, and a significant overall effect was observed. When evaluating HbA1c-related risks, there were obvious differences between the results presented by the OR and the HR. OR is used to measure the strength of the association between an intervention and an outcome. Although it can comprehensively reflect the overall effect, it often tends to overestimate the actual risk; in addition, this indicator has static characteristics and is difficult to capture information on the dynamic changes in event incidence over time (62). In contrast, HR focuses on the temporal differences in event occurrence and can more intuitively reflect the impact of an intervention on the timing of specific events. HR is usually estimated using the Cox proportional hazards model, which is suitable for analyzing the effect of covariates on the "time to first event," thereby describing the dynamic process of risk changes over time and can be regarded as a measure of instantaneous risk intensity (63). It is particularly important to note that compared with HR, OR often shows an overestimation of risk, and a similar phenomenon was observed in this study—this was particularly evident in the correlation analysis between HbA1c SD/CV and cardiovascular outcomes in patients with T2DM.

Currently, there is no consensus on the optimal follow-up duration for HbA1c monitoring. This study innovatively explored the impact of different follow-up durations on cardiovascular incidence and mortality. Subgroup analysis in this study used a median follow-up period of 5 years as the cutoff, suggesting that 5 years may be a more effective follow-up indicator. In addition, SD, HGI, and HVS showed an upward trend in risk from the lowest quartile to the highest quartile, while CV did not exhibit a similar trend.

The key point is that each index captures a distinct glycemic signature: SD/CV reflects the amplitude of oscillations, HVS captures the frequency of clinically relevant jumps, while HGI quantifies individual glycation susceptibility. This meta-analysis shows that amplitude (SD/CV) carries the strongest and most consistent signal for CVD, an observation that aligns with *in-vitro* data demonstrating that larger glucose excursions generate more superoxide than chronic hyperglycemia of the same mean (64). For HVS, although the pooled estimate did not reach statistical significance, the upper confidence limit still extended to a 78% excess risk. Mechanistic studies indicate that every >0.5% HbA1c swing activates the NLRP3 inflammasome and leaves a persistent epigenetic footprint (H3K9me3)—the so-called "metabolic memory" (65). On the other hand, HGI may link to cardiovascular injury independently of ambient glucose: a high HGI signifies rapid hemoglobin glycation, paralleling band-3 protein glycation on the red-cell membrane, which reduces erythrocyte deformability and predisposes to micro-vascular sludging (66). Thus, HGI operates via a "blood-rheology" axis rather than the classic glucose-toxicity axis,

explaining why its association with CVD remains positive yet weaker than that of SD/CV.

This study is the first meta-analysis to explore the association between multiple HbA1c variability indicators (SD, CV, HVS, HGI) and cardiovascular disease-related risk from multiple perspectives. A total of 31 cohort studies were included, with Newcastle-Ottawa Scale (NOS) quality scores ranging from 6 to 9. This indicates that the included studies have an overall high methodological quality, which enhances the credibility of the results. The results of extensive subgroup analyses and sensitivity analyses are consistent, further supporting the robustness of the main conclusions.

However, this study still has several limitations. First, there are differences in the detection frequency, time intervals, measurement equipment, and methods of HbA1c among the original studies, which may introduce heterogeneity. Second, some potential confounding factors have not been fully adjusted for, which may interfere with the estimation of effect sizes. Furthermore, this study aims to synthesize evidence from observational studies to address questions concerning HbA1c variability in real-world settings. The controlled environment of an RCT, including fixed follow-up schedules and strict intervention protocols, inherently influences the pattern of HbA1c variability, making it less generalizable to the fluctuations that occur in routine clinical practice. Therefore, while RCTs are superior for establishing causality, their applicability to our research objective is limited and *post-hoc* analyses of RCTs were excluded. Finally, this study focused on cardiovascular outcomes and did not involve other typical diabetic microvascular and macrovascular complications such as retinopathy, neuropathy, and kidney disease; therefore, caution should be exercised when extrapolating the conclusions.

In conclusion, this study indicates that HbA1c variability is positively correlated with the progression of incidence and mortality of cardiovascular disease-related events in patients with T2DM. Individualized treatment based on HbA1c variability may be a key component of precision medicine for T2DM.

5 Conclusion

This study confirmed through meta-analysis that there is a significant positive correlation between HbA1c variability and cardiovascular complications as well as all-cause mortality in patients with T2DM. This result suggests that HbA1c variability should be regarded as an important and independent predictive risk factor for T2DM patients. In particular, CV, SD, and HGI can serve as significant indicators for predicting the risk of CVD occurrence and mortality, and thus deserve greater attention in clinical practice and risk stratification.

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.

Author contributions

CW: Validation, Investigation, Supervision, Project administration, Methodology, Conceptualization, Funding acquisition, Software, Visualization, Formal analysis, Resources, Writing – review & editing, Data curation, Writing – original draft. AL: Data curation, Software, Project administration, Investigation, Conceptualization, Resources, Methodology, Visualization, Writing – original draft, Validation, Funding acquisition, Writing – review & editing, Supervision, Formal analysis. QZ: Writing – original draft, Visualization, Software, Resources, Investigation, Data curation, Formal analysis, Conceptualization, Project administration, Funding acquisition, Methodology, Writing – review & editing, Validation, Supervision. JG: Writing – review & editing, Project administration, Writing – original draft, Data curation. YL: Conceptualization, Validation, Writing – original draft, Writing – review & editing. XG: Writing – review & editing, Writing – original draft, Data curation. AS: Writing – review & editing, Methodology, Writing – original draft, Supervision. MW: Data curation, Methodology, Visualization, Conceptualization, Investigation, Supervision, Validation, Project administration, Resources, Funding acquisition, Writing – review & editing, Software, Formal analysis, Writing – original draft. YG: Formal analysis, Software, Writing – original draft, Data curation, Resources, Methodology, Visualization, Project administration, Conceptualization, Validation, Investigation, Supervision, Writing – review & editing, Funding acquisition.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. The authors acknowledge support from the National Administration of Traditional Chinese Medicine Young Qi Huang Scholars support project (National Traditional Chinese Medicine Human Education Development (2020) No.7), the Fundamental Research Funds for the Central Universities (2023-JYB-JBZD-010), Postdoctoral Fellowship Program of China Postdoctoral Science Foundation (GZC20230324), China Postdoctoral Science Foundation (2024M750263) and Leading Talent Training Program Project of Dongzhimen Hospital of Beijing University of Chinese Medicine (No. DZMG-LJRC0004).

Acknowledgments

The authors gratefully acknowledge Beijing University of Traditional Chinese Medicine and Dongzhimen Hospital for their generous support of this study, and especially thank the reviewers for allowing the authors to improve the manuscript.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1698360/full#supplementary-material

References

1. Ogle GD, Wang F, Haynes A, Gregory GA, King TW, Deng K, et al. Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: Results from the International diabetes Federation Atlas, 11th Edition, and the T1D Index Version 3.0. *Diabetes Res Clin Pract*. (2025) 225:112277. doi: 10.1016/j.diabres.2025.112277

2. Chatterjee S, Riewpaiboon A, Piyauthakit P, Riewpaiboon W, Boupaijit K, Panpuwong N, et al. Cost of diabetes and its complications in Thailand: a complete picture of economic burden. *Health Soc Care Community*. (2011) 19:289–98. doi: 10.1111/j.1365-2524.2010.00981.x

3. Sacco RL, Roth GA, Reddy KS, Arnett DK, Bonita R, Gaziano TA, et al. The heart of 25 by 25: achieving the goal of reducing global and regional premature deaths from cardiovascular diseases and stroke. *Circulation*. (2016) 133. doi: 10.1161/cir.0000000000000395

4. Stratton IM. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ (Clinical Res ed)*. (2000) 321:405–12. doi: 10.1136/bmj.321.7258.405

5. Kohnert K-D, Augstein P, Heinke P, Zander E, Peterson K, Freyse E-J, et al. Chronic hyperglycemia but not glucose variability determines HbA1c levels in well-controlled patients with type 2 diabetes. *Diabetes Res Clin Pract*. (2007) 77:420–6. doi: 10.1016/j.diabres.2007.01.021

6. Gorst C, Kwok CS, Aslam S, Buchan I, Kontopantelis E, Myint PK, et al. Long-term glycemic variability and risk of adverse outcomes: A systematic review and meta-analysis. *Diabetes Care*. (2015) 38:2354–69. doi: 10.2337/dc15-1188

7. Guo R, Pandey A, Chandramouli C, Wu MZ, Cai AP, Liu YX, et al. The effect of sodium-glucose cotransporter 2 inhibitors on HbA1c variability and cardiovascular and renal adverse outcome in patients with T2DM. *Diabetes Obes Metab*. (2025) 27:4720–8. doi: 10.1111/dom.16509

8. Hsu JC, Yang YY, Chuang SL, Huang KC, Lee JK, Lin LY. Long-term visit-to-visit glycemic variability as a predictor of major adverse limb and cardiovascular events in patients with diabetes. *J Am Heart Assoc*. (2023) 12. doi: 10.1161/jaha.122.025438

9. Norhammar A, Tenerz Å, Nilsson G, Hamsten A, Efendíc S, Rydén L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. (2002) 359:2140–4. doi: 10.1016/s0140-6736(02)09089-x

10. Su G, Mi S-h, Tao H, Li Z, Yang H-X, Zheng H, et al. Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. *Diabetes Care*. (2013) 36:1026–32. doi: 10.2337/dc12-0925

11. Hempe JM, Liu S, Myers L, McCarter RJ, Buse JB, Fonseca V. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. *Diabetes Care*. (2015) 38:1067–74. doi: 10.2337/dc14-1844

12. Chen J, Yi Q, Wang Y, Wang J, Yu H, Zhang J, et al. Long-term glycemic variability and risk of adverse health outcomes in patients with diabetes: A systematic review and meta-analysis of cohort studies. *Diabetes Res Clin Pract*. (2022) 192:110085. doi: 10.1016/j.diabres.2022.110085

13. Sartore G, Ragazzi E, Caprino R, Lapolla A. Long-term HbA1c variability and macro-/micro-vascular complications in type 2 diabetes mellitus: a meta-analysis update. *Acta Diabetol*. (2023) 60:721–38. doi: 10.1007/s00592-023-02037-8

14. Wang T, Zhang X, Liu J. Long-term glycemic variability and risk of cardiovascular events in type 2 diabetes: A meta-analysis. *Horm Metab Res*. (2022) 54:84–93. doi: 10.1055/a-1730-5029

15. Kim H, Jung DY, Lee SH, Cho JH, Yim HW, Kim HS. Long-term risk of cardiovascular disease among type 2 diabetes patients according to average and visit-to-visit variations of hbA1c levels during the first 3 years of diabetes diagnosis. *J Korean Med Sci*. (2023) 38:e24. doi: 10.3346/jkms.2023.38.e24

16. Cardoso CRL, Leite NC, Salles GF. Importance of the hemoglobin glycation index for risk of cardiovascular and microvascular complications and mortality in individuals with type 2 diabetes. *Endocrinol Metab (Seoul)*. (2024) 39:732–47. doi: 10.3803/EnM.2024.2001

17. Kim MK, Jeong JS, Yun JS, Kwon HS, Baek KH, Song KH, et al. Hemoglobin glycation index predicts cardiovascular disease in people with type 2 diabetes mellitus: A 10-year longitudinal cohort study. *J Diabetes Complicat*. (2018) 32:906–10. doi: 10.1016/j.jdiacomp.2018.08.007

18. Li F, Zhang L, Shen Y, Liu HH, Zhang ZY, Hu G, et al. Higher glucose fluctuation is associated with a higher risk of cardiovascular disease: Insights from pooled results among patients with diabetes. *J Diabetes*. (2023) 15:368–81. doi: 10.1111/1753-0407.13386

19. Liu X, Yang X, Wu N. Relationship between glycosylated hemoglobin variability and the severity of coronary artery disease in patients with type 2 diabetes mellitus. *J Diabetes Res*. (2024) 2024:9958586. doi: 10.1155/2024/9958586

20. Global B. M. I. M. C., Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. (2016) 388:776–86. doi: 10.1016/s0140-6736(16)30175-1

21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed)*. (2021) 74:790–9. doi: 10.1016/j.rec.2021.07.010

22. Brooke BS, Schwartz TA, Pawlik TM. MOOSE reporting guidelines for meta-analyses of observational studies. *JAMA Surg*. (2021) 156:787–8. doi: 10.1001/jamasurg.2021.0522

23. Motschall E, Falck-Ytter Y. Searching the MEDLINE literature database through PubMed: a short guide. *Onkologie*. (2005) 28:517–22. doi: 10.1159/000087186

24. Xin C, Yao J, Li H, Sun X, Wang H. Relationship between ghrelin and thyroid disease: a meta-analysis. *Front Endocrinol (Lausanne)*. (2025) 16:1505085. doi: 10.3389/fendo.2025.1505085

25. Yao Q, Song L, Xu J, Wu Z. Medium- and long-term recurrence after radioiodine therapy for differentiated thyroid carcinoma with recombinant human thyrotropin: a meta-analysis. *Front Endocrinol (Lausanne)*. (2024) 15:1474121. doi: 10.3389/fendo.2024.1474121

26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

27. Service FJ, O'Brien PC. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care*. (2007) 30:186–6. doi: 10.2337/dc06-1782

28. Hempe JM, Gomez R, McCarter RJ Jr., Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. *J Diabetes Complicat*. (2002) 16:313–20. doi: 10.1016/s1056-8727(01)00227-6

29. Bouchi R, Babazono T, Mugishima M, Yoshida N, Nyumura I, Toya K, et al. Fluctuations in HbA1c are associated with a higher incidence of cardiovascular disease in Japanese patients with type 2 diabetes. *J Diabetes Investig*. (2012) 3:148–55. doi: 10.1111/j.2040-1124.2011.00155.x

30. Luk AOY, Ma RCW, Lau ESH, Yang X, Lau WWY, Yu LWL, et al. Risk association of HbA_{1c} variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. *Diabetes Metab Res Rev*. (2013) 29:384–90. doi: 10.1002/dmrr.2404

31. Takao T, Matsuyama Y, Yanagisawa H, Kikuchi M, Kawazu S. Association between HbA1c variability and mortality in patients with type 2 diabetes. *J Diabetes Complicat*. (2014) 28:494–9. doi: 10.1016/j.jdiacomp.2014.02.006

32. Yang HK, Kang B, Lee SH, Yoon KH, Hwang BH, Chang K, et al. Association between hemoglobin A1c variability and subclinical coronary atherosclerosis in subjects with type 2 diabetes. *J Diabetes Complicat*. (2015) 29:776–82. doi: 10.1016/j.jdiacomp.2015.04.008

33. Bonke FC, Donnachie E, Schneider A, Mehring M. Association of the average rate of change in HbA1c with severe adverse events: a longitudinal evaluation of audit data from the Bavarian Disease Management Program for patients with type 2 diabetes mellitus. *Diabetologia*. (2016) 59:286–93. doi: 10.1007/s00125-015-3797-z

34. Ahn CH, Min SH, Lee DH, Oh TJ, Kim KM, Moon JH, et al. Hemoglobin glycation index is associated with cardiovascular diseases in people with impaired glucose metabolism. *J Clin Endocrinol Metab*. (2017) 102:2905–13. doi: 10.1210/jc.2017-00191

35. Lee MY, Hsiao PJ, Huang YT, Huang JC, Hsu WH, Chen SC, et al. Greater HbA1c variability is associated with increased cardiovascular events in type 2 diabetes patients with preserved renal function, but not in moderate to advanced chronic kidney disease. *PloS One*. (2017) 12:e0178319. doi: 10.1371/journal.pone.0178319

36. Cardoso CRL, Leite NC, Moram CBM, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol*. (2018) 17. doi: 10.1186/s12933-018-0677-0

37. Gu J, Fan YQ, Zhang JF, Wang CQ. Association of hemoglobin A1c variability and the incidence of heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus and arterial hypertension. *Hellenic J Cardiol*. (2018) 59:91–7. doi: 10.1016/j.hjc.2017.08.001

38. Kaze AD, Santhanam P, Erqou S, Ahima RS, Echouffo-Tcheugui JB. Long-term variability of glycemic markers and risk of all-cause mortality in type 2 diabetes: the Look AHEAD study. *BMJ Open Diabetes Res Care*. (2020) 8. doi: 10.1136/bmjdrc-2020-001753

39. Li S, Nemeth I, Donnelly L, Hapca S, Zhou K, Pearson ER. Visit-to-visit hbA(1c) variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes. *Diabetes Care*. (2020) 43:426–32. doi: 10.2337/dc19-0823

40. Li S, Tang X, Luo Y, Wu B, Huang Z, Li Z, et al. Impact of long-term glucose variability on coronary atherosclerosis progression in patients with type 2 diabetes: a 2.3 year follow-up study. *Cardiovasc Diabetol*. (2020) 19:146. doi: 10.1186/s12933-020-01126-0

41. Wan EYF, Yu EYT, Chin WY, Ng FTY, Chia SMC, Wong ICK, et al. Age-specific associations of glycated hemoglobin variability with cardiovascular disease and mortality in patients with type 2 diabetes mellitus: A 10-year cohort study. *Diabetes Obes Metab*. (2020) 22:1316–27. doi: 10.1111/dom.14034

42. Akselrod D, Friger M, Biderman A. HbA1C variability among type 2 diabetic patients: a retrospective cohort study. *Diabetol Metab Syndrome*. (2021) 13. doi: 10.1186/s13098-021-00717-5

43. Moosaie F, Mouodi M, Sheikhy A, Fallahzadeh A, Deravi N, Rabizadeh S, et al. Association between visit-to-visit variability of glycemic indices and lipid profile and the incidence of coronary heart disease in adults with type 2 diabetes. *J Diabetes Metab Disord*. (2021) 20:1715–23. doi: 10.1007/s40200-021-00930-z

44. Sato M, Inaishi J, Saisho Y, Sato Y, Komuro I, Itoh H. Association of visit-to-visit glycemic variability with risk of cardiovascular diseases in high-risk Japanese patients with type 2 diabetes: A subanalysis of the EMPATHY trial. *J Diabetes Investig*. (2021) 12:2190–6. doi: 10.1111/jdi.13597

45. Shen Y, Zhou J, Shi L, Nauman E, Katzmarzyk PT, Price-Haywood EG, et al. Association between visit-to-visit HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes. *Diabetes Obes Metab*. (2021) 23:125–35. doi: 10.1111/dom.14201

46. Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Franzén S, Svensson AM, et al. HbA1c variability predicts cardiovascular complications in type 2 diabetes regardless of being at glycemic target. *Cardiovasc Diabetol*. (2022) 21:13. doi: 10.1186/s12933-022-01445-4

47. Ma C, Zhang W, Xie R, Wan G, Yang G, Zhang X, et al. Effect of hemoglobin A1c trajectories on future outcomes in a 10-year cohort with type 2 diabetes mellitus. *Front Endocrinol (Lausanne)*. (2022) 13:846823. doi: 10.3389/fendo.2022.846823

48. Wu T-E, Su Y-W, Chen H-S. Mean HbA1c and HbA1c variability are associated with differing diabetes-related complications in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. (2022) 192:110069. doi: 10.1016/j.diabres.2022.110069

49. Manosroi W, Phimphilai M, Waisayanand N, Buranapin S, Deerochanawong C, Gunaparn S, et al. Glycated hemoglobin variability and the risk of cardiovascular events in patients with prediabetes and type 2 diabetes mellitus: A post-hoc analysis of a prospective and multicenter study. *J Diabetes Investig*. (2023) 14:1391–400. doi: 10.1111/jdi.14073

50. Zhang F, Shi T, Feng X, Shi Y, Zhang G, Liu Y, et al. Visit-to-visit HbA1c variability is associated with poor prognosis in peritoneal dialysis patients with type 2 diabetes mellitus. *BMC Nephrol*. (2023) 24. doi: 10.1186/s12882-023-03348-2

51. Lin CC, Li CI, Liu CS, Lin CH, Yang SY, Li TC. Association of carotid atherosclerosis markers with all-cause and cardiovascular disease–specific mortality in persons with type 2 diabetes: a causal mediation analysis with glucose variation. *Acta Diabetol*. (2024) 61:657–69. doi: 10.1007/s00592-024-02243-y

52. Maajani K, Nasli-Esfahani E, Fahimfar N, Sheidaei A, Mansournia MA, Yazdani K. Long-term glycemic variability and the risk of cardiovascular diseases in type 2 diabetic patients: Effect of hypothetical interventions using parametric g-formula in a population-based historical cohort study. *PloS One*. (2025) 20:e0319975. doi: 10.1371/journal.pone.0319975

53. Teh XR, Looareesuwan P, Pattanaprateep O, Pattanateepapon A, Attia J, Thakkinstian A. Predictive ability of visit-to-visit glucose variability on diabetes complications. *BMC Med Inform Decis Mak*. (2025) 25. doi: 10.1186/s12911-025-02964-2

54. Wan EY, Fong DY, Fung CS, Lam CL. Incidence and predictors for cardiovascular disease in Chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study. *J Diabetes Complicat*. (2016) 30:444–50. doi: 10.1016/j.jdiacomp.2015.12.010

55. Tabesh M, Sacre JW, Mehta K, Chen L, Sajjadi SF, Magliano DJ, et al. The association of glycemic risk factors and diabetes duration with risk of heart failure in people with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab*. (2024) 26:5690–700. doi: 10.1111/dom.15938

56. Kim S, Hwang J, Yon, Dong K, Sang H, Woo S, et al. Dual roles of hbA1c variability and body composition for cardiovascular risk: A cohort study of 8224 adults with type 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle*. (2025) 16. doi: 10.1002/jcsm.70028

57. Hsu H, Kocis PT, Pichardo-Lowden A, Hwang W. Major adverse cardiovascular events' reduction and their association with glucose-lowering medications and glycemic control among patients with type 2 diabetes: A retrospective cohort study using electronic health records. *J Diabetes*. (2024) 16. doi: 10.1111/1753-0407.13604

58. Wang Y, Liu H, Hu X, Wang A, Wang A, Kang S, et al. Association between hemoglobin glycation index and 5-year major adverse cardiovascular events: the REACTION cohort study. *Chin Med J (Engl)*. (2023) 136:2468–75. doi: 10.1097/cm9.0000000000002717

59. Gagnon DR, Zhang T-J, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease—The Framingham Study: A 34-year follow-up. *Am Heart J*. (1994) 127:674–82. doi: 10.1016/0002-8703(94)90679-3

60. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, et al. Anemia as a risk factor for cardiovascular disease in the atherosclerosis risk in communities (aric) study. *J Am Coll Cardiol*. (2002) 40:27–33. doi: 10.1016/s0735-1097(02)01938-1

61. Astle WJ, Elding H, Jiang T, Allen D, Ruklisa D, Mann AL, et al. The allelic landscape of human blood cell trait variation and links to common complex disease. *Cell*. (2016) 167:1415–1429.e1419. doi: 10.1016/j.cell.2016.10.042

62. VanderWeele TJ. Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics*. (2020) 76:746–52. doi: 10.1111/biom.13197

63. George A, Stead TS, Ganti L. What's the risk: differentiating risk ratios, odds ratios, and hazard ratios? *Cureus*. (2020). doi: 10.7759/cureus.10047

64. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. (2006) 295:1681–7. doi: 10.1001/jama.295.14.1681

65. Asare AL, Gao Z, Carey VJ, Wang R, Seyfert-Margolis V. Power enhancement via multivariate outlier testing with gene expression arrays. *Bioinformatics*. (2009) 25:48–53. doi: 10.1093/bioinformatics/btn591

66. Wang Z, Liu Y, Xie J, Liu NF. Association between hemoglobin glycation index and subclinical myocardial injury in the general population free from cardiovascular disease. *Nutr Metab Cardiovasc Dis*. (2022) 32:469–78. doi: 10.1016/j.numecd.2021.10.018

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 17 November 2025
DOI 10.3389/fendo.2025.1531525

Check for updates

OPEN ACCESS

EDITED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States

REVIEWED BY
Kai P. Law,
University of Derby, United Kingdom
Vinay Tanwar,
Beckman Research Institute of City of Hope,
United States
Ibrahim Hamed,
National Research Centre, Egypt

*CORRESPONDENCE
Jassim Al Suwaidi
jalsuwaidi@hamad.qa

RECEIVED 20 November 2024
ACCEPTED 20 October 2025
PUBLISHED 17 November 2025

CITATION
Elshrif M, Isufaj K, El-Menyar A, Ullah E, Beotra A, Al-Maadheed M, Mohamed-Ali V, Saad M and Al Suwaidi J (2025) Coronary heart disease and type 2 diabetes metabolomic signatures in the Middle East. *Front. Endocrinol.* 16:1531525. doi: 10.3389/fendo.2025.1531525

COPYRIGHT
© 2025 Elshrif, Isufaj, El-Menyar, Ullah, Beotra, Al-Maadheed, Mohamed-Ali, Saad and Al Suwaidi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Coronary heart disease and type 2 diabetes metabolomic signatures in the Middle East

Mohamed Elshrif[1], Keivin Isufaj[1], Ayman El-Menyar[2,3], Ehsan Ullah[1], Alka Beotra[4], Mohammed Al-Maadheed[4], Vidya Mohamed-Ali[4], Mohamad Saad[1] and Jassim Al Suwaidi[5]*

[1]Qatar Computing Research Institute, Hamad Bin Khalifa University, Doha, Qatar, [2]Clinical Research, Trauma & Vascular Surgery, Hamad Medical Corporation, Doha, Qatar, [3]Department of Clinical Medicine, Weill Cornell Medical College, Doha, Qatar, [4]Anti-doping Lab Qatar, Doha, Qatar, [5]Department of Cardiology, Heart Hospital, Hamad Medical Corporation, Doha, Qatar

Background: The growing field of metabolomics has opened new venues for identifying biomarkers of type 2 diabetes (T2D) and predicting its consequences, such as coronary heart disease (CHD). Despite their large size, Middle Eastern populations are underrepresented in omics research. In this study, we aim at investigating metabolomics profiles of T2D stratified by the CHD comorbidity for Middle Eastern population, such as Qatari population.

Methods: In this cross-sectional study, we used a total of 641 metabolites from a large cohort of 3,679 Qatari adults from the Qatar BioBank (QBB; 272 T2D and 2,438 non-T2D individuals) and Qatar Cardiovascular Biorepository (QCBio; all CHD patients; 488 T2D and 481 non-T2D individuals). Univariate and pathway enrichment analyses were performed to identify metabolites associated with T2D in the absence or presence of CHD. Machine learning (ML) models, and metabolite risk scores were developed to assess the predictive power of the different combinations of T2D and CHD.

Results: Many metabolites were significantly associated with T2D in both the QBB and QCBio cohorts. Among these, we observed 1,5-anhydroglucitol (1,5-AG) ($P = 1.33 \times 10^{-68}$ [-5.20, -4.16] in QBB vs 9.82×10^{-33} [-2.51, -1.80] in QCBio), glucose ($P = 7.14 \times 10^{-57}$ [4.09, 5.23] in QBB vs. 3.26×10^{-29} [1.41, 2.00] in QCBio), and mannose ($P = 2.61 \times 10^{-54}$ [2.68, 3.45] in QBB vs. 1.01×10^{-27} [1.45, 2.09] in QCBio). Other metabolites were significantly associated with T2D only in one cohort, e.g., gamma-glutamylglutamine ($P = 1.79 \times 10^{-20}$ and $\beta = -2.61$ in QBB vs. $P = 5.12 \times 10^{-1}$ and $\beta = 0.10$ in QCBio). The enriched pathways (FDR $P < 0.05$), common to both cohorts, included galactose metabolism and valine leucine, and isoleucine biosynthesis and degradation. Few pathways were significantly associated with T2D in only one cohort: fructose and mannose, and Pantothenate and CoA biosynthesis metabolisms were significant in the QCBio cohort, whereas Arginine biosynthesis, and Alanine, aspartate and glutamate metabolisms were significant in the QBB cohort. ML models performed well in predicting T2D with high accuracy (>80% in both QBB and QCBio). The metabolite risk score (MRS) developed in the QCBio and tested in the QBB while adjusting for hemoglobin A1C yielded an odds ratio (OR) of 21.18 for the top quintile vs. the remaining quintiles.

Conclusions: Metabolomic profiling has the potential for the early detection of metabolic alterations that precede clinical symptoms of T2D and CHD in the presence of T2D. Risk scores showed great performance in predicting T2D and CHD, but longitudinal data are required to provide evidence for disease risk. Early detection allows timely interventions and improved management strategies for both T2D and CHD patients.

KEYWORDS

type 2 diabetes, coronary heart disease, metabolomics, Middle Eastern populations, supervised learning, predictive modeling, pathway enrichment analysis, metabolite risk score

1 Introduction

The number of people, who live with diabetes is quickly increasing globally, driven by many factors including ageing, urbanization, and the growing prevalence of obesity (1–3). Diabetes is estimated to affect more than 500 million people worldwide, with severe impacts on health and the economy (4). The prevalence of diabetes is continuously increasing worldwide, and it is expected that the number of patients with diabetes will approach 550 million by 2030 and 700 million by 2045 (5–7). However, the burden of Type 2 Diabetes (T2D) is not shared equally between different ethnic groups globally. Non-White ethnic populations are three-to-five times higher prevalence of T2D than people of White-European background (8). In the US several recent studies discussed disparities in the prevalence of diabetes (9–12). For example, Cheng et al. (10), showed that the Hispanic American adults having the highest prevalence with 22.1% followed by non-Hispanic Black with 20.4%, and non-Hispanic Asian American with 19.1% compared with the non-Hispanic White American adult population with 12.1%. South Asians ethnic populations develop T2D five-to-ten years earlier and possess higher risk of developing T2D compared to White European population (two-to six-fold) (13). Similarly, 9% of White European population are diagnosed with T2D under the age of 40 years compared with the Black African-Caribbean populations of 23% (14). The Middle East, North Africa, and especially the Gulf region show a high prevalence of diabetes, exceeding 17% in some countries, such as Qatar (4, 15). In addition, the incidence of young-onset diabetes is rapidly increasing in Gulf countries (all countries that have coasts in the Arabic Gulf, which includes Kuwait, Saudi Arabia, Bahrain, Qatar, Emirates, and Oman). These populations have high rates of metabolic syndrome at a young age, with a prevalence 10-15% higher than that in most developed countries (16). The etiology of type 2 diabetes (T2D) is complex and is associated with diverse complications (17–20). Individuals with T2D have greater cardiovascular morbidity and mortality, and the risk of cardiovascular disease (CVD) and CVD-related death is two to four times greater among T2D patients (21–23). A recent study showed that two-thirds of deaths in patients with T2D are caused by CVD (24). Furthermore, the risk of developing coronary heart disease (CHD) and heart failure (HF) in T2D patients increased two-to-four fold and two-to-eight fold, respectively (25–27). Prevention and early detection of T2D are crucial for improving treatment to avoid/delay major complications (28–31). T2D and CHD are partly caused by complex interactions between genetic and metabolic profiles (32–34). Metabolic alteration is the leading hallmark of diabetes, as it was assumed that T2D individuals' metabolic pathways are affected and play an important role in their total metabolomic dysfunction (35, 36). For example, in one study Chen et al. (36), impaired glucose metabolic homeostasis led to hyperglycemia, which is a hallmark of diabetes mellitus. Numerous studies have investigated the associations between metabolites and T2D (30, 37, 38) and between metabolites and CHD (39–41). Stratification of metabolomics signatures of T2D patients with respect to CHD is important to shed light on the biological mechanisms of these two diseases. The relationship at the metabolomics level for T2D and CHD was studied previously (42), but to the best of our knowledge, this has rarely been examined for Middle Eastern populations. Hence, this is the first large-scale metabolomics study of T2D and CHD in a Qatari population, providing insights from an underrepresented region. The identification of differential metabolic profiles of T2D patients who have CHD vs. T2D patients who do not develop CHD may lead to therapeutic approaches to reduce the occurrence of CHD in T2D patients. In this study, we assessed the differences between the metabolomics profiles of T2D patients stratified by the absence or presence of CHD in a Middle Eastern (Qatari) dataset using univariate and multivariate analyses, pathways enrichment analysis, machine learning, and metabolite risk score analysis. Metabolomic data were generated by Metabolon for two cohorts collected by the Qatar BioBank [QBB, 2,710 samples, (43)] and

Abbreviations: T2D, Type 2 Diabetes; CHD, Coronary Heart Disease; QBB, Qatar BioBank; QCBio, Qatar Cardiovascular Biorepository; MRS, Metabolite Risk Score; OR, Odds Ratio; SD, Standard Deviation; AUC, Area Under the Curve; ML, Machine Learning; CVD, Cardiovascular Disease.

Qatar Cardiovascular Biorepository (QCBio, 969 samples, (40, 44, 45).

2 Materials and methods

2.1 Study cohort

Our cross-sectional study included two cohorts: (1) the QBB cohort, which comprised 2,710 participants (272 T2D patients and 2,438 non-T2D controls), none with CHD based on the survey completed by participants, and (2) the QCBio cohort, which comprised 969 CHD patients (481 T2D patients and 488 non-T2D patients) (Supplementary Figure 1). CHD patients were identified from the Cardiac Catheterization Laboratory, Coronary Care Unit, and Heart Hospital Clinics at Hamad Medical Corporation (HMC), Doha, Qatar. Patients with a history of acute coronary syndrome or stable angina were included in the study (44). For patients with CHD and T2D, T2D occurs first. The study was approved by the Institutional Review Boards of HMC and QBB. Written informed consent was obtained from all patients before their participation. The cohorts' characteristics are shown in Table 1. The diagnostic criteria used for identifying T2D and CHD were as follows: T2D status in QCBio cohort was defined as fasting blood glucose ≥ 126 mg/dL, random glucose ≥ 200 mg/dL, hemoglobin A1C ≥ 6.5%, or a prior diagnosis with oral hypoglycemic or insulin therapy. Within QBB cohort, patients with hemoglobin A1C ≥ 6.5% were considered to have T2D. The age at onset of both T2D and CHD was not available in our dataset, which prevented the analysis accounting for age at onset.

As indicated in Table 1, for QCBio cohort, the number of T2D patients was almost matched with non-T2D individuals and the females represent 38%, whereas the males represent 62%. For T2D patients, the age and BMI were statistically different between males vs females with P = 0.91 and P = 1.63×10^{-11}, respectively. The number of hypertension individuals was 391 patients. For non-T2D individuals, the age and BMI were statistically different between males vs females with P = 0.03 and P = 0.91, respectively. The number of hypertension individuals was 141 patients. For QBB cohort, the number of T2D patients was 272, whereas the non-T2D individuals was 2,438. The gender distribution was equal between females and males. The age and BMI were statistically different between T2D for females vs males with P = 1.66×10^{-4} and P = 2.05×10^{-5}, respectively, whereas P = 0.35 and P = 0.07, respectively for non-T2D individuals. None of the QBB cohort individuals has hypertension.

2.2 Metabolomics profiling and data quality control

Serum metabolites for the QCBio and QBB cohorts were jointly quantified by untargeted, ultrahigh-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and curated by Metabolon Inc. We used the HD4 platform, which exactly mimics and is accredited by Metabolon Inc. More specifically, we used 96-well plates, with 40 samples per plate, each with 5 internal QCs, 3 blanks and 1 pooled sample prepared from the 144 samples, to check for any drift between plates (46, 47). The obtained data were normalized across batches to generate batch-normalized data and to correct for minor instrument technical variation that could occur from one batch to another. Each compound was corrected in instrument batch blocks by registering the medians of each batch to equal one and normalizing each data point proportionally. A total of 641 out of the 1,159 metabolites were analyzed from both cohorts in our study after standard quality control steps were performed by Ullah and his colleagues (40). Figure 1 shows the details of the selection process in both cohorts. Briefly, 296 metabolites and seven samples with > 20% missing data were discarded. Principal component analysis (PCA) was used to detect and remove 40 outliers from our dataset, with a criterion based on the first five principal component values falling outside the range of [$\mu \pm 5$ SD]. To mitigate the influence of

TABLE 1 Cohorts characteristics.

Cohort Name	Diabetes Status	Gender	Participants N (%)	Age, Mean (SD) years	P value (Gender ~ Age)	BMI, Mean (SD) $kg.m^{-2}$	P value (Gender ~ BMI)	Hypertension
QCBio	T2D+	Females Males All	179 (37.21) 302 (62.79) 481 (100)	59.07 (10.05) 58.96 (11.29) 59.01 (10.84)	9.13E-01	34.08 (6.38) 30.05 (5.11) 31.55 (5.93)	1.63E-11	148 243 391
	T2D-	Females Males	191 (39.14) 297 (60.86)	44.57 (15.21) 47.64 (15.09)	2.96E-02	29.56 (5.04) 29.51 (4.86)	9.12E-01	41 (10 NA) 100 (12 NA)
		All	488 (100)	46.45 (15.20)		29.53 (4.93)		141 (22 NA)
QBB	T2D+	Females Males All	137 (50.37) 135 (49.63) 272 (100)	53.59 (8.98) 48.81 (10.84) 51.22 (10.20)	1.66E-04	33.24 (6.24) 29.93 (5.52) 31.60 (6.12)	2.05E-05	NA
	T2D-	Females Males	1191 (48.85) 1247 (51.15)	38.34 (11.88) 37.92 (10.65)	3.51E-01	28.82 (6.20) 28.40 (5.40)	7.43E-02	
		All	2438 (100)	38.13 (11.57)		28.60 (5.81)		

T2D status in the QCBio dataset was defined as fasting blood glucose ≥126 mg/dL, random glucose ≥ 200 mg/dL, hemoglobin A1C ≥ 6.5%, or a prior diagnosis with oral hypoglycemic or insulin therapy. Within controls, hemoglobin A1C ≥ 6.5% was used to define T2D patients. T2D+: T2D patient; T2D-: non-T2D patient. * is part of the metabolite name↑ increased, ↓decreased.

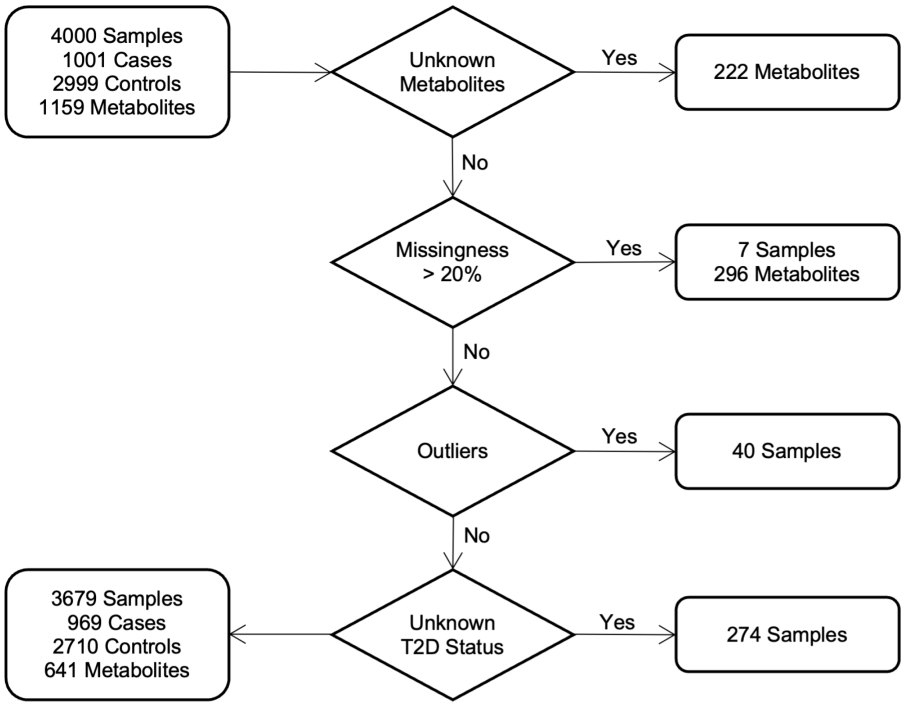


FIGURE 1
Study cohorts and quality control: workflow diagram indicates the selection process of individuals in both cohorts.

extreme values in the metabolite data, metabolites were winsorized using 80% winsorization: values for a metabolite below the 10^{th} percentile were set to the 10^{th} percentile, and values above the 90^{th} percentile were set to the 10^{th} percentile. For more details, see Supplementary Material.

2.3 Statistical analysis

Statistical and machine learning analyses were performed with R software (version 4.1.2) and Python software (version 3.11.13) for both cohorts. The packages' versions are detailed in Supplemental Material.

2.3.1 Univariate analysis

The first analysis was conducted to compare T2D vs non-T2D patients in the QCBio cohort, where 136 all individuals had CHD. The same analysis was performed in the QBB cohort as a replication stage for the QCBio results. The analysis was separately performed in each cohort using logistic regression, adjusting for age, sex, and body mass index (BMI) as covariates. The threshold chosen for the Bonferroni correction was$< 7.8 \times 10^{-5}$ (0.05/641). The effect size was used to identify the direction of the changes in the metabolite concentrations with respect to disease status. A metabolite has a positive effect size if its concentration was greater in T2D patients than in controls. Metabolites that were significantly associated with T2D in the QCBio cohort (CHD patients) but not in the QBB cohort were investigated to evaluate the interplay between T2D and CHD, and to explore the underlying biological mechanisms involved. The most significant metabolites were tested with several cardiometabolic traits: Glucose, HbA1C, and lipid traits (LDL, HDL, Triglycerides, and Total Cholesterol). This analysis was performed only in the QBB cohort because the tested traits were not available in the QCBio cohort. Alongside Bonferroni correction, we applied the Benjamini–Hochberg False Discovery Rate (FDR) procedure at a threshold of 0.05. This method calculates an adjusted value $q_i$for each metabolite, representing the expected proportion of false positives among discoveries up to the i^{th} ranked test. Unlike the conservative Bonferroni threshold ($0.05/641 \sim 7.8 \times 10^{-5}$), which controls family-wise error, FDR is more flexible and allows greater power to detect true associations while still limiting false positives (48).

2.4 Machine learning-based predictive modeling

Machine learning (ML) models were used to predict the occurrence of T2D. Random Forest (RF), support vector machine (SVM), extreme gradient boosting (XGBoost), and linear discriminant analysis (LDA) methods were used. Details on the selection criteria for the ML models and the rationale behind the chosen settings can be found in the Supplementary Material. For both cohorts, the prediction was based on four settings (Figure 2):

- Covariates only: The model included only age, sex, and BMI.

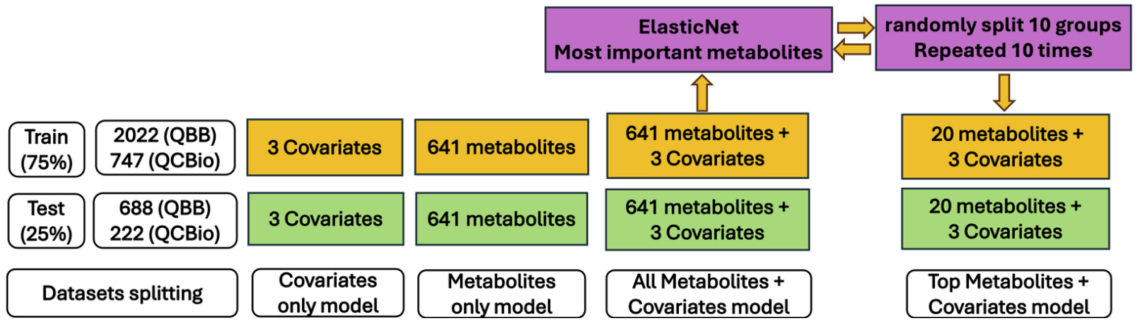


FIGURE 2
General overview of dataset splitting and different settings of models' prediction.

- Metabolites only: The model included only the 641 metabolites.
- Metabolites + covariates: The model included both covariates and metabolites.
- Top metabolites + covariates: The model included the 20 most significant metabolites plus the covariates.

For all ML experiments, the samples were divided randomly into a training set (75%) and a testing set (25%). Ten-fold cross-validation was used in all ML models where all individuals in the training set were randomly splitted into ten equal-sized groups. Each group was treated separately as a test set, and the analysis was repeated ten times. The final predictive power was evaluated based on the average accuracy and the area under the curve (AUC) for all ten predictive models. For the potential implementation of these ML models in healthcare, selecting fewer metabolites in an ML model with good predictive power is more practical and cost efficient. Hence, a feature selection technique was applied to select the most important metabolites while preserving the performance of the ML model. ElasticNet (49), which is a combination of two regularization techniques, L2 regularization (used in ridge regression) and L1 regularization (used in LASSO), has been shown to outperform LASSO when the data are highly correlated. We followed the Zou and Hastie (49) procedure for feature selection using 10-fold cross-validation. The most important metabolites were used in the ML model, and the performance was assessed (top metabolites + covariates). In this process, we avoid overfitting by running ElasticNet method on the training dataset for all 641 metabolites and extracted the most important metabolites related to T2D. Then, the performance of this model was evaluated using these important metabolites in the testing dataset. Furthermore, to avoid bias due to imbalanced classes (e.g., the number of T2D patients was much smaller than that of non-T2D individuals), especially in the QBB cohort, we performed additional analyses by reducing the sample size of non-T2D individuals (100 random selections) and assessed the performance of the ML models using the average accuracy across 100 runs. In addition, we compared models trained with Synthetic Minority Over-sampling Technique (SMOTE) (50) to those trained without SMOTE (i.e., using the 100 random downsampling runs) on the QBB cohort. In general, SMOTE is a technique used to address severe class imbalance by generating synthetic minority samples. This allowed us to evaluate whether synthetic oversampling improved predictive performance or introduced potential overfitting due to the large class imbalance. The details of how we tackled the imbalanced dataset can be found in the Supplementary Material.

2.5 Metabolite correlation and pathway enrichment analysis

Pearson's correlation (R) was utilized to measure the strength of correlation between the most significant metabolites. Pathway enrichment analysis was performed using MetaboAnalyst 6.0 (51) (https://www.metaboanalyst.ca/) to determine the biological pathways that are highly enriched in a metabolite list than would be anticipated in random setting. For compound matching purposes, we utilized the MetaboAnalyst 6.0 software to match the Human Metabolome Database IDs with the provided compounds. Three analyses were performed, selecting the significant metabolites after Bonferroni correction in 1) the QCBio dataset, 2) the QBB dataset, and 3) the metabolites that were associated with T2D in both cohorts. Metabolite pathways with False Discovery Rate (FDR) and $P< 0.05$ were selected.

2.6 Metabolite risk score analysis

We calculated the metabolite risk scores (MRSs) using the top 20 most important metabolites derived from ElasticNet algorithm. The ElasticNet approach will use the 641 metabolites and rank them based on their importance to predict T2D. MRS is calculated as an aggregated average of metabolite values and their pre-defined effect sizes. The effect sizes are estimated using ElasticNet in the training dataset, and evaluation of MRS performance is assessed in the testing dataset. AUC, OR per 1 SD increase, and OR for top decile/quintile vs the remaining deciles/quintiles are used as performance metrics. In addition, we developed two MRS scores. One in QCBio cohort and tested in the QBB cohort and the other one developed in QBB and evaluated in QCBio.

2.7 Code availability

The analysis was performed in R and Python, and the code is available upon request.

3 Results

3.1 Univariate analysis

In the QCBio cohort, 42 out of 641 metabolites were significantly different between T2D patients and non-T2D patients at $P < 10^{-8}$ (Table 2). These metabolites included 20 lipids, 10 amino acids, 8 carbohydrates, 2 peptides, and 2 xenobiotics. Twenty-seven metabolites (64.3%) were increased in T2D, and 15 metabolites (35.7%) were decreased. Thirty-six metabolites were replicated in the QBB cohort using the Bonferroni threshold (same effect size direction and $P < 7.8 \times 10^{-5}$) (Table 2). When applying the FDR threshold of 0.05, 40 metabolites were replicated, leaving only glucuronate and N6-carboxymethyllysine as nonsignificant. This demonstrates that while the strict Bonferroni criterion identifies a robust subset of associations, the FDR procedure, by accounting for correlation structure among metabolites, recovers additional biologically consistent signals. Among the replicated metabolites in QBB, 1,5-anhydroglucitol (1,5-AG) ($P = 1.33 \times 10^{-68}$ [-5.20, -4.16] in QBB), glucose ($P = 7.14 \times 10^{-57}$ [4.09, 5.23] in QBB), mannose ($P = 2.61 \times 10^{-54}$ [2.68, 3.45] in QBB), methylsuccinoylcarnitine ($P = 1.2 \times 10^{-45}$ [1.22, 1.61] in QBB), and fructosyllysine ($P = 1.38 \times 10^{-35}$ [1.80, 2.46] in QBB) were detected (Table 2). The 6 non-replicated metabolites were N6-carboxymethyllysine ($P = 0.38$ [-0.09, 0.33]), glucuronate ($P = 0.16$ and $\beta = 0.17$ [-0.06, 0.41]), 2-aminoheptanoate ($P = 0.015$ [0.06, 0.64]), phenylacetylglutamine ($P = 7.2 \times 10^{-3}$ [0.04, 0.33]), prolylglycine ($P = 1.72 \times 10^{-3}$ [0.11, 0.42]), and ribulonate/xylulonate/lyxonate* ($P = 4.14 \times 10^{-4}$ [0.19, 0.69]) (Tables 2, 3).

Additionally, to assess the robustness of the observed metabolites with respect to lipid profiles, we performed a univariate analysis in the QBB cohort and adjusted for LDL, HDL, Triglycerides, and Total cholesterol. The results remained largely unchanged (Table 2). The significance of the top 42 metabolites in the QBB cohort ranged between 1.33×10^{-68} and 6.3×10^{-15} (Supplementary Table 1). The 5 most significant metabolites were 1,5-anhydroglucitol (1,5-AG), glucose, fructose, mannose, andmannonate* (Supplementary Table 1). These 5 metabolites were all significant in the QCBio cohort, all having $P < 3.38 \times 10^{-11}$ and the same effect size direction (Supplementary Table 1). Twelve out of 42 metabolites did not pass the Bonferronithreshold ($P < 7.8 \times 10^{-5}$), and 6 were not nominally significant in the QCBio data ($P < 0.05$): N,N,N-trimethyl-alanylproline betaine (TMAP), 3-(3-amino-3-carboxypropyl) uridine*, pseudouridine, glutamine, gamma-glutamylthreonine, and gamma-glutamylglutamine (Table 3). All 6 metabolites showed opposite effect sizes in QBB vs QCBio (negative in the QBB cohort and positive in the QCBio cohort; Table 3), except for gamma-glutamylthreonine (negative effect size in both datasets).

3.2 Association between top metabolites and cardiometabolic traits

We tested the association between the most significant metabolites obtained in the QCBio cohort with several cardiometabolic traits: Glucose, HbA1C, LDL, HDL, Triglycerides, and total cholesterol (Table 3 and Online Supplementary Table 1). Glucose was associated with 40 of the 42 metabolites after Bonferroni correction (Online Supplementary Table 1). The highest evidence of association was expectedly observed for carbohydrates (e.g., fructose and mannose both with $P< 10^{-300}$, Online Supplementary Table 1). HbA1C was associated with 20 of the 42 metabolites, with all amino acid metabolites being significant except 6-bromotryptophan, which was nominally significant ($P = 6.28 \times 10^{-4}$; Online Supplementary Table 1). Only 4 out of 20 lipid metabolites were associated with HbA1C using Bonferroni significance. On the other hand, for LDL and total cholesterol, 23 and 22 metabolites were significant, respectively (Online Supplementary Table 1). All carbohydrates did not show significant associations for both traits (Online Supplementary Table 1). Only two lipid metabolites were not significantly associated with LDL and total cholesterol (deoxycholic acid 12-sulfate* and 3-hydroxydecanoate; Online Supplementary Table 1). LDL and total cholesterol were not associated with the 4 peptide and xenobiotics metabolites (Online Supplementary Table 1). Triglyceride levels were associated with 33 of the 42 metabolites across the 4 classes of metabolites (Online Supplementary Table 1). Interestingly for N6-carboxymethyllysine, which was associated with T2D only in the cohort with CHD patients, no significant association was observed with any of the considered cardiometabolic traits (Online Supplementary Table 1).

3.3 Metabolite correlation and pathway enrichment analysis

Pearson's correlation was calculated between the top 42 metabolites separately in QCBio and QBB cohorts (Figure 3). In both datasets, two main groups of metabolites with positive correlations were observed. These groups contained the same set of metabolites in both datasets (Figure 3). The largest group of correlated metabolites contained the 8 sphingomyelin metabolites (Figure 3). Mannose, glucose, and fructose were negatively correlated with 1,5-anhydroglucitol (1,5-AG) (Figure 3). This is concordant with the opposite direction effect sizes with T2D (e.g., increase of glucose was associated with an increased risk of T2D whereas increase of 1,5-anhydroglucitol (1,5-AG) was associated with a decreased risk of T2D) (Online Supplementary Table 1). Mannose, glucose, fructose, methylsuccinoylcarnitine, gluconate, mannonate*, and eryhtronate* expectedly formed a group of positively correlated metabolites.

TABLE 2 The significant metabolite in the QCBio cohort with P< 10^{-8} and their corresponding results in the QBB cohort.

Biochemical		QCBio				QBB				QBB-Lipids	
		β	P	FDR q_i	95% CI	β	P	FDR q_i	95% CI	β	P
Amino Acids	methylsuccinoylcarnitine (↑)	0.74	1.09E-18	3.12E-04	[0.58 – 0.90]	1.44	1.20E-45	4.68E-04	[1.22 – 1.61]	1.41	3.53E-43
	fructosyllysine (↑)	1.28	1.29E-16	4.68E-04	[0.98 – 1.59]	2.12	1.38E-35	6.24E-04	[1.80 –.2.46]	2.04	7.03E-33
	1-carboxyethylphenylalanine (↑)	0.48	2.40E-14	6.24E-04	[0.36 – 0.60]	0.76	1.71E-19	1.56E-03	[0.59 – 0.91]	0.72	2.84E-17
	N,N,N-trimethyl-5-aminovalerate (↑)	0.96	1.09E-13.	7.02E-04	[0.71 – 1.22]	1.24	4.26E-15	3.20E-03	[0.89 – 1.50]	1.22	1.48E-14
	2-hydroxybutyrate/2-hydroxyisobutyrate(↑)	0.71	5.51E-13.	8.58E-04	[0.53 – 0.91]	0.98	1.20E-26	7.80E-04	[0.79 – 1.15]	0.95	5.40E-25
	3-methyl-2-oxovalerate (↑)	1.17	5.20E-11	1.33E-03	[0.79 – 1.47]	1.85	3.87E-19	1.64E-03	[1.27 – 1.99]	1.78	2.69E-17
	1-carboxyethylvaline (↑)	0.45	1.54E-10	1.48E-03	[0.32 – 0.59]	0.79	2.59E-18	1.79E-03	[0.62 – 0.96]	0.76	8.57E-17
	6 bromotryptophan (↓)	-1.43	5.39E-10	1.87E-03	[-1.90 – -0.99]	-2.73	4.76E-22	1.09E-03	[-3.25 – -2.15]	-2.78	2.49E-22
	3-methyl-2-oxobutyrate (↑)	1.36	3.84E-09	2.34E-03	[0.91 – 1.80]	2.52	1.27E-20	1.33E-03	[1.89 – 2.89]	2.46	3.26E-19
	4-methyl-2-oxopentanoate (↑)	0.95	2.15E-08	2.81E-03	[0.61 – 1.25]	1.51	2.50E-15	2.89E-03	[1.02 – 1.70]	1.47	3.71E-14
Carbohydrates	1,5-anhydroglucitol (1,5-AG) (↓)	-2.15	9.82E-33	7.80E-05	[-2.51 – -1.80]	-4.64	1.33E-68	7.80E-05	[-5.20 – -4.16]	-4.68	4.40E-67
	glucose (↑)	1.7	3.26E-29	1.56E-04	[1.41 – 2.00]	4.68	7.14E-57	1.56E-04	[4.09 – 5.23]	4.64	2.99E-55
	mannose (↑)	1.76	1.01E-27	2.34E-04	[1.45 – 2.09]	3.05	2.61E-54	3.12E-04	[2.68 – 3.45]	2.97	7.85E-52
	erythronate* (↑)	1.07	2.24E-11	1.09E-03	[0.77 – 1.40]	1.7	7.68E-14	3.82E-03	[1.28 – 2.17]	1.68	1.63E-13
	fructose (↑)	0.81	3.38E-11	1.17E-03	[0.57 – 1.05]	3.15	2.25E-55	2.34E-04	[2.77 – 3.56]	3.13	9.74E-54
	ribulonate/xylulonate/lyxonate* (↑)	0.72	6.62E-10	1.95E-03	[0.49 – 0.94]	0.46	4.14E-04	1.61E-02	[0.19 – 0.69]	0.46	4.41E-04
	glucuronate (↑)	0.62	2.57E-09	2.18E-03	[0.42 – 0.83]	0.17	1.63E-01	3.17E-02	[-0.06 – 0.41]	0.18	1.39E-01
	N6-carboxymethyllysine (↑)	0.37	2.24E-08	2.89E-03	[0.25 – 0.51]	0.1	3.80E-01	3.87E-02	[-0.09 – 0.33]	0.07	4.77E-01
Lipids	sphingomyelin (d18:2/24:2)* (↓)	-1.74	1.12E-13	7.80E-04	[-2.04 – -1.18]	-2.59	1.88E-21	1.17E-03	[-2.93 – -1.92]	-2.48	9.00E-20
	sphingomyelin (d18:1/20:1, d18:2/20:0)* (↓)	-2.11	1.56E-11	9.36E-04	[-2.56 – -1.40]	-2.57	3.17E-15	3.12E-03	[-3.10 – -1.88]	-2.42	8.91E-14
	3-hydroxyoctanoate (↑)	0.51	2.23E-11	1.01E-03	[0.37 – 0.67]	0.5	1.43E-09	6.86E-03	[0.34 – 0.66]	0.48	6.38E-09
	1-(1-enyl-palmitoyl)-GPC (P-16:0)* (↓)	-1.26	3.57E-11	1.25E-03	[-1.62 – -0.89]	-1.94	6.30E-15	3.28E-03	[-2.45 – -1.48]	-1.79	8.23E-13
	sphingomyelin (d18:2/24:1, d18:1/24:2)* (↓)	-1.73	8.17E-11	1.40E-03	[-2.17 – -1.17]	-2.9	1.29E-19	1.48E-03	[-3.43 – -2.22]	-2.78	2.97E-18
	sphingomyelin (d18:2/14:0, d18:1/14:1)* (↓)	-1.35	3.73E-10	1.64E-03	[-1.60 – -0.82]	-1.84	7.89E-15	3.35E-03	[-2.04 – -1.21]	-1.79	2.88E-14
	lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) (↓)	-1.58	3.74E-10	1.72E-03	[-2.08 – -1.10]	-1.7	5.78E-10	6.55E-03	[-2.27 – -1.19]	-1.67	1.43E-09
	sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2)* (↓)	-1.54	5.35E-10	1.79E-03	[-1.90 – -0.98]	-2.29	1.68E-16	2.34E-03	[-2.65 – -1.64]	-2.2	1.93E-15

(Continued)

10.3389/fendo.2025.1531525

TABLE 2 Continued

Biochemical		QCBio				QBB				QBB-Lipids	
		β	P	FDR q_i	95% CI	β	P	FDR q_i	95% CI	β	P
	deoxycholic acid 12-sulfate* (↑)	0.27	1.49E-09	2.03E-03	[0.18 – 0.36]	0.29	5.25E-16	2.57E-03	[0.22 – 0.36]	0.28	9.63E-15
	3-hydroxydecanoate (↑)	0.39	2.53E-09	2.11E-03	[0.26 – 0.52]	0.66	2.90E-12	4.84E-03	[0.47 – 0.83]	0.64	1.44E-11
	1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)* (↓)	-0.99	3.02E-09	2.26E-03	[-1.32 – -0.67]	-1.47	8.21E-16	2.65E-03	[-1.84 – -1.13]	-1.43	1.54E-14
	1-stearoyl-2-arachidonoyl-GPE (18:0/20:4) (↑)	0.66	4.93E-09	2.42E-03	[0.43 – 0.87]	1.02	8.36E-17	2.26E-03	[0.72 – 1.19]	0.92	1.18E-12
	sphingomyelin (d18:2/23:1)* (↓)	-1.22	5.44E-09	2.50E-03	[-1.56 – -0.78]	-1.69	3.17E-13	4.13E-03	[-2.03 – -1.18]	-1.65	6.99E-13
	1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)* (↑)	0.52	5.49E-09	2.57E-03	[0.33 – 0.68]	0.96	1.31E-23	9.36E-04	[0.72 – 1.09]	0.89	1.10E-18
	sphingomyelin (d18:2/18:1)* (↓)	-1.42	5.94E-09	2.65E-03	[-1.80 – -0.89]	-1.82	1.23E-12	4.52E-03	[-2.25 – -1.29]	-1.75	6.22E-12
	2-aminoheptanoate (↑)	0.73	1.30E-08	2.73E-03	[0.48 – 0.98]	0.35	1.53E-02	2.29E-02	[0.06 – 0.64]	0.36	1.48E-02
	sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2)* (↓)	-0.91	2.72E-08	2.96E-03	[-1.17 – -0.56]	-1.38	1.47E-15	2.81E-03	[-1.62 – -0.98]	-1.36	7.68E-15
	1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)* (↓)	-1.23	3.95E-08	3.04E-03	[-1.67 – -0.80]	-1.38	1.44E-09	6.94E-03	[-1.85 – -0.95]	-1.24	5.77E-08
	1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6)* (↑)	0.39	5.95E-08	3.20E-03	[0.24 – 0.52]	0.51	8.32E-12	5.07E-03	[0.34 – 0.62]	0.45	6.13E-09
	1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)* (↓)	-1.15	5.99E-08	3.28E-03	[-1.57 – -0.75]	-1.69	1.19E-13	4.06E-03	[-2.16 – -1.27]	-1.56	1.73E-11
Peptides	phenylacetylglutamine (↑)	0.36	2.74E-10	1.56E-03	[0.26 – 0.48]	0.2	7.20E-03	2.10E-02	[0.04 – 0.33]	0.21	4.80E-03
	prolylglycine (↑)	0.39	4.52E-08	3.12E-03	[0.26 – 0.54]	0.25	1.72E-03	1.84E-02	[0.11 – 0.42]	0.23	4.05E-03
Xenobiotics	mannonate* (↑)	0.99	3.06E-17	3.90E-04	[0.77 – 1.23]	2.34	2.11E-47	3.90E-04	[2.04 – 2.67]	2.29	6.88E-45
	gluconate (↑)	0.92	2.02E-15	5.46E-04	[0.69 – 1.14]	1.9	2.07E-41	5.46E-04	[1.58 – 2.13]	1.88	4.03E-40

The β and P values come from the regression models (effect sizes and P-values); QBB-Lipids is the analysis that includes LDL, HDL, Total cholesterol, and Triglycerides as covariates. Underlined metabolites are not associated with Bonferroni significance threshold. * is part of the metabolite name.

10.3389/fendo.2025.1531525

Five pathways were obtained in the QCBio dataset Table 4). The most significant pathway was Valine, leucine and isoleucine biosynthesis (FDR P = 1.69×10^{-4}). Galactose metabolism, Valine, leucine and isoleucine degradation, Fructose and mannose metabolism, and Pantothenate and CoA biosynthesis were also significant with FDR P< 0.05. The results from the QCBio and QBB common metabolites yielded 3 significant pathways, which were also present in the QCBio analysis (Valine, leucine and isoleucine degradation and biosynthesis, and galactose metabolism; Table 4). In the QBB dataset, only Valine, leucine and isoleucine biosynthesis was common with previous analysis (Table 4). Arginine biosynthesis, Alanine, aspartate and glutamate metabolism, Glyoxylate and dicarboxylate metabolism, and Glycerophospholipid metabolism were the remaining significant pathways (FDR P< 0.05; Table 4).

3.4 Sensitivity analysis and robustness

Although age was added as a covariate to mitigate the age difference between T2D patients and controls in the QBB cohort, we ran further analysis by selecting an age matched non-T2D set from the QBB cohort. Forty-one of the top 42 metabolites identified in the full data analysis remained significant (Supplementary Table 1). Additionally, to further address the large sample size difference between the T2D and non-T2D groups in the QBB cohort, we randomly selected 272 non-T2D individuals from the QBB cohort and ran the analysis (with covariates) 100 times. We found that 41 metabolites were always significantly different according to the Bonferroni threshold across the 100 runs (Supplementary Table 1).

Furthermore, we performed another analysis on the QBB cohort that considered AGEs. Since AGEs play an important role in the pathogenesis of chronic complications of diabetes and are closely related to blood lipids, we performed univariate analysis between AGEs and LDL, HDL, and total cholesterol in the QBB cohort. Our results did not show significant differences between AGEs and lipids (Supplementary Table 2).

3.5 Machine learning-based predictive modeling

3.5.1 Binary classification of T2D

In the QCBio cohort, SVM showed the highest performance based on the AUC for all ML models except for the top metabolites + covariates model, where it was outperformed by LDA (AUC = 0.904 for LDA vs 0.878 for SVM; Figure 4A). The RF and SVM performances were similar, which made them the preferred predictive ML models. For SVM, the metabolites only, metabolites + covariates, and top metabolites + covariates models yielded similar AUCs (0.885, 0.886, and 0.878, respectively; Figure 4A). In the QBB cohort, similar trends were observed in both analyses (balanced and imbalanced data): adding covariates did not significantly improve the performance, choosing the top 20 metabolites showed comparable performance to the full model with a slight decrease in performance, and RF and SVM showed the highest performances (AUCs > 0.93; Figure 4B).

The performance of XGBoost and LDA was much lower than that of SVM and RF for most models, and the AUC difference with the best model exceeded 0.2 (i.e., LDA vs SVM in the QCBio cohort for the Metabolites + covariates model; Figure 4A). In terms of accuracy, SVM and RF for the metabolites + covariates and top metabolites + covariates models showed accuracies greater than 80% in the QCBio cohort and greater than 87% in the QBB cohort (Supplementary Figure 2).

In the QBB cohort, we contrasted our baseline no-SMOTE approach with models trained with SMOTE (Supplementary Material Figure 3). Across all four feature sets, SMOTE did not produce a systematic improvement in AUC. Without SMOTE, the leading algorithms were LDA (covariates only), SVM (metabolites only), SVM (metabolites + covariates), and RF (top metabolites + covariates). With SMOTE, the best methods shifted slightly to LDA, RF, RF, and SVM, respectively, but their AUCs were very close to those of the corresponding no-SMOTE leaders. These results indicate that our undersampling-with replication strategy provides equal or better predictive accuracy than SMOTE while limiting the risk of overfitting.

Among the top 20 metabolites selected by the ElasticNet algorithm for both QCBio and QBB, five metabolites were common in both cohorts: 1,5-anhydroglucitol (1,5-AG), mannose, glucose, acisoga, and N,N,N-trimethyl-5-aminovalerate (Figure 5). Eight and nine metabolites had negative effect sizes in QCBio and QBB, respectively (Figure 5). The effect sizes were relatively larger in the QBB cohort (e.g., the effect size of 1,5-anhydroglucitol (1,5-AG) was -0.92 in QCBio vs -1.76 in QBB; 0.32 for glucose in QCBio and 1.63 in QBB). The use of ElasticNet to select the 20 most important metabolites did not decrease the accuracy of the ML models in predicting T2D in either cohort. We compared all ML algorithms quantitatively using the DeLong test to compare AUCs. For both cohorts, the AUCs of XGBoost were significantly different from those of other ML algorithms, whereas the AUCs of RF, SVM, and LDA were not significantly different (Supplementary Table 3).

3.6 Metabolite risk score to predict T2D

In each cohort, one model was developed in the training dataset and evaluated in the testing dataset. Both models performed well in discriminating T2D patients. The odds ratios (ORs) were 2.153 (P = 1.2×10^{-15}) and 2.32 (P = 2.91×10^{-20}) for QCBio and QBB, respectively (Figures 6A, B). The AUC was greater in QBB (0.958 for QBB vs 0.872 for QCBio; Figures 6A, B). We also developed an MRS in one cohort and evaluated its performance in the other cohort. The MRSdeveloped in QCBio and tested in QBB (MRS_{qcbio}) performed much better than the MRS developed in QBB and tested in QCBio (MRS_{qbb}) (Figures 6C, D). The OR for MRS_{qcbio} was 10.52 (AUC = 0.934, P = 2.27×10^{-85}; Figure fFig: MRS C). The OR for MRS_{qbb} was 6.285 (AUC = 0.863, P = 1.1×10^{-53}; Figure 6D). To evaluate the robustness of the MRS_{qcbio} results with respect to the lower number of T2D+ |CHD- individuals (N = 272) compared to

TABLE 3 The list of metabolites that were exclusively significant with T2D in only one cohort. .

Biochemical	QCBio		QBB		HbA1C		Glucose		LDL		HDL		Triglyceride		Total cholesterol	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Significant in QBB but not in QCBio																
gamma-glutamylglutamine	0.10	5.12E-01	-2.61	1.79E-20	-0.43	4.07E-02	-0.22	4.03E-19	-0.16	4.19E-02	0.04	1.35E-01	-0.48	1.87E-18	-0.33	1.01E-07
gamma-glutamylthreonine	-0.16	4.02E-01	-2.66	1.47E-17	-0.29	1.73E-01	-0.13	2.30E-07	-0.16	4.97E-03	-0.04	1.20E-01	-0.15	8.97E-03	-0.26	5.70E-05
glutamine	0.30	2.68E-01	-4.87	1.43E-18	-1.15	7.03E-03	-0.32	4.30E-10	-0.06	6.02E-01	-0.11	2.68E-02	-0.52	2.57E-06	-0.39	1.79E-03
pseudouridine	0.26	1.37E-01	-3.27	3.81E-18	-0.25	3.82E-01	-0.23	5.60E-11	-0.02	8.07E-01	-0.08	2.71E-02	0.29	1.34E-04	0.029	7.55E-01
3-(3-amino-3-carboxypropyl)uridine*	0.17	1.22E-01	-1.96	2.18E-17	-0.30	1.04E-01	-0.12	2.30E-07	0.03	5.78E-01	-0.14	2.70E-11	0.28	5.63E-09	0.005	9.23E-01
N,N,N-trimethyl-alanylproline betaine (TMAP)	0.26	6.88E-02	-2.49	3.09E-15	0.29	1.12E-01	-0.024	2.80E-01	0.24	2.47E-06	-0.29	9.92E-42	0.28	3.43E-09	0.07	1.92E-01
3-methoxytyrosine	-0.37	3.17E-02	-3.38	4.19E-25	-0.49	1.93E-02	-0.17	6.60.E-12	-0.12	4.32E-02	0.04	1.31E-01	-0.33	1.56E-09	-0.21	7.55E-04
gamma-glutamylcitrulline*	-0.28	1.53E-02	-1.98	4.18E-22	-0.34	2.24E-02	-0.11	4.20E-10	-0.008	8.46E-01	0.10	6.98E-09	-0.25	1.77E-10	-0.015	7.30E-01
choline phosphate	0.61	1.41E-02	2.99	6.55E-17	1.76	1.67E-08	0.43	1.40E-30	0.45	1.87E-07	0.05	1.82E-01	0.61	6.88E-14	0.78	7.76E-17
pyruvate	0.43	1.43E-03	2.87	4.92E-28	1.32	2.26E-08	0.61	1.40E-107	0.11	1.05E-01	-0.25	1.19E-19	1.04	8.72E-66	0.30	2.31E-05
methyl glucopyranoside (alpha + beta)	-0.12	1.04E-03	-0.74	2.62E-15	-0.02	6.97E-01	-0.022	2.50E-09	-0.009	2.33E-01	0.003	3.99E-01	0.001	8.56E-01	-0.008	3.49E-01
1-palmitoyl-GPE (16:0)	0.48	8.12E-05	1.01	1.00E-15	0.51	1.92E-05	0.16	5.20E-28	0.19	9.53E-09	0.004	7.90E-01	0.79	6.22E-156	0.53	6.10E-51
Significant in QCBio but not in QBB																
N6-carboxymethyllysine	0.37	2.24E-08	0.10	3.80E-01	0.32	7.17E-04	0.023	4.60E-02	0.04	9.22E-02	-0.02	3.56E-02	0.06	2.53E-02	0.04	1.47E-01
glucuronate	0.62	2.57E-09	0.17	1.63E-01	0.33	4.10E-03	0.16	1.80E-32	-0.02	5.89E-01	-0.03	3.88E-02	0.22	2.75E-13	0.05	1.33E-01
2-aminoheptanoate	0.73	1.30E-08	0.35	1.53E-02	0.10	4.46E-01	0.087	8.80E-08	-0.22	3.79E-09	-0.05	1.29E-03	0.005	8.93E-01	-0.26	1.31E-10
phenylacetylglutamine	0.36	2.74E-10	0.20	7.20E-03	0.25	1.06E-03	0.041	1.30E-05	-0.04	7.53E-02	0.03	1.95E-03	-0.02	3.02E-01	-0.02	5.00E-01
prolylglycine	0.39	4.52E-08	0.25	1.72E-03	0.09	2.24E-01	0.061	1.60E-10	-0.06	5.25E-03	-0.07	6.37E-15	0.25	1.22E-34	-0.03	2.67E-01
ribulonate/xylulonate/lyxonate*	0.72	6.62E-10	0.46	4.14E-04	0.19	1.06E-01	0.18	2.20E-34	-0.12	5.99E-04	0.001	9.31E-01	0.09	3.25E-03	-0.08	3.90E-02

The columns of HbA1C, Glucose, LDL, HDL, Triglycerides, and Total Cholesterol show the results of association between the listed metabolites and these cardiometabolic traits in the QBB cohort only. Underlined metabolites are not associated with Bonferroni significance threshold.

10.3389/fendo.2025.1531525

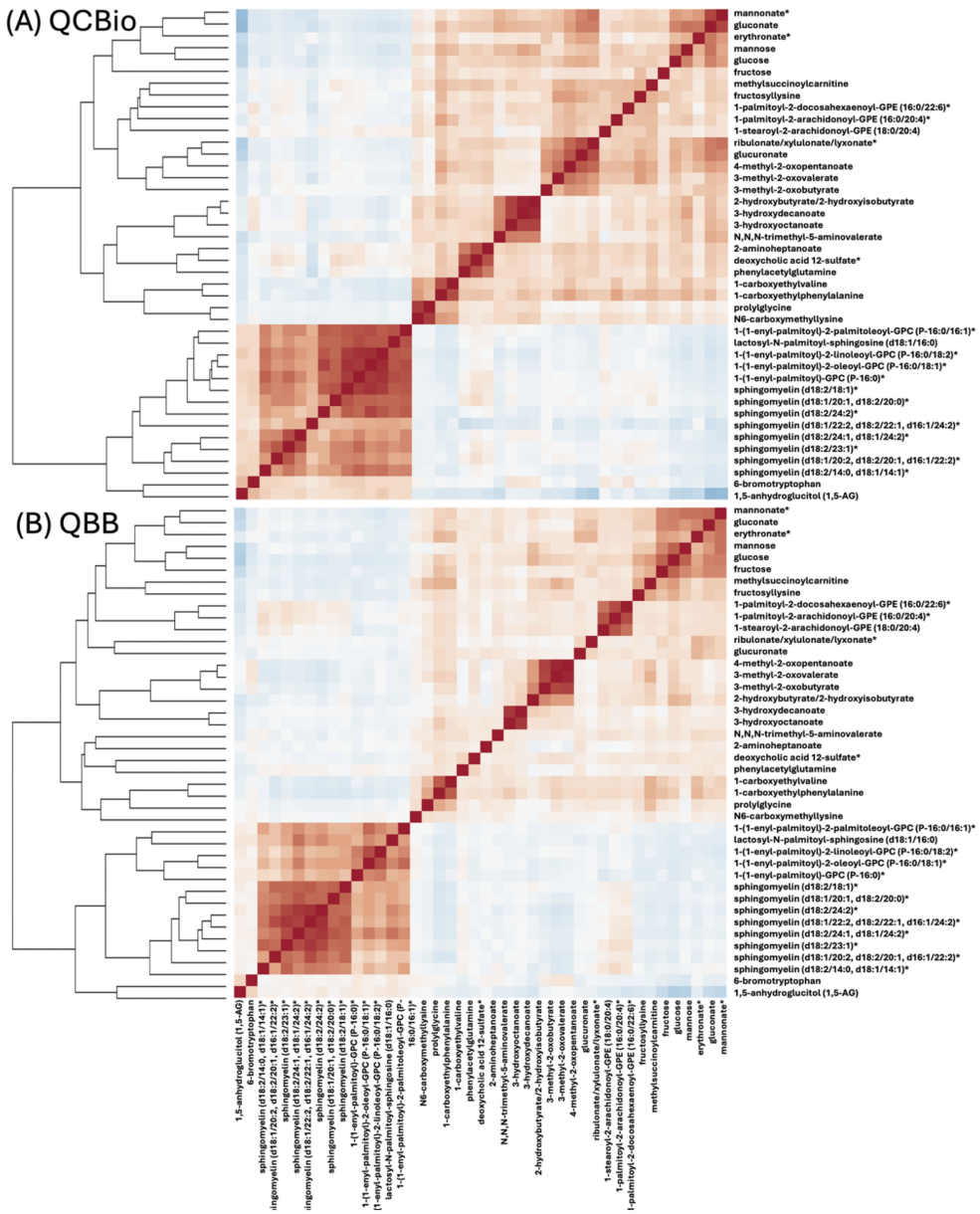


FIGURE 3
A heat map representation of Pearson's correlation matrix of top-42 metabolites in **(A)** QCBio and **(B)** QBB cohorts. Correlations among metabolites were obtained by deriving a Pearson's correlation coefficient between each pair of metabolites. The color scheme corresponds to correlation direction (red: positive and blue: negative).

that of T2D- |CHD- individuals (N = 2,438), we selected 272 individuals from the T2D- |CHD- group and tested MRS_{qcbio}. The performance improved, and the OR was 19.334 [11.921 - 31.357] (Supplementary Figure 4). The OR of the top quintile vs remaining quintiles of MRS_{qbb} tested in the QCBio data was 24.77 ($P = 4.58 \times 10^{-54}$) (Supplementary Table 4). Adjusting the model for HbA1C decreased the OR to 21.18 (Supplementary Table 4). Removing the 3 metabolites with the highest coefficients (i.e., 1,5-anhydroglucitol (1,5-AG), mannose, and glucose) led to ORs of 5.96 and 9.26 when accounting for HbA1C vs not accounting for HbA1C, respectively (Supplementary Table 4). After splitting by deciles, the ORs were expectedly greater than those after splitting by quintiles (OR = 31.87 for the decile model vs 24.77 for the quintile model) (Supplementary Table 4). The list of metabolites that were used for MRS_{qcbio} and MRS_{qbb} and their effect sizes are shown in Table 5. Furthermore, we ran an extra analysis to test the association between risk scores and HbA1C in non-diabetic individuals. The aim of this analysis was to determine whether these risk scores could be valuable for predicting the latent variable that is commonly used to define T2D. Hence, we used the QBB dataset after removing T2D patients (2,438 individuals). Then, we ran regression analysis between MRS and HbA1C in non-T2D patients including

10.3389/fendo.2025.1531525

covariates (sex, age, and BMI). The analysis revealed a significant association ($P = 3.09 \times 10^{-7}$) and a positive correlation between HbA1C and risk scores (data 345 not shown).

4 Discussion

We studied the metabolomic signatures of T2D patients stratified by the presence or absence of CHD in a Middle Eastern cohorts from the Qatar BioBank and Qatar Cardiovascular Biorepository. Univariate analysis was performed to identify metabolites that were differentially expressed between T2D patients who had CHD and T2D patients without CHD. In addition, matching and resampling methods were used to tackle the cohorts class imbalance problem. Pathway enrichment analysis was utilized to observe the significant metabolic alterations on a pathway level related to T2D, in the presence and absence of CHD. ML modeling was used to predict T2D in the presence and absence of CHD. Metabolite risk scores were developed and showed great discriminative power for T2D, especially in the CHD cohort. This study is important for dissecting the metabolomics signatures of two metabolic diseases that are biologically interlinked. This study sheds light on metabolites that behave differently between T2D patients and non T2D patients with respect to CHD status. Delaying or preventing CHD in T2D patients can have a major clinical impact.

In our study, we compared several ML models that included all metabolites and covariates, and we also developed a model that only included the top metabolites. The aim of this model was to assess the performance of using a smaller set of metabolites as a practical and cost-effective choice in clinical practice. Our results provide strong evidence that many metabolites are altered in T2D patients with CHD. Therefore, this small panel of metabolites can be used as a diagnostic/predictive tool after further clinical validation. The discovered metabolites could be further investigated for therapeutic interventions to reduce the incidence of CHD in T2D patients.

Our study identified several previously reported metabolites that are associated with T2D. These metabolites were replicated in both the QCBio and QBB cohorts. 1,5-anhydroglucitol (1,5-AG) was the most significant metabolite in both cohorts. This metabolite has been identified as a marker for glycemic control (38, 52, 53). The metabolite was decreased in T2D patients, but the decrease in the cohort without CHD was two-fold lower than that in the cohort with CHD. Other known carbohydrates, including glucose, mannose, and fructose, were associated with T2D in both cohorts.

We investigated metabolites that were associated with T2D in QCBio (CHD cohort) but not in QBB. Since the size of the QCBio dataset is much smaller (one-third) than the QBB dataset (Supplementary Figure 1), the identification of such metabolites is unlikely because of the lower statistical power of QCBio. One of these metabolites is N6-carboxymethyllysine (CML), which is a type of advanced glycation end product (AGE) that is commonly used as a marker for analyzing AGEs in food (54, 55). AGEs are a group of bioactive molecules that result from nonenzymatic glycation of proteins, lipids, and nucleic acids and are associated with the progression of degenerative diseases such as diabetes and atherosclerosis (56, 57). AGEs may also contribute to vascular complications in T2D patients (58). In patients with CHD, elevated serum AGEs have been reported even without any comorbidities, such as T2D (59). Increased CML levels are known to be associated with arterial stiffness (60). In the present study, CML levels were found to be significantly associated with CHD in individuals with T2D, while mean CML levels were similar between CHD patients and non-CHD patients without T2D. Moreover, the levels of CML increased significantly in patients with both CHD and T2D (Supplementary Figure 5).

Phenylacetylglutamine (PAGln) was also significant in the QCBio cohort but not in the QBB cohort. Recently, PAGln was identified as a novel metabolic biomarker for ischemic stroke (61). PAGln is a gut microbiota-derived metabolite that may induce cardiovascular events by activating platelets and increasing the risk of thrombosis (62). The PAGln level appeared to be significantly increased in T2D patients in recent studies (63, 64). In our study, the levels of PAGln were increased in both the QCBio and QBB cohorts for T2D patients, but the highest levels were observed in T2D patients who had CHD (Supplementary Figure 5). These findings are consistent with the results of Nemet et al. (63), who indicated that elevated levels of PAGln can predict the occurrence of adverse cardiac events such as heart attack and stroke in patients with T2D.

Another metabolite that showed statistical significance in the CHD cohort but not in the QBB cohort was glutamine. Glutamine is

TABLE 4 Pathway enrichment analysis using MetaboAnalyst 6.0.

Metabolite Set	Total	Hits	FDR P
QCBio			
Valine, leucine and isoleucine biosynthesis	8	4	1.69E-04
Galactose metabolism	27	4	0.0178
Valine, leucine and isoleucine degradation	39	4	0.0395
Fructose and mannose metabolism	20	3	0.0395
Pantothenate and CoA biosynthesis	20	3	0.0395
QBB			
Valine, leucine and isoleucine biosynthesis	8	5	3.91E-05
Arginine biosynthesis	14	6	3.91E-05
Alanine, aspartate and glutamate metabolism	28	6	0.00242
Glyoxylate and dicarboxylate metabolism	31	5	0.0296
Glycerophospholipid metabolism	36	5	0.0472
QCBio + QBB			
Valine, leucine and isoleucine biosynthesis	8	4	2.36E-05
Valine, leucine and isoleucine degradation	39	4	0.0118
Galactose metabolism	27	3	0.0411

Total: the number of metabolites in the set; Hits: the number of metabolites intersecting with our top metabolites and the metabolite set; FDR P: the FDR corrected P value; QCBio + QBB signifies the analysis that included metabolites observed in both cohorts; Colors shows the common results between analyses.

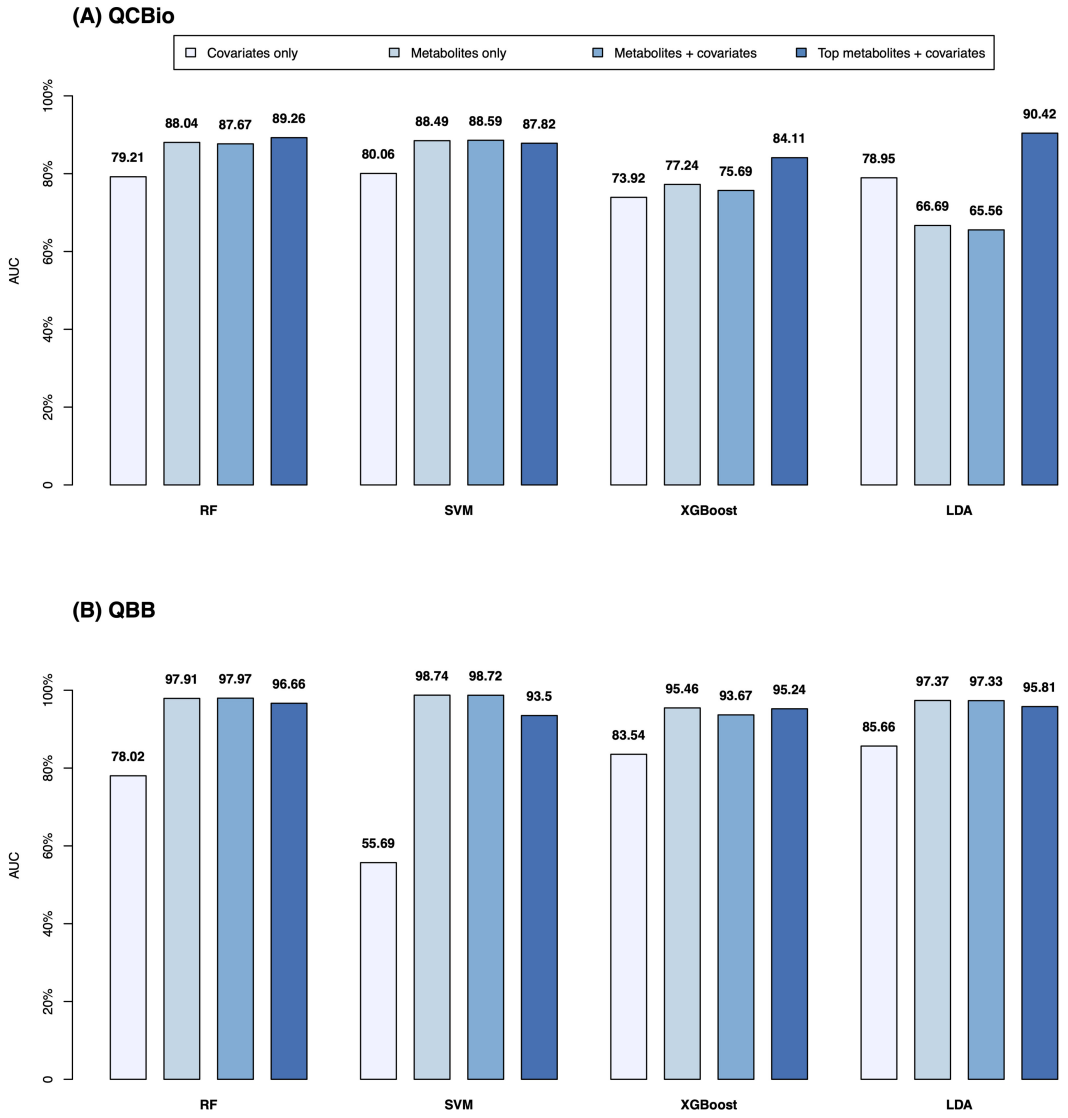


FIGURE 4
AUC of various ML models to predict T2D for 4 different settings. The ML models, RF, SVM, XGboost, and LDA are presented on the X-axis. Y-axis is the AUC. The numbers on top of each bar are the actual AUC values (in %). The bars from left to right of each model, colored as ice blue represent the Covariates only setting; light blue represent Metabolites only setting; cyan represent Metabolites and covariates setting; and dark blue represent Top 20 metabolites + covariates setting. **(A)** The AUC was computed in the QCBio cohort; and **(B)** The AUC was computed in the QBB cohort.

an amino acid that plays a significant role in the biosynthesis of proteins. Glutamine deficiency is associated with many conditions, including type 2 diabetes (65, 66) and insulin resistance (67, 68), which are considered risk factors for CVD (69). In our study, glutamine levels were reduced in T2D patients compared with non-T2D patients in the QCBio cohort, in accordance with previous findings (66, 70–72). Glutamine serves as an L-arginine precursor for the production of nitric oxide and mitigates risk factors for CVD (73). A recent research proposal aimed at investigating the hypothesis that targeting glutamine-dependent pathways in monocytes/macrophages may limit the inflammatory phenotype and cardiovascular events in diabetic patients (https://anr.fr/Project-ANR-19-CE17-0030). Since gamma-glutamylthreonine and gamma-glutamylglutamine are associated with pathways involving glutamine as a substrate, their levels expectedly showed similar trends in our data.

Our study showed results consistent with those of metabolomics studies of T2D in other regions of the world. For example, our analysis showed that the 1,5-anhydroglucitol carbohydrate content was significantly decreased in T2D patients, regardless of CHD status, which is consistent with the findings of Suhre et al. (37), who studied the German population. Similar observations were observed for increased levels of glucose, mannose, 3-methyl-2-oxovalerate, and erythronate in T2D patients. An identical trend was observed in a Chinese cohort for the glucose metabolite, where its level was increased in T2D patients who also had CHD (74). Another study (75) confirmed previous observations and showed a significant increase in glucose

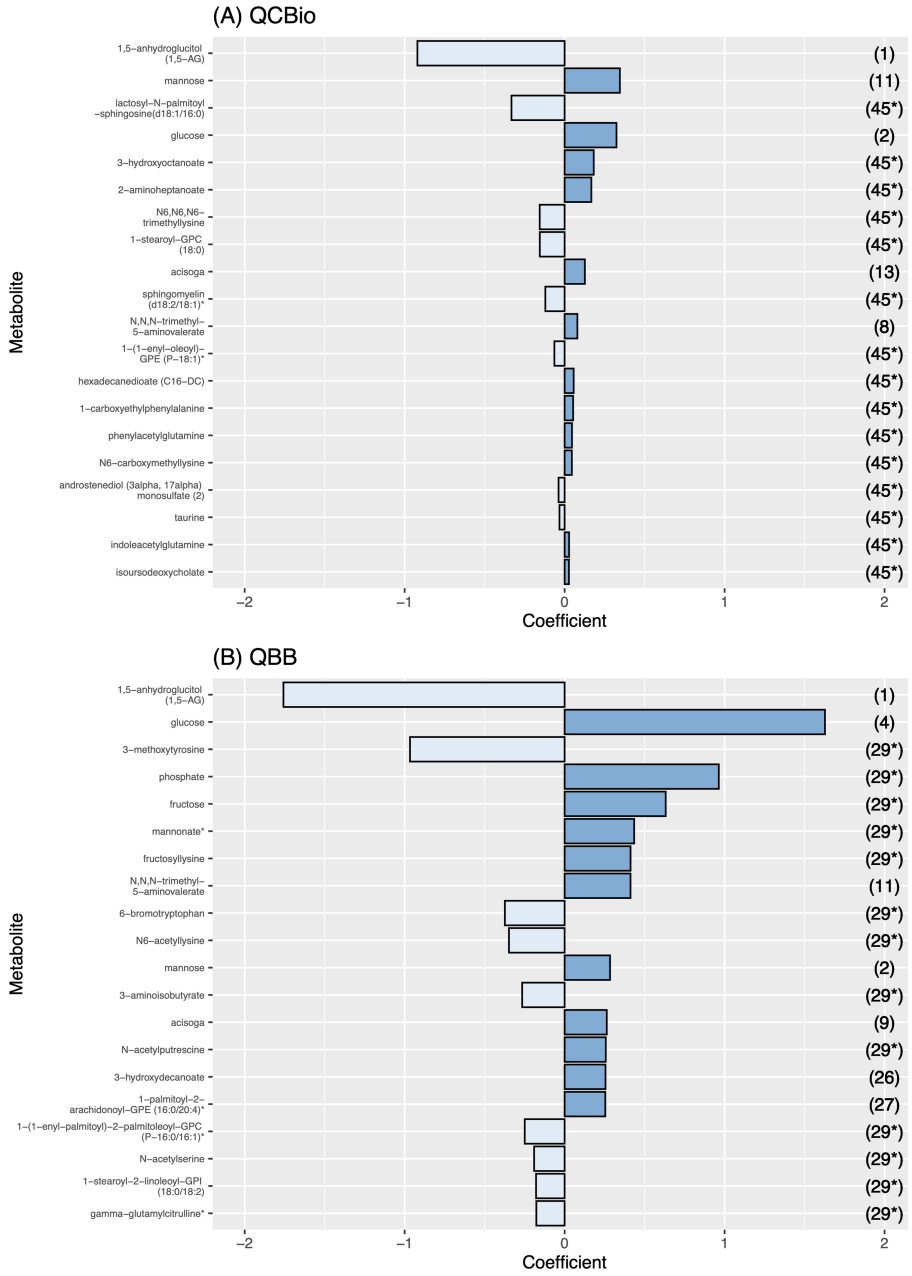


FIGURE 5
The effect size of the 20 most important metabolites for each cohort. The effect size is presented in the X-axis. Metabolite names are presented in the Y-axis. The dark blue bars represent a positive effect, while the light blue ones represent a negative effect. The numbers in the right Y-axis represent the rank of the metabolite in the other cohort. **(A)** Metabolite effect size on QCBio cohort; and **(B)** Metabolite effect size on QBB cohort.

metabolite levels in T2D patients with CHD in a Chinese population. A study (76) of a Malaysian cohort showed that N6-carboxymethyllysine metabolite levels were significantly increased in diabetic and ischemic heart disease (IHD) patients compared with those in T2D patients but not in IHD patients, which matches our findings, where these metabolite levels increased in diabetic CHD patients compared with those in T2D patients without CHD.

Furthermore, we investigated the CHD-specific metabolites, where we compared the metabolites from non-T2D patients in QBB and non-T2D CHD patients in QCBio. CHD-related metabolites were identified and were consistent with the literature including ornithine, 3-amino-2-piperidone, Sphingosine-1-phosphate (S1P), aspartate (see Online Table 2). For instance, Virak et al. (77), indicated that the citrulline-to-ornithine ratio is a critical risk factor for HF and CHD. Similar findings have been observed in other studies (78, 79). As a consequence, any disturbance in the ornithine cycle causes increase of the 3-amino-2-piperidone levels, which damages cardiovascular system (80). Previous study showed that the Sphingosine-1-phosphate plays an important role in the occurrence and development of many

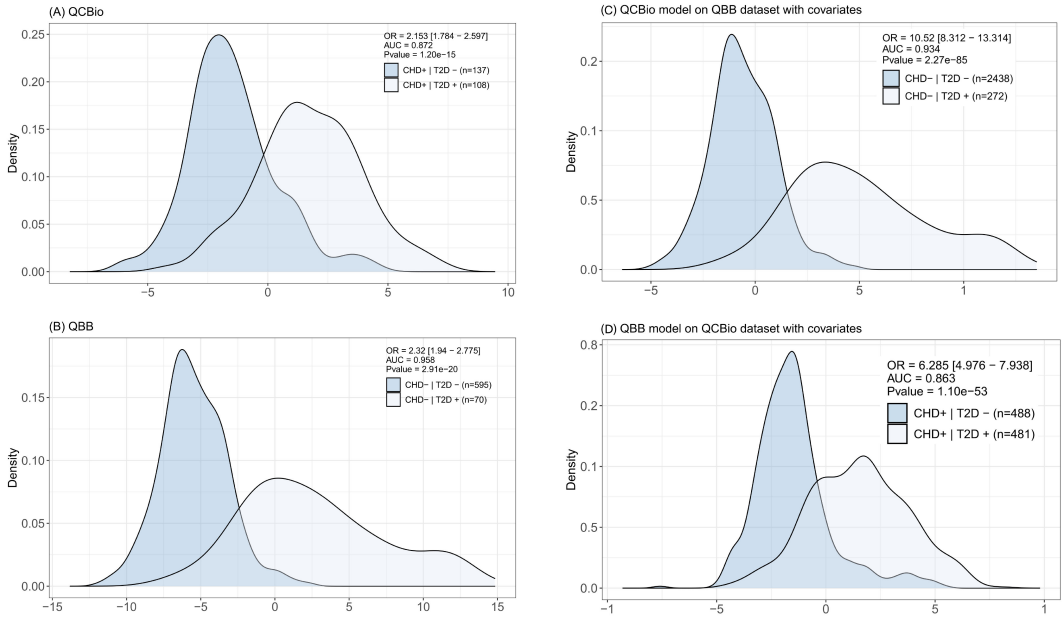


FIGURE 6
Distribution of the metabolite risk scores (MRS) for each of the reported classes. In top-right we report the OR value, AUC (0–1 scale), and the P value. For (C, D) the model is trained in one of the cohorts and tested in the other. Covariates (Gender, BMI, Age) are included in the model. **(A)** The MRS was computed in the QCBio dataset and tested in the QCBio dataset. Light blue represents the patients with both diseases (CHD+T2D +) and dark blue represents the CHD patients (CHD+T2D-); and **(B)** The MRS was computed in the QBB dataset and tested in the QBB dataset. Light blue represents the T2D patients (CHD-T2D+) and dark blue represents the healthy individuals (CHD-T2D-). **(C)** The MRS was computed in the QCBio dataset and tested in the QBB dataset. Light blue represents the T2D patients (CHD-T2D+) and dark blue represents the healthy individuals (CHD-T2D-); and **(D)** The MRS was computed in the QBB dataset and tested in the QCBio dataset. Light blue represents the patients with both diseases (CHD+T2D+) and dark blue represents the CHD patients (CHD+T2D-).

cardiovascular diseases (81–84). Numerous studies investigated the association between aspartate metabolite and CVD diseases (85–87). They revealed that elevated aspartate level may indicate an increased CVD risk (85–87).

Pathway enrichment analysis showed that the galactose metabolism was, as expected, significantly associated with T2D in both cohorts. This has been observed in previous studies (38, 88, 89). Leucine, isoleucine, and valine, which are branched-chain amino acids (BCAAs), also showed significant association with T2D in both cohorts (Table 4). There has been consensus that this class of amino acids is among the strongest biomarkers of T2D as well as other pathogenesis metabolic disturbances in obesity and cardiovascular diseases (90–92). Also, Starch and sucrose metabolism was among the top significant metabolisms in both cohorts (Table 4), which is in accordance with many previous studies (93–95). For instance, Sun et al. (95) performed metabolic pathway analysis with the MetPA tool, and they found that starch and sucrose metabolism was one of the potential biomarkers for T2D. Furthermore, Arginine biosynthesis was found associated with T2D in the QBB cohort only. Arginine is a precursor for nitric oxide, and was shown to be reduced in patients with T2D due to a decreased conversion of arginine to nitric oxide (96). Moreover, the long-term oral L-Arginine administration showed an improvement of hepatic insulin in patients with T2D (97). This validates our findings and adds evidence to the importance of Arginine in the pathophysiology of T2D. The non-significance of Arginine biosynthesis pathway in our CHD cohort might be due to a reduced sample size, or due to the disruption of Arginine metabolite with the CHD cohort as shown on the same data previously (40).

ML models were applied to predict T2D in the presence and absence of CHD using metabolites and demographic data. These models account for nonlinear relationships between metabolites and might yield better predictions. The F_1 scores for predicting T2D in the QBB (non-CHD) cohort were greater than those in the QCBio cohort. The scores were > 74% for both the RF and SVM models for all classes. The accuracy values were relatively high and reached 80%. In the present study, we accounted for class imbalance to mitigate the potential of bias in ML results by selecting subsets of each class to make them balanced. So, we (i) established an age-matched non-T2D control group from the QBB cohort, which validated 41 of the 42 metabolites found in the complete analysis and (ii) downsized the non-T2D group (n=272) 100 times, redoing the analysis with covariates each time. In all 100 resampled datasets, 41 metabolites continued to be significant following the Bonferroni correction. These outcomes show that our results are resilient to both age disparity and class disparity and are not influenced by the unequal case-control ratios across groups (Supplementary

10.3389/fendo.2025.1531525

TABLE 5 The list of top 20 metabolites in the metabolite risk score developed in QCBio and QBB.

MRS_{qcbio}		MRS_{qbb}	
Metabolite name	Effect size	Metabolite name	Effect size
1,5-anhydroglucitol (1,5-AG)	-0.920	1,5-anhydroglucitol (1,5-AG)	-1.758
lactosyl-N-palmitoyl-sphingosine(d18:1/16:0)	-0.332	3-methoxytyrosine	-0.967
N6,N6,N6-trimethyllysine	-0.156	6-bromotryptophan	-0.373
1-stearoyl-GPC (18:0)	-0.155	N6-acetyllysine	-0.348
sphingomyelin (d18:2/18:1)*	-0.120	3-aminoisobutyrate	-0.265
1-(1-enyl-oleoyl)-GPE (P-18:1)*	-0.064	1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)*	-0.249
androstenediol (3alpha, 17alpha) monosulfate (2)	-0.038	N-acetylserine	-0.191
taurine	-0.032	1-stearoyl-2-linoleoyl-GPI (18:0/18:2)	-0.178
isoursodeoxycholate	0.027	gamma-glutamylcitrulline*	-0.177
indoleacetylglutamine	0.028	1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)*	0.254
N6-carboxymethyllysine	0.045	3-hydroxydecanoate	0.255
phenylacetylglutamine	0.046	N-acetylputrescine	0.257
1-carboxyethylphenylalanine	0.053	acisoga	0.264
hexadecanedioate (C16-DC)	0.056	mannose	0.284
N,N,N-trimethyl-5-aminovalerate	0.080	N,N,N-trimethyl-5-aminovalerate	0.412
acisoga	0.127	fructosyllysine	0.412
2-aminoheptanoate	0.167	mannonate*	0.435
3-hydroxyoctanoate	0.182	fructose	0.632
glucose	0.324	phosphate	0.964
mannose	0.345	glucose	1.628

* is part of the metabolite name.

Material). For binary classification, which we used to predict T2D vs non-T2D within each cohort, selecting 20 metabolites instead of the 641 tested metabolites led to similar performance (similar AUC and similar accuracy). The RF and SVM models exhibited similar performances and outperformed the XGBoost and LDA models. The RF model in the QBB showed an AUC of 0.96 for the top metabolites + covariates model, which was greater than the AUC in QCBio (0.89). Since CHD is a cardiometabolic disorder, metabolism is disrupted and might overlap with T2D metabolism disruption, which makes the prediction of T2D in CHD patients slightly more difficult.

Metabolite risk scores were also developed to predict T2D using the QCBio and QBB cohorts. MRS assumes linear relationships between metabolites and can be easily integrated in clinical practice. It is calculated as a weighted sum of metabolites and prespecified coefficients. Similar MRSs were developed previously in 4 Finnish cohorts using 3 metabolites (98). In the Finnish study, the top 20% of individuals with respect to their MRS had a ten-fold increased risk of developing T2D, and the OR per 1 standard deviation (SD) increase was 1.76. Our MRS comprised 20 metabolites, which is 17 more metabolites than in the Finnish study. In our study, the OR per 1 SD increase was 10.52 in MRS_{qcbio}, which was developed in the CHD cohort (QCBio). Individuals in the top MRS_{qcbio}quintile had a 24.77-fold increased risk of developing T2D. Adjusting for HbA1C reduced the performance to an OR of 21.18. Removing the most important metabolites from MRS_{qcbio}, such as glucose and mannose, and adjusting for HbA1C led to an OR of 13.19 for the top quintile. MRS_{qcbio}performed better than MRS_{qbb}in predicting T2D, potentially because T2D patients are better defined in the QCBio cohort, and they are older. MRS_{-seq}can eventually be used in clinical practice with other types of risk scores for better interventions and treatments of individuals at high risk of developing T2D. However, these MRSs need validation in a new independent cohort to replicate our findings. Metabolic risk scores are dynamic and modifiable, unlike genetic risk scores. They complement existing genetic and clinical risk scores and can be an alternative in the absence of the other scores. They are particularly helpful for preclinical disease stages and hold promise for early detection. Genetic risk scores are fixed over time, and do not reflect recent changes in the biological process. Implementation of MRS, and other types of risk scores, is crucial for personalized prevention and treatment plans, but face difficulties. All scores need to be well-validated, ultimately across ancestral groups. Moreover, healthcare systems should be equipped with state-of-art techniques that generate the various omics data that is required to build all these scores.

Our study has a few limitations. First, there was an imbalance of the different disease combinations, where the number of T2D patients was relatively smaller in the QBB cohort. A cohort of well-defined T2D patients is needed to confirm our results and increase the sample size. A longitudinal design would be preferable to a retrospective design. T2D patients could be followed up over time to assess CHD incidence and link it to metabolomics data, which should be generated at multiple time points. This optimal study design raises challenges about the cost of generating multiple metabolomics datasets, also the reproducibility and accuracy of metabolomics data generation, which might vary because of data generation artifacts. There have been proposed approaches to deal with systematic differences across metabolomics datasets, which can be used to improve reproducibility of our results (99). The results from this study might also be affected by the statistical power and low sample size of some disease groups. Therefore, the validation and reproducibility of our results should be explored in future studies from the same population, ideally with larger sample size. A well-designed study with well-defined T2D and CHD cases is likely

to yield more robust results, even with smaller sample sizes and therefore lower cost.

Second, although QBB and QCBio cohorts were different in terms of age, we tried to mitigate for the age difference impact on the resulting metabolites by adding age as covariate in all regression models. Ideally, both cohorts should be matched on sex and age, but because of small sample size, especially for T2D patients in QBB, this was difficult to achieve in our study. Age at onset is another important variable that could be checked with respect to obtained metabolites, but this variable was absent in our data. Furthermore, while Age, BMI and Gender, were already included as covariates, we did not consider cultural, dietary or genetic factors, which could bring new important insights to our study.

Third, all carried analysis has been done on datasets that belong to the same Qatari population. This limits our generalizability claims. Hence, we are in the process of generating new independent metabolomics data, which will be used to validate these scores, however that will take some time. In addition, our plan is to include other datasets from the Gulf region like Saudi Arabia for generalizability purposes.

5 Conclusion

In this study, focusing on circulating metabolites in Middle Eastern cohorts from the QCBio and QBB, we identified and replicated metabolites that are associated with T2D. Several metabolites associated with T2D were identified only by stratifying for CHD status. Pathway enrichment analysis was utilized to observe the significant metabolic pathways that were associated with T2D in the presence and absence of CHD. ML models were applied and showed good predictive power to predict T2D in the presence and absence of CHD. RF and SVM were the best models in our study. A metabolite risk score for the prediction of T2D was developed and showed great performance, especially the score developed from the QCBio cohort.

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 study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hamad Medical Corporation. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ME: Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. KI: Data curation, Formal Analysis, Software, Visualization, Writing – original draft. AE-M: Data curation, Writing – review & editing. KK: Writing – review & editing. EU: Writing – review & editing. RE: Data curation, Writing – review & editing. HM: Data curation, Writing – review & editing. EA: Data curation, Writing – review & editing. MA-N: Data curation, Writing – review & editing. AB: Data curation, Writing – review & editing. MA-M: Data curation, Writing – review & editing. VM-A: Data curation, Writing – review & editing. MS: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. JA: Data curation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This study was supported in part by the National Qatar Research Fund (NPRP: 5-1024-3–225 with MRC: MRC-01-17-005) awarded by Dr. Jassim Al Suwaidi and Anti-Doping Lab Qatar. QCRI researchers were funded by QCRI and did not receive external funding.

Acknowledgments

The authors thank all the Qatar Biobank cohort participants and staff. Also, we thank Khalid Kunji, Reem Elsousy, Haira R. Mokhtar, Eiman Ahmad, and Maryam A. Al-Nesf Al-Mansour for their valuable discussions, and contribution to data collection and sample preparation.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial

intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1531525/full#supplementary-material

References

1. Kokkorakis M, Folkertsma P, van Dam S, Sirotin N, Taheri S, Chagoury O, et al. Effective questionnaire-based prediction models for type 2 diabetes across several ethnicities: a model development and validation study. *EClinicalMedicine*. (2023) 64. doi: 10.1016/j.eclinm.2023.102235

2. Rathmann W, Giani G. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030: Response to wild et al. *Diabetes Care*. (2004) 27:2568–9. doi: 10.2337/diacare.27.10.2568

3. Kokkorakis M, Katsarou A, Katsiki N, Mantzoros CS. Milestones in the journey towards addressing obesity; past trials and triumphs, recent breakthroughs, and an exciting future in the era of emerging effective medical therapies and integration of effective medical therapies with metabolic surgery. *Metabolism*. (2023) 148:155689. doi: 10.1016/j.metabol.2023.155689

4. Ogurtsova K, da Rocha Fernandes J, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. Idf diabetes atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. (2017) 128:40–50. doi: 10.1016/j.diabres.2017.03.024

5. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas. *Diabetes Res Clin Pract*. (2019) 157:107843. doi: 10.1016/j.diabres.2019.107843

6. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. Idf diabetes atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

7. Whiting DR, Guariguata L, Weil C, Shaw J. Idf diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract*. (2011) 94:311–21. doi: 10.1016/j.diabres.2011.10.029

8. Goff LM, Ladwa M, Hakim O, Bello O. Ethnic distinctions in the pathophysiology of type 2 diabetes: a focus on black african-caribbean populations. *Proc Nutr Soc*. (2020) 79:184–93. doi: 10.1017/S0029665119001034

9. Hassan S, Gujral UP, Quarells RC, Rhodes EC, Shah MK, Obi J, et al. Disparities in diabetes prevalence and management by race and ethnicity in the usa: defining a path forward. *Lancet Diabetes Endocrinol*. (2023) 11:509–24. doi: 10.1016/S2213-8587(23)00129-8

10. Cheng YJ, Kanaya AM, Araneta MRG, Saydah SH, Kahn HS, Gregg EW, et al. Prevalence of diabetes by race and ethnicity in the United States 2011-2016. *Jama*. (2019) 322:2389–98. doi: 10.1001/jama.2019.19365

11. Wang L, Li X, Wang Z, Bancks MP, Carnethon MR, Greenland P, et al. Trends in prevalence of diabetes and control of risk factors in diabetes among us adults 1999-2018. *Jama*. (2021) 326:704–16. doi: 10.1001/jama.2021.9883

12. Elhussein A, Anderson A, Bancks MP, Coday M, Knowler WC, Peters A, et al. Racial/ethnic and socioeconomic disparities in the use of newer diabetes medications in the look ahead study. *Lancet Regional Health–Americas*. (2022) 6. doi: 10.1016/j.lana.2021.100111

13. Banerjee A, Shah B. Differences in prevalence of diabetes among immigrants to Canada from south asian countries. *Diabetic Med*. (2018) 35:937–43. doi: 10.1111/dme.13647

14. Paul SK, Owusu Adjah ES, Samanta M, Patel K, Bellary S, Hanif W, et al. Comparison of body mass index at diagnosis of diabetes in a multi-ethnic population: A case-control study with matched non-diabetic controls. *Diabetes Obes Metab*. (2017) 19:1014–23. doi: 10.1111/dom.12915

15. El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Consanguinity and major genetic disorders in saudi children: a community-based cross-sectional study. *Ann Saudi Med*. (2008) 28:169–73.

16. Mabry R, Reeves M, Eakin E, Owen N. Gender differences in prevalence of the metabolic syndrome in gulf cooperation council countries: a systematic review. *Diabetic Med*. (2010) 27:593–7. doi: 10.1111/j.1464-5491.2010.02998.x

17. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clinics*. (2004) 88:787–835. doi: 10.1016/j.mcna.2004.04.013

18. Gregg EW, Li Y, Wang J, Rios Burrows N, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States 1990–2010. *New Engl J Med*. (2014) 370:1514–23. doi: 10.1056/NEJMoa1310799

19. Leahy JL. Pathogenesis of type 2 diabetes mellitus. *Arch Med Res*. (2005) 36:197–209. doi: 10.1016/j.arcmed.2005.01.003

20. Reutens AT, Prentice L, Atkins RC. The epidemiology of diabetic kidney disease. *Epidemiol Diabetes mellitus*. (2008), 499–517. doi: 10.1016/j.mcna.2012.10.001

21. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol*. (2018) 17:1–19. doi: 10.1186/s12933-018-0728-6

22. Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, et al. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the american heart association. *Circulation*. (2022) 145:e722–59. doi: 10.1161/CIR.0000000000001040

23. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the san antonio heart study. *Diabetes Care*. (1998) 21:1167–72. doi: 10.2337/diacare.21.7.1167

24. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus–mechanisms, management, and clinical considerations. *Circulation*. (2016) 133:2459–502. doi: 10.1161/CIRCULATIONAHA.116.022194

25. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the american heart association and the heart failure society of america: this statement does not represent an update of the 2017 acc/aha/hfsa heart failure guideline update. *Circulation*. (2019) 140:e294–324. doi: 10.1161/CIR.0000000000000691

26. Fujita Y, Morimoto T, Tokushige A, Ikeda M, Shimabukuro M, Node K, et al. Women with type 2 diabetes and coronary artery disease have a higher risk of heart failure than men, with a significant gender interaction between heart failure risk and risk factor management: a retrospective registry study. *BMJ Open Diabetes Res Care*. (2022) 10:e002707. doi: 10.1136/bmjdrc-2021-002707

27. Park JJ. Epidemiology, pathophysiology, diagnosis and treatment of heart failure in diabetes. *Diabetes Metab J*. (2021) 45:146–57. doi: 10.4093/dmj.2020.0282

28. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. *Nat Rev Endocrinol*. (2022) 18:525–39. doi: 10.1038/s41574-022-00690-7

29. Yu MG, Gordin D, Fu J, Park K, Li Q, King GL. Protective factors and the pathogenesis of complications in diabetes. *Endocrine Rev*. (2024) 45:227–52. doi: 10.1210/endrev/bnad030

30. Jin Q, Ma RCW. Metabolomics in diabetes and diabetic complications: insights from epidemiological studies. *Cells*. (2021) 10:2832. doi: 10.3390/cells10112832

31. Bailes BK. Diabetes mellitus and its chronic complications. *AORN J*. (2002) 76:265–82. doi: 10.1016/S0001-2092(06)61065-X

32. Ma RCW, Lin X, Jia W. Causes of type 2 diabetes in China. *Lancet Diabetes Endocrinol*. (2014) 2:980–91. doi: 10.1016/S2213-8587(14)70145-7

33. Nowlin SY, Hammer MJ, D' Eramo Melkus G. Diet, inflammation, and glycemic control in type 2 diabetes: an integrative review of the literature. *J Nutr Metab*. (2012) 2012:542698. doi: 10.1155/2012/542698

34. Yousri NA, Albagha OM, Hunt SC. Integrated epigenome, whole genome sequence and metabolome analyses identify novel multi-omics pathways in type 2 diabetes: A middle eastern study. *BMC Med*. (2023) 21:347. doi: 10.1186/s12916-023-03027-x

35. Bragg F, Trichia E, Aguilar-Ramirez D, Bešević J, Lewington S, Emberson J. Predictive value of circulating nmr metabolic biomarkers for type 2 diabetes risk in the uk biobank study. *BMC Med*. (2022) 20:159. doi: 10.1186/s12916-022-02354-9

36. Chen Y, Zhao X, Wu H. Metabolic stress and cardiovascular disease in diabetes mellitus: The role of protein o-glcnac modification. *Arteriosclerosis thrombosis Vasc Biol*. (2019) 39:1911–24. doi: 10.1161/ATVBAHA.119.312192

37. Suhre K, Meisinger C, Döring A, Altmaier E, Belcredi P, Gieger C, et al. Metabolic footprint of diabetes: a multiplatform metabolomics study in an epidemiological setting. *PloS One*. (2010) 5:e13953. doi: 10.1371/journal.pone.0013953

38. Yousri NA, Suhre K, Yassin E, Al-Shakaki A, Robay A, Elshafei M, et al. Metabolic and metabo-clinical signatures of type 2 diabetes, obesity, retinopathy, and dyslipidemia. *Diabetes*. (2022) 71:184–205. doi: 10.2337/db21-0490

39. Chen H, Wang Z, Qin M, Zhang B, Lin L, Ma Q, et al. Comprehensive metabolomics identified the prominent role of glycerophospholipid metabolism in coronary artery disease progression. *Front Mol Biosci*. (2021) 8:632950. doi: 10.3389/fmolb.2021.632950

40. Ullah E, El-Menyar A, Kunji K, Elsousy R, Mokhtar HR, Ahmad E, et al. Untargeted metabolomics profiling reveals perturbations in arginine-no metabolism in middle eastern patients with coronary heart disease. *Metabolites*. (2022) 12:517. doi: 10.3390/metabo12060517

41. Wang Z, Zhu C, Nambi V, Morrison AC, Folsom AR, Ballantyne CM, et al. Metabolomic pattern predicts incident coronary heart disease: findings from the atherosclerosis risk in communities study. *Arteriosclerosis thrombosis Vasc Biol*. (2019) 39:1475–82. doi: 10.1161/ATVBAHA.118.312236

42. Smith E, Ericson U, Hellstrand S, Orho-Melander M, Nilsson PM, Fernandez C, et al. A healthy dietary metabolic signature is associated with a lower risk for type 2 diabetes and coronary artery disease. *BMC Med*. (2022) 20:122. doi: 10.1186/s12916-022-02326-z

43. Al Thani A, Fthenou E, Paparrodopoulos S, Al Marri A, Shi Z, Qafoud F, et al. Qatar biobank cohort study: study design and first results. *Am J Epidemiol*. (2019) 188:1420–33. doi: 10.1093/aje/kwz084

44. El-Menyar A, Al Suwaidi J, Badii R, Mir F, Dalenberg AK, Kullo IJ. Discovering novel biochemical and genetic markers for coronary heart disease in Qatari individuals: the initiative Qatar cardiovascular biorepository. *Heart Views*. (2020) 21:6–16. doi: 10.4103/HEARTVIEWS.HEARTVIEWS_98_19

45. Saad M, El-Menyar A, Kunji K, Ullah E, Al Suwaidi J, Kullo IJ. Validation of polygenic risk scores for coronary heart disease in a middle eastern cohort using whole genome sequencing. *Circulation: Genomic Precis Med*. (2022) 15:e003712. doi: 10.1161/CIRCGEN.122.003712

46. Al-Khelaifi F, Diboun I, Donati F, Botre,` F, Alsayrafi M, Georgakopoulos C, et al. A pilot study comparing the metabolic profiles of elite-level athletes from different sporting disciplines. *Sports medicine-open*. (2018) 4:1–15. doi: 10.1186/s40798-017-0114-z

47. Al-Nesf A, Mohamed-Ali N, Acquaah V, Al-Jaber M, Al-Nesf M, Yassin MA, et al. Untargeted metabolomics identifies a novel panel of markers for autologous blood transfusion. *Metabolites*. (2022) 12:425. doi: 10.3390/metabo12050425

48. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat society: Ser B (Methodological)*. (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

49. Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Stat Soc Ser B: Stat Method*. (2005) 67:301–20. doi: 10.1111/j.1467-9868.2005.00503.x

50. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. Smote: synthetic minority over-sampling technique. *J Artif Intell Res*. (2002) 16:321–57. doi: 10.1613/jair.953

51. Pang Z, Lu Y, Zhou G, Hui F, Xu L, Viau C, et al. Metaboanalyst 6.0: towards a unified platform for metabolomics data processing, analysis and interpretation. *Nucleic Acids Res*. (2024) 52:gkae253. doi: 10.1093/nar/gkae253

52. Kim MJ, Jung HS, Hwang-Bo Y, Cho SW, Jang HC, Kim SY, et al. Evaluation of 1, 5-anhydroglucitol as a marker for glycemic variability in patients with type 2 diabetes mellitus. *Acta diabetologica*. (2013) 50:505–10. doi: 10.1007/s00592-011-0302-0

53. Yamanouchi T, Akanuma Y. Serum 1, 5-anhydroglucitol (1, 5 ag): new clinical marker for glycemic control. *Diabetes Res Clin Pract*. (1994) 24:S261–8. doi: 10.1016/0168-8227(94)90259-3

54. Ames JM. Determination of n-(carboxymethyl) lysine in foods and related systems. *Ann New York Acad Sci*. (2008) 1126:20–4. doi: 10.1196/annals.1433.030

55. Assar SH, Moloney C, Lima M, Magee R, Ames JM. Determination of n-(carboxymethyl) lysine in food systems by ultra performance liquid chromatography-mass spectrometry. *Amino Acids*. (2009) 36:317–26. doi: 10.1007/s00726-008-0071-4

56. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *Journals Gerontol Ser A: Biomed Sci Med Sci*. (2010) 65:963–75. doi: 10.1093/gerona/glq074

57. Vistoli G, De Maddis D, Cipak A, Zarkovic N, Carini M, Aldini G. Advanced glycoxidation and lipoxidation end products (ages and ales): an overview of their mechanisms of formation. *Free Radical Res*. (2013) 47:3–27. doi: 10.3109/10715762.2013.815348

58. Ramasamy R, Yan SF, D'Agati V, Schmidt AM. Receptor for advanced glycation endproducts (rage): a formidable force in the pathogenesis of the cardiovascular complications of diabetes & aging. *Curr Mol Med*. (2007) 7:699–710. doi: 10.2174/156652407783220732

59. Kanauchi M, Tsujimoto N, Hashimoto T. Advanced glycation end products in nondiabetic patients with coronary artery disease. *Diabetes Care*. (2001) 24:1620–3. doi: 10.2337/diacare.24.9.1620

60. Semba RD, Najjar SS, Sun K, Lakatta EG, Ferrucci L. Serum carboxymethyl–lysine, an advanced glycation end product, is associated with increased aortic pulse wave velocity in adults. *Am J hypertension*. (2009) 22:74–9. doi: 10.1038/ajh.2008.320

61. Yu F, Li X, Feng X, Wei M, Luo Y, Zhao T, et al. Phenylacetylglutamine, a novel biomarker in acute ischemic stroke. *Front Cardiovasc Med*. (2021) 8:798765. doi: 10.3389/fcvm.2021.798765

62. Yu F, Feng X, Li X, Luo Y, Wei M, Zhao T, et al. Gut-derived metabolite phenylacetylglutamine and white matter hyperintensities in patients with acute ischemic stroke. *Front Aging Neurosci*. (2021) 13:675158. doi: 10.3389/fnagi.2021.675158

63. Nemet I, Saha PP, Gupta N, Zhu W, Romano KA, Skye SM, et al. A cardiovascular disease-linked gut microbial metabolite acts via adrenergic receptors. *Cell*. (2020) 180:862–77. doi: 10.1016/j.cell.2020.02.016

64. Porcu E, Gilardi F, Darrous L, Yengo L, Bararpour N, Gasser M, et al. Triangulating evidence from longitudinal and mendelian randomization studies of metabolomic biomarkers for type 2 diabetes. *Sci Rep*. (2021) 11:6197. doi: 10.1038/s41598-021-85684-7

65. Morze J, Wittenbecher C, Schwingshackl L, Danielewicz A, Rynkiewicz A, Hu FB, et al. Metabolomics and type 2 diabetes risk: an updated systematic review and meta-analysis of prospective cohort studies. *Diabetes Care*. (2022) 45:1013–24. doi: 10.2337/dc21-1705

66. Stančáková A, Civelek M, Saleem NK, Soininen P, Kangas AJ, Cederberg H, et al. Hyperglycemia and a common variant of gckr are associated with the levels of eight amino acids in 9,369 finnish men. *Diabetes*. (2012) 61:1895–902. doi: 10.2337/db11-1378

67. Dollet L, Kuefner M, Caria E, Rizo-Roca D, Pendergrast L, Abdelmoez AM, et al. Glutamine regulates skeletal muscle immunometabolism in type 2 diabetes. *Diabetes*. (2022) 71:624–36. doi: 10.2337/db20-0814

68. Palmer ND, Stevens RD, Antinozzi PA, Anderson A, Bergman RN, Wagenknecht LE, et al. Metabolomic profile associated with insulin resistance and conversion to diabetes in the insulin resistance atherosclerosis study. *J Clin Endocrinol Metab*. (2015) 100:E463–8. doi: 10.1210/jc.2014-2357

69. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part i. *Eur Heart J*. (2013) 34:2436–43. doi: 10.1093/eurheartj/eht149

70. Cheng S, Rhee EP, Larson MG, Lewis GD, McCabe EL, Shen D, et al. Metabolite profiling identifies pathways associated with metabolic risk in humans. *Circulation*. (2012) 125:2222–31. doi: 10.1161/CIRCULATIONAHA.111.067827

71. Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez-González MA, Salas-Salvadó J, et al. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. *Diabetes Care*. (2016) 39:833–46. doi: 10.2337/dc15-2251

72. Urpi-Sarda M, Almanza-Aguilera E, Llorach R, Vázquez-Fresno R, Estruch R, Corella D, et al. Non-targeted metabolomic biomarkers and metabotypes of type 2 diabetes: A cross-sectional study of predimed trial participants. *Diabetes Metab*. (2019) 45:167–74. doi: 10.1016/j.diabet.2018.02.006

73. Durante W. The emerging role of l-glutamine in cardiovascular health and disease. *Nutrients*. (2019) 11:2092. doi: 10.3390/nu11092092

74. Zhang L, Zhang Y, Ma Z, Zhu Y, Chen Z. Altered amino acid metabolism between coronary heart disease patients with and without type 2 diabetes by quantitative 1h nmr based metabolomics. *J Pharm Biomed Anal*. (2021) 206:114381. doi: 10.1016/j.jpba.2021.114381

75. Liu X, Gao J, Chen J, Wang Z, Shi Q, Man H, et al. Identification of metabolic biomarkers in patients with type 2 diabetic coronary heart diseases based on metabolomic approach. *Sci Rep*. (2016) 6:30785. doi: 10.1038/srep30785

76. Ahmed KA, Muniandy S, Ismail IS. Role of nε-(carboxymethyl) lysine in the development of ischemic heart disease in type 2 diabetes mellitus. *J Clin Biochem Nutr*. (2007) 41:97–105. doi: 10.3164/jcbn.2007014

77. Virak V, Nov P, Chen D, Zhang X, Guan J, Que D, et al. Exploring the impact of metabolites function on heart failure and coronary heart disease: insights from a mendelian randomization (mr) study. *Am J Cardiovasc Dis*. (2024) 14:242. doi: 10.62347/OQXZ7740

78. Dehghanbanadaki H, Dodangeh S, Parhizkar Roudsari P, Hosseinkhani S, Khashayar P, Noorchenarboo M, et al. Metabolomics profile and 10-year atherosclerotic cardiovascular disease (ascvd) risk score. *Front Cardiovasc Med*. (2023) 10:1161761. doi: 10.3389/fcvm.2023.1161761

79. Molek P, Zmudzki P, Wlodarczyk A, Nessler J, Zalewski J. The shifted balance of arginine metabolites in acute myocardial infarction patients and its clinical relevance. *Sci Rep*. (2021) 11:83. doi: 10.1038/s41598-020-80230-3

80. Oravilahti A, Vangipurapu J, Laakso M, Fernandes Silva L. Metabolomics-based machine learning for predicting mortality: Unveiling multisystem impacts on health. *Int J Mol Sci*. (2024) 25:11636. doi: 10.3390/ijms252111636

81. Wang N, Li J-Y, Zeng B, Chen G-L. Sphingosine-1-phosphate signaling in cardiovascular diseases. *Biomolecules*. (2023) 13:818. doi: 10.3390/biom13050818

82. Mantovani A, Bonapace S, Lunardi G, Canali G, Dugo C, Vinco G, et al. Associations between specific plasma ceramides and severity of coronary-artery stenosis assessed by coronary angiography. *Diabetes Metab*. (2020) 46:150–7. doi: 10.1016/j.diabet.2019.07.006

83. Spijkers LJ, van den Akker RF, Janssen BJ, Debets JJ, De Mey JG, Stroes ES, et al. Hypertension is associated with marked alterations in sphingolipid biology: a potential role for ceramide. *PloS One*. (2011) 6:e21817. doi: 10.1371/journal.pone.0021817

84. Li N, Zhang F. Implication of sphingosin-1-phosphate in cardiovascular regulation. *Front bioscience (Landmark edition)*. (2016) 21:1296. doi: 10.2741/4458

85. Ndrepepa G. Aspartate aminotransferase and cardiovascular disease—a narrative review. *J Lab Precis Med*. (2021) 6:2335-2342. doi: 10.21037/jlpm-20-93

86. Ndrepepa G, Holdenrieder S, Cassese S, Xhepa E, Fusaro M, Laugwitz K-L, et al. Aspartate aminotransferase and mortality in patients with ischemic heart disease. *Nutrition Metab Cardiovasc Dis*. (2020) 30:2335–42. doi: 10.1016/j.numecd.2020.07.033

87. Zoppini G, Cacciatori V, Negri C, Stoico V, Lippi G, Targher G, et al. The aspartate aminotransferase-to-alanine aminotransferase ratio predicts all-cause and cardiovascular mortality in patients with type 2 diabetes. *Medicine*. (2016) 95:e4821. doi: 10.1097/MD.0000000000004821

88. Ercan N, Nuttall F, Gannon M, Redmon J, Sheridan K. Effects of glucose, galactose, and lactose ingestion on the plasma glucose and insulin response in persons with non-insulin-dependent diabetes mellitus. *Metabolism*. (1993) 42:1560–7. doi: 10.1016/0026-0495(93)90151-D

89. Liu Y, Gan L, Zhao B, Yu K, Wang Y, Männistö S, et al. Untargeted metabolomic profiling identifies serum metabolites associated with type 2 diabetes in a cross-sectional study of the alpha tocopherol, beta-carotene cancer prevention (atbc) study. *Am J Physiology-Endocrinol Metab*. (2023) 324:E167–75. doi: 10.1152/ajpendo.00287.202

90. Cuomo P, Capparelli R, Iannelli A, Iannelli D. Role of branched-chain amino acid metabolism in type 2 diabetes, obesity, cardiovascular disease and non-alcoholic fatty liver disease. *Int J Mol Sci*. (2022) 23:4325. doi: 10.3390/ijms23084325

91. Vanweert F, Schrauwen P, Phielix E. Role of branched-chain amino acid metabolism in the pathogenesis of obesity and type 2 diabetes-related metabolic disturbances bcaa metabolism in type 2 diabetes. *Nutr Diabetes*. (2022) 12:35. doi: 10.1038/s41387-022-00213-3

92. White PJ, McGarrah RW, Herman MA, Bain JR, Shah SH, Newgard CB. Insulin action, type 2 diabetes, and branched-chain amino acids: a two-way street. *Mol Metab*. (2021) 52:101261. doi: 10.1016/j.molmet.2021.101261

93. Kanehara R, Goto A, Sawada N, Mizoue T, Noda M, Hida A, et al. Association between sugar and starch intakes and type 2 diabetes risk in middle-aged adults in a prospective cohort study. *Eur J Clin Nutr*. (2022) 76:746–55. doi: 10.1038/s41430-021-01005-1

94. Rani L, Saini S, Shukla N, Chowdhuri DK, Gautam NK. High sucrose diet induces morphological, structural and functional impairments in the renal tubules of drosophila melanogaster: A model for studying type-2 diabetes mediated renal tubular dysfunction. *Insect Biochem Mol Biol*. (2020) 125:103441. doi: 10.1016/j.ibmb.2020.103441

95. Sun H, Zhang S, Zhang A, Yan G, Wu X, Han Y, et al. Metabolomic analysis of diet-induced type 2 diabetes using uplc/ms integrated with pattern recognition approach. *PloS One*. (2014) 9:e93384. doi: 10.1371/journal.pone.0093384

96. Tessari P, Cecchet D, Cosma A, Vettore M, Coracina A, Millioni R, et al. Nitric oxide synthesis is reduced in subjects with type 2 diabetes and nephropathy. *Diabetes*. (2010) 59:2152–9. doi: 10.2337/db09-1772

97. Piatti P, Monti LD, Valsecchi G, Magni F, Setola E, Marchesi F, et al. Long-term oral l-arginine administration improves peripheral and hepatic insulin sensitivity in type 2 diabetic patients. *Diabetes Care*. (2001) 24:875–80. doi: 10.2337/diacare.24.5.875

98. Ahola-Olli AV, Mustelin L, Kalimeri M, Kettunen J, Jokelainen J, Auvinen J, et al. Circulating metabolites and the risk of type 2 diabetes: a prospective study of 11,896 young adults from four finnish cohorts. *Diabetologia*. (2019) 62:2298–309. doi: 10.1007/s00125-019-05001-w

99. Ghosh T, Philtron D, Zhang W, Kechris K, Ghosh D. Reproducibility of mass spectrometry based metabolomics data. *BMC Bioinf*. (2021) 22:1–25. doi: 10.1186/s12859-021-04336-9

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 18 November 2025
DOI 10.3389/fendo.2025.1651416

Check for updates

OPEN ACCESS

EDITED BY
James Harper,
Sam Houston State University, United States

REVIEWED BY
Enrico Buccheri,
Università di Catania, Italy
Bo Jiang,
Rice University, United States

*CORRESPONDENCE
Ying Pan
py97183@163.com
Shao Zhong
drzhong@163.com

†These authors have contributed equally to this work

RECEIVED 21 June 2025
ACCEPTED 29 October 2025
PUBLISHED 18 November 2025

CITATION
Zhang J, Wang Z, Wang Q, Liu Y, Shao Q, Pan Y and Zhong S (2025) The association between residual cholesterol to high-density lipoprotein cholesterol ratio and type 2 diabetes risk in elderly populations. *Front. Endocrinol.* 16:1651416. doi: 10.3389/fendo.2025.1651416

COPYRIGHT
© 2025 Zhang, Wang, Wang, Liu, Shao, Pan and Zhong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The association between residual cholesterol to high-density lipoprotein cholesterol ratio and type 2 diabetes risk in elderly populations

Jinting Zhang[1†], Zhaoxiang Wang[1†], Qianqian Wang[1], Yang Liu[2], Qi Shao[1], Ying Pan[3,4*] and Shao Zhong[1,4*]

[1]Department of Endocrinology, Kunshan Hospital Affiliated to Jiangsu University, Kunshan, Jiangsu, China, [2]Department of Critical Care Medicine, Shanghai East Hospital, Tongji University School of Medicine, Tongji University, Shanghai, China, [3]Department of General Medicine, Kunshan Hospital Affiliated to Jiangsu University, Kunshan, Jiangsu, China, [4]Biomedical Big Data Innovation Application Laboratory, The First People's Hospital of Kunshan, Kunshan, Jiangsu, China

Purpose: The remnant cholesterol to high-density lipoprotein cholesterol ratio (RC/HDL-C) is a novel biomarker of metabolic disturbances. Prior studies have indicated a close association between elevated RC/HDL-C and the occurrence and progression of cardiovascular, cerebrovascular, and metabolic diseases. However, longitudinal data on the relationship between RC/HDL-C and type 2 diabetes (T2D) risk remain limited, particularly among high-risk elderly populations. This study aims to clarify the association between RC/HDL-C and incident T2D in Chinese adults, offering evidence for early prevention and detection of T2D.

Patients and methods: A follow-up study was conducted in Kunshan, China, from January 2018 to July 2021, involving 7655 participants aged 60 years or older. Cox proportional hazards models were used to evaluate the independent effect of the RC/HDL-C level on the risk of T2D. The relationship between RC/HDL-C and T2D risk was visually demonstrated using the Kaplan-Meier method and restricted cubic splines (RCS).

Results: During a median follow-up of 3.87 years, 783 participants (10.23%) developed T2D. A fully adjusted Cox proportional hazards model showed a positive and independent association between RC/HDL-C and T2D risk (HR = 1.12, 95% CI: 1.06-1.17, $P < 0.001$). The highest RC/HDL-C quartile (Q4) had the highest cumulative incidence of T2D (Log-rank test, $P < 0.001$). Furthermore, RCS analysis revealed a non-linear relationship between RC/HDL-C and T2D risk. Receiver operating characteristic (ROC) curve analysis revealed that the RC/HDL-C ratio exhibited the largest area under the curve (AUC = 0.601, 95% CI: 0.580–0.623), indicating modest but statistically significant predictive ability. Subgroup analysis further validated the robustness of these results.

Conclusion: We found that older adults with elevated RC/HDL-C levels have a higher risk of incident T2D. RC/HDL-C is an independent predictor of incident T2D in the elderly and may serve as a valuable adjunct to enhance risk stratification within existing prediction models.

KEYWORDS

RC/HDL-C, T2D, cohort study, elderly population, incident T2D

1 Introduction

With global socioeconomic development, lifestyle changes, and rising obesity, the incidence of type 2 diabetes (T2D) is increasing in parallel worldwide (1). The disease arises from multifactorial mechanisms driven by complex interactions among genetic, metabolic, and lifestyle factors. Obesity-related anthropometric measures remain simple and effective tools for screening dysglycemia, complemented by hypertension and physical activity levels (2–4). Moreover, lipid parameters, notably high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), continue to constitute foundational components for metabolic risk assessment and have been incorporated into diabetes risk prediction models (5). Abnormal glucose metabolism—including prediabetes and overt diabetes—is now a major public health concern. Notably, projections from 2017 estimate that more than 600 million individuals will develop prediabetes by 2045, with a similar number progressing to T2D (6). The prevalence of T2D is increasing most rapidly among the elderly population across all age groups. In China, studies indicate that elderly T2D patients face disproportionately higher complication rates, imposing significant clinical, familial, and societal burdens. Early diagnosis and intervention for T2D significantly improve cost-effectiveness and health outcomes (7, 8). Consequently, there is an urgent need for novel, easily measurable biomarkers to facilitate early screening and improve management of at-risk populations.

Previous research has confirmed that dyslipidemia is a risk factor for both macrovascular diseases and T2D. The limited effectiveness of statins in adequately managing diabetic dyslipidemia has shifted research interest from conventional lipid profiles to triglyceride-rich lipoproteins (TRLs) (9). Remnant cholesterol (RC), a novel non-traditional lipid parameter introduced recently, reflects cholesterol within TRLs that may more directly promote insulin resistance (IR) than triglycerides (TG), including remnants from very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and chylomicrons (10). A large-scale Chinese cohort study showed that RC is more strongly associated with diabetes than LDL-C, possibly mediated through IR and proinflammatory pathways (11). HDL-C has antioxidant properties and an enhanced capacity for cholesterol efflux, whereas its relationship with T2D involves complex interactions among lipid metabolism, inflammation, and oxidative stress. Clinical data indicate an inverse relationship between HDL-C levels and the risk of T2D (12, 13). Reduced HDL-C levels are a key factor in the pathogenesis and etiology of T2D and prediabetes, and are consistently associated with increased atherosclerosis risk in both T2D patients and experimental models (14–16). Emerging evidence indicates that lipid or lipoprotein ratios have greater predictive value than individual lipid measures for T2D risk, as they more effectively capture interactions among lipid components (17–22). Although a high RC/HDL-C ratio is strongly linked to cardiovascular, cerebrovascular, and metabolic disorders, studies investigating its association with incident diabetes risk are limited, especially among elderly populations.

Given the positive association between RC and disease development, contrasted with the inverse correlation of HDL-C, this study examines the relationship between the RC/HDL-C ratio and incident T2D in Chinese adults, aiming to provide evidence for early prevention and detection to enhance health outcomes.

2 Methods

2.1 Study population and design

This population-based cohort study utilized electronic health records (EHRs) derived from the Kunshan Elderly Cohort. The cohort collected residents' health records, annual physical examination data, and follow-up information on chronic diseases via the medical information management system of the regional healthcare consortium. Personal identifiers were anonymized, and data were processed to ensure participant confidentiality. Detailed specifications of the cohort design have been previously documented (23–25). All participants provided written informed consent for the use of their comprehensive EHR data. This study was conducted in accordance with the Declaration of Helsinki, and the study's protocol was reviewed and approved by the Ethics Committee of the Kunshan First People's Hospital (Grant No: 2023-03-014-H01-K01).

We enrolled older adult residents who underwent community health screenings in Kunshan between January 2018 and July 2021. Participants meeting any of the following criteria were excluded: (i) insufficient baseline data (RC and HDL-C), (ii) baseline age <60 years, (iii) diagnosis of type 1 diabetes or other specific diabetes types. The final analysis included 7,655 non-diabetic participants.

2.2 Exposure and outcome definitions

RC was calculated as total cholesterol (TC) minus HDL-C minus LDL-C (26). The RC/HDL-C ratio was derived by dividing RC by HDL-C (27). The primary endpoint was incident T2D during follow-up, defined by either ICD-10 codes (E11-E14) or fasting plasma glucose (FPG) ≥7.0 mmol/L (24). The time to T2D onset was calculated as the interval between baseline assessment and diabetes diagnosis. For participants without a T2D diagnosis during follow-up, follow-up duration was determined from baseline assessment to the final investigation date.

2.3 Covariate definitions

Comprehensive clinical characteristics were extracted from the EHR health screening database, encompassing demographic data, annual lifestyle questionnaires (smoking status, alcohol consumption), and anthropometric measurements (height, weight, waist circumference, blood pressure). Annual laboratory tests for elderly participants included: aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (SUA), TC, TG, and FPG (28). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. According to Chinese BMI classification criteria, weight status categories were defined as: 18.5–23.9 kg/m² (normal weight), 24.0–27.9 kg/m² (overweight), and ≥28 kg/m² (obesity) (29). Estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation (30). Hypertension diagnosis criteria included ICD-10 codes (I10-I15), mean systolic blood pressure (SBP) ≥140 mmHg, and/or mean diastolic blood pressure (DBP) ≥90 mmHg (31). Cardiovascular disease (CVD) diagnoses encompassed coronary artery disease (ICD-10: I20-I25) and cerebrovascular disease (ICD-10: I60-I64), documented in the EHR database (28). The chronic disease registry and follow-up database systematically recorded disease incidence, management protocols, and clinical outcomes. Additionally, outpatient prescription data and biochemical measurements improved the accuracy of T2D outcome assessment.

2.4 Statistical analyses

Baseline characteristics are summarized as means ± standard deviations (SD) for continuous variables and as counts (n, %) for categorical variables. Participants were grouped based on the presence of T2D or quartiles of the RC/HDL-C ratio. Differences between groups were evaluated using Student's t-test, analysis of variance, or the chi-square test. Cox proportional hazards models were employed to examine the association between baseline RC/HDL-C levels (as both continuous and categorical variables) and the risk of developing T2D. Variables with clinical or prognostic relevance were included in the models. Model 1 was unadjusted; Model 2 was adjusted for age and sex; and Model 3 further adjusted for BMI, systolic and DBP, FPG, ALT, AST, BUN, Scr, SUA, eGFR, smoking status, alcohol consumption, hypertension, and CVD. The cumulative incidence of T2D events in the RC/HDL-C quartile groups was estimated using the Kaplan-Meier method, and differences between groups were tested with the log-rank test. The dose-response relationship between baseline RC/HDL-C levels and T2D risk was analyzed using restricted cubic splines (RCS) with four knots. Additionally, receiver operating characteristic (ROC) curves were constructed to evaluate the predictive ability of RC/HDL-C and other conventional indicators for incident diabetes. Subgroup analyses were performed stratified by sex (male/female), age (<75/≥75 years), BMI (<24, 24-28, ≥28 kg/m²), CVD (yes/no), hypertension (yes/no), and eGFR (<60, 60-90, ≥90 mL/min/1.73 m²) to assess the stability of the findings. All statistical analyses were conducted using R version 4.2.2 and EmpowerStats software (http://www.empowerstats.com). A two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 7,655 participants without T2D at baseline were enrolled, with a mean age of 66.96 ± 4.49 years; among them, 3,689 were males (48.19%) (Table 1). Over a median follow-up duration of 3.87 years, 783 participants (10.23%) developed incident T2D.

Baseline characteristics stratified by RC/HDL-C quartiles are summarized in Table 2: Q1 (0.037–0.292), Q2 (0.294–0.437), Q3 (0.444–0.692), and Q4 (0.692–20.50). Participants in the highest RC/HDL-C quartile exhibited significantly higher BMI, systolic and DBP, ALT, SUA, and FPG levels compared to those in the lowest quartile, with a higher prevalence of hypertension (P < 0.001). Conversely, the same group showed lower eGFR levels (P < 0.001). Additionally, levels of BUN and alcohol consumption varied significantly across the quartiles of RC/HDL-C (P < 0.05). There was no statistically significant association between RC/HDL-C quartiles and smoking prevalence. The highest RC/HDL-C quartile had a higher proportion of females compared to the lowest quartile (P < 0.001), while the proportion of males was lower in the highest quartile than in the lowest (P < 0.001) (Table 3).

3.2 Relationship between RC/HDL-C and T2D incidence

Cox proportional hazards regression models were used to assess the independent association between RC/HDL-C and incident T2D. RC/HDL-C was identified as a significant risk factor across unadjusted, partially adjusted, and fully adjusted models (all P < 0.001). In the fully adjusted model (Table 4), each 1-unit increase in RC/HDL-C correlated with a 12% higher risk of T2D (HR = 1.12; 95% CI: 1.06–1.17; P < 0.001). When analyzed by quartiles, the multivariable-adjusted HR for incident T2D were 1.37 (95% CI: 1.09–1.73) in Q3 (P < 0.05) and 1.78 (95% CI: 1.43–2.22) in Q4 (P < 0.001).

10.3389/fendo.2025.1651416

TABLE 1 Baseline characteristics of the study population.

Characteristics	Total (N=7,655)	Non-diabetes group (N=6,872)	Diabetes group (N=783)	*P* value
Age, years	66.96 ± 4.49	66.84 ± 4.38	68.07 ± 5.25	<0.001
Sex, men	3689 (48.19%)	3358 (48.86%)	331 (42.27%)	<0.001
BMI, kg/m2	24.51 ± 3.23	24.35 ± 3.19	25.87 ± 3.29	<0.001
Smoking				0.161
Never	5751 (75.95%)	5146 (75.74%)	605 (77.76%)	
Former	282 (3.72%)	262 (3.86%)	20 (2.57%)	
Current	1539 (20.32%)	1386 (20.40%)	153 (19.67%)	
Drinking				0.019
None	6032 (79.66%)	5379 (79.17%)	653 (83.93%)	
Light	495 (6.54%)	456 (6.71%)	39 (5.01%)	
Moderate	146 (1.93%)	135 (1.99%)	11 (1.41%)	
Heavy	899 (11.87%)	824 (12.13%)	75 (9.64%)	
SBP, mmHg	139.06 ± 19.19	138.67 ± 19.25	142.50 ± 18.33	<0.001
DBP, mmHg	81.44 ± 10.66	81.35 ± 10.74	82.22 ± 9.97	0.019
ALT, U/L	19.87 ± 12.81	19.44 ± 12.52	23.60 ± 14.56	<0.001
AST, U/L	22.53 ± 10.54	22.31 ± 10.20	24.38 ± 12.98	0.001
BUN, mmol/L	5.67 ± 3.88	5.65 ± 4.06	5.82 ± 1.57	<0.001
Scr, μmol/L	72.57 ± 22.03	72.48 ± 22.43	73.39 ± 18.21	0.146
SUA, mg/dL	324.89 ± 83.97	322.64 ± 83.14	344.66 ± 88.62	<0.001
eGFR, ml/min/1.73 m^2	84.47 ± 12.98	84.77 ± 12.81	81.80 ± 14.06	<0.001
FPG, mmol/L	5.45 ± 0.66	5.38 ± 0.63	6.06 ± 0.58	<0.001
TC, mg/dL	184.70 ± 35.90	184.86 ± 35.64	183.26 ± 38.09	0.133
TG, mg/dL	145.89 ± 107.39	142.12 ± 102.80	179.04 ± 137.09	<0.001
Hypertension	3776 (49.33%)	3310 (48.17%)	466 (59.51%)	<0.001
Cardiovascular disease	324 (4.23%)	239 (3.48%)	85 (10.86%)	<0.001
RC/HDL-C	0.60 ± 0.66	0.58 ± 0.61	0.79 ± 0.95	<0.001
RC	0.71 ± 0.48	0.69 ± 0.46	0.85 ± 0.59	<0.001

Continuous variables are shown as mean±SD, and categorical variables are presented as n (%) numbers.
RC was calculated as TC minus HDL-C minus LDL-C.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; RC/HDL-C, Residual Cholesterol to High-Density Lipoprotein Cholesterol Ratio.

As shown in Figure 1, the Kaplan–Meier curves indicated that participants in the highest quartile (Q4) of RC/HDL-C exhibited a significantly greater cumulative incidence of T2D during follow-up (log-rank test, $P < 0.001$). Moreover, as shown in Figure 2, RCS analysis revealed a significant non-linear association between the RC/HDL-C ratio and the risk of T2D (P_non-linear < 0.001). A positive association was observed between higher RC/HDL-C levels and increased T2D risk up to a threshold of 0.934 (overall $P < 0.001$). Overall, the risk of T2D increased non-linearly with increasing RC/HDL-C levels.

Table 2 presents the area under the receiver operating characteristic curve (AUROC) for RC/HDL-C and other conventional lipid parameters in predicting incident diabetes among older adults. Compared to RC, TC, HDL-C, and LDL-C, RC/HDL-C demonstrated the highest AUROC (0.601), with a sensitivity of 63.60%, a specificity of 52.28%, and an optimal cutoff value of 0.455 (Figure 3), indicating modest but statistically significant predictive ability.

3.3 Subgroup analysis

Stratified analyses were performed to evaluate the association between RC/HDL-C and T2D risk across subgroups defined by sex

TABLE 2 ROC curve of different indicators for predicting the risk of new-onset T2D in the elderly.

Test	AUROC	95% CI	Best threshold	Specificity	Sensitivity
RC/HDL-C	0.601	0.580-0.623	0.455	0.523	0.636
RC	0.596	0.575-0.617	0.600	0.558	0.586
LDL-C	0.542	0.520-0.565	90.875	0.673	0.414
HDL-C	0.427	0.405-0.448	9.668	0.001	1.000
TC	0.484	0.462-0.506	241.688	0.946	0.073

AUROC, area under the receiver operating curve; RC/HDL-C, Residual Cholesterol to High-Density Lipoprotein Cholesterol Ratio; RC, remnant cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

TABLE 3 Baseline characteristics of the study population according to RC/HDL-C quartiles.

RC/HDL-C	Quartile 1 (0.037-0.292)	Quartile 2 (0.294-0.437)	Quartile 3 (0.444-0.692)	Quartile 4 (0.692-20.50)	*P* value
N	1913	1903	1916	1923	
Age, years	67.03 ± 4.55	67.04 ± 4.57	66.89 ± 4.56	66.90 ± 4.29	0.620
Sex, men	1045 (54.63%)	892 (46.87%)	906 (47.29%)	846 (43.99%)	<0.001
BMI, kg/m2	23.17 ± 3.23	24.23 ± 3.06	24.97 ± 3.13	25.65 ± 2.98	<0.001
Smoking					0.315
Never	1393 (74.06%)	1447 (76.89%)	1461 (76.89%)	1450 (75.96%)	
Former	68 (3.62%)	73 (3.88%)	69 (3.63%)	72 (3.77%)	
Current	420 (22.33%)	362 (19.23%)	370 (19.47%)	387 (20.27%)	
Drinking					0.035
None	1453 (77.25%)	1481 (78.69%)	1543 (81.21%)	1555 (81.46%)	
Light	125 (6.65%)	130 (6.91%)	120 (6.32%)	120 (6.29%)	
Moderate	43 (2.29%)	36 (1.91%)	37 (1.95%)	30 (1.57%)	
Heavy	260 (13.82%)	235 (12.49%)	200 (10.53%)	204 (10.69%)	
SBP, mmHg	136.41 ± 18.85	138.71 ± 18.62	139.57 ± 19.49	141.54 ± 19.46	<0.001
DBP, mmHg	79.88 ± 10.69	81.30 ± 10.54	81.63 ± 10.71	82.93 ± 10.49	<0.001
ALT, U/L	18.40 ± 9.96	19.27 ± 14.66	20.16 ± 13.29	21.63 ± 12.65	<0.001
AST, U/L	22.72 ± 10.26	22.22 ± 11.29	22.50 ± 11.18	22.67 ± 9.32	0.457
BUN, mmol/L	5.90 ± 2.22	5.64 ± 1.45	5.68 + 7.13	5.46 ± 1.45	0.005
Scr, μmol/L	72.98 ± 32.22	71.91 ± 17.02	72.40 ± 17.72	73.00 ± 17.32	0.354
SUA, mg/dl	302.73 ± 79.88	315.97 ± 79.03	330.24 ± 83.29	350.39 ± 85.99	<0.001
eGFR, ml/min/1.73 m2	85.87 ± 13.45	84.55 ± 12.68	84.30 ± 12.53	83.15 ± 13.08	<0.001
FPG, mmol/L	5.39 ± 0.63	5.41 ± 0.65	5.44 ± 0.67	5.55 ± 0.68	<0.001
Hypertension	841 (43.96%)	924 (48.55%)	970 (50.63%)	1041 (54.13%)	<0.001
Cardiovascular disease	68 (3.55%)	89 (4.68%)	83 (4.33%)	84 (4.37%)	0.358
T2D incidence	126 (6.59%)	157 (8.25%)	200 (10.44%)	300 (15.60%)	<0.001

Continuous variables are shown as mean±SD, and categorical variables are presented as n (%) numbers.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; RC/HDL-C, Residual Cholesterol to High-Density Lipoprotein Cholesterol Ratio.

TABLE 4 The association between RC/HDL-C and the incidence of T2D during follow-up.

Type 2 diabetes, HR 95%CI, *P* value			
RC/HDL-C	Model 1	Model 2	Model 3
Continuous	1.19 (1.14, 1.24), <0.001	1.20 (1.14, 1.25), <0.001	1.12 (1.06, 1.17), <0.001
RC/HDL-C quartile			
Q1	Reference	Reference	Reference
Q2	1.36 (1.08, 1.72), 0.0098	1.33 (1.05, 1.69), 0.0165	1.20 (0.95, 1.53), 0.1332
Q3	1.77 (1.42, 2.22), <0.001	1.76 (1.41, 2.20), <0.001	1.37 (1.09, 1.73), 0.0073
Q4	2.63 (2.14, 3.24), <0.001	2.58 (2.10, 3.18), <0.001	1.78 (1.43, 2.22), <0.001
P for trend	<0.001	<0.001	<0.001

HR, hazards ratio.
95% CI: 95% confidence interval.
Model 1: no covariates were adjusted.
Model 2: adjusted for age and gender.
Model 3: adjusted for age, gender, smoking status, drinking status, hypertension, cardiovascular disease, BMI, SBP, DBP, FPG, ALT, AST, BUN, Scr, SUA, and eGFR.

(male/female), age (<75 vs. ≥75 years), BMI (<24, 24–28, or ≥28 kg/m^2), CVD status (yes/no), hypertension (yes/no), and eGFR (<60/60-90/≥90 ml/min/1.73 m^2). As shown in Figure 4, the positive association between RC/HDL-C and T2D risk remained consistent across all subgroups, indicating the robustness of the findings.

4 Discussion

In this large-scale retrospective cohort study, participants with elevated RC/HDL-C ratios at baseline exhibited a higher incidence of T2D. To our knowledge, this is the first study to examine the association between RC/HDL-C and T2D risk in an older adult cohort. This novel and straightforward biomarker can serve as a non-invasive and easily accessible diagnostic indicator for T2D, and it is expected to supplement established risk factors (such as age and BMI) in comprehensive risk prediction models.

Previous studies have demonstrated that dyslipidemia induces inflammation, endoplasmic reticulum stress, and lipotoxicity, ultimately contributing to IR (32, 33). This relationship may be mediated by excessive cholesterol accumulation in β-cells, leading to dysfunction, impaired glucose tolerance, and reduced insulin secretion. Elevated RC levels have been associated with increased risks of diabetic complications, hypertension, and non-alcoholic fatty liver disease (NAFLD) (34–37). Women exposed to elevated RC levels exhibit increased susceptibility to diabetes, which may be associated with distinct dietary patterns, estrogen status, and cholesterol metabolism. Estrogen deficiency in females promotes atherosclerotic dyslipidemia, visceral adiposity, and IR, collectively elevating the risk of diabetes and cardiometabolic disorders (38, 39). Consistent with these findings, our observations showed that females predominated in the highest RC/HDL-C quartile (P < 0.001), whereas males were underrepresented in this quartile relative to lower quartiles (P < 0.001). Further mechanistic studies are needed to elucidate the pathophysiological roles of these

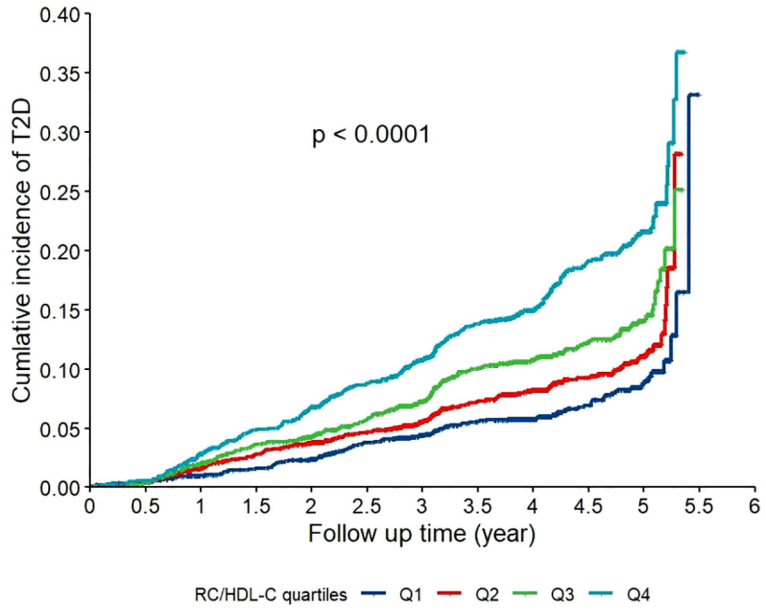


FIGURE 1
Kaplan-Meier curves for the cumulative incidence of type 2 diabetes (T2D) stratified by quartiles of the residual cholesterol to high-density lipoprotein cholesterol ratio (RC/HDL-C) in the study population (N = 7,655). Participants were categorized into quartiles based on their baseline RC/HDL-C ratio: Q1 (0.037-0.292), Q2 (0.294-0.437), Q3 (0.444–0.692), and Q4 (0.692-20.50). Differences between the curves were assessed using the log-rank test (P < 0.001).

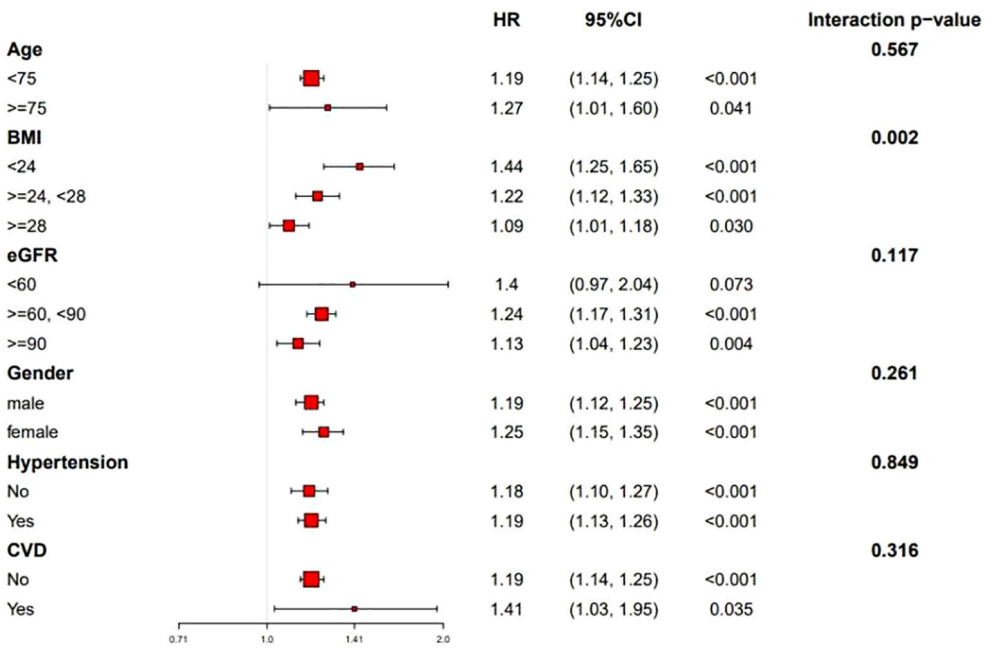


FIGURE 2
Dose-response relationship between the RC/HDL-C and the risk of incident T2D analyzed using restricted cubic splines (RCS) in a Cox proportional hazards model. The solid line represents the hazard ratio (HR), and the shaded area represents the 95% confidence interval. The reference value (HR = 1) was set at an RC/HDL-C ratio of 0.3. The model was adjusted for age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (SUA), estimated glomerular filtration rate (eGFR), smoking status, alcohol consumption, hypertension, and cardiovascular disease. The *P* value for the overall association and for non-linearity are presented. *P*-overall<0.05 indicates a significant association between RC/HDL-C and T2D risk. *P*-nonlinear <0.05 indicated a significant nonlinear relationship between RC/HDL-C and T2D risk.

parameters in the progression of diabetes in the elderly. In summary, the interaction between RC and T2D involves complex mechanisms, including metabolic dysregulation, inflammatory cascades, and vascular pathology.

HDL-C, a multifunctional structural lipoprotein with anti-inflammatory, antioxidant, and cholesterol efflux properties, is widely recognized as "good cholesterol" in cardiovascular pathophysiology (40). HDL-C facilitates reverse cholesterol

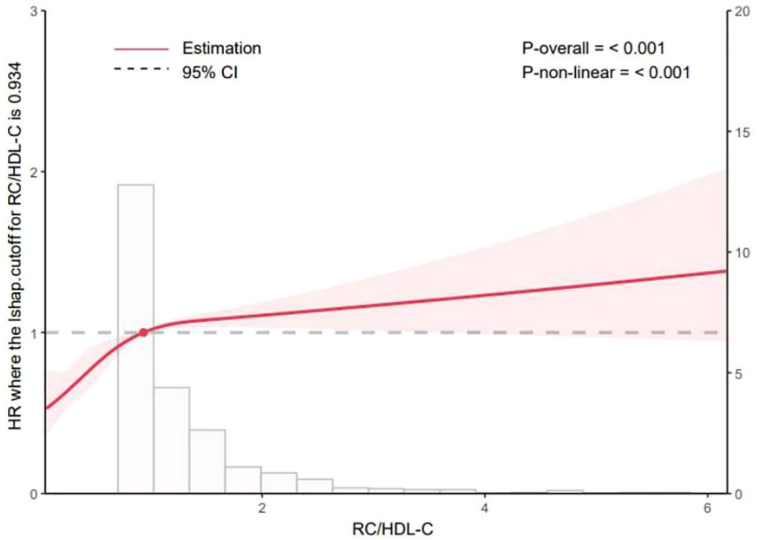


FIGURE 3
Receiver operating characteristic (ROC) curves comparing the predictive performance of the RC/HDL-C, remnant cholesterol (RC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) for incident T2D. The area under the ROC curve (AUROC) for each indicator is provided in Table 2.

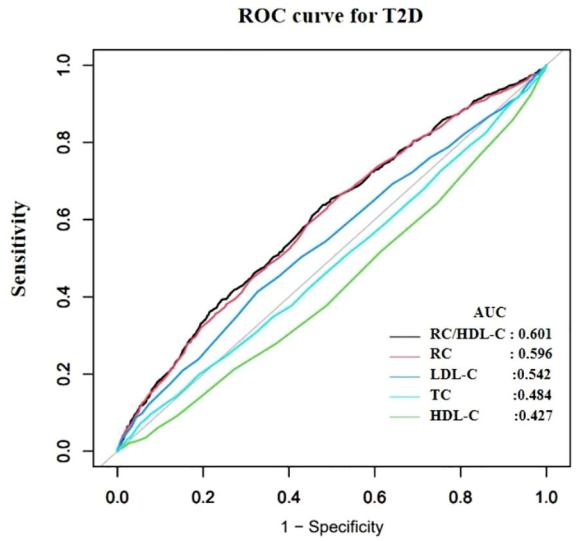


FIGURE 4
Subgroup analyses of the association between the RC/HDL-C ratio and incident T2D risk (N=7,655). Hazard ratios (squares) with 95% CIs (horizontal lines) are shown for each subgroup. *P* values for interaction are indicated.

transport by extracting cholesterol from atherosclerotic vessel walls and delivering it to the liver for metabolic elimination. Reduced HDL-C levels impair glucose homeostasis through mechanisms such as decreased insulin secretion, reduced insulin sensitivity, and downregulation of AMP-activated protein kinase (AMPK) activity (41).

Current longitudinal evidence on the association between the RC/HDL-C ratio and T2D risk remains limited, especially in high-risk elderly populations. Our study identified a positive association between the RC/HDL-C ratio and incident T2D, which remained significant after adjusting for multiple confounders (see Statistical analyses section for details). These confounders included BMI, systolic and DBP, FPG, ALT, AST, BUN, Scr, SUA, eGFR, TC, smoking status, alcohol intake, hypertension, and CVD. Sensitivity analyses confirmed that neither the RC/HDL-C ratio nor T2D risk estimates were substantially affected by these covariates, supporting the robustness of the findings.

The mechanisms underpinning the relationship between the RC/HDL-C ratio and T2D pathogenesis remain poorly elucidated and likely involve multiple pathways. (1) RC transports cholesterol species that are toxic to pancreatic β-cells (PBCs), inducing apoptosis and impairing insulin biosynthesis and secretion. HDL facilitates reverse transport of RC, with elevated HDL levels potentially reflecting both increased clearance and promoting efficient removal of RC — a vital process, given the atherogenic and proinflammatory effects of accumulated RC particles (42). (2) The TG/HDL-C ratio has been established as a robust surrogate marker for IR with strong predictive capacity (43). However, conventional enzymatic assays for TG measure both lipoprotein-bound TG and free glycerol, which limits the ability to directly substitute TG for RC, possibly conferring an analytical advantage to the RC/HDL-C ratio. (3) Sexual dimorphism: Estrogenic activity may dysregulate glucose homeostasis in cerebral and pancreatic tissues, promoting peripheral insulin desensitization (44). Elevated estrogen levels can also drive atherogenic dyslipidemia, visceral adiposity, and IR progression, thereby increasing hepatopathic and cardiometabolic risks (38, 45). These proposed mechanisms require rigorous validation through dedicated experimental studies.

Our findings indicate an independent association between higher RC/HDL-C ratios and increased T2D risk in elderly individuals. This association can be interpreted as a reflection of an imbalance between RC-driven atherogenic/proinflammatory pathways and the protective functions of HDL-C. Specifically, elevated RC may promote IR and β-cell dysfunction through lipid accumulation, inflammatory activation, and oxidative stress, whereas HDL-C supports insulin sensitivity via anti-inflammatory, antioxidant, and cholesterol efflux mechanisms. In our study, restricted cubic spline analysis reveals a nonlinear relationship between RC/HDL-C and T2D risk, with a inflection point at 0.934. This threshold may mark a critical level at which RC–mediated atherogenic and proinflammatory effects accelerate IR and β-cell dysfunction. Values below the threshold suggest that HDL-C can sufficiently counteract the deleterious effects of residual cholesterol through reverse cholesterol transport, whereas values above the threshold imply insufficient counterregulation by HDL-C against the rising RC burden. This pathophysiological framework helps explain the observed nonlinear risk relationship and moderate yet significant predictive value in our elderly cohort. Previous studies reporting nonlinear associations—thresholds for Diabetic retinopathy (DR) and NAFLD at RC/HDL-C of 0.460 and 0.619, respectively—point to threshold effects, beyond which compensatory mechanisms are overwhelmed (46). Prospective cohort studies are required to validate these thresholds for risk stratification and preventive applications, and to assess generalizability across populations. In clinical practice, RC/HDL-C > 0.934 may serve as a practical biomarker to identify high-risk elderly individuals, informing preventive strategies and the frequency of glucose metabolism

assessments. For those with RC/HDL-C > 0.934, intensified lifestyle guidance and closer monitoring should be considered, with potential for earlier interventions in high-risk patients. Given our study population of older adults, age-related HDL dysfunction and accumulation of RC may amplify the clinical significance of RC/HDL-C imbalance.

As noted, our study focused on adults aged 60 years and older. The pathophysiological mechanisms linking dyslipidemia to T2D are widely considered to be universal throughout adulthood. Several studies focusing on middle-aged and general adult populations have also reported significant associations between non-traditional lipid markers and T2D (47). This suggests that the biological pathways underpinning our findings are not exclusive to the elderly. However, the RC/HDL-C ratio might hold particular clinical relevance for risk stratification in the elderly due to several age-specific factors: 1) Competing Risks: In the elderly, competing risks of mortality from other conditions (e.g., CVD) can dilute observed associations with T2D. Despite this, we detected a robust independent association, which underscores the potency of this biomarker in this age group. 2)Shift in Pathophysiology: The capacity for βoraci self-replication declines with age, suggesting younger individuals may possess greater regenerative potential (48). Previous studies indicate that younger prediabetic patients are more likely to achieve normoglycemia (49). T2D in the elderly often manifests with more pronounced β-cell function decline rather than pure IR. Future research would be valuable to explore whether RC/HDL-C is more strongly linked to β-cell dysfunction in the context of aging. 3)Polypharmacy and Comorbidities: Our elderly cohort had a high prevalence of hypertension, CVD, and likely concomitant medication use (e.g., statins). Our fully adjusted model demonstrated that the association of RC/HDL-C with T2D was independent of these factors, a finding critical for its potential application in older adults with complex clinical presentations. Conversely, compared to the elderly, younger individuals often adopt unhealthy dietary habits and sedentary lifestyles, which significantly impact IR (50). Future studies directly comparing the predictive value of RC/HDL-C across different age strata are necessary to elucidate potential age-specific effects.

This study's strengths include its longitudinal assessment of the association between the RC/HDL-C ratio and incident T2D, with significant clinical implications. The investigation was further supported by a median follow-up of 8.2 years, a low attrition rate (<5%), and stable cohort characteristics. Comprehensive sensitivity analyses using multiple models reinforced the robustness of our findings.

Although the RC/HDL-C ratio demonstrated the strongest predictive value among lipid parameters, its AUROC of 0.601 indicates only modest discrimination when used as a standalone biomarker—an expected feature for single biomarkers. The potential advantage lies in its complementarity within established risk-prediction models that integrate multiple factors. This study has not developed or validated an integrated T2D risk prediction model, which represents one of its limitations. The growing role of artificial intelligence (AI) in medicine offers a promising avenue to enhance diabetes screening and risk stratification (51). AI models excel at integrating multifaceted data to improve predictive accuracy, a trend evident across diabetology, cardiology, and musculoskeletal medicine (52–54). In this context, easily measurable and low-cost biomarkers, such as the RC/HDL-C ratio identified in this study, are attractive inputs for scalable screening tools. Future work should explore AI-driven prediction models that integrate RC/HDL-C with additional clinical and anthropometric variables to achieve higher precision in identifying high-risk elderly individuals. Additionally, several other limitations warrant consideration: First, as a retrospective study based on EHRs, key variables such as family history of diabetes, educational attainment, dietary habits, and physical activity levels were not available. This omission may lead to residual confounding, although we adjusted for a comprehensive set of clinically relevant covariates. Future prospective studies that incorporate these important lifestyle and genetic factors are needed to confirm our findings. Second, our study population was exclusively derived from a single center in Eastern China, which may limit the generalizability of our findings to other ethnic or regional groups. Although we identified a significant association between RC/HDL-C and T2D risk, external validation in independent cohorts is necessary to confirm its predictive value before it can be considered for broader clinical application. Future studies should aim to validate our findings in other populations, including international cohorts. Third, the underlying mechanisms linking the RC/HDL-C ratio to diabetic complications require further mechanistic research.

5 Conclusion

Elevated RC/HDL-C ratio was significantly associated with a higher risk of incident T2D during longitudinal follow-up in elderly populations. RC/HDL-C shows promise as a research tool for understanding T2D risk, but validation in larger and more diverse populations is needed before consideration of clinical implementation. Future prospective studies should focus on integrating the RC/HDL-C ratio with other established risk factors to develop and validate a robust multivariable diabetes risk prediction model tailored for older adults.

Data availability statement

The dataset involves privacy information of the elderly population in Kunshan and is part of an ongoing follow-up study. To ensure data accuracy and security, and to comply with ethical restrictions, access is restricted. Any requests for access should be submitted to the Ethics Committee of the Kunshan First People's Hospital. Requests to access these datasets should be directed to Jinting Zhang, 18896660180@163.com.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki, and the study's protocol was reviewed and approved by the Ethics Committee of the Kunshan First People's Hospital (Grant No: 2023-03-014-H01-K01). The studies were conducted in

accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JZ: Data curation, Investigation, Writing – original draft. ZW: Methodology, Writing – review & editing. QW: Formal Analysis, Visualization, Writing – review & editing. YL: Methodology, Writing – review & editing. QS: Data curation, Investigation, Writing – review & editing. YP: Conceptualization, Writing – review & editing. SZ: Conceptualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This study was supported by the Suzhou Major Diseases Multicenter Clinical Research Program (DZXYJ202419).

Acknowledgments

We are grateful to all participants of this study and the research team.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* (2018) 138:271–81. doi: 10.1016/j.diabres.2018.02.023

2. Buccheri E, Dell'Aquila D, Russo M. Artificial intelligence in health data analysis: The Darwinian evolution theory suggests an extremely simple and zero-cost large-scale screening tool for prediabetes and type 2 diabetes. *Diabetes Res Clin Pract.* (2021) 174:108722. doi: 10.1016/j.diabres.2021.108722

3. Buccheri E, Dell'Aquila D, Russo M. Stratified analysis of the age-related waist circumference cut-off model for the screening of dysglycemia at zero-cost. *Obes Med.* (2022) 31:100398. doi: 10.1016/j.obmed.2022.100398

4. Wu J, Hou X, Chen L, Chen P, Wei L, Jiang F, et al. Development and validation of a non-invasive assessment tool for screening prevalent undiagnosed diabetes in middle-aged and elderly Chinese. *Prev Med.* (2019) 119:145–52. doi: 10.1016/j.ypmed.2018.12.025

5. Zhang M, Zhang H, Wang C, Ren Y, Wang B, Zhang L, et al. Development and validation of a risk-score model for type 2 diabetes: A cohort study of a rural adult Chinese population. *PLoS One.* (2016) 11:e0152054. doi: 10.1371/journal.pone.0152054

6. Yuan D, Jiang P, Zhu P, Jia S, Zhang C, Liu Y, et al. Prognostic value of fibrinogen in patients with coronary artery disease and prediabetes or diabetes following percutaneous coronary intervention: 5-year findings from a large cohort study. *Cardiovasc Diabetol.* (2021) 20:143. doi: 10.1186/s12933-021-01335-1

7. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet (London England).* (2010) 375:2215–22. doi: 10.1016/S0140-6736(10)60484-9

8. Bragg F, Holmes MV, Iona A, Guo Y, Du H, Chen Y, et al. Association between diabetes and cause-specific mortality in rural and urban areas of China. *JAMA.* (2017) 317:280–9. doi: 10.1001/jama.2016.19720

9. Sascău R, Clement A, Radu R, Prisacariu C, Stătescu C. Triglyceride-rich lipoproteins and their remnants as silent promoters of atherosclerotic cardiovascular disease and other metabolic disorders: A review. *Nutrients.* (2021) 13:1774. doi: 10.3390/nu13061774

10. Jørgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjærg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J.* (2013) 34:1826–33. doi: 10.1093/eurheartj/ehs431

11. Hu X, Liu Q, Guo X, Wang W, Yu B, Liang B, et al. The role of remnant cholesterol beyond low-density lipoprotein cholesterol in diabetes mellitus. *Cardiovasc Diabetol.* (2022) 21:117. doi: 10.1186/s12933-022-01554-0

12. Abbasi A, Corpeleijn E, Gansevoort RT, Gans RO, Hillege HL, Stolk RP, et al. Role of HDL cholesterol and estimates of HDL particle composition in future development of type 2 diabetes in the general population: the PREVEND study. *J Clin Endocrinol Metab.* (2013) 98:E1352–1359. doi: 10.1210/jc.2013-1680

13. Okin PM, Hille DA, Wiik BP, Kjeldsen SE, Lindholm LH, Dahlöf B, et al. In-treatment HDL cholesterol levels and development of new diabetes mellitus in hypertensive patients: the LIFE Study. *Diabetic Med.* (2013) 30:1189–97. doi: 10.1111/dme.12213

14. Ozder A. Lipid profile abnormalities seen in T2DM patients in primary healthcare in Turkey: a cross-sectional study. *Lipids Health Dis.* (2014) 13:183. doi: 10.1186/1476-511X-13-183

15. Wu L, Parhofer KG. Diabetic dyslipidemia. *Metabolism: Clin Exp.* (2014) 63:1469–79. doi: 10.1016/j.metabol.2014.08.010

16. von Eckardstein A, Sibler RA. Possible contributions of lipoproteins and cholesterol to the pathogenesis of diabetes mellitus type 2. *Curr Opin lipidology.* (2011) 22:26–32. doi: 10.1097/MOL.0b013e3283412279

17. Ren XY, Shi D, Ding J, Cheng ZY, Li HY, Li JS, et al. Total cholesterol to high-density lipoprotein cholesterol ratio is a significant predictor of nonalcoholic fatty liver: Jinchang cohort study. *Lipids Health Dis.* (2019) 18:47. doi: 10.1186/s12944-019-0984-9

18. Fan N, Peng L, Xia Z, Zhang L, Song Z, Wang Y, et al. Triglycerides to high-density lipoprotein cholesterol ratio as a surrogate for nonalcoholic fatty liver disease: a cross-sectional study. *Lipids Health Dis.* (2019) 18:39. doi: 10.1186/s12944-019-0986-7

19. Pacifico L, Bonci E, Andreoli G, Romaggioli S, Di Miscio R, Lombardo CV, et al. Association of serum triglyceride-to-HDL cholesterol ratio with carotid artery intima-media thickness, insulin resistance and nonalcoholic fatty liver disease in children and adolescents. *Nutrition metabolism Cardiovasc diseases: NMCD.* (2014) 24:737–43. doi: 10.1016/j.numecd.2014.01.010

20. Zhang M, Zhou J, Liu Y, Sun X, Luo X, Han C, et al. Risk of type 2 diabetes mellitus associated with plasma lipid levels: The rural Chinese cohort study. *Diabetes Res Clin Pract*. (2018) 135:150–7. doi: 10.1016/j.diabres.2017.11.011

21. Zou Y, Zhong L, Hu C, Zhong M, Peng N, Sheng G. LDL/HDL cholesterol ratio is associated with new-onset NAFLD in Chinese non-obese people with normal lipids: a 5-year longitudinal cohort study. *Lipids Health Dis*. (2021) 20:28. doi: 10.1186/s12944-021-01457-1

22. Yang MH, Sung J, Gwak GY. The associations between apolipoprotein B, A1, and the B/A1 ratio and nonalcoholic fatty liver disease in both normal-weight and overweight Korean population. *J Clin lipidology*. (2016) 10:289–98. doi: 10.1016/j.jacl.2015.11.017

23. Wu P, Liu Z, Tian Z, Wu B, Shao J, Li Q, et al. CYP2C19 loss-of-function variants associated with long-term ischemic stroke events during clopidogrel treatment in the Chinese population. *Clin Pharmacol Ther*. (2023) 114:1126–33. doi: 10.1002/cpt.3028

24. Liu Y, Pan Y, Tian Z, Wang J, Chen F, Geng Z, et al. Association of mitochondrial DNA copy number with chronic kidney disease in older adults. *BMC geriatrics*. (2023) 23:514. doi: 10.1186/s12877-023-04203-7

25. Tian Z, Chen F, Wang J, Wu B, Shao J, Liu Z, et al. CAS Array: design and assessment of a genotyping array for Chinese biobanking. *Precis Clin Med*. (2023) 6: pbad002. doi: 10.1093/pcmedi/pbad002

26. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet (London England)*. (2014) 384:626–35. doi: 10.1016/S0140-6736(14)61177-6

27. Zeng RX, Li S, Zhang MZ, Li XL, Zhu CG, Guo YL, et al. Remnant cholesterol predicts periprocedural myocardial injury following percutaneous coronary intervention in poorly-controlled type 2 diabetes. *J Cardiol*. (2017) 70:113–20. doi: 10.1016/j.jjcc.2016.12.010

28. Chen F, Pan Y, Liu Z, Huang R, Wang J, Shao J, et al. Impact of visit-to-visit triglyceride-glucose index variability on the risk of cardiovascular disease in the elderly. *Int J Endocrinol*. (2022) 2022:5125884. doi: 10.1155/2022/5125884

29. Wang W, Zhou L, Hu Q, Gao Y, Wei Y, Tang X, et al. Correlative relationship between body mass index and heart rate variability in psychiatric disorders. *Eur Arch Psychiatry Clin Neurosci*. (2024) 275:1015–1024. doi: 10.1007/s00406-024-01768-1

30. Zhang B, Liang H, Yu Z, Wei FF, Wu Y. Clinical implications of estimating glomerular filtration rate with different equations in heart failure patients with preserved ejection fraction. *High Blood Pressure Cardiovasc Prev*. (2024) 31:205–13. doi: 10.1007/s40292-024-00631-7

31. Pan Y, Zhong S, Zhou K, Tian Z, Chen F, Liu Z, et al. Association between diabetes complications and the triglyceride-glucose index in hospitalized patients with type 2 diabetes. *J Diabetes Res*. (2021) 2021:8757996. doi: 10.1155/2021/8757996

32. Drew BG, Rye KA, Duffy SJ, Barter P, Kingwell BA. The emerging role of HDL in glucose metabolism. *Nat Rev Endocrinol*. (2012) 8:237–45. doi: 10.1038/nrendo.2011.235

33. Ikonen E. Cellular cholesterol trafficking and compartmentalization. *Nat Rev Mol Cell Biol*. (2008) 9:125–38. doi: 10.1038/nrm2336

34. Pastori D, Baratta F, Novo M, Cocomello N, Violi F, Angelico F, et al. Remnant lipoprotein cholesterol and cardiovascular and cerebrovascular events in patients with non-alcoholic fatty liver disease. *J Clin Med*. (2018) 7:378. doi: 10.3390/jcm7110378

35. Chin J, Mori TA, Adams LA, Beilin LJ, Huang RC, Olynyk JK, et al. Association between remnant lipoprotein cholesterol levels and non-alcoholic fatty liver disease in adolescents. *JHEP reports: Innovation Hepatol*. (2020) 2:100150. doi: 10.1016/j.jhepr.2020.100150

36. Li K, Fan F, Zheng B, Jia J, Liu B, Liu J, et al. Associations between remnant lipoprotein cholesterol and central systolic blood pressure in a Chinese community-based population: a cross-sectional study. *Lipids Health Dis*. (2021) 20:60. doi: 10.1186/s12944-021-01490-0

37. Cao YX, Zhang HW, Jin JL, Liu HH, Zhang Y, Gao Y, et al. The longitudinal association of remnant cholesterol with cardiovascular outcomes in patients with diabetes and pre-diabetes. *Cardiovasc Diabetol*. (2020) 19:104. doi: 10.1186/s12933-020-01076-7

38. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nat Rev Endocrinol*. (2021) 17:47–66. doi: 10.1038/s41574-020-00431-8

39. Gado M, Tsaousidou E, Bornstein SR, Perakakis N. Sex-based differences in insulin resistance. *J Endocrinol*. (2024) 261:e230245. doi: 10.1530/JOE-23-0245

40. Cao C, Hu H, Zheng X, Zhang X, Wang Y, He Y. Non-linear relationship between high-density lipoprotein cholesterol and incident diabetes mellitus: a secondary retrospective analysis based on a Japanese cohort study. *BMC endocrine Disord*. (2022) 22:163. doi: 10.1186/s12902-022-01074-8

41. You Y, Hu H, Cao C, Han Y, Tang J, Zhao W. Association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of gestational diabetes mellitus: a second analysis based on data from a prospective cohort study. *Front Endocrinol*. (2023) 14:1153072. doi: 10.3389/fendo.2023.1153072

42. Kontush A. HDL and reverse remnant-cholesterol transport (RRT): relevance to cardiovascular disease. *Trends Mol Med*. (2020) 26:1086–100. doi: 10.1016/j.molmed.2020.07.005

43. Qin YG, Zhu LY, Wang CY, Zhang BY, Wang QY, Li RY, et al. Retraction Note: Glycol chitosan incorporated retinoic acid chlorochalcone (RACC) nanoparticles in the treatment of Osteosarcoma. *Lipids Health Dis*. (2020) 19:246. doi: 10.1186/s12944-020-01416-2

44. Elliott A, Walters RK, Pirinen M, Kurki M, Junna N, Goldstein JI, et al. Distinct and shared genetic architectures of Gestational diabetes mellitus and Type 2 Diabetes Mellitus. *medRxiv*. (2023) 56:377–382. doi: 10.1101/2023.02.16.23286014

45. Rahnemaei FA, Pakzad R, Amirian A, Pakzad I, Abdi F. Effect of gestational diabetes mellitus on lipid profile: A systematic review and meta-analysis. *Open Med (Warsaw Poland)*. (2022) 17:70–86. doi: 10.1515/med-2021-0408

46. Xuan Y, Hu W, Wang Y, Li J, Yang L, Yu S, et al. Association between RC/HDL-C ratio and risk of non-alcoholic fatty liver disease in the United States. *Front Med*. (2024) 11:1427138. doi: 10.3389/fmed.2024.1427138

47. Kim J, Shin SJ, Kim YS, Kang HT. Positive association between the ratio of triglycerides to high-density lipoprotein cholesterol and diabetes incidence in Korean adults. *Cardiovasc Diabetol*. (2021) 20:183. doi: 10.1186/s12933-021-01377-5

48. Yazıcı D, Sezer H. Insulin resistance, obesity and lipotoxicity. *Adv Exp Med Biol*. (2017) 960:277–304. doi: 10.1007/978-3-319-48382-5_12

49. Huang C, Zhang Y, Yang X, Li G, Gao Z. Associations between non-traditional lipid parameters and normoglycemic reversion in Chinese adults with prediabetes: a retrospective analysis. *Front Endocrinol*. (2025) 16:1502861. doi: 10.3389/fendo.2025.1502861

50. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care*. (2008) 31:661–6. doi: 10.2337/dc07-2046

51. Guan Z, Li H, Liu R, Cai C, Liu Y, Li J, et al. Artificial intelligence in diabetes management: Advancements, opportunities, and challenges. *Cell Rep Med*. (2023) 4:101213. doi: 10.1016/j.xcrm.2023.101213

52. Singh M, Kumar A, Khanna NN, Laird JR, Nicolaides A, Faa G, et al. Artificial intelligence for cardiovascular disease risk assessment in personalised framework: a scoping review. *EClinicalMedicine*. (2024) 73:102660. doi: 10.1016/j.eclinm.2024.102660

53. Buccheri E, Dell'Aquila D, Russo M, Chiaramonte R, Musumeci G, Vecchio M. Can artificial intelligence simplify the screening of muscle mass loss? *Heliyon*. (2023) 9: e16323. doi: 10.1016/j.heliyon.2023.e16323

54. Buccheri E, Dell'Aquila D, Russo M, Chiaramonte R, Vecchio M. Appendicular skeletal muscle mass in older adults can be estimated with a simple equation using a few zero-cost variables. *J geriatric Phys Ther*. (2024) 47:E149–e158. doi: 10.1519/JPT.0000000000000420

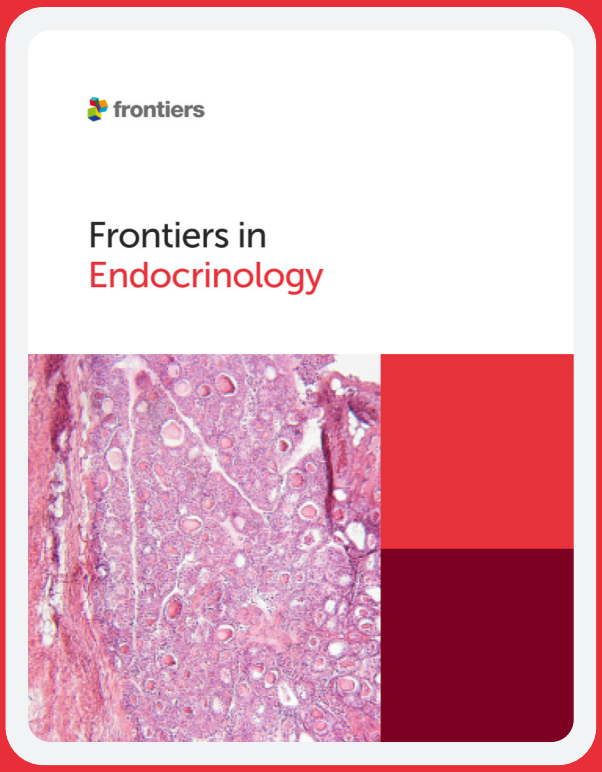
Frontiers in Endocrinology

Explores the endocrine system to find new therapies for key health issues

The second most-cited endocrinology and metabolism journal, which advances our understanding of the endocrine system. It uncovers new therapies for prevalent health issues such as obesity, diabetes, reproduction, and aging.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact