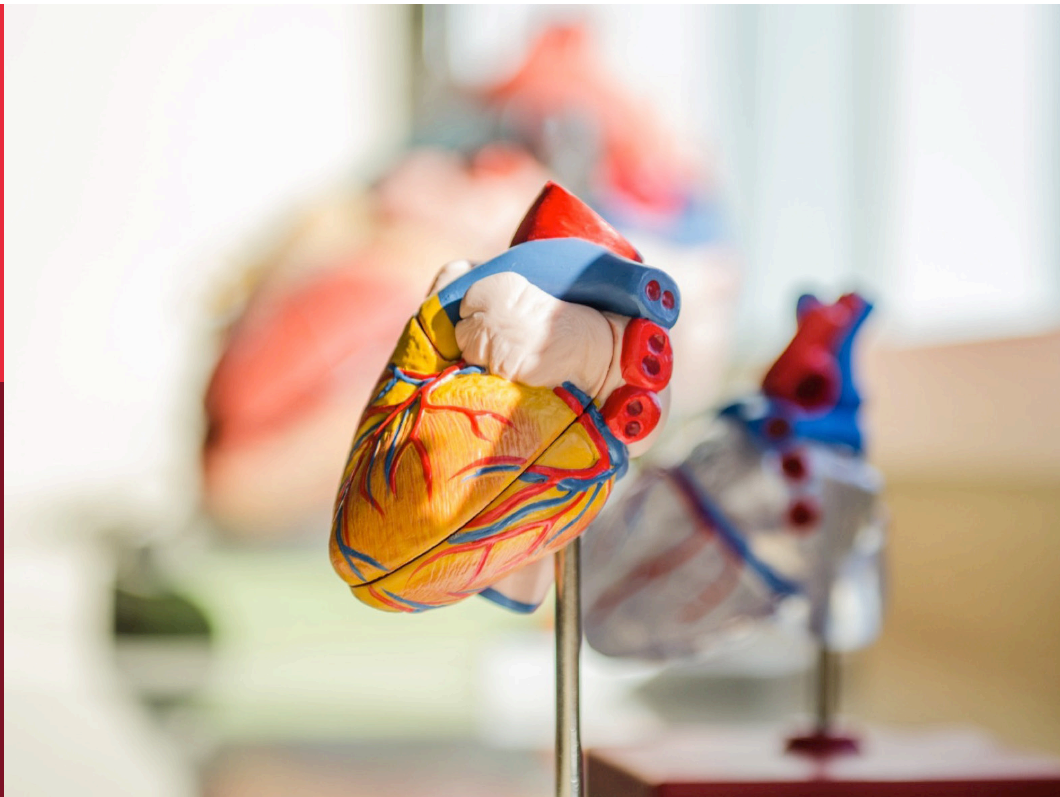
frontiers | Research Topics

The newer paradigms in hypertension research and management

Edited by
Komal Marwaha, Indranill Basu-Ray, Freny Vaghaiwalla Mody
and Keith Curtis Norris

Published in
Frontiers in Cardiovascular Medicine
Frontiers in Medicine
Frontiers in Public Health



ISSN 1664-8714
ISBN 978-2-8325-7229-0
DOI 10.3389/978-2-8325-7229-0

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

The newer paradigms in hypertension research and management

Topic editors
Komal Marwaha — Texas Tech University Health Sciences Center, United States
Indranill Basu-Ray — Memphis VA Medical Center, United States Department of Veterans Affairs, United States
Freny Vaghaiwalla Mody — University of California, Los Angeles, United States
Keith Curtis Norris — University of California, Los Angeles, United States

Citation
Marwaha, K., Basu-Ray, I., Mody, F. V., Norris, K. C., eds. (2025). *The newer paradigms in hypertension research and management*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-7229-0

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 23 January 2026
DOI 10.3389/fmed.2026.1781466

OPEN ACCESS

EDITED AND REVIEWED BY
Arch Mainous,
University of Florida, United States

*CORRESPONDENCE
Komal Marwaha
✉ drkmarwaha@gmail.com

RECEIVED 05 January 2026
ACCEPTED 09 January 2026
PUBLISHED 23 January 2026

CITATION
Marwaha K, Norris K and Mody FV (2026) Editorial: The newer paradigms in hypertension research and management. *Front. Med.* 13:1781466.
doi: 10.3389/fmed.2026.1781466

Editorial: The newer paradigms in hypertension research and management

Komal Marwaha[1]*, Keith Norris[2] and Freny Vagaiwalla Mody[2,3]

[1]College of Medicine, University of Illinois, Peoria, IL, United States, [2]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, United States, [3]Division of Cardiology, Veterans Affairs Greater Los Angeles Health Care System, Los Angeles, CA, United States

KEYWORDS

age of hypertension onset shapes long-term renal risk, chronotherapy in hypertension treatment, recurrent hypoglycemia triggered secondary hypertension, nasal turbinate lymphatic obstruction in the pathogenesis of essential hypertension, impact of cuff placement on blood pressure readings, lay advisor-led interventions in hypertension management, elevated hemoglobin an independent predictor of hypertension, hypertension knowledge and adherence among primary care patients

Editorial on the Research Topic
The newer paradigms in hypertension research and management

Hypertension remains a major global health challenge, affecting more than 1.2 billion individuals worldwide and contributing to substantial cardiovascular morbidity and premature mortality (1). Despite decades of epidemiological insight and therapeutic innovation, population-level control remains inadequate: fewer than one in five individuals with hypertension achieve guideline-based targets (2). In addition to underdiagnosis and therapeutic inertia, poor adherence, especially among socioeconomically disadvantaged populations continues to limit effective management (3, 4). These persistent gaps underscore the need for fresh perspectives that extend beyond conventional risk stratification and pharmacologic control.

The articles included in this Research Topic collectively reflect the diverse and evolving paradigms shaping contemporary hypertension research. They examine the condition across multiple dimensions, temporal and mechanistic insights, circadian pharmacology, emerging neurovascular hypotheses, precision in measurement, population-specific determinants, and community- and system-level interventions. Together, these contributions offer a holistic view of hypertension as a complex interplay of biological, behavioral, and structural factors, while pointing toward novel strategies for prevention, diagnosis, and management.

At the temporal and mechanistic level, Qiu and Wu analyzed NHANES data to examine how the age of hypertension onset shapes long-term renal risk. Their cross-sectional study demonstrated that individuals diagnosed with hypertension before the age of 35 had more than double the risk of developing chronic kidney disease compared with normotensive peers. This finding underscores that hypertension is not simply a hemodynamic state but a reflection of progressive vascular burden that begins early, highlighting the need for screening for not only blood pressure, but end-organ changes in younger adults in the second decade with recommendations for lifestyle intervention and aggressive early therapeutic intervention to reduce vascular effects. Complementing this, Tsige and Ayele revisited malignant hypertension, one of the most severe clinical presentations. Their review emphasized current guideline-based treatment, endorsing intravenous labetalol and nicardipine as first-line agents, while stressing controlled reduction to avoid ischemic complications. Together, these studies span the disease's temporal extremes, from silent early onset to life-threatening crises and emphasize the necessity of timely detection and evidence-based management.

Building on these clinical insights, Nadeem et al. explored chronotherapy through a meta-analysis comparing morning vs. bedtime low-dose aspirin administration. Across more than 1,300 participants, bedtime dosing produced greater reductions in both systolic and diastolic blood pressure compared to morning dosing. These results highlight the interplay between circadian biology, vascular tone, and pharmacologic response, offering a low-cost, personalized strategy that leverages biological rhythms to optimize therapeutic outcomes.

Beyond established mechanisms, several contributions challenge conventional paradigms and open new investigative avenues. Mijalkovic and Sacic proposed that pancreatic insulinoma–induced recurrent hypoglycemia may trigger secondary hypertension through catecholamine surges and renal sodium retention. This opinion draws attention to neuroendocrine factors that may underlie secondary forms of hypertension. And additional novel pathobiological mechanism for secondary hypertension, with potential reversible management was proposed by Phillips and Schwartz, They advanced an innovative hypothesis implicating nasal turbinate lymphatic obstruction in the pathogenesis of essential hypertension. Drawing on nuclear imaging, they propose that nasal turbinate vasodilation impedes cerebrospinal fluid drainage, increases intracranial pressure, and triggers compensatory hypertension via the Cushing mechanism. This "selfish brain" model offers a novel neurovascular perspective and suggests unconventional therapeutic targets focused on autonomic modulation and nasal lymphatic pathways.

Another critical dimension explored in this Research Topic relates to measurement precision. Zhu et al. examined the impact of sphygmomanometer and cuff placement on blood pressure readings. In a large methodological study, measurements taken at the elbow fossa were consistently lower than those at the upper arm by 3–4 mmHg for both systolic and diastolic pressures. Given that treatment effect in large clinical trials is frequently in this range of change in BP in mmHg, this reinforces the importance of standardized technique and adherence to validated protocols, especially in large-scale screening or telemonitoring programs where even small deviations can shift diagnostic and treatment thresholds.

Expanding outward to system-level approaches, Patil et al. conducted a comprehensive systematic review and meta-analysis of lay advisor–led interventions, evaluating their effectiveness and implementation using the (Reach, Effectiveness, Adoption, Implementation, and Maintenance) RE-AIM framework. High-intensity lay advisor programs achieved greater reductions in both systolic and diastolic blood pressures compared with low-intensity or control groups. However, the authors noted limited reporting on adoption, implementation, and maintenance, underscoring the need to embed such interventions within sustainable health systems to achieve lasting impact.

Population-specific studies further enrich this Research Topic. Hongyu et al. examined high-altitude populations in China and identified elevated hemoglobin as an independent predictor of both carotid intima–media thickness and hypertension, with a threshold of 131 g/L. Their findings shed light on how chronic hypoxia and hematological adaptations shape vascular remodeling and may inform both local interventions and insights relevant to sea-level populations. Similarly, Al-Hazmi et al. conducted a cross-sectional study in eastern Saudi Arabia to assess hypertension knowledge and adherence among primary care patients. Only a small proportion of participants demonstrated high levels of knowledge, particularly regarding drug compliance, and knowledge was positively correlated with adherence. This emphasizes the critical role of culturally tailored patient education in improving long-term control. Finally, Hou et al. analyzed the cost drivers of hypertension hospitalizations in traditional Chinese medicine hospitals. They identified length of stay, age, and admission pathways as key factors and advocated integrating TCM's strengths in chronic disease management with standardized modern protocols to reduce economic burden and enhance efficiency.

Taken together, these contributions expand the landscape of hypertension research. From early onset risk and malignant hypertension to chronotherapy, neurovascular hypotheses, measurement precision, community engagement, and population-specific insights, they exemplify a shift from reductionist approaches toward integrated frameworks linking biology, behavior, and systems. Future progress will depend on bridging mechanistic discovery with clinical implementation, leveraging digital technologies, addressing sociocultural barriers, and personalizing care across diverse populations. The research presented in The Newer Paradigms in Hypertension Research and Management represents an important step toward redefining how hypertension is understood and managed in the coming decades.

Author contributions

KM: Conceptualization, Methodology, Writing – review & editing, Writing – original draft. KN: Methodology, Conceptualization, Writing – review & editing. FM: Methodology, Conceptualization, Writing – review & editing.

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

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. (2021) 398:957–980. doi: 10.1016/s0140-6736(21)01330-1

2. Schutte AE, Jafar TH, Poulter NR, Damasceno A, Khan NA, Nilsson PM, et al. Addressing global disparities in blood pressure control: perspectives of the International Society of Hypertension. *Cardiovasc Res*. (2023) 119:381–409. doi: 10.1093/cvr/cvac130

3. Carey RM, Moran AE, Whelton PK. Treatment of hypertension: a review. *JAMA*. (2022) 328:1849–1861. doi: 10.1001/jama.2022.19590

4. Choudhry NK, Kronish IM, Vongpatanasin W, Ferdinand KC, Pavlik VN, Egan BM, et al. Medication adherence and blood pressure control: a scientific statement from the american heart association. *Hypertension*. (2022) 79:e1–e14. doi: 10.1161/hyp.0000000000000203

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 25 April 2024
DOI 10.3389/fpubh.2024.1329768

OPEN ACCESS

EDITED BY
Komal Marwaha,
Texas Tech University Health Sciences Center,
United States

REVIEWED BY
Anees Ur Rehman,
Bahauddin Zakariya University, Pakistan
Muhammad Fawad Rasool,
Bahauddin Zakariya University, Pakistan

*CORRESPONDENCE
Zhong-hua Luo
✉ psxlzh@163.com

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

RECEIVED 29 October 2023
ACCEPTED 01 April 2024
PUBLISHED 25 April 2024

CITATION
Hou H-j, Cong T-z, Cai Y, Ba Y-h, Chen M-e, Yang J-y and Luo Z-h (2024) Influencing factors of hospitalization cost of hypertension patients in traditional Chinese medicine hospitals.
Front. Public Health 12:1329768.
doi: 10.3389/fpubh.2024.1329768

Influencing factors of hospitalization cost of hypertension patients in traditional Chinese medicine hospitals

Hao-jia Hou[1†], Tian-zhen Cong[1†], Yu Cai[1†], Ya-hui Ba[2], Meng-en Chen[3], Jing-yu Yang[2] and Zhong-hua Luo[4*]

[1]School of Public Health, Gansu University of Chinese Medicine, Lanzhou, China, [2]School of Business and Management, Gansu University of Chinese Medicine, Lanzhou, China, [3]School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, [4]School of Marxism Studies, Gansu University of Chinese Medicine, Lanzhou, China

Objectives: This study aimed to analyze the influencing factors of hospitalization cost of hypertensive patients in TCM (traditional Chinese medicine, TCM) hospitals, which can provide a scientific basis for hospitals to control the hospitalization cost of hypertension.

Methods: In this study, 3,595 hospitalized patients with a primary diagnosis of tertiary hypertension in Tianshui City Hospital of TCM, Gansu Province, China, from January 2017 to June 2022, were used as research subjects. Using univariate analysis to identify the relevant variables of hospitalization cost, followed by incorporating the statistically significant variables of univariate analysis as independent variables in multiple linear regression analysis, and establishing the path model based on the results of the multiple linear regression finally, to explore the factors influencing hospitalization cost comprehensively.

Results: The results showed that hospitalization cost of hypertension patients were mainly influenced by length of stay, age, admission pathways, payment methods of medical insurance, and visit times, with length of stay being the most critical factor.

Conclusion: The Chinese government should actively exert the characteristics and advantages of TCM in the treatment of chronic diseases such as hypertension, consistently optimize the treatment plans of TCM, effectively reduce the length of stay and steadily improve the health literacy level of patients, to alleviate the illnesses pain and reduce the economic burden of patients.

KEYWORDS

hypertension, TCM hospitals, characteristic advantages of TCM, hospitalization cost, length of stay

1 Introduction

Hypertension is a common chronic cardiovascular disease, with persistently high blood pressure, causes damage to the heart, cerebral blood vessels, kidneys, and other organs, and can increase the risk of heart disease, stroke, and other diseases (1). By category, hypertension can typically be divided into essential hypertension, secondary hypertension, and pregnancy-induced hypertension (2). Hypertension has been identified as an essential risk factor for death, with an estimated 9.4 million premature deaths and 92 million disabilities attributable to hypertension each year (3–5).

Based on available surveys, more than 1 billion people worldwide with hypertension in 2019, the number has doubled since 1990 (6). The largest global study of hypertension trends to date, led by Imperial College London and the World Health Organization in 2021 and involving more than 1,100 doctors and scientists, found the number of adults aged 30–79 with hypertension has increased from 650 million to 1.28 billion in the last 30 years and more than 700 million of these don't know they have (7). By 2019, China managed about 109 million registered hypertensive patients, the standardized management rate of hypertensive patients has increased by 29.28%, and the blood pressure control rate in the population managed for hypertension has increased by 16.84% in the past decade, with an average annual growth rate of 3.28% (8). In addition to the high prevalence of hypertension, the financial burden of this disease is also significant. The global healthcare costs due to hypertension exceed $500 billion per year, and only the United States incurs more than $300 billion per year, with Europe being the region with the highest healthcare costs for hypertension (9, 10). China's direct medical costs due to hypertension from 1993 to 2003 grew from RMB 4.531 billion to RMB 30.030 billion, with an average annual growth rate as high as 20.82%, which is faster than the GDP, and even faster than the growth rate of the total health costs and the total medical costs in the same period (11). The annual per capita cost of hypertension among Chinese residents in the period of 2006–2011 was RMB 6,271.80, accounting for 45.58% of the annual per capita income (12), and the medical cost of hypertension in China in 2019 was as high as RMB 74.06 billion, accounting for 5.1% of the total national medical cost (13, 14). With the aging of China's population, China's hypertensive population is bound to increase continually, and the hypertensive disease burden will continue to increase. Hypertension has become a worldwide public health problem bringing a heavy economic burden of disease to the world (15–17), and hypertensive patients with other comorbidities and complications will consume more medical resources and incur more healthcare costs (18, 19), so the need for research on hypertension cost control is particularly urgent (20–22).

As an essential part of China's healthcare system, TCM hospitals make comprehensive use of the correlation of all four examinations as well as traditional resources and therapeutic means, such as traditional Chinese medicine, acupuncture and moxibustion, and tuina, to carry out diagnosis and treatment for diseases. The TCM hospitals' therapy process emphasizes mutually the overall concept and individualized diagnosis, which focuses on regulating the balance and coordination of the systems within the human body while formulating targeted treatment plans according to the patient's specific condition and physical characteristics. Meanwhile, TCM hospitals inherit and carry forward the essence of TCM, as well as actively introduce modern medical technology, and promote the development of integrated Chinese medicine and Western medicine diagnosis and treatment modes, to satisfy the demand for patients' all-around diagnosis and treatment service. In recent years, the Chinese government has paid more and more attention to the inheritance and innovation of Chinese medicine and focused on the dominant therapy of TCM in the treatment of chronic diseases, such as cupping, scraping, acupuncture, and tuina (23–25). In particular, the publication of "Expert Consensus on the Diagnosis and Treatment of Hypertension with Traditional Chinese Medicine" (26, 27) has further improved the system of diagnostic and therapeutic protocols for the treatment of hypertension with Chinese medicine in China. Undeniably, TCM tonics, oral CPMs (Chinese patent medicines, CPMs), and TCM injections have been widely used in the treatment of hypertension and have achieved remarkable efficacy (28–30), which reflects unique TCM advantages in improving clinical efficacy, reducing BP levels, and improving the quality of life. In a word, TCM provides an excellent alternative for hypertensive patients who cannot tolerate conventional Western medications.

The Global Report on Hypertension released by WHO in September 2023, estimates the economic benefits of improved hypertension treatment options are ∼18 times greater than the costs. As an important treatment method for hypertension in China, Chinese medicine, including herbal formulas, acupuncture, acupoints, footbaths, and other Chinese medical treatments, as well as the combination of Chinese medicine and Western medicine, not only achieve effective clinical results in the treatment of hypertension but also have an absolute advantage in terms of cost. In this regard, the overall cost of treating hypertension in TCM hospitals is much lower than Western medicine due to the vast area of cultivation of Chinese herbal medicine in China and the high availability and circulation of Chinese medicine resources. Therefore, this paper reviewed and analyzed the relevant information of 3,595 patients with hypertension who were hospitalized in Tianshui Hospital of TCM in Gansu Province, China from January 2017 to June 2022, to explore the influencing factors of hospitalization cost of patients. In this study, targeted countermeasures and suggestions were also proposed to control hospitalization cost and give full play to the price advantages of chronic diseases in TCM, to effectively alleviate the economic pressure brought by hypertension to the national economy.

2 Materials and methods

2.1 Study design and population

The data for this study came from the National Health Big Data Platform (a governmental non-full public database) of the Health Commission of Gansu Province, China, and the data content mainly involved information on the front page of TCM hospital cases, with detailed on hypertensive hospitalized patients in Tianshui City TCM Hospital, Gansu Province, for January 2017–June 2022. Inclusion criteria: patients with a primary diagnosis of tertiary hypertension I10.x05 (in accordance with ICD-10). Exclusion criteria: the length of stay is <1 day, logically inconsistent in medical information, and diagnostic information with incomplete and could not be effectively supplemented. Following the above inclusion and exclusion criteria, 3,595 valid cases were finally included. As the research data need to be treated confidentially and should not be made public, the corresponding author can be contacted if necessary.

TABLE 1 Variable assignment processing case.

Variables	Variable codes	Variable names	Dummy variables	Variable assignment
Endogenous variables	Y_1	Length of stay (days)	—	Log (length of stay)
	Y_2	Hospitalization cost (CNY¥)	—	Log (hospitalization cost)
Exogenous variables	X_1	Gender	—	0 = male, 1 = female
	X_2	Nationality	—	0 = han, 1 = other ethnic groups
	X_{3-0}-X_{3-2}	Age (years)	<45 (reference)	0, 0
			45–60	1, 0
			>60	0, 1
	X_4	Marital status	—	0 = married, 1 = others (unmarried, widowed or divorced)
	X_5	Visit times	—	0 = one time, 1 = two or more times
	X_{6-0}-X_{6-3}	Payment methods of medical insurance	UEBMI[a] (reference)	0, 0, 0
			URBMI[b]	1, 0, 0
			NCMS[c]	0, 1, 0
			Others	0, 0, 1
	X_7	Occupations	—	0 = retired personnel, 1 = non-retired personnel
	X_{8-0}-X_{8-2}	Admission pathways	Emergency (reference)	0, 0
			Outpatients	1, 0
			Others	0, 1
	X_{9-0}-X_{9-2}	Treatment categories	—	0 = Chinese medicine 1 = integrated Chinese and western medicines
	X_{10-0}-X_{10-2}	Clinical Pathways	Chinese medicine (reference)	0, 0
			Western medicine	1, 0
			No clinical pathway	0, 1
	X_{11}	Use of TCM[d] preparations	—	0 = no, 1 = yes
	X_{12}	Use of TCM[d] diagnosis and treatment equipment	—	0 = no, 1 = yes
	X_{13}	Use of TCM[d] diagnosis and treatment techniques	—	0 = no, 1 = yes
	X_{14}	Disease severity	—	0 = non-extremely high risk, 1 = extremely high risk
	X_{15}	Surgery and procedures	—	0 = no, 1 = yes

[a]UEBMI, the urban employee basic medical insurance system; [b]URBMI, the urban residents' basic medical insurance system; [c]NCMS, the new cooperative medical scheme; [d]TCM, traditional Chinese medicine.

2.2 Data processing

Since the key indicator of hospitalization cost in this study is economic data, to eliminate the bias effect of inflation and other factors on the study of hospitalization cost in hypertension, the cost adjustment was made based on the Consumer Price Index (CPI) for healthcare in Gansu Province from 2017 to 2022, with 2016 as the base period for statistical correlation analysis.

According to the existing research, hospitalization cost is affected by factors such as length of stay (31–34). In this study, the length of stay and hospitalization cost were endogenous variables, while gender, ethnicity, age, marital status, visit times, payment methods of medical insurance, occupations, admission pathways, treatment categories, clinical pathways, use of TCM preparations, use of TCM diagnosis and treatment equipment, use of TCM diagnosis and treatment techniques, disease severity, and surgery and procedures were exogenous variables. In addition, relevant variables should be classified or integrated according to the actual analysis. The specific variable assignment processing was shown in Table 1.

TABLE 2 Description of the study sample (length of stay and hospitalization cost).

Variable names	Variable categories	*N* (%)	Length of stay (days)		Hospitalization cost (CNY ¥)	
			M (P_{25}, P_{75})[e]	*Z*/*H*-value[f]/*p*-value	*M* (P_{25}, P_{75})	*Z*/*H*-value/*p*-value
Gender	Male	1,727 (48.04%)	12 (9, 14)	−0.278/0.781	6,208.289 (4,991.133, 7,463.729)	−1.284/0.199
	Female	1,868 (51.96%)	12 (9, 14)		6,266.977 (5,081.495, 7,517.017)	
Nationality	Han	3,501 (97.39%)	12 (9, 14)	−1.070/0.285	6,245.893 (5,052.704, 7,479.793)	−0.630/0.528
	Other ethnic groups	94 (2.61%)	11 (9, 13)		6,304.742 (4,970.031, 7,745.187)	
Age (years)	<45	182 (5.06%)	10 (9, 13)	28.622/<0.001	5,448.945 (4,738.820, 6,776.972)	81.317/<0.001
	45–60	1,184 (32.93%)	11 (9, 14)		5,917.072 (4,769.390, 7,181.638)	
	>60	2,229 (62.00%)	12 (10, 14)		6,441.065 (5,303.748, 7,659.316)	
Marital status	Married	3,461 (96.27%)	12 (9, 14)	−0.437/0.662	6,227.116 (5,022.163, 7,470.215)	−2.761/0.006
	Others	134 (3.73%)	12 (10, 13.25)		6,592.672 (5,581.839, 7,861.733)	
Visit times	One time	2,124 (59.08%)	12 (9, 14)	−4.681/<0.001	6,086.396 (4,835.231, 7,334.465)	−6.552/ <0.001
	Two or more times	1,471 (40.92%)	12 (10, 14)		6,484.139 (5,330.546, 7,704.961)	
Payment methods of medical insurance	UEBMI[a]	2,309 (64.23%)	12 (10, 14)	27.940/<0.001	6,330.094 (5,159.746, 7,515.878)	12.178/0.007
	URBMI[b]	606 (16.86%)	11 (9, 14)		6,060.021 (4,834.210, 7,353.051)	
	NCMS[c]	596 (16.58%)	11 (9, 13)		6,180.217 (4,948.426, 7,535.548)	
	Others	84 (2.34%)	11 (8, 14.75)		5,834.281 (3,973.610, 7,395.272)	
Occupations	Retired personnel	1,385 (38.53%)	12 (9, 13)	−2.231/0.026	6,320.342 (5,060.134, 7,481.272)	−0.723/0.469
	Non-retired personnel	2,210 (61.47%)	12 (9, 14)		6,198.538 (5,035.872, 7,486.123)	
Admission pathways	Emergency	830 (23.09%)	11 (9, 13)	269.393/<0.001	6,201.436 (4,907.115, 7,457.158)	104.115/<0.001
	Outpatients	2,217 (61.67%)	11 (9, 14)		6,089.061 (4,896.043, 7,346.399)	
	Others	548 (15.24%)	14 (12, 16)		6,933.002 (5,793.101, 8,240.037)	
Treatment categories	Chinese medicine	2,374 (66.04%)	12 (9, 14)	−3.395/0.001	6,260.372 (5,077.969, 7,469.626)	−0.375/0.708
	Integrated Chinese and Western medicines	1,221 (33.96%)	12 (9, 14)		6,218.038 (4,956.771, 7,533.129)	
Length of stay (days)	1–7	453 (12.60%)	6 (5, 7)	2,404.479/<0.001	3,901.713 (3,249.464, 4,605.480)	1,281.254/<0.001
	8–14	2,483 (69.07%)	11 (10, 13)		6,196.272 (5,256.654, 7,198.669)	
	15–21	611 (17.00%)	16 (15, 17)		7,880.837 (6,969.960, 8,984.650)	

(Continued)

TABLE 2 (Continued)

Variable names	Variable categories	*N* (%)	Length of stay (days)		Hospitalization cost (CNY ¥)	
			M (P_{25}, P_{75})[e]	*Z*/*H*-value[f]/*p*-value	*M* (P_{25}, P_{75})	*Z*/*H*-value/*p*-value
	22 and above	48 (1.34%)	23 (22, 25)		9,101.600 (8,317.079, 1,0924.638)	
Clinical pathways	Chinese medicine	2,471 (68.73%)	11 (9, 13)	62.088/<0.001	6,207.420 (5,069.242, 7,400.979)	5.722/0.057
	Western medicine	28 (0.78%)	13.5 (12, 16)		6,832.700 (5,439.879, 8,619.730)	
	No clinical pathway	1,096 (30.49%)	12 (10, 15)		6,331.794 (4,942.251, 7,742.514)	
Use of TCM[d] preparations	Yes	1,880 (52.29%)	12 (9, 14)	−0.958/0.338	6,245.983 (5,138.758, 7,524.630)	−1.008/0.313
	No	1,715 (47.71%)	12 (9, 14)		6,246.410 (4,970.603, 7,455.126)	
Use of TCM[d] diagnosis and treatment equipment	Yes	3,263 (90.76%)	12 (9, 14)	−4.582/<0.001	6,211.532 (5,018.061, 7,459.125)	−2.992/0.003
	No	332 (9.24%)	13 (10, 15)		6,526.797 (5,378.767, 7,832.870)	
Use of TCM[d] diagnosis and treatment techniques	Yes	3,512 (97.69%)	12 (9, 14)	−0.447/0.655	6,252.858 (5,052.493, 7,480.795)	−0.640/0.522
	No	83 (2.31%)	12 (9, 14)		5,866.920 (4,900.576, 7,730.989)	
Disease severity	Extremely high risk	2,473 (68.79%)	11 (9, 13)	−14.290/<0.001	6,090.096 (4,894.673, 7,333.047)	−7.695/<0.001
	Non-extremely high risk	1,122 (31.21%)	13 (10, 15)		6,523.289 (4,894.673, 7,842.733)	
Surgery and procedures	Yes	773 (21.50%)	11 (9, 13)	−7.148/<0.001	5,992.718 (4,805.164, 7,134.159)	−5.431/<0.001
	No	2,822 (78.50%)	12 (9, 14)		6,291.816 (5,146.004, 7,595.878)	

[a]UEBMI, the urban employee basic medical insurance system; [b]URBMI, the urban residents' basic medical insurance system; [c]NCMS, the new cooperative medical scheme; [d]TCM, traditional Chinese medicine; [e]M (P_{25}, P_{75}), median (the first quartile, the third quartile); [f]Z/H-value, Mann–Whitney *U*-test statistical value or Kruskal–Wallis *H*-test statistical value.

2.3 Statistical analysis

Firstly, univariate analysis of length of stay and hospitalization cost was performed using SPSS 26.0. Since the original data of hospitalization cost and length of stay did not follow the normal distribution, the *Mann-Whitney U*-test and *Kruskal-Wallis H*-test were used to process and analyze according to the data types, and the length of stay and hospitalization cost were expressed in the median and quartile. Secondly, variables that were statistically significant in the univariate analysis selected as independent variables, and the dependent variables length of stay and hospitalization cost, which did not obey normal distribution, were logarithmically transformed into Log (Length of stay) and Log (Hospitalization cost) to approximate the requirement of obeying normality, to establish multiple linear regression models. Based on multiple linear regression analysis model, Amos 24.0 software was used to establish a path model with statistically significant variables in multiple linear regression results as independent variables, Log (Length of stay) as mediator variables, and Log (Hospitalization cost) as dependent variables, to explore the influencing factors and its rank relationship of hospitalization cost in patients with hypertension comprehensively. The test level of the above analysis was $\alpha = 0.05$.

3 Results

3.1 Univariate analysis results of length of stay and hospitalization cost

As can be seen from Table 2, there were significant differences ($p < 0.05$) in the length of stay among hypertensive patients with different ages, visit times, payment methods of medical insurance, occupations, admission pathways, treatment categories, clinical pathways, use of TCM diagnosis and treatment equipment, disease severity, and whether surgery and procedures were performed, and more comparison of differences can be seen in Figure 1. Furthermore, there were also statistical differences ($p < 0.05$) in

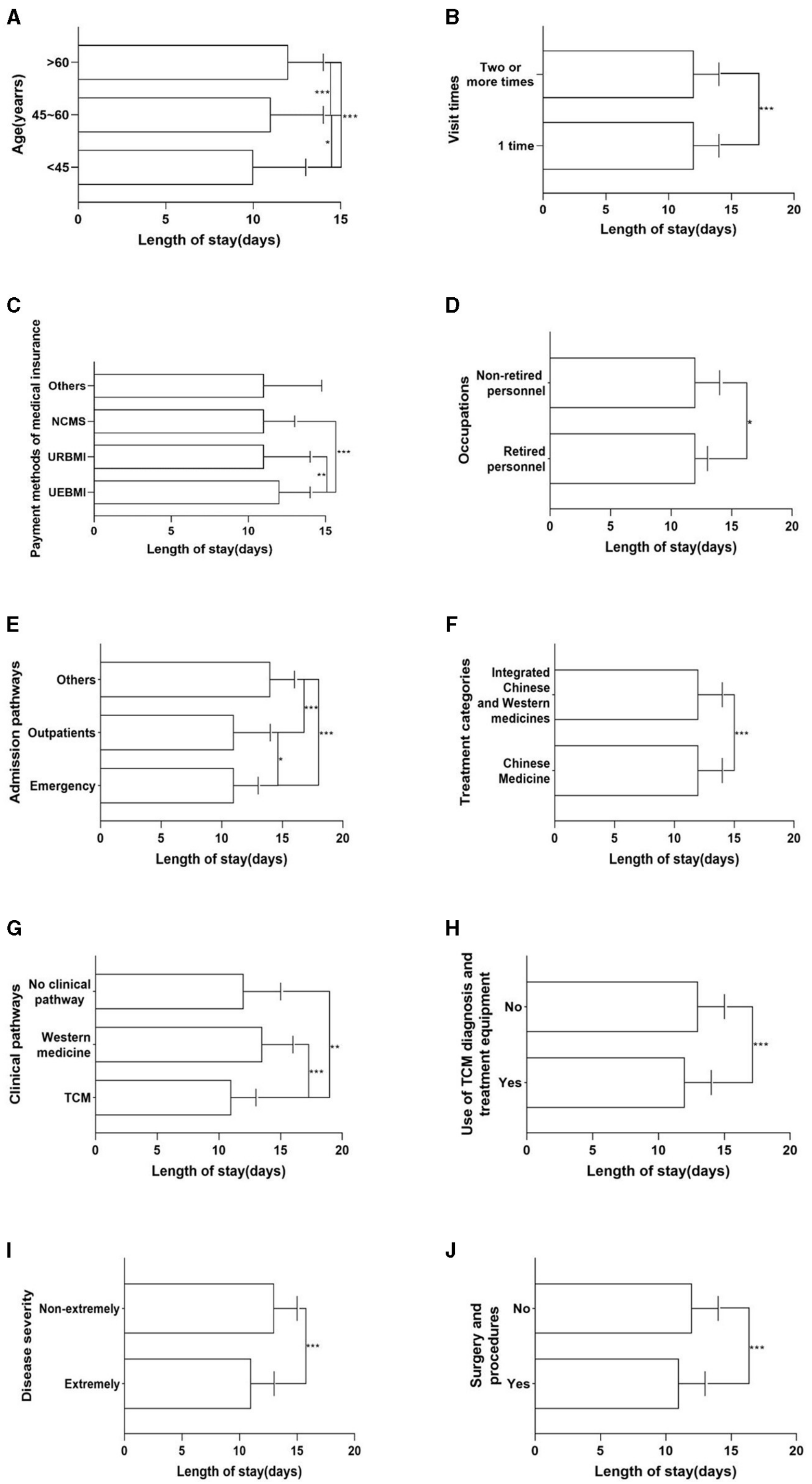


FIGURE 1
Univariate analysis results of length of stay. **(A)** Age. **(B)** Visit times. **(C)** Payment methods of medical insurance. **(D)** Occupations. **(E)** Admission pathways. **(F)** Treatment categories. **(G)** Clinical pathways. **(H)** Use of TCM diagnosis and treatment equipment. **(I)** Disease severity. **(J)** Surgery and procedures. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

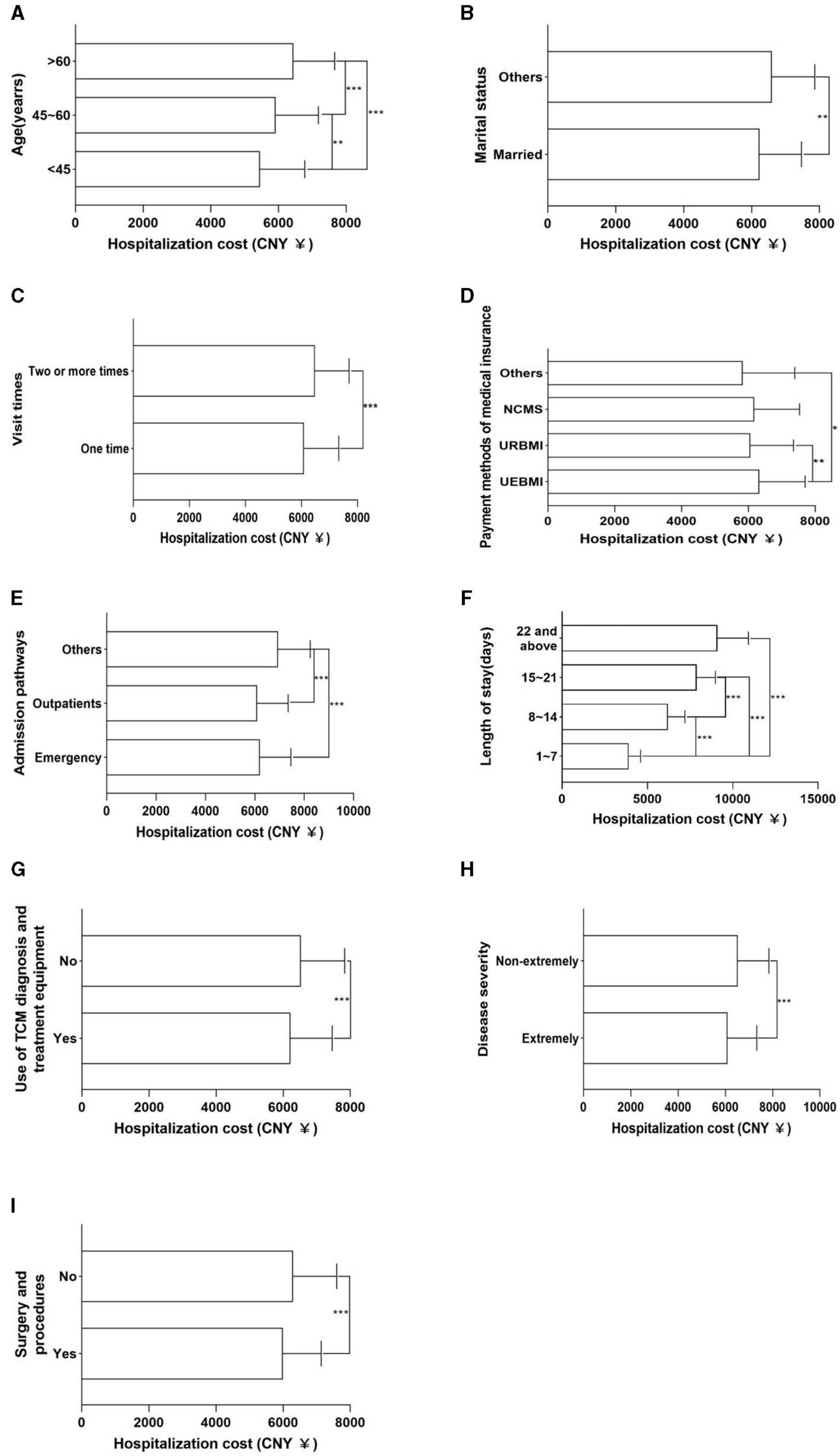


FIGURE 2
Univariate analysis results of hospitalization cost. **(A)** Age. **(B)** Marital status. **(C)** Visit times. **(D)** Payment methods of medical insurance. **(E)** Admission pathways. **(F)** Length of stay. **(G)** Use of TCM diagnosis and treatment equipment. **(H)** Disease severity. **(I)** Surgery and procedures. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

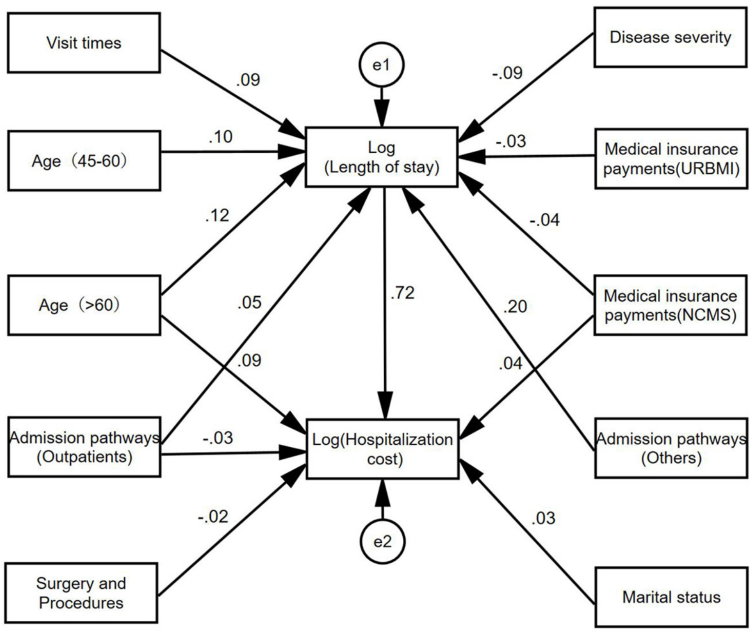


FIGURE 3
Path diagram of influencing factors of hospitalization cost of hypertension patients.

the hospitalization cost of hypertensive patients by different ages, marital status, visit times, payment methods of medical insurance, admission pathways, length of stay, use of TCM diagnosis and treatment equipment, disease severity, and whether surgery and procedures were performed, and more comparison of differences can be seen in Figure 2.

3.2 Multivariate linear regression results of length of stay and hospitalization cost

Results of multivariate linear regression showed that the length of stay of hypertensive patients was affected by age, visit times, payment methods of medical insurance, other ways of admission pathways, and disease severity ($p < 0.05$), and the regression equation of length of stay ($F = 20.322$, $p < 0.001$, $R^2 = 0.078$) was as follows:

$$\boldsymbol{Y_1 = 0.953 + 0.037^*X_{3-1} + 0.042^*X_{3-2} + 0.032^*X_5 - 0.020^*X_{6-1} - 0.027^*X_{6-2} + 0.015^*X_{8-1} + 0.098^*X_{8-2} - 0.028^*X_{14}}.$$

Hospitalization cost was affected by age, marital status, payment methods of medical insurance, admission pathways, surgery and procedures, and length of stay ($p < 0.05$), and the regression equation of hospitalization cost ($F = 327.863$, $p < 0.001$, $R^2 = 0.543$) was as follows:

$$\boldsymbol{Y_2 = 3.103 + 0.038^*X_{3-2} + 0.019^*X_4 + 0.015^*X_{6-2} - 0.012^*X_{8-1} - 0.010^*X_{15} + 0.610^*Y_1}.$$

The results are summarized in Table 3. Further calculation based on analysis results showed that the residual path coefficient was 0.676 ($P_e = \sqrt{1 - R^2} = 0.676$), which is lower than the standardized coefficient of Y_1, indicating that there are other influencing factors existing as well. Path models can be developed based on the results of multiple linear regressions to explore other influences on hospitalization cost comprehensively.

3.3 Path analysis results of hospitalization cost

As shown in Figure 3, visit times, age (45–60), admission pathways (Outpatient, Others), disease severity, and payment methods of medical insurance could indirectly affect the hospitalization cost through the length of stay. In addition, age (>60), admission pathways (Outpatients), marital status, payment methods of medical insurance (NCMS), and surgery and procedures could also affect the hospitalization cost directly.

Based on the path model, the effects decomposition of the influencing factors of hospitalization cost could be derived, and the specific results were summarized in Table 4. The effect of each factor on hospitalization cost ranked as follows: length of stay, age (>60), admission pathways (Others), payment methods of medical insurance (NCMS), visit times, disease severity, admission pathways (Outpatients), marital status, payment methods of medical insurance (URBMI), surgery and procedures.

4 Discussion

Current research on the cost of hypertension mainly focuses on comprehensive (Western medicine) hospitals, while our study is based on the TCM hospitals' official database from local governments in China, with rigorous and appropriate statistical methods to analyze the influence factors on hospitalization cost of hypertensive patients. As a result, this study will powerfully enrich and expand the content of the current research on cost control of

TABLE 3 Multiple linear regression results of the length of stay and hospitalization cost of hypertension patients.

Variables	Log (length of stay)				Log (hospitalization cost)			
	B[e]	Beta[f]	t-value	p-value	B	Beta	t-value	p-value
Constant	0.953	—	35.476	<0.001	3.103	—	180.744	<0.001
Age (ref = <45)								
45–60	0.037	0.100	2.741	0.006	0.013	0.040	1.583	0.113
>60	0.042	0.116	3.023	0.003	0.038	0.123	4.773	<0.001
Marital status	—	—	—	—	0.019	0.024	2.069	0.039
Visit times	0.032	0.089	5.133	<0.001	0.006	0.021	1.707	0.088
Payment methods of medical insurance (ref = URRBMI[a])								
URBMI[b]	−0.020	−0.042	−2.254	0.024	−0.003	−0.009	0.733	0.464
NCMS[c]	−0.027	−0.057	−2.910	0.004	0.015	0.037	3.062	0.002
Others	−0.034	0.030	−1.813	0.070	−0.021	−0.021	−1.850	0.064
Occupation	0.003	0.008	0.349	0.727	—	—	—	—
Admission pathways (ref = emergency)								
Outpatients	0.015	0.042	2.084	0.037	−0.012	−0.039	−2.802	0.005
Others	0.098	0.200	7.238	<0.001	−0.010	−0.025	−1.419	0.156
Treatment category	0.012	0.033	1.784	0.075	—	—	—	—
Clinical pathway (ref = Chinese medicine)								
Western medicine	0.046	0.023	1.414	0.157	—	—	—	—
No clinical pathway	−0.012	−0.031	−1.672	0.095	—	—	—	—
Use of TCM[d] diagnosis and treatment equipment	−0.010	−0.017	−1.017	0.309	−0.002	−0.004	−0.321	0.748
Disease severity	−0.028	−0.073	−2.827	0.005	−0.001	−0.004	−0.272	0.785
Surgery and procedures	−0.014	−0.032	−1.780	0.075	−0.010	−0.029	−22.323	0.020
Log (length of stay)	—	—	—	—	0.610	0.721	61.342	<0.001
R^2-value	0.078				0.543			
F-value	20.322				327.863			
P-value	<0.001				<0.001			

[a]UEBMI, the urban employee basic medical insurance system; [b]URBMI, the urban residents' basic medical insurance system; [c]NCMS, the new cooperative medical scheme; [d]TCM, traditional Chinese medicine; [e]B, unstandardized coefficients; [f]Beta, standardized coefficients.

hypertension, promote the development of health economics with Chinese characteristics, and be of great practical significance in giving full play to the advantages of traditional Chinese medicine in the treatment of chronic diseases such as hypertension and the reduction of the economic burden of disease in China.

Through the research, we found the length of stay of male patients with hypertension in TCM hospitals is basically equal to female patients, while the hospitalization cost of male patients is slightly higher than female patients. What's more, the age of patients is a stronger factor on hospitalization cost, which increases with growing age. What made this possible is that the older adult due to the continuous aging of the patient's organism and decreasing resistance, have a higher risk of disease and are prone to repeat and prolonged hospitalization, which consumes more healthcare resources (35, 36). Additionally, patients admitted by other pathways, such as medical referral and cross-province medical treatment, will significantly increase hospitalization cost (37). The fact that medical insurance policies of some insured places have set up differential treatment for medical referral and cross-provincial medical treatment so that their reimbursement ratio is lower than other groups, is the main reason for the current Chinese government's continuous implementation of medical insurance reform. In terms of visit times, patients with repeat visit may have relatively complex and severe conditions that show a tendency toward poorer outcomes, of which hospitalization cost will also be relatively high. As the condition progressed to critical, the risk of increased hospitalization cost rose dramatically, implying a greater possibility of resuscitation, and further increasing the risk of higher hospitalization cost.

In complete harmonization with existing studies, hospitalization cost is higher for older patients, the greater the number of visit times, and longer length of stay (38–40). Meanwhile, we found the length of stay and hospitalization cost are higher among non-retired personnel patients (41–43), which may

TABLE 4 Effect decomposition table of influencing factors of hospitalization cost of hypertension patients (tertiary).

Variables	Direct effect	Indirect effect	Total effect	Ranking of total effect
Age (45–60)	–	0.074	0.074	4
Age (> 60)	0.092	0.066	0.158	2
Marital status	0.028	–	0.028	9
Visit times	–	0.064	0.064	6
Payment methods of medical insurance (URBMI[a])	–	−0.024	−0.024	10
Payment methods of medical insurance (NCMS[b])	0.041	0.030	0.071	5
Admission pathways (Outpatients)	−0.029	−0.021	−0.05	8
Admission pathways (Others)	–	0.144	0.144	3
Disease severity	–	−0.063	−0.063	7
Surgery and procedures	−0.024	–	−0.024	11
Length of stay	0.722	–	0.722	1

[a]URBMI, the urban residents basic medical insurance system; [b]NCMS, the new cooperative medical scheme.

be due to the fact that higher work pressure induces more serious hypertensive disorders with more hospitalization cost (44–46). This result coincided with multiple existing studies (47, 48), which indicate that young and middle-aged working hypertension patients tend to have a predominantly cerebral workload, older retired hypertension patients are mostly engaged in physical work, as well as working mental work face more pressure, whose prevalence of hypertension and severity of the disease also increase continuously. In addition, patients with hypertension admitted through other pathways have longer length of stay and higher hospitalization cost, mainly because patients' conditions are more complex or severe with more special investigations and treatments. At the same time, the referral pathway may result in poor transfer of information between multiple providers, which increases duplication of tests and treatments and further increases hospitalization cost (49, 50).

Confusingly, hypertensive patients with more critical diseases and undergoing surgeries and procedures had fewer length of stay and lower hospitalization cost than patients with non-critical diseases and without surgeries and procedures. Combined with the characteristics of TCM syndrome differentiation and treatment, the explanations conjecture are as follows: Firstly, the more critical the disease, the more standardized the treatment, surgical operation, and medical service process are performed. Subsidiary, surgery and procedures in the sense of TCM, such as acupuncture, moxibustion, cupping therapy, tuina, qigong, and other external treatment methods, have always been safer, more convenient, and less costly than Western surgeries (51–53), which reduces the length of stay and hospitalization cost with excellent therapeutic results. Moreover, according to the relevant policies of Chinese medical insurance, and surgery and procedures will receive greater reimbursement support from medical insurance, so the actual hospitalization cost is relatively low.

In general, in addition to the length of stay and age, the hospitalization cost of hypertension patients in TCM hospitals is also affected by the admission pathways, payment methods of medical insurance, and visit times, among which the length of stay has the greatest impact on the hospitalization cost of patients with hypertension (5, 54, 55). The longer the length of stay, the greater the medical-economic pressure the patients face. Notably, the health literacy level of hypertensive patients also affects hospitalization cost (56). Health literacy affects patients' lifestyle, medication adherence treatment behavior, etc., which in turn affects the disease management and prognosis of patients with chronic diseases (57–59). Some studies have shown that the proportion of hypertension patients with health literacy was 10.10%, which was lower than 16.13% of the general population (60), indicating that improving health literacy is an important strategy to prevent and control hypertension and other chronic diseases.

5 Conclusions

In this study, 3,595 inpatients with a primary diagnosis of tertiary hypertension in Tianshui Hospital of Traditional Chinese Medicine, Gansu Province, China from January 2017 to June 2022 were selected as the research objects, to explore the influencing factors of hospitalization cost of hypertension patients. From our analysis results, the hospitalization cost of hypertensive patients is mainly affected by length of stay, age, admission pathways, payment methods of medical insurance, and visit times, and the length of stay is the most important and core influencing factor. As chronic diseases such as hypertension intensify and threaten the quality of life and health of all human beings, the Chinese government should continue to optimize the methods of diagnosis and treatment of TCM, incorporate the "combining disease and syndrome" into the process of treating illnesses to classify and define treatments, and actively exert the characteristics and advantages of TCM in the treatment of chronic diseases such as hypertension. Meanwhile, the China government should continue to deepen the reform of medical insurance policies, enhance the strength of outpatient medical insurance for chronic diseases, and optimize the structure of medical insurance treatment for patients with chronic diseases. More importantly, the China government should innovate a compensation mechanism for TCM to incentivize patients to actively use TCM to improve their health literacy, thereby reducing the length of stay, relieving their pain, and lowering the burden of medical costs.

Data availability statement

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

Author contributions

H-jH: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. T-zC: Investigation, Validation, Writing – review & editing. YC: Formal analysis, Validation, Writing – review & editing. Y-hB: Validation, Writing – original draft. M-eC: Software, Writing – original draft. J-yY: Resources, Supervision, Writing – review & editing. Z-hL: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Funding

The author (s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by the National Social Science Foundation of China, grant number 19BZX082.

Acknowledgments

Thanks for the financial support from the National Social Science Foundation and the support from the Key Discipline Construction Program of Marxism in Gansu University of Traditional Chinese Medicine.

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.

References

1. Tschanz MP, Cushman WC, Harrell TE, Berlowitz DR, Sall JL. Synopsis of the 2020 U.S. Department of Veterans Affairs/U.S. Department of Defense Clinical Practice Guideline: The Diagnosis and Management of Hypertension in the Primary Care Setting. *Ann Int Med.* (2020) 173:904–13. doi: 10.7326/M20-3798

2. Yin R, Yin L, Li L, Silva-Nash J, Tan J, Pan Z, et al. Hypertension in China: burdens, guidelines, and policy responses: a state-of-the-art review. *J Hum Hypertens.* (2022) 36:126–34. doi: 10.1038/s41371-021-00570-z

3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* (2012) 380:2224–60. doi: 10.1016/s0140-6736(12)61766-8

4. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2019) 393:1958–72. doi: 10.1016/S0140-6736(19)30041-8

5. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. *Circ Res.* (2019) 124:1045–60. doi: 10.1161/CIRCRESAHA.118.313236

6. Nguyen TN, Chow CK. Global and national high blood pressure burden and control. *Lancet.* (2021) 398:932–3. doi: 10.1016/S0140-6736(21)01688-3

7. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet.* (2021) 398:957—80. doi: 10.1016/S0140-6736(21)0 1330-1

8. You L, Zhao J, Chen X, Yang L, Liu M, Pan Y, et al. National essential public health services programs over the past decade research report two: progress and achievements of the lmplementation of national essential public health services programs over the past decade. *Chin General Pract.* (2022) 25:3209–20. doi: 10.12114/j.issn.1007-9572.2022.0407

9. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation.* (2016) 134:441–50. doi: 10.1161/CIRCULATIONAHA.115.018912

10. Feng YJ, Wang HC Li YC, Zhao WH. Hypertension screening and follow-up management by primary health care system among Chinese population aged 35 years and above. *Biomed Environ Sci.* (2015) 28:330–40. doi: 10.3967/bes2015.047

11. Kejun L, Mei W. Economic burden of main chronic non-infectious diseases in China. *Chin Health Econ.* (2005) 77–80. doi: 10.3969/j.issn.1003-0743.2005.10.031

12. Liu M, Sun L, Liu G. Economic burden and economic risk of five major chronic diseases among Chinese urban residents. *J Peking Univ.* (2014) 46:782–9. doi: 10.3969/j.issn.1003-0743.2005.10.03

13. Zhang Y, Chai P, Zhai T, Wan Q. Study on accounting and analysis of curative expenditure on cardio-cerebrovascular diseases in China. *Chin Circ J.* (2020) 35:859–65. doi: 10.3969/j.issn.1000-3614.2020.09.003

14. Zhou P, Cheng J, Gu S, Liu C. Analysis on the treatment cost and influencing factors of hypertension patients in Hainan province. *Chin Health Econ.* (2020) 39:62–4. doi: 10.7664/CHE20200416

15. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* (2017) 390:1151–210. doi: 10.1016/S0140-6736(17)32152-9

16. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet.* (2013) 381:1987–2015. doi: 10.1016/S0140-6736(13)61097-1

17. GBD 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* (2017) 390:1084–150. doi: 10.1016/s0140-6736(17)31833-0

18. Gregory AN, Anastasia U, Anouk D-L, Maureen O-R, Kimberly GB. Health care costs by type of expenditure across eGFR stages among patients with and without diabetes, cardiovascular disease, and heart failure. *J Am Soc Nephrol.* 31:1594–601. doi: 10.1681/asn.2019121308

19. Blakely T, Kvizhinadze G, Atkinson J, Dieleman J, Clarke P. Health system costs for individual and comorbid noncommunicable diseases: an analysis of publicly funded health events from New Zealand. *PLoS Med.* (2019) 16:1002716. doi: 10.1371/journal.pmed.1002716

20. Wierzejska E, Giernaś B, Lipiak A, Karasiewicz M, Cofta M, Staszewski R. A global perspective on the costs of hypertension: a systematic review. *Arch Med Sci*. (2020) 16:92689. doi: 10.5114/aoms.2020.92689

21. Gheorghe A, Griffiths U, Murphy A, Legido-Quigley H, Lamptey P, Perel P, et al. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. *BMC Public Health*. (2018) 18:975. doi: 10.1186/s12889-018-5806-x

22. Muka T, Imo D, Jaspers L, Colpani V, Chaker L, van der Lee JS, et al. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. *Eur J Epidemiol*. (2015) 30:25177. doi: 10.1007/s10654-014-9984-2

23. Li L, Yang M, Song J, Yu Y, Huang H. Network meta-analysis of the antihypertensive effect of traditional Chinese exercises on patients with essential hypertension. *J Healthc Eng*. (2022) 2022:9419037. doi: 10.1155/2022/9419037

24. Zhong D, Li J, Yang H, Li Y, Huang Y, Xiao Q, et al. Tai Chi for essential hypertension: a systematic review of randomized controlled trials. *Curr Hypertens Rep*. (2020) 3:25. doi: 10.1007/s11906-020-1031-y

25. Dai L, Jiang Y, Wang P, Chen K. Effects of three traditional Chinese fitness exercises combined with essential hypertension: a systematic review and network meta-analysis of randomized controlled trials. *Evid Based Comp Altern Med*. (2021) 22:70472. doi: 10.1155/2021/2570472

26. Expert Consensus on Diagnosis and Treatment of Hypertension with Traditional Chinese Medicine. *Chin J Exp Trad Med Form*. (2019) 25:217–21.

27. Xing M, Xiong X. Interpretation of expert consensus on diagnosis and treatment of hypertension with traditional Chinese medicine. *Chin J Exp Trad Med Form*. (2022) 28:192–205. doi: 10.13422/j.cnki.syfjx.20221191

28. Wu S, Jiang N, Shi Y, Zhao X, Guo Z, Liu J, et al. Observation on the therapeutic effect of Xiaochaihu decoction on hypertension vertigo with liver heat and phlegm dampness syndrome. *Chin Arch Trad Chin Med*. (2022) 40:169–72. doi: 10.13193/j.issn.1673-7717.2022.01.040

29. Cui S, Li R, Zhou Y. Clinical effect of Xinkeshu tablets combined with irbesartan on abdominal obesity complicated with essential hypertension and hyperlipidemia. *Chin Jo Clin Ration Drug Use*. (2022) 15:103–5. doi: 10.15887/j.cnki.13-1389/r.2022.16.032

30. Zhang J, Wei W. Clinical study on Puerarin injection combined with irbesartan for primary hypertension of type of static blood obstructing the internal. *New China Med*. (2022) 54:94–6. doi: 10.13457/j.cnki.jncm.2022.12.020

31. He J, Sun N, Yang Z, Shu T, Huang W, Fang Q. Analysis of hospitalization costs and their influencing factors in patients with primary diagnosis of pulmonary arterial hypertension. *Chongqing Med*. (2023) 52:2685–9. doi: 10.3969/j.issn.1671-8348.2023.17.024

32. Chen M, Kong F, Su B, Wei X, Yang J. Factors influencing hospitalization cost for diabetic patients in traditional Chinese medicine hospitals in Qingyang City, China. *Int J Environ Res Public Health*. (2022) 19:13859. doi: 10.3390/ijerph192113859

33. Deng X, Ma W, Xia X, Wang Y. Analysis of hospitalization expenses and influencing factors of hypertension patients based on multilevel model. *J Med Inf*. (2020) 33:57–60+64. doi: 10.3969/j.issn.1006-1959.2020.15.019

34. Gong X. Hospitalization costs and the influencing factors of drug costs in the patients with unstable Angina. *China J Pharm Econ*. (2023) 18:28–31. doi: 10.12010/j.issn.1673-5846.2023.03.005

35. Liu G, Fang Q, Ji X, Ouyang J, Zhu Y, Wang L. Medical expenditure and its influencing factors of patients with hypertension in Shanxi Province, China: a study based on 'System of Health Accounts 2011' and multiple-layer perceptron neural network. *BMJ Open*. (2022) 12:e048396. doi: 10.1136/bmjopen-2020-048396

36. Wang Y, Xu P, Zhu M. A study of hospitalization costs of hypertensive patients and their influencing factors. *Chin J Health Stat*. (2019) 36:574–7.

37. Han X, Han X, Shan H, Zuo L, He W. DRGs-based analysis of hospitalization costs for patients with tertiary hypertension. *Chin J Health Stat*. (2019) 36:412–5.

38. Gao H, Feng Q, Chen H, Xu T, Luo G, Zhao J. Influencing factors of hospitalization costs of elderly hypertensive patients in Guangxi. *Chin J Gerontol*. (2020) 40:5290–4. doi: 10.3969/j.issn.1005-9202.2020.24.042

39. Zhang B, Zhao L, Wang J. Analysis on hospitalization and cost influencing factors of the elderly in a hospital from 2015 to 2021. *Chin Med Rec*. (2023) 24:54–7. doi: 10.3969/j.issn.1672-2566.2023.08.019

40. Deng Y, Ou W, Lin Z, Lin W, Lin Y, Zeng C, et al. The Third Affiliated Hospital of Guangzhou Medical University. Status and influencing factors of hospitalization expenses of hypertension kidney disease: an analysis with ordinal logistic regression based on medica record front pages. *Chin Med Rec*. (2020) 21:66–70. doi: 10.3969/j.issn.1672-2566.2020.09.025

41. Ma J, Xu A. Utilization of health services in hypertensive patients enjoying 4 different types of basic medical insurance: a comparative analysis. *Modern Prev Med*. (2018) 21:3518–22. doi: 10.12114/j.issn.1007-9572.2018.00.072

42. Wen X, Xu D, Liu X. Relationship between overweight/obesity and hypertension, hyperlipidemia and fatty liver among railway workers in Jinan. *Chinese J Prev Control Chron Dis*. (2015) 23:588–91. doi: 10.16386/j.cjpccd.issn.1004-6194.2015.08.008

43. Shen Y, Wang X, Wang Z, Chen Z, Zhu M, Chang C, et al. Survey on knowledge, attitude, practice, and associated risk factors of hypertension among working population in China. *Chin J Hypertens*. (2018) 26:865–70. doi: 10.16439/j.cnki.1673-7245.2018.09.023

44. Rodwin AB, Spruill TM, Ladapo JA. Economics of psychosocial factors in patients with cardiovascular disease. *Progr Cardiovasc Dis*. (2013) 6:55. doi: 10.1016/j.pcad.2013.03.006

45. Lim L-F, Solm M, Cortese S. Association between anxiety and hypertension in adults: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. (2021) 131:31. doi: 10.1016/j.neubiorev.2021.08.031

46. Jian W. An investigation of the effect of different occupations on hypertension. *Psychol Month*. (2019) 14:154.

47. Fu A, Liu X, Li Z, Liu J. Department of Medical Record Management, Tumor Hospital Affiliated to Xinjiang Medical University. Interaction a between occupational stress and dyslipidemia on the prevalence of hypertension. *Chin J Dis Control Prev*. (2023) 27:1091–5.

48. Ren Y. Interpretation of the expert consensus on the diagnosis and treatment of stress-related hypertension in adults. *Chin J Clin*. (2022) 50:397–9. doi: 10.3969/j.issn.2095-8552.2022.04.007

49. Liu Y, Guo M. Research on the characteristics and expenses of direct settlement of cross-provincial medical treatment among rural insured population taking Hainan Province as an Example. *China Health Insur*. (2022) 33–6+40.

50. Xu Z, Xu W, Wu Y. Analysis of influencing factors of hospitalization expenses of patients across provinces in Jiangsu Province. *Med Soc*. (2022) 35:72–5+84.

51. Hao P, Fan J, Jing C, Ma L, Zhang Y, Zhao Y. Traditional Chinese medicine for cardiovascular disease. *J Am Coll Cardiol*. (2017) 69:2952–66. doi: 10.1016/j.jacc.2017.04.041

52. Xiong X. Integrating traditional Chinese medicine into Western cardiovascular medicine: an evidence-based approach. *Nat Rev Cardiol*. (2015) 12:374–374. doi: 10.1038/nrcardio.2014.177-c1

53. Yagüe E, Sun H, Hu Y. East Wind, West Wind: toward the modernization of traditional Chinese medicine. *Front Neurosci*. 16:1057817. doi: 10.3389/fnins.2022.1057817

54. Zheng E, Xu J, Xu J, Zeng X, Tan Wj, Li J, et al. Health-related quality of life and its influencing factors for elderly patients with hypertension: evidence from Heilongjiang Province, China. *Front Public Health*. (2021) 16:654822. doi: 10.3389/fpubh.2021.654822

55. Singh AJ, Shaohua YU. Emergency department and inpatient healthcare utilization due to hypertension. *BMC Health Serv Res*. (2016) 16:303. doi: 10.1186/s12913-016-1563-7

56. Pedersen SS, Känel Rv, Tully PJ, Denollet J. Psychosocial perspectives in cardiovascular disease. *Eur J Prev Cardiol*. (2017) 24:108–15. doi: 10.1177/2047487317703827

57. Zhu X, Sun X, Zhang X, Shen Y, Wang T, Hu K, et al. A4367 Effect of education on health literacy of hypertensive patients. *J Hypertens*. (2018) 36:e294. doi: 10.1097/01.hjh.0000549202.49537.31

58. Liu Y, Wang R, Huang R, Cao Y, Wang J, Feng D. Influencing factors and their relationships of risk perception and decision-making behavior of polypharmacy in patients with chronic diseases: a qualitative descriptive study. *BMJ Open*. (2021) 11:e043557. doi: 10.1136/bmjopen-2020-043557

59. Varga B, Oláh A, Csákvári T, Fusz K, Boncz I, Karácsony I, et al. Pcv78 Assessment of health literacy and therapeutic adherence among patients with hypertension. *Value Health*. (2020) 23:180. doi: 10.1016/j.jval.2020.04.180

60. Nie X, Wang X, Li Y, Li L, Zhang G, Wang L, et al. Comparative study on health literacy between hypertensive patients and general population. *Chin J Health Educ*. (2021) 37:387–91.

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 20 May 2024
DOI 10.3389/fmed.2024.1305190

OPEN ACCESS

EDITED BY
Komal Marwaha,
Texas Tech University Health Sciences Center,
United States

REVIEWED BY
Elaine C. Khoong,
University of California, San Francisco,
United States
Mohammad Saiful Islam,
Bangladesh Livestock Research Institue,
Bangladesh
Frits Lekkerkerker,
Consultant, Amsterdam, Netherlands

*CORRESPONDENCE
Sonal Patil
spatil@metrohealth.org

RECEIVED 07 November 2023
ACCEPTED 22 April 2024
PUBLISHED 20 May 2024

CITATION
Patil SJ, Bhayani V, Yoshida Y, Bushweller L, Udoh E-O, Todorov I, Saper R, Stange KC and Bolen S (2024) Lay advisor interventions for hypertension outcomes: A Systematic Review, Meta-analysis and a RE-AIM evaluation.
Front. Med. 11:1305190.
doi: 10.3389/fmed.2024.1305190

Lay advisor interventions for hypertension outcomes: A Systematic Review, Meta-analysis and a RE-AIM evaluation

Sonal J. Patil[1]*, Vishwa Bhayani[2], Yilin Yoshida[3], Leila Bushweller[4], Eno-Obong Udoh[4], Irina Todorov[5], Robert Saper[5], Kurt C. Stange[6] and Shari Bolen[7]

[1]Center for Health Equity, Engagement, Education, and Research (CHEEER), Department of Family Medicine, The MetroHealth Campus of Case Western Reserve University, Cleveland, OH, United States, [2]Department of Public Health, University of Missouri, Columbia, MO, United States, [3]Department of Medicine, School of Medicine, Tulane University, New Orleans, LA, United States, [4]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, United States, [5]Department of Wellness and Preventive Medicine, Primary Care Institute, Cleveland Clinic, Cleveland, OH, United States, [6]Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, OH, United States, [7]Department of Medicine, Center for Health Care Research and Policy, The MetroHealth Campus of Case Western Reserve University, Cleveland, OH, United States

Introduction: Lay advisor interventions improve hypertension outcomes; however, the added benefits and relevant factors for their widespread implementation into health systems are unknown. We performed a systematic review to: (1) summarize the benefits of adding lay advisors to interventions on hypertension outcomes, and (2) summarize factors associated with successful implementation in health systems using the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework.

Methods: We systematically searched several databases, including Ovid MEDLINE, CINAHL, PsycINFO from January 1981 to May 2023. All study designs of interventions delivered solely by lay advisors for adults with hypertension were eligible. If both arms received the lay advisor intervention, the study arm with lower intensity was assigned as the low-intensity intervention.

Results: We included 41 articles, of which 22 were RCTs, from 7,267 screened citations. Studies predominantly included socially disadvantaged populations. Meta-analysis (9 RCTs; $n = 4,220$) of eligible lay advisor interventions reporting outcomes showed improved systolic blood pressure (BP) [−3.72 mm Hg (CI −6.1 to −1.3; I^2 88%)], and diastolic BP [−1.7 mm Hg (CI −1 to −0.9; I^2 7%)] compared to control group. Pooled effect from six RCTs ($n = 3,277$) comparing high-intensity with low-intensity lay advisor interventions showed improved systolic BP of −3.6 mm Hg (CI −6.7 to −0.5; I^2 82.7%) and improved diastolic BP of −2.1 mm Hg (CI −3.7 to −0.4; I^2 70.9%) with high-intensity interventions. No significant difference in pooled odds of hypertension control was noted between lay advisor intervention and control groups, or between high-intensity and low-intensity intervention groups. Most studies used multicomponent interventions with no stepped care elements or reporting of efficacious components. Indicators of external validity (adoption, implementation, maintenance) were infrequently reported.

Discussion: Lay advisor interventions improve hypertension outcomes, with high intensity interventions having a greater impact. Further studies need to identify successful intervention and implementation factors of multicomponent interventions for stepped upscaling within healthcare system settings as well as factors used to help sustain interventions.

KEYWORDS

allied health personnel, lay advisors, community health workers, health care systems, implementation sciences, hypertension, RE-AIM

1 Introduction

Hypertension is the leading risk factor for heart disease, and 31.3% of adults worldwide have hypertension (1, 2). It is estimated that only 13.8% of patients with hypertension globally achieve hypertension control (2). Traditional clinic-based care has not successfully improved hypertension control rates, which are worse in underserved communities (1). Community-based support improves outcomes in socially disadvantaged populations, especially when delivered by lay advisors who belong to the same social groups (3). Prior reviews of lay health advisors and community health workers (CHWs) have shown improved blood pressure and hypertension control (4–6). These reviews have been limited by including studies that evaluated lay advisor interventions with team-based care or additional health professional interventions and infrequent inclusion of broader community-based lay advisors such as barbers and faith-based lay advisors. Most health systems do not have the resources and staff to include multilevel interventions as reimbursement structure for team-based care is unclear, and it is difficult to know which level of intervention intensity can improve outcomes and in which contexts. The Community Preventive Services Task Force's (CPSTF) systematic review of CHW interventions for heart disease and stroke prevention reported an evidence gap in incremental effectiveness of CHW interventions (7). Therefore, there is a need to identify the sole benefit of adding lay advisors to improve their adoption into routine healthcare teams, assess their generalizability or external validity, and understand the level of intensity and context needed to have an impact on blood pressure.

Thus, we conducted a systematic review which aims to assess the additional benefit of lay advisor interventions (including varying intensity levels) on hypertension outcomes from a health system perspective. We defined lay advisor interventions as those provided by anyone who does not have a health professional degree, including CHWs, health coaches, hairdressers, and faith-based workers. We aim to summarize reported factors that may inform decisions on implementation choices in clinical settings using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework, which is useful for assessing internal and external validity and context of interventions (8).

2 Methods

The PRISMA statement was used to report the findings of this systematic review (9).

2.1 Search strategy and study selection

(See Supplementary material S1 for the detailed search strategy for the Ovid MEDLINE database)

2.2 Data sources

Librarians with expertise in screening citations for systematic reviews searched English language articles from 1981 through May 2023, using Ovid MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, PsycINFO, Scopus, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, and Sociological Abstracts. We reviewed references in published reviews for any additional articles. Two reviewers (SJP and VB) independently screened citations and confirmed the final included studies.

2.3 Search terms

Groups of search terms included keywords for (1): lay lead, peer, community health worker, promotora, expert patient, barber, hairdresser, volunteer aide, faith-based, and (2); hypertension, high blood pressure, blood pressure.

2.3.1 Population and setting

Randomized and non-randomized studies published in English where the lay advisor intervention was evaluated as a sole additional intervention in adults with hypertension were included. As this review is designed for upscaling lay advisor interventions for hypertension care from a health system perspective, we did not include population-level screening studies that excluded adults with hypertension or population-level studies that did not report outcomes for the proportion of individuals diagnosed with hypertension. We excluded studies focused on pregnancy related hypertension disorders (preeclampsia, gestational hypertension).

2.3.2 Intervention

We defined lay advisor interventions as those including navigation, education, or support provided by anyone who does not have a health professional degree, as they typically belong to the same social groups as study participants (10). Common lay advisor interventions include *promotoras*, health coaches, peer supporters, faith-based workers, hairdressers, and community health workers. We excluded studies that included additional health professional intervention, including physician education or intervention

10.3389/fmed.2024.1305190

components, as it is typically uncompensated time. We excluded studies of blood pressure screenings in the community or health insurance linkages where patients with hypertension were excluded or there was no follow-up information on the group of patients with confirmed clinical diagnosis of hypertension. If both arms received the lay advisor intervention, the study arm with lower intensity was assigned as the low-intensity intervention. We assigned low-intervention intensity when the lay advisors delivered a synchronous intervention targeting hypertension education or management. It was not considered an intervention if the lay advisors only checked BP or collected data.

2.3.3 Comparator

We included control groups where the only difference between the intervention and control group was the lay advisor delivered intervention. We included studies even if the control group received any form of low-intensity lay advisor interventions to provide insight into the incremental benefit of low-intensity versus high-intensity lay advisor interventions. Pre-post, process evaluations, and non-randomized studies were included. Studies that compared lay advisor interventions with active comparators such as health professionals or research staff were excluded.

2.3.4 Outcomes

For quantitative outcomes, the primary outcome was reduction in blood pressure (BP). We included change in systolic BP and diastolic BP as our joint primary outcome. Secondary outcome was the difference in the change in the proportion of patients with controlled hypertension from baseline to post intervention between intervention and control arms. If reported, we used the proportion of patients with BP <140/90 mmHg to define controlled hypertension if the study did not explicitly state the proportion of patients with controlled hypertension (2). For RE-AIM dimension outcomes, we looked at the characteristics and presence or absence of each RE-AIM dimension component.

2.4 Quality assessment

Two authors assessed study quality using the Cochrane Collaboration's risk of bias tool for RCTs (11). The primary author (S.J.P.) made final decisions where conflicts existed after reviewing all the articles independently.

2.5 Data extraction

Two authors independently reviewed titles, abstracts, and full articles to identify eligible studies and conflicts were resolved by joint re-review and consensus. Prior to data extraction, two authors created a codebook with all variables of interest. Two authors extracted data independently, and discrepancies were resolved by consensus between reviewers or by a third author if needed.

2.5.1 Data

We extracted data on characteristics of the study setting, participants, lay advisor training and recruitment, and intervention characteristics. We defined any intervention with more than one component as multicomponent intervention. For example, if an intervention included education sessions and recurring follow-up telephone calls, it was considered a multicomponent intervention.

Quantitative values and measures of statistical variation for BP and hypertension control rates were extracted from baseline and at the end of the study. When there were multiple study arms, we included quantitative values for the two arms, where the only difference was the lay advisor-led intervention or varying levels of lay advisor intervention.

Internal and external validity indicators using RE-AIM coding and scoring: A previously published tool was used to code eligible articles on the degree to which internal and external validity indicators of the RE-AIM framework were reported (12). We looked at protocols if referenced in the main articles. Supplementary Table S1 details how each dimension and component of RE-AIM was defined and measured.

2.6 Statistical analysis and data synthesis

A descriptive synthesis of the study setting, participants, lay advisors, intervention components, and control group was performed and reported as a study description table. Proportions of total, RCTs, and nonRCT studies reporting each of the RE-AIM dimensions and components are reported as a table. *Quantitative synthesis:* If we had three or more eligible studies of added lay advisor intervention or varying levels of lay advisor interventions, the primary author (SJP.) performed the statistical analysis using Comprehensive Meta-analysis Software version 3 (Biostat Inc., Englewood, NJ). We adjusted sample sizes for cluster RCTs using the documented intra-cluster coefficient (ICC) (13). We used the random-effects model to compute conservative effect sizes incorporating both within-study and between-study variations. We calculated the difference in means with 95% confidence intervals, and we considered a p-value of <0.05 statistically significant for all analyses other than the Q statistic. A correlation coefficient of 0.5 was assumed between initial and final values. Heterogeneity among studies was evaluated using the Q statistic, with a p-value <0.10 indicating heterogeneity, and using I^2 statistics (I^2 values <40% may indicate less substantial heterogeneity and 75–100% indicates substantial heterogeneity) (14). If substantial heterogeneity existed, we planned *a priori* meta-regression if we had 20 or more studies or subgroup analysis if we had <10 studies. We identified the following study characteristics that may explain between-study variability: presence or absence of intention to treat analysis; presence or absence of home visits; settings in developed or developing countries; lay advisor training duration; study duration; and intervention components of group education, individualized intervention, or combined intervention. Publication bias was assessed with funnel plots and the Egger regression test (15). We conducted sensitivity analysis by removing one study at a time.

3 Results

Of 7,267 unique citations, 41 studies were eligible for inclusion in our review. See PRISMA Flow Diagram. (Figure 1) All study characteristics are shown in Table 1.

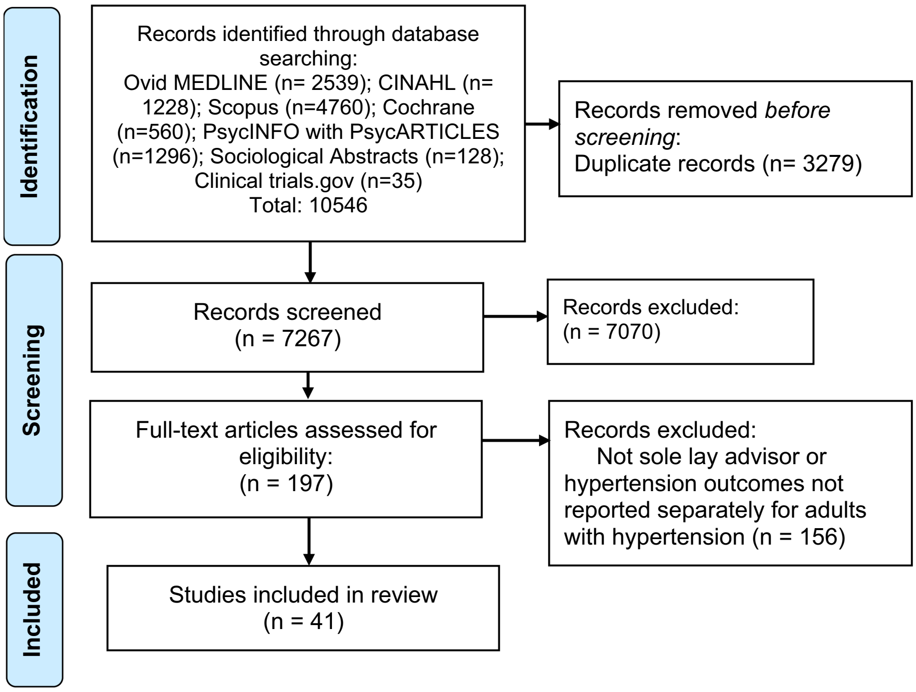


FIGURE 1
PRISMA flow diagram - identification of studies via databases and registers.

3.1 Study characteristics

Of the 41 articles meeting inclusion criteria, 22 were RCTs (16–37) and 19 were non-randomized studies including process assessments and matched cohort studies (38–56). Of the 22 RCTs, 13 RCTs were done in the US (16, 17, 21, 24, 26, 27, 29–31, 33, 35–37). Of the 19 non-randomized studies, 14 were done in the United States. Twenty-nine studies were from developed economies, and 12 were from developing economies. Studies mainly included racial/ethnic minority populations or were conducted in socioeconomically deprived areas of the country. Seven RCTs conducted in the United States included low-intensity lay advisor interventions in the control group (21, 24, 27, 30, 31, 35, 37). The participants' mean age was 54 years and, in most studies, varied between 50 to 65 years.

Most studies mentioned lay advisors were matched demographically with study participants. The least intense interventions were outreach phone calls to promote access to care (29). Most intense intervention included monthly group education with home visits every other month with follow-up biweekly phone calls (35). Other than two studies, all lay advisor interventions were multicomponent. Seven studies compared low-intensity interventions with high-intensity lay advisor interventions. No studies specifically compared stratified or stepped care models of modifying lay advisor intervention intensity based on patient characteristics or hypertension control state with usual care.

3.2 Study quality

Supplementary Table S2 summarizes the assessment of risk of bias for individual randomized studies. All studies had at least one domain judged as unclear risk of bias and 18 studies had at least one domain, mainly blinding or intention to treat, regarded as high risk of bias. No studies had all domains regarded as low risk of bias. Dropout rates varied from 0 to 31% and 6 RCTs had dropout rates of >20% with higher dropouts from intervention groups.

3.3 Outcomes

Of RCTs where control groups did not receive any lay advisor interventions, nine reported systolic BP outcomes, eight reported diastolic BP outcomes and six reported hypertension control outcomes at baseline and end of study. See Table 2 for improvement in BP and hypertension control noted in all included RCTs and Table 3 for improvement in BP and hypertension control in included non-RCTs.

3.3.1 Effect on blood pressure outcomes

The overall pooled effect of lay advisor interventions from nine RCTs ($n = 4{,}220$ participants) showed a mean improvement in systolic BP of −3.7 mmHg (CI −6.1 to −1.3; p 0.002, I^2 88%). (Figure 2) A sensitivity analysis where each study was removed had no significant impact on the results. (Supplementary Figure S1: Forest plot with each study removed) The pooled effect from eight RCTs ($n = 3{,}056$) of lay advisor interventions which measured diastolic BP showed an improvement of −1.8 mmHg (CI −2.5 to −1.0; $p < 0.001$, I^2 7%). (Figure 3) A sensitivity analysis where each study was removed had no significant impact on the results. (See Supplementary Figure S2).

3.3.2 Effect on hypertension control outcomes

Meta-analysis of six RCTs ($n = 3{,}762$) showed a pooled odds ratio of 1.2 (CI 0.75 to 2.0; $p = 0.4$, I^2 85.8%) for controlled hypertension

TABLE 1 Study description table.

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Hovell, 1984	NonRCT $n = 20$ >3 months	United States White 53 y/o	High school graduates or college students. Trained in blood pressure measurement, adherence assessment, interviewing, and counseling in three two-hour sessions (Total 6 h training) by a nurse and a psychologist.	Individual visits twice monthly: monitoring of BP and emphasis on appointment attendance and adherence to medications. Phone calls if visit was missed. Community based: no Home visits: no	None
Krieger, 1999	RCT $n = 421$ 3 months	United States Urban African American predominantly and White Age mainly 40–64 year old.	Community health workers, predominantly African American and from neighborhoods similar to study subjects. 100 h of training on hypertension, cardiovascular system, risk factors for CVD, community resources, research methods, stress management, alcohol/ drugs. Certified as blood pressure measurement specialists.	Phone calls, variable frequency and duration: tracking and outreach to participants with hypertension to promote access to care and keeping appointments. Community based: No Home visits: no	Usual care
Morisky, 2002	RCT $n = 1{,}367$ 48 months	United States Urban African American 54 y/o	Community health workers of same ethnic group assigned to each participant. 1 month training in BP measurement and monitoring, adherence counseling, barriers to care.	High intensity intervention condition: Home visits with counseling similar to low intensity intervention but also involves family/household members in supporting lifestyle and medication adherence with further opportunities to participate in discussion groups. Higher frequency of home visits done for patients with uncontrolled hypertension and low adherence. Group education: Yes in home visit intervention Community based: no Home visits: yes in home visit intervention	Low intensity intervention by CHWs: Individualized patient counseling following each clinic visit, for 5–10 min. Emphasis on lifestyle modifications, medication adherence, appointment-keeping. Assesses health literacy, barriers, social and family support.
Levine, 2003	RCT $n = 789$ 40 months	United States Urban African American 43 y/o	Community health workers, local to the area, trained over 3 months in BP management, monitoring, education, counseling, social support mobilization, community outreach and follow-up.	High-intensity intervention: Less intensive intervention plus 5 additional home visits over a 30-month period. Emphasis on reducing barriers, increasing adherence, lifestyle modifications, family and social support. Addressed issues of health insurance and social/human service needs. Community-based: yes Home visits: yes	Low-intensity intervention: home visit with education, counseling, and referrals to promote access. Emphasis on adherence and monitoring. No control group without lay advisor intervention.
Hess, 2007	NonRCT $n = 107$ 14 months	United States Low-middle income area of Dallas County (Urban) African-American Mean Age 51 years	Each barber underwent an initial four-hour training session that included BP measurement technique, BP interpretation, informed consent, and utilization of written project materials. In addition, barbers participated in monthly one-hour motivational booster sessions on intervention protocol fidelity.	BP measured with haircut, BP report card given with model story and patients were told to share BP report cards with their providers. If signed reports card returned- customer got a free haircut. Community based: yes Home visits: no	None

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Balcazar, 2009	RCT $n=98$ 2 months	United States Urban Hispanic, 82% immigrants 52 y/o	Lay Hispanic community health workers (promotora) from surrounding communities. Trained for 4 days using the National Heart, Lung, and Blood Institute's promotora curriculum, Salud Para Su Corazon (SPSC). Curriculum consists of educational materials designed to address CVD risk in the Hispanic community in the United States.	Group education: Nine-week program with educational modules in Spanish in 2-h sessions in weeks 1, 2, 3, and 8 for groups of 15–20. Modules focused on patient education, lifestyle modifications, and overcoming barriers, and a hypertension module with photonovela. Phone calls: Yes, during week 4 to 7 phone calls done to answer questions, schedule makeup classes, and discuss lifestyle changes discussed during educational modules Community based: Yes Home visits: No	Usual treatment, plus Spanish educational materials related to overall health provided in week 1
Jafar 2009	Cluster RCT $N=674$ 24 months	Pakistan Urban Asian Mean Age:53 years	Trained CHWs in behavior changing communications over 6 weeks.	First 90-min home health education visit session with all members of household, reinforcement visits of 30 min every 3 months for 2 yrs	Usual Care (No intervention)
Hayes, 2010	Non-RCT (Program description and adoption by peer leaders) 18 months	United States Rural and urban	27 peer leaders recruited from 15 veteran service organization posts. Initial 8-h training session followed by monthly/bimonthly 2-h meetings to introduce new health materials and review project activities. Topics covered hypertension, self-management and peer education/ motivation. 63 y/o (peer leaders) 78% peer leaders were males	Monthly group education: Educational materials, health scripts, BP check stations, and promotion of self-monitoring at routine veteran's service organization meetings. Community based: No Home visits: No	No control arm
Truncali, 2010	NonRCT $n=244$ 6 months	United States Urban Ethnicity variable depending on site (Greek, Hispanic, Asian American, Jewish) 73 y/o	Community health workers recruited from members of senior center. Selection based on enthusiasm and availability. Trained for 12 h by health educators in BP measurement, record keeping, communication to participants.	Sessions every other week include checking and recording BP on program and participant record cards followed by information on BP status and recommended action steps Community based: Yes Home visits: no	No control arm

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Victor, 2011	Cluster RCT $N = 1,297$ 10-month	United States Urban, Dallas County African American 50-year-old	Barbers from black-owned barbershops with ≥95% black male clientele. Barbers trained, equipped, and paid to get consent, offer BP check, discuss a model story and give BP card to clientele	Community based: yes, Barber shops Baseline BP screening. Barbers continue BP monitoring and health and role model messages. If BP not at goal, barber discusses role model stories–real stories of other male customers modeling the desired changes in health behavior. Referral cards to physicians with incentive for returning physician signed card.	Baseline BP screenings followed by control group shops delivering standard pamphlets written by AHA. No BP monitoring.
Margolius, 2012	RCT $n = 237$ 6 months	United States Urban 46% Hispanic and 35% Asian primarily (8% White and 11% Black also included) 60 y/o	Health coaches recruited from health center employees and volunteers with bachelor's degrees. Trained for 16–20 h HTN, HTN medications, lifestyle modifications, adherence counseling.	High Intensity intervention of home BP monitoring, weekly health coaching, and home titration of BP medications Phone cells: weekly, to both study arms. Discuss well-being, adherence, BP values. Participants who reported elevated BP and adherence to medications could increase dose according to predetermined algorithm. Health worker advised physician to fax prescription and updated EHR. Community based: no Home visits: no	Low intervention: Home BP monitoring and weekly health coaching (no home titration). No control group without intervention.
Sanchez, 2014	NonRCT $n = 96$ 2 months	United States Rural Hispanic 59 y/o	Lay Hispanic community health workers (promotora) from surrounding communities. Trained for 2 days using the National Heart, Lung, and Blood Institute's promotora curriculum, Salud Para Su Corazon (SPSC). Curriculum consists of educational materials designed to address CVD risk in the Hispanic community in the US.	Group education: weekly session with 10–15 participants, 9-week curriculum. Plus, additional evidence-based mental health session and managing medicines session. Community based: Yes Home visits: Yes, reviewed and emphasized group education concepts.	No control arm
Ursua, 2014	Non RCT $N = 88$ 4 months	United States Urban Asian Americans (Filipino) 53yo	Trained bilingual Filipino CHWs between 25 and 63 years of age. Previous CHW leadership and extensive community organizing experience. Number of training hours not reported	Group education: Yes for 90-min group education sessions delivered monthly, held in local library, community centers apartment buildings Phone: Yes, twice monthly phone calls Community based: yes Home visits: Yes, monthly as needed for individual visits at locations convenient for participants	No control arm

(Continued)

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Dye, 2015	NonRCT $n = 205$ 4 months	United States Rural 86% White 72 y/o	Community health workers recruited from community. Trained for 30 h in knowledge in modules. Required to score at least 80% on a post-training knowledge test and on a human subject's protection test. Role plays to demonstrate proficiency in classroom instruction.	Group education: 8 core scripted modules plus 8 optional supplemental modules, each ~1.5 h long. Participants received notebook with interactive session activities, BP home monitors, cookbooks, pedometers, and relaxation CDs depending on modules completed. Participants counseled on developing personal action plans and use of a personal health diary. Following group training, health coaches met weekly with participants for an additional 7 weeks to implement core modules. Community based: yes Home visits: no	No control arm
Johnson, 2015	RCT $n = 54$ but only 37 completed the study 6 months	United States Urban African American 59 y/o	Experienced community health workers trained in International Society on Hypertension in Blacks (ISHIB) cardiovascular risk reduction toolkit. Training duration not mentioned.	Individual education session with community health worker based on ISHIB toolkit. Education included training in BP self-monitoring. Follow-up monthly visits included review of home BP measurements. Written reminder and 1 week phone call reminder for each appointment to confirm or reschedule. Community based: No (Physician offices) Home visits: no	Usual care, received similar assessments of outcome measures by CHWs for attention control
Dye, 2016	RCT $n = 185$ 2 months	United States Rural White 65 y/o	Community health workers recruited who resembled demographic profile of the community. Training not reported. Required to achieve at least 80% on a knowledge test and demonstrate effective small group teaching skills.	Group education: 8 weekly small group classes, 90-min each, following scripted manual. Sessions focused on measuring BP, lifestyle modifications, relaxation using visualization CD, and long-term action plans. Focused on building self-efficacy. Participants provided with notebook with session notes, blood pressure monitor, pedometer, cookbook, relaxation CD. Community based: Yes Home visits: no	Usual care
Woods, 2016	Non-RCT $n = 6$ 6 weeks	United States Urban free clinic 67% African American 52 y/o	CHWs recruited in partnership with a nonprofit agency. Trained during three 1-h sessions on HTN, BP monitoring, BP medications, and lifestyle modifications.	Community based: Yes Home visits: Yes, 3x, every 2 weeks for 6 weeks to review 2-week home BP records. CHWs discussed educational information based on AHA guidelines (HTN, medication, DASH diet, lifestyle modifications)	None

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Goudge, 2018	RCT *n* = 3,413 18 months	South Africa Rural 55 y/o	Community health workers selected from the local community based on completion of secondary education. Trained by a local primary healthcare nurse with training qualification.	CHWs in clinics with usual care: appointment management, filing, health education on adherence and lifestyle, vitals measurements and prepackaging of medicines. Phone calls (or text): for appointment reminders Community based: no Home visits: no	Usual care
Neupane, 2018	Cluster RCT *n* = 1,638 12 months	Nepal Rural/urban: mixed Not reported 50 y/o	Female community health workers program includes 18 days basic training in primary healthcare training. Additional 5-day intensive training on hypertension for selected 46 CHWs for the study	Community based: Yes Home visits: Yes, every 4 months for a year (3 total visits). Provided lifestyle counseling and BP monitoring. Referred individuals with high BP to nearest health facility and followed for medication adherence.	
Ursua, 2018	RCT *n* = 240 8 months	United States Urban Asian 54 y/o	Community health workers were Filipino immigrants fluent in English and native languages. All had at minimum a bachelor's degree and most lived in the same community as participants. Trained for 60 h in core competencies, HTN, lifestyle modifications.	Group education: yes, 4, 1x/monthly 90 min sessions consisting of health education using adult learning techniques and other culturally appropriate games. Individual visits between group sessions, 1x/month. Convenient locations including home, employer, community setting. Develop individual goals, remove barriers to access, promote adherence, provide referrals (including mental health or tobacco cessation). Phone: yes, as needed, to follow up with participants. Community based: yes Home visits: yes, as needed for individual visits.	One CHW delivered health education session was attended by control group.
Islam, 2018 (Beasley[d], 2021) (37, 60)	RCT *n* = 187 6 months	United States Urban Asian Mean Age: 57 years (comorbid diabetes)	CHWs trained for 105 h in core competencies.	Group education: yes, monthly (5 total), 60 min health education sessions in English or South Asian language using culturally adapted curriculum. Phone calls: No 2 in-person 1-on-1 visits for action-planning and goal setting to improve diabetes management, conducted by CHWs in participants' preferred language using standardized documentation tools	Usual care plus a single CHW-led 60 min group-based health education session in English or South Asian language using culturally adapted curriculum. Waitlist Control for 6 months

(Continued)

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Gamage, 2019	RCT $n = 1{,}736$ 3 months	India Rural Not reported 57 y/o	Community health workers recruited from accredited social health activists already serving the region. Trained for 5 days to deliver specific program.	Group education: every 2 weeks, for six 90 min sessions. Measured BP and educated participants on HTN and its management in local language. Education included medication adherence, lifestyle modifications. Community based: yes Home visits: no	Usual care
Joshi, 2019	RCT $n = 3{,}261$ 12 months	India Rural Not reported 62 y/o	CHWs recruited from the community who had at minimum high school education. Trained for 4 weeks in survey methods, BP measurement, lifestyle counseling.	Community based: Yes Home visits: yes, every 2 months for 30–45 min, 6 total visits. Measured BP, assessed and reinforced medication adherence, delivered risk-reduction advice, links to physician for medication management.	Usual care defined as access to a clinic within 0 to 7 kilometers distance similar to Intervention group
Khetan, 2019	RCT $n = 650$ 24 months	India Semi urban 52 y/o	CHWs recruited from community based on written test scores and 2 rounds of interviews. Trained for 7 days, 3 h/day (total 21 h) in 1–2-week blocks followed by 5 h supervised field work. Refresher training midway through study	Community based: Yes Home visits: yes, 1 h, every 2 months. Behavior change strategy focused on lifestyle, improving healthcare seeking, and addressing barriers to medication adherence. Communication in native language of patient using pictorial information.	Educational handout
Ojji, 2019	RCT $n = 60$ 4 weeks	Nigeria Urban 43 y/o	Community health workers: training and selection not reported.	Two interventions (1): home blood pressure support ($n = 20$) and (2) community health worker support ($n = 20$). Community based: Yes In (2) community health worker support: Group education: yes, 4 education sessions over 4 weeks. Home visits: yes, 8 visits over 4 weeks for tailored counseling on health behaviors, adherence	Usual care ($n = 20$)
Poggio[c], 2019	RCT $n = 1{,}954$ 41 months	Argentina Urban 55 y/o	CHWs recruited from the primary care staff of public care centers. From the community, with similar ethnicity, language, SES, and life experiences. Trained for 2 days in motivational interviewing techniques, measuring BP, behavior change, adherence counseling, lifestyle modifications. Training followed by onsite field testing and certification.	CHW and text messaging intervention: Weekly, from web-based platform to participants and family members using a one-way outgoing system. Individualized to promote lifestyle changes and reminders for medication adherence. Community based: Yes Home visits: Yes, monthly for the first 6 months and every other month thereafter. Initial visit lasting 90 min with subsequent visits of 60 min. Family-based intervention to discuss general HTN knowledge at first visit. At subsequent visit, tailored counseling to participants and their families on adherence, home BP monitoring, and lifestyle modifications. Focus on goal setting, problem solving, social support, and motivation.	Usual care

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Yi, 2019	NonRCT $n = 146$ 6 months	United States, New York, Urban Asian 55 year old	Trained bilingual consultants recruited a team of Faith-based organization (FBO) volunteers. Participated in 2-day train the trainer program	Volunteers advertised programs. Worked through co-located senior center, every 2 weeks to quarterly, conducted free blood pressure screening, lifestyle counseling, weight management, coaching for clinical encounters.	No control group
Reininger, 2021	Non-RCT (RE-AIM Framework) $n = 2{,}508$ (12 locations) 5 years	United States Both urban and rural Hispanic 44 year old	CHWs recruited from local community and advocate for local needs. Trained to collect information from individuals on demographics, health habits, BMI, BP. Monthly training sessions throughout to ensure consistency and time for troubleshooting.	Community-wide campaign in 10 municipalities. CHWs lead the culturally tailored efforts of social support, risk factor screening, exercise groups, healthy cooking classes. Community based: Yes Group education: Yes Home visits: Yes	No control group
Schwalm, 2021	NonRCT $n = 41$ 6 months	Canada Urban 69 y/o	CHWs and Firefighters: CHWs recruited from preexisting Community Health Center-associated individuals. 1-week CHW training Firefighters leveraged due to integration into the community via community fire check safety program with training in implementation of the intervention package.	CHWs and firefighters supported by tablets for data management and decision support, identified participants with poorly controlled hypertension, recommending evidence-based management strategy, supported lifestyle counseling Group education: no Individual education: yes. Each participant had a tailored intervention designed for their barriers, based on the 3 components above. Four total visits over 6 months. Online: No, but mobile health technology leveraged by CHWs. Community based: yes Home visits: no	None (compared to baseline)
Isiguzo, 2022	NonRCT $n = 104$ 6 months	Nigeria Both urban and rural 57 y/o	Study participants recruited from selected religious centers. Role-model patients selected from enrolled patients. Must also have secondary education. Trained for 1 day in HTN, BP measurements, signs of uncontrolled HTN. CHWs helping with implementation trained for 3 days.	Peer-support adherence clubs led by role-model patients to motivate and facilitate medication adherence, BP monitoring. Once a month for 6 months in local community center. Group education: Yes, small groups (10–15) of patients with a role-model patient as facilitator Community based: yes Home visits: no	None (compared to baseline)

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Samuel-Hodge, 2022	NonRCT $n=215$ 4 months	United States Rural 87% Non-Hispanic Black 57 y/o	CHWs hired from the community. Intensive 4-day training (20 h) on study protocols, intervention content, counseling principles, community referral resources, and data collection methods.	Carolina Heart Alliance Networking for Greater Equity (CHANGE) Program. Low intensity behavioral lifestyle interventions. Group education: no Home visits: Yes, 4 monthly counseling sessions in home (or at local venue selected by participant). Including goal setting, action planning, and resource referral. Phone calls: Yes, booster call after first three counseling visits Community based: Yes	None (compared to baseline)
Manavalan, 2022	NonRCT $n=14$ 4 weeks	Tanzania Urban Persons living with HIV (PLWH) 54.5 y/o	CHWs with a secondary level education & volunteer position with the local HIV advisory board. Two-week training by physician researcher on BP measurement techniques, risk factors, causes, symptoms, treatment, diagnosis, and prevention of hypertension. Review of intervention curriculum and mock intervention sessions.	Educational intervention based on the Health Belief Model delivered by CHW as part of HIV clinic appointments. Group education: No Phone calls: Yes (three in person sessions and two phone sessions). Remind patients of next appointment and to foster therapeutic relationship with CHW. Online: No Community-based: No Home visits: No	None. Comparison to baseline.
Suseela, 2022	RCT $n=1952$ 6 months	India Urban Asian 56.8 y/o	Pre-existing locally funded women's self-help group (SHG) members were nominated by elected local representative to be trained to become peer educators. 1 per 20–30 households SHG members were provided a training module consisting of a facilitator's guide, participant's guide, presentations, and exercises on BP an anthropometry measurement. Modules included information on normal BP values, complications of HTN and diabetes, diet, and exercise recommendations as well as smoking cessation. SHGs were also trained on conducting patient support group meetings and guiding participants through goal setting. Trainings were conducted in groups of 15 and lasted for 21 h over 3 days. 6-h refresher was conducted 2 months later.	SHGs provided help with daily HTN management, encourage healthy behaviors via social and emotional support, and referral to primary healthcare centers. Group education: Yes. SHG members were assigned 1 to 20–30 households that met monthly. Each meeting lasted for an hour. Phone calls: No Online: No Community-based: Yes Home visits: Yes. SHG members visited participants at their homes to record their BPs, weight and provided counsel on diet, physical activity, and smoking cessation. Participants were also asked about their medication adherence and encouraged to take on healthy behaviors.	Usual care through clinics, private and public hospitals, and Urban Public Health Centers

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Rimawi, 2022	Non-RCT *n* = 33 Patients graduated after 6 months at highest level of control	Refugees Palestine (Aida and Beit Jibrin camps, Bethlehem) Urban (Demographics provided only for patients with diabetes not hypertension)	CHW (Health for Palestine – H4P) aged 19–26 y/o Recruited by the Lajee Center via announcements in camp and via social media. CHWs were trained by IM physician and medical student using a guide from published CHW manuals. Training lasted for six weeks and consisted of lectures, role paying, hands-on training, and guided home visits with a physician or nurse.	Patients receive home visits by the CHWs based on the level of their disease control. An accompaniment approach, which encompasses medication and appointment adherence and support including transportation. Motivational interviewing to address the primary risk factors of diet, exercise, medication adherence, and smoking with integrated psychosocial counseling. Group education: No Phone calls: No Online: No Community-based: Yes Home visits: Yes	No matched controls for hypertension as BP data was not universally available.
Islam, 2023[d]	RCT *n* = 291 6 months	United States (New York City) Urban South Asian Americans 56.8 y/o	CHWs were chosen based on their representation of the patient population. They consisted of men and women, who spoke Bangla, Hindi, Punjabi and/or Urdu. They received standardized CHW core competency training after which they provided translation services to clinical staff, medication reminders, and appointment scheduling.	CHWs Group education: Yes. There were 5 monthly 60–90 min group education sessions. Phone calls: Yes, for follow up every two weeks. During follow-up, participants were guided to set goals for hypertension control (medication, activity, and nutrition). Some follow ups were completed in-person at primary care offices and community spaces. Online: No Community-based: Yes Home visits: No	Usual care plus a single initial CHW-led 60 min group-based health education

(Continued)

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Kisigo, 2023	Non-RCT *n* = 50 1 year	Mwanza City, Tanzania Not Reported 61 y/o	Peer counselors were themselves patients with hypertension but a well-controlled blood pressure and receiving care at the outpatient clinic. Training duration: 2 weeks by medical doctors and social scientists.	The peer counselors provided five sessions on hypertension management over 3 months. Each session lasted about an hour except for the fourth telephone session lasting for 5-10 min Sessions focused on social connecting, medication adherence, lifestyle modifications including herbal options, following up in clinic and insurance coverage. Group education: No Phone calls: Yes, visit 4 was telephone call to check progress on medication adherence, going to clinic, and lifestyle changes. Online: No Community-based: Yes Home visits: Yes. First, third and fifth session were at patient's home but patient could chose alternative location.	Historical controls receiving standard of care
Nelson, 2023	RCT *n* = 264 12 months	United States Veterans Washington, United States 60.6 y/o Black 28%	Seven peer health coaches were recruited to provide social support, assist with health education and goal setting and connect participants to community resources. Peer health coaches received 100 hours of comprehensive training in health coaching, and motivational interviewing by health psychologist and a clinician trained the health coaches in blood pressure monitor use.	Participants in this study received coaching for 12 months as well as educational materials, a blood pressure monitor, scale, pill organizer and healthy nutrition tools. Five required modules were completed during health coaching sessions: blood pressure, physical activity, nutrition, medication adherence, and communication with medical team or physician. Elevated BP was reported to primary care team. Group education: No Phone calls: Yes, for check-ins on progress related to goals. Online: No Community-based: Yes, Recruitment of both participants and coaches were based on the neighborhood. Home visits: Yes. 5 home visits and 5calls. Due to the COVID-19 pandemic, the protocol was changed to telephone only.	Usual care and same educational materials as intervention group. Elevated BP at enrollment or exit visit was reported to primary care team

(Continued)

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Bush, 2023	Non-RCT $n = 192$ 12 months	Northeast Texas, United States Rural 82% non-Hispanic	CHWs led several self-management blood pressure (SBMP) program workshop series to help improve participants' health outcomes by providing heart health education. Information on CHW training was not reported.	The participants engaged in structured workshops, regular follow up, and were connected to community resources by the CHWs. Each workshop lasted for about an hour bi-weekly for 12 weeks. Group education: Yes Phone calls: No Online: No Community-based: Yes Home visits: No	None
Safford-Shikany, 2023	Cluster RCT $N = 830$[b] 12 months	Black Belt AL and NC United States Rural Black 56% Age 58	Peer coaches provided support to patients as they made lifestyle changes to improve their blood pressure. This included goal planning, connection to community resources etc. Peer coaches received training and certification by staff members of the Southeastern Collaboration to Improve Blood Pressure Control (SEC). The coaches were members of the community just like the patients in the study. They also had chronic medical conditions but were not health professions and were not required to provide medical advice. They worked with patients for 12 months.	Assist engagement in hypertension self-management (including dietary changes and physical activity), to carry out the recommendations of the healthcare team (including taking medications and keeping appointments), to provide emotional support, and to link patients to the practice for care. Group education: No Phone calls: Yes, a one-on-one telephone delivered structured program intensive intervention phase of 8 weekly topic-focused sessions followed by monthly check-ins over the 12-month intervention period. Longer booster sessions were offered if BP control slipped after the intensive intervention phase. Online: No Community-based: Yes Home visits: No	Enhanced usual care - Each practice received a laptop computer, the freely available web-based patient education platform-Patient Activated Learning System (PALS), 25 home BP monitors and BP logs, and a binder of practice tips including flow sheets and an evidence-based BP titration algorithm designed for African Americans.
Thomas, 2023	Non-RCT $n =$ not mentioned 8 participating barbers collected 236 BP readings 9 months	Barbershop clients BAME (Black, Asian, and Minority Ethnic) men Croydon, London	Barbers in an existing BAME barber network in south London, UK were recruited from 5 barbershops. Barbers were educated on offering BP checks to clients and providing education when needed. Trained online (1.5 h) and face-to-face (3 h)	Barbers provided BP healthcare advice and measured participants BP Group education: No Phone calls: No Online: No Community-based: Yes Home visits: No	None

(Continued)

10.3389/fmed.2024.1305190

TABLE 1 (Continued)

Study, year published	Study design, number of participants[a], duration	Population, setting[b] country urban/ rural dominant ethnicity (>40%) mean age	Interventionist, lay advisor selection and training[b]	Intervention[b,c] components group education phone calls online community-based home visits	Comparison[b,c]
Brewer, 2023	Non-RCT $n=16$	Minneapolis-St Paul, MN African American 52.6 y/o	African American CHWs were hired for the study. CHWs monitored patient engagement on the app for self-monitoring and medication adherence. CHWs were trained by study PI on FAITH! App usage, content modules and NIH/NHLBI training manual. CHWs also received training for two months from the Association of Black Cardiologists Community Health Advocate Training (CHAT)	Patients utilized FAITH! Hypertension app and met with CHW weekly via telephone or zoom for 10 weeks. Group education: No Phone calls: Yes Online: Yes Community-based: No Home visits: No	None

[a]Only sample size of patients with hypertension is mentioned. [b]If data on population/setting such as age or urban/rural location was not reported, we did not include the missing components in the study rows. [c]For multi-arm studies, we limited the sample size intervention, and control group descriptions to groups where the only difference between groups was either a lay advisor intervention or a low-intensity versus a high intensity lay advisor intervention. [c]original article for BP improvement included physician education component so was excluded but the current included article focused on lifestyle modifications supported by only CHWs with text messages. BP and hypertension control outcomes were not included in the review for the original article due to physician education component for medication management. [d]Report of two RCTs with comorbid DM and HTN, included study information where CHW intervention was tailored for diabetes as the RCT with hypertension is separately included.

with lay advisor interventions compared to the control group. (See Figure 4).

Subgroup analyses of studies grouped by presence of intention to treat did not show any significant differences in BP between groups. (Supplementary Figures S3, S4) There were not enough studies to conduct subgroup analyses of studies grouped by developed or developing country setting, and mode of interventions. The funnel plot and Eggers regression test ($p=0.008$) indicate publication bias for systolic BP outcomes but not for diastolic BP or hypertension control outcomes. (Supplementary Figures S5, S6).

3.3.3 Effect on systolic blood pressure, diastolic blood pressure, and hypertension control with high-intensity compared to low-intensity lay advisor interventions

Seven RCTs from the United States compared low-intensity interventions with high-intensity interventions, of which six reported BP outcomes. Pooled effect from these six RCTs ($n=2{,}644$) showed a mean improvement in systolic BP of −3.6 mmHg (CI −6.7 to −0.46; p 0.02, I^2 82.7%) and in diastolic BP of −2.1 mmHg (CI −3.7 to −0.4; p 0.01, I^2 70.9%) in high-intensity lay advisor interventions compared to low-intensity interventions (See Figures 5, 6). The funnel plot and Eggers regression test ($p=0.4$) did not indicate publication bias for these pooled BP outcomes. A sensitivity analysis where each study was removed showed reduced significance of results. (See Supplementary Figures S7, S8) Meta-analysis of seven RCTs ($n=3{,}277$) showed a pooled odds ratio of 1.29 (CI 0.79 to 2.1; $p=0.3$, I^2 90.79%) for controlled hypertension with high-intensity lay advisor interventions compared to the low-intensity lay advisor intervention group (Supplementary Figure S10). There were not enough studies in groups to conduct subgroup analyses for high intensity compared to low intensity interventions.

3.3.4 RE-AIM criteria reporting In studies

There was no significant difference in the frequency of reporting of RE-AIM components between randomized and non-randomized studies other than qualitative assessments of efficacy, which were more frequently reported in nonRCTs. See Table 4 and Supplementary Table S1. One study specifically reported study results in RE-AIM format (45) and one recent study specifically reported reach and adoption of peer coaching intervention in primary care practices (33, 57).

3.3.4.1 Reach

Six of the nine studies with sample sizes >1000 were conducted in developing countries (18–20, 23, 25, 34) and three were done in the United States (27, 31, 45). Participation rate varied from 2 to 98% with clinic-based recruitment showing higher participation rates compared to population-level recruitment. When reported, nonparticipating individuals had higher systolic BP or a lower proportion of their BP controlled at baseline, but this information was not reported in most studies (18, 29). Clinic-based recruitment showed higher participation rates as fewer patients needed to be approached in clinics (denominators were lower) with higher recruitment success (21).

3.3.4.2 Efficacy/effectiveness reporting

Eight non-randomized studies reported qualitative assessments to understand outcomes (39, 41, 42, 50–53, 56); one

10.3389/fmed.2024.1305190

TABLE 2 Improvement in BP in RCTs[a].

First authors	Reduction in SBP	Reduction in DBP	% Change in achievement of hypertension control (or proportion of patients achieving Hypertension control at end of study)
Krieger, 1999	−0.5 mm Hg in intervention vs. 0.5 mm Hg in control group	0 mm Hg in intervention vs. −0.1 mm Hg in control group	Not available
Morisky, 2002 (High-intensity intervention compared to low intensity intervention)	Not available	Not available	Hypertension control improved in the tracking group (by 7.8%, $p<0.01$) and in the counseling group (by 13%, $p<0.01$) compared to the control group (by 1.4%)
Levine, 2003 (High-intensity intervention compared to low intensity intervention)	−3.3 mm Hg in intensive intervention and − 5.6 mm Hg in less intensive intervention ($p<0.05$)	−2.6 mm Hg in intensive intervention and − 3.8 mm Hg in less intensive intervention ($p<0.05$)	Hypertension control improved by 20% in intensive intervention and by 16% in less intensive intervention
Balcazar, 2009	No statistically significant change in SBP/DBP between the intervention and control groups after adjusting for confounders	Not available	Hypertension control improved in intervention group (by 15%) and worsened in control group (−16%)
Jafar, 2009	−5.6 (95% CI −3.7 to −7.4)in CHW intervention group vs. −5.8 (95% CI −3.9 to −7.7) in control group($p=0.89$)	No statistically significant difference between intervention and control	Hypertension control improved in CHW intervention group by 23% and in control group by 27.3%, $p=0.003$
Victor, 2011 (High-intensity intervention compared to low intensity intervention)	−7.8 mm Hg in intervention vs. −5.3 mm Hg in control group; absolute group difference of −2.5 mmHg [95% CI −5.3 to 0.3 mmHg] ($p=0.087$)	−2.8 mm Hg in intervention vs. −1.9 mm Hg in control group; absolute group difference of −0.9 [95% CI −2.6 to 0.8] ($p=0.183$)	Hypertension control improved in intervention group (by 19.9%) compared to control group (by 11.1%); absolute group difference 8.8% [95% CI 0.8 to 16.9%], $p=0.036$
Margolius, 2012 (High-intensity intervention compared to low intensity intervention)	−23.9 mm Hg in home medication titration arm and − 19.3 mm Hg in no home titration; combined mean reduction of −21.8 mm Hg ($p<0.001$)	−5.9 mm Hg in home medication titration arm and 5.4 mm Hg in no home titration; combined mean reduction of −5.7 mm Hg ($p<0.001$)	Not available
Wallace-Johnson, 2015	−34.75 mm Hg [95% CI −46.55 to −22.95 mm Hg] in intervention group vs. −5.65 mm Hg [95% CI −12.84 to 1.54 mm Hg] in control group ($p<0.001$)	−16.19 mm Hg [95% CI −24 to −8.39 mm Hg] in intervention group vs. −4.36 mm Hg [95% CI −8.26 to −0.46 mm Hg] in control group ($p=0.009$)	At follow up, 83% of patients in intervention had hypertension control vs. 60% in usual care ($p=0.263$)
Dye, 2016	Small (not reported) changes observed ($p=0.001$) for both treatment and control groups	Small (not reported) changes observed ($p=0.018$) for both treatment and control groups	Not available
Goudge, 2017	Not available	Not available	Hypertension control increased by 4.7% in intervention vs. 1% in control
Neupane, 2018	−4.9 mm Hg [95% CI −7.78 to −2.00 mmHg, $p=0.001$] significant improvement in intervention participants compared to control group of hypertensive participants	−2.63 mm Hg [95% CI −4.59 to −0.67 mmHg, $p=0.008$] significant improvement in intervention participants compared to control group of hypertensive participants	Not available
Ursua, 2018 (High-intensity intervention compared to low intensity intervention)	−20 mm Hg in intervention ($p<0.001$) vs. −4.3 mm Hg in control group ($p<0.001$) Intervention effect after adjustment for all covariates was −6.2 ($p<0.001$)	−7.4 mm Hg in intervention ($p<0.001$) vs. −0.2 mm Hg in control group ($p=0.829$) Intervention effect after adjustment for all covariates was −2.8 ($p<0.001$)	Hypertension control improved in intervention group (by 83.3%) compared to control (by 42.7%), $p<0.001$. The adjusted odds of controlled BP for intervention was 3.2 times the odds for control [95% CI 1.9 to 5.4, $p<0.001$]
Gamage,2019	−8.2 mm Hg [95% CI −10.0 to −6.3 mmHg] in intervention group vs. −2.1 mm Hg [95% CI −3.4 to −0.8 mmHg] in control group ($p<0.001$)	−4.2 mm Hg [95% CI −5.3 to −3.1 mmHg] in intervention group vs. −2.2 mm Hg [95% CI −3.0 to −1.4 mmHg] in control group ($p=0.004$)	Hypertension control improved in intervention group (by 20.3%) compared to control group (by 9.5%); odds ratio 1.6 [95% CI 1.2 to 2.1, $p=0.001$]

(Continued)

TABLE 2 (Continued)

First authors	Reduction in SBP	Reduction in DBP	% Change in achievement of hypertension control (or proportion of patients achieving Hypertension control at end of study)
Joshi, 2019	+0.4 mm Hg in intervention group vs. −0.5 mm Hg in control group over 12 months; no significant difference between groups	Not available	Not available
Khetan, 2019	−12.2 ± 19.5 mm Hg in intervention vs. −6.4 ± 26.1 mm Hg in control group; adjusted difference of −8.9 mm Hg [95% CI −3.5 to −14.4 mm Hg, $p = 0.001$]	−5.1 ± 13.5 mm Hg in intervention group vs. −3.0 ± 14.7 mm Hg in control group; adjusted difference of −2.1 mm Hg [95% CI −4.5 to 0.3, $p = 0.09$]	Hypertension control improved in the intervention group (by 17.6%) compared to control (by 8.6%), $p = 0.23$
Ojji, 2019	−31 mm Hg in intervention group vs. −21 mm Hg in control group, $p = 0.02$	−18 mm Hg in intervention group vs. −16 mm Hg in control group, $p = 0.88$	Not available
Poggio, 2019[b]	Not available	Not available	Not available
Islam, 2018 (Beasley, 2021)(60) (High-intensity intervention compared to low intensity intervention)	−5.7 mm Hg in intervention group ($p < 0.001$) vs. 0 mm Hg in control group ($p = 0.98$); adjusted odds ratio – 6.2 [95% CI −10.4 to −2.1]	−4.2 mm Hg in intervention group ($p < 0.001$) vs. 0 mm Hg in control group ($p = 0.1$); adjusted odds ratio – 4.0 [95% CI −6.3 to −1.7]	Hypertension control improved in the intervention group (by 24%, $p < 0.001$) compared to the control group (by 5.2%, $p = 0.2$); adjusted odds ratio 1.4 [95% CI 1.1 to 1.8]
Islam, 2023 (High-intensity intervention compared to low intensity intervention)	−6.8 mm Hg [95% CI −9.5 to −4.2 mmHg], significant improvement in intervention participants compared to control group participants	−4.7 mm Hg [95% CI −9.5 to −4.2 mmHg], significant improvement in intervention participants compared to control group participants	68.2% of the intervention group and 41.6% of the control group had controlled BP ($p < 0.001$)
Suseela, 2022	−4.1 mm Hg [95% CI −2.2 to −4.2 mmHg], significant improvement in intervention participants compared to control group participants	−1.5 mm Hg [95% CI −0.4 to −2.6 mmHg], significant improvement in intervention participants compared to control group participants	Not available
Nelson, 2023	No significant difference between intervention and control groups −2.05 [95%CI −7.00 to 2.55]	Not available	Not available
Safford, 2023	Results not reported	Results not reported	Results not reported

[a]*p*-values are not reported if they were not reported in the original article. [b]Original article for BP improvement included physician education component so was excluded but the current included article focused on lifestyle modifications supported by only CHWs with text messages.

of these was mainly a process evaluation of a sustained peer leader program for Veterans (39). One pragmatic randomized study included process evaluation in their protocol, but published article mentions challenges with balancing external validity and intervention assessments (19, 58). Few studies reported reasons for lay advisor withdrawals, which included personal reasons of health issues or relocation as well as an inability to perform certain required intervention tasks such as properly reading BP measurements (25, 39).

3.3.4.3 Adoption

Method to identify the target delivery agent was reported mainly as the selection and nomination of volunteers with matching sociodemographic characteristics to participants. Two studies reported adding activities to a pre-existing program, but repeated visitor rate (43%) was only reported in one study (39, 44). One author of a randomized study shared a follow-up process evaluation using mixed methods assessment with surveys and focus group discussions (18, 59).

3.3.4.4 Implementation

Four studies mention compensation for lay advisors reflecting the pay scale of the respective countries otherwise studies reported lay advisor compensation for completing study activities (18, 25, 28, 32). One study reported CHWs worked 40 to 60 h per month to care for 120 participants (28).

3.3.4.5 Maintenance

Seven studies indicate the continued feasibility of maintaining intervention using already available infrastructure or public funding (25, 28, 32, 39, 44, 45, 60).

4 Discussion

We contribute to the literature by reporting a systematic review that evaluates the additional benefit of lay advisor interventions for hypertension outcomes where the lay advisor interventions are the sole additional intervention. We limited contamination by

10.3389/fmed.2024.1305190

TABLE 3 Improvement in BP in non-RCTs[a,b].

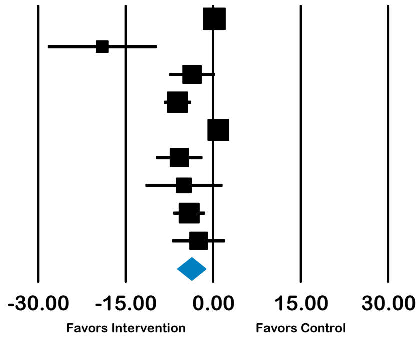
	[c]Reduction in SBP ± SD, mm Hg	[c]Reduction in DBP ± SD, mm Hg	% change in achievement of Hypertension control (or proportion of patients achieving Hypertension control at end of study)
Hovell, 1984 (Lay advisor intervention compared to Control group)	−10 mm Hg in intervention group ($p < 0.05$) vs. −2.4 mm Hg in control group. Follow up after intervention discontinued: −7 mm Hg in intervention vs. −13 mm Hg in control group.	−7 mm Hg in intervention group ($p < 0.05$) vs. −0.1 mm Hg in control group. Follow up after intervention discontinued: −7 mm Hg in intervention vs. 8 mm Hg in control group.	Not available
Hess, 2007	Not available	Not available	Hypertension control increased from mean 20% in those who did not participate to 51% in those with maximum intervention exposure. ($p = 0.01$)
Hayes, 2010	Not available	Not available	Not available
Truncali, 2010	−3.9 mm Hg in intervention participants with multiple visits [95% CI −7.6 to −0.1, $p = 0.04$]	Not available	Hypertension with controlled SBP increased by from 35 to 45% in intervention group ($p = 0.16$)
Sanchez, 2014	Not available	Not available	Not available
Ursua, 2014	−12.8 mm Hg reduction ($p < 0.001$)	−6.8 mm Hg reduction ($p < 0.001$)	Hypertension control increased by 27% from baseline to 4 months
Dye, 2015	−5.781 mm Hg in intervention group ($p = 0.001$)	−1.116 mm Hg in intervention group ($p = 0.128$)	Hypertension control increased by 11% in intervention group
Woods, 2016	Significant reduction in intervention group	Not available	Not available
Yi, 2019	−3.9 mm Hg in intervention group ($p = 0.005$)	−2.4 mm Hg in intervention group ($p = 0.01$)	Not available
Reninger, 2021 (High-intensity intervention compared to low intensity intervention)	−0.96% adjusted mean difference for intensive intervention compared to less intensive [95% CI −1.57 to −0.35, $p = 0.002$]	−1.61% adjusted mean difference for intensive intervention compared to less intensive [95% CI −2.42 to −0.81, $p < 0.0001$]	Low exposure (2–3 CHW visits) group was more likely than high exposure (4−5CHW visits) to recover to normal BP, OR 0.92 ($p = 0.4$) Hypertension control increased by 25% in the intervention group
Schwalm, 2021	−16.4 mm Hg ($p < 0.01$)	Not available	Hypertension control increased by 51% in the intervention group ($p < 0.01$)
Isiguzo, 2022	−13 ± 20.9 in intervention group ($p < 0.0001$)	−3.6 ± 12.1 in intervention group ($p = 0.02$)	28 of 65 patients changed from uncontrolled to controlled hypertension, 18 continued to have controlled hypertension
Samuel-Hodge, 2022	−2.9 ± 18.6 in intervention group ($p = 0.03$)	−2.1 ± 11.8 in intervention group ($p = 0.007$)	Hypertension control increased by 7% ($p = 0.05$) and DSB by 9% ($p = 0.005$) in intervention group
Manavalan, 2022	Median SBP reduced from 164 to 146 ($p = 0.0029$)	Median DBP reduced from 102 to 89 (p −0.0023)	Not available
Rimawi, 2022	−7.3 (95% CI −1.93 to −12.25, $p = 0.009$) in intervention group	−4.3 (95% CI −0.80 to −7.91, $p = 0.018$) in intervention group	Hypertension control increased by 58% after intervention
Kisigo, 2023	Not available	Not available	Combined rates of hospitalization and /or death were 18% in intervention cohort and 35% in historical controls.
Brewer, 2023	Mean pre-post SBP reduction −6.5 mm Hg ($p = 0.15$)	Mean pre-post DBP reduction −2.8 mm Hg ($p = 0.78$)	Proportion of patients with controlled Bp increased from 0 to 29%
Bush, 2023	Mean SBP reduced by 4.48 mm Hg ($p < 0.05$)	Significant reduction in DBP by −2.73 mm Hg	Not available
Thomas, 2023	Not available	Not available	Not available

[a]p-values are not reported if they were not reported in the original article. [b]Other than Hovell, 1984 and Reninger, 2021, all non RCTs were pre- to post comparisons. [c]Only included results for participants diagnosed with hypertension additional requirements. PRISMA checklist attached as a separate Supplementary Table.

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value
Jafar, 2009	0.20	0.12	-0.03	0.43	0.08
Johnson, 2015	-19.00	4.76	-28.32	-9.68	0.00
Neupane, 2018	-3.62	1.97	-7.48	0.24	0.07
Gamage, 2019	-6.10	1.17	-8.40	-3.80	0.00
Joshi, 2019	0.90	0.90	-0.86	2.66	0.32
Khetan, 2019	-5.80	2.01	-9.74	-1.86	0.00
Ojji, 2019	-5.00	3.35	-11.56	1.56	0.14
Suseela, 2022	-4.10	1.38	-6.80	-1.40	0.00
Nelson, 2023	-2.50	2.29	-6.98	1.98	0.27
Pooled	-3.72	1.22	-6.12	-1.32	0.00

Statistics for each study

Difference in means and 95% CI



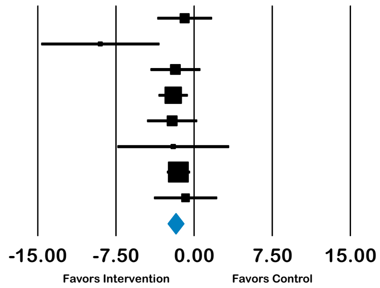
P=0.002, I2 88.7%

FIGURE 2
Forest plot of Systolic BP - Effect of lay advisor interventions on Systolic BP compared to control group.

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value
Jafar, 2009	-0.900	1.334	-3.514	1.714	0.500
Johnson, 2015	-9.000	2.887	-14.658	-3.342	0.002
Neupane, 2018	-1.790	1.217	-4.176	0.596	0.141
Gamage, 2019	-2.000	0.713	-3.397	-0.603	0.005
Khetan, 2019	-2.100	1.222	-4.494	0.294	0.086
Ojji, 2019	-2.000	2.729	-7.350	3.350	0.464
Suseela, 2022	-1.500	0.560	-2.598	-0.402	0.007
Nelson, 2023	-0.810	1.539	-3.826	2.206	0.599
Pooled	-1.765	0.388	-2.526	-1.004	0.000

Statistics for each study

Difference in means and 95% CI



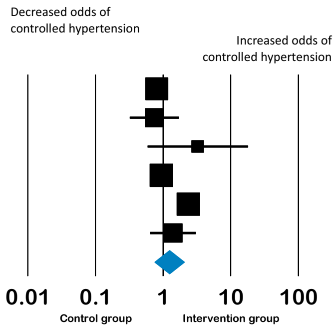
P<0.001, I2 7%

FIGURE 3
Forest plot of Diastolic BP - Effect of lay advisor interventions on Diastolic BP compared to control group.

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Jafar, 2009	0.808	0.569	1.145	0.231
Balacazar, 2009	0.744	0.323	1.711	0.486
Johnson, 2015	3.255	0.591	17.917	0.175
Goudge, 2018	0.946	0.725	1.235	0.683
Gamage, 2019	2.368	1.817	3.084	0.000
Nelson, 2023	1.400	0.642	3.051	0.397
Pooled	1.239	0.751	2.043	0.402

Statistics for each study

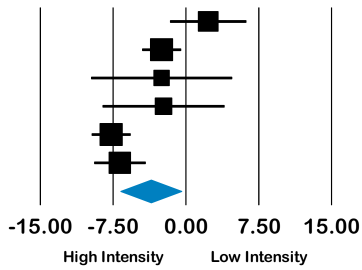
Odds ratio and 95% CI



P=0.4; I^2 85.8%

FIGURE 4
Forest plot of pooled effect on hypertension control - Effect of lay advisor interventions on hypertension control compared to control group.

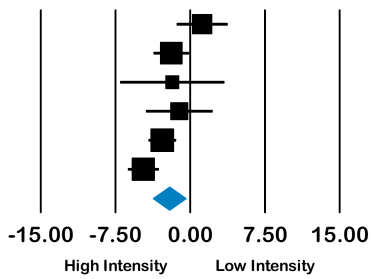
Study name	Difference in means	Lower limit	Upper limit	p-Value
Levine, 2003	2.300	-1.620	6.220	0.250
Victor, 2011	-2.500	-4.499	-0.501	0.014
Margolius, 2012	-2.500	-9.752	4.752	0.499
Islam, 2018	-2.300	-8.572	3.972	0.472
Ursua, 2018	-7.700	-9.699	-5.701	0.000
Islam, 2023	-6.800	-9.438	-4.162	0.000
Pooled	-3.594	-6.726	-0.462	0.024



P=0.2; I2 82.7%

FIGURE 5
Forest plot of pooled effect of high intensity compared to low intensity interventions on Systolic BP.

Study name	Difference in means	Lower limit	Upper limit	p-Value
Levine, 2003	1.200	-1.348	3.748	0.356
Victor, 2011	-1.900	-3.664	-0.136	0.035
Margolius, 2012	-1.800	-7.021	3.421	0.499
Islam, 2018	-1.100	-4.432	2.232	0.518
Ursua, 2018	-2.800	-4.172	-1.428	0.000
Islam, 2023	-4.700	-6.243	-3.157	0.000
Pooled	-2.088	-3.743	-0.433	0.013



P=0.1; I2 70.9%

FIGURE 6
Forest plot of pooled effect of high intensity compared to low Intensity interventions on Diastolic BP.

separating the analysis where the control group received any lay advisor intervention to inform this additional benefit and to inform differing intensity levels of interventions. We note improvement in blood pressure outcomes with added lay advisor interventions compared to usual care and with high-intensity interventions compared to low-intensity interventions in populations with lower socioeconomic states or racial/ethnic minority populations. Control groups and low-intensity interventions also showed BP improvements in most studies. No studies examined the impact of minimally burdensome lay advisor interventions with stepped-up care to high-intensity interventions in people with continued unmet needs.

Our results are similar to most reviews showing positive effects of CHWs on hypertension outcomes. Previous Community Preventive Services Task Force (CPSTF) found that team-based care with community health workers (CHWs) is effective for hypertension and cardiovascular disease prevention, but they did not look at the add-on benefit of CHWs (4). Team-based care and lay advisor interventions are difficult to translate into clinical care settings as reimbursement policies remain unclear for both, and staff time is limited (4, 5, 61). A recent review reported individual studies of CHW interventions in low-income and middle-income countries showed improved hypertension control (6). Most previous reviews focused on CHW interventions delivered by mainly government-trained CHWs or CHWs specifically recruited for the studies; lay advisors such as barbers and faith-based workers are infrequently included in previous reviews. We included a broader lay advisor definition and assessed the additional benefit of adopting lay advisors for hypertension care without adding burden to already overworked limited clinic staff within health systems. No previous reviews have compared the effectiveness of varying intensities of lay advisor interventions on hypertension outcomes. We strengthen the literature by showing the additional benefit of lay advisors interventions for improving hypertension outcomes and showing increasing effects with higher intensity interventions. Lastly, this is the first comprehensive systematic review of the state of lay advisor interventions for hypertension from internal and external validity perspectives using the RE-AIM framework. We also demonstrate areas for needed future research such as reporting on elements of the RE-AIM framework for the context of and validity of interventions as well as the need for examining stepped-up intervention intensity approaches for patients with continued uncontrolled hypertension which may help balance the intervention burden and limited healthcare resources.

TABLE 4 Publications reporting on RE-AIM elements.

Reach	Total (n = 41)	RCT (n = 22)	Non-RCT (n = 19)
Method to identify target population	100% (41)	100% (22)	100% (19)
Inclusion criteria	95% (39)	100% (22)	89% (17)
Exclusion criteria	53.6% (22)	68% (15)	36.8% (7)
Sample size	95% (39)	100% (22)	89% (17)
Participation rate	43.9%% (18)	50% (11)	36.8% (7)
Characteristics of both participation and non-participation	2% (1)	4.5% (1)	0% (0)
Representativeness of study population with target population	21.9% (9)	18% (4)	26% (5)
Efficacy/Effectiveness			
Measures/results (at shortest assessment)	97.6% (40)	95% (21)	100% (19)
Intent to treat (Only applicable to RCTs)		45% (10)	
Imputation procedures (specify)		18% (4)	
Quality of life measure	7% (3)	13.6% (3)	0% (0)
Effects at longest (specify time)	39% (16)	40.9% (9)	36.8% (7)
Percent attrition	78% (32)	86% (19)	68% (13)
Qualitative assessment	19.5% (8)	0 (0)	42% (8)
Adoption			
Method to identify target delivery agent	80.5% (33)	77.3% (17)	84% (16)
Level of expertise of delivery agent	68% (28)	72.7% (16)	63% (12)
Inclusion criteria	90% (26)	100% (22)	78.9% (15)
Rate	19.5% (8)	18% (4)	21% (4)
Characteristics of adoption/non-adoption	7% (3)	4.5% (1)	10.5% (2)
Qualitative assessment	24% (10)	13.6% (3)	36.8% (7)
Implementation			
Intervention type and intensity	100% (41)	100% (22)	100% (19)
Extent protocol delivered as intended (%)	34% (14)	22.7% (5)	47% (9)
Measures of cost	29% (12)	27% (6)	31.6% (6)
Qualitative assessment	29% (12)	22.7% (5)	42% (8)
Maintenance			
Was individual behavior assessed at least 6 months following the completion of the intervention?	14.6% (6)	9% (2)	21% (4)
Is the program still in place?	17% (7)	13.6% (3)	21% (4)
Was the program modified? Specify	14.6% (6)	9% (2)	21% (4)

4.1 RE-AIM assessment discussion

Similar to most literature, our RE-AIM assessments show frequent reporting of individual-level (Reach, Effectiveness) but insufficient reporting of organizational-level dimensions (Adoption, Implementation, and Maintenance) that affect the external validity of the interventions. Below we discuss each element of the RE-AIM Framework.

4.1.1 Reach

Characteristics or contexts that interact with an individual's willingness to participate may influence the potential of these interventions to improve health disparities, as most studies included socially disadvantaged populations.

4.1.2 Effectiveness

Studies have rarely reported reasons for improvement in outcomes and characteristics of participants who may not benefit from these interventions or continue to have unmet needs. Assessments of multicomponent interventions to identify the least and most efficacious individual components are missing and may help tailor upscaling.

4.1.3 Adoption

It is unclear what characteristics or contextual factors would encourage the uptake of a lay advisor role by individuals not already engaged in community-level leadership. Settings for lay advisor interventions were mostly predetermined with outside funding;

hence, the characteristics of settings that otherwise may or may not participate are unclear.

4.1.4 Implementation and maintenance

The time required for interventions' key components and supervision needs to be quantified from the individual and organizational perspectives. Costs from a societal perspective or grant-funded compensation are frequently reported but may not be helpful for health systems with limited resources or budget margins.

4.2 Limitations

Our review has several limitations due to the way studies report information and limitations of meta-analyses. We strictly limited our review to studies with lay advisor-delivered intervention without additional health professional or research staff-delivered components. We did not want to combine two interventions with unclear reimbursement structures, and lay advisors are generally not yet part of core healthcare teams; however, lay advisors alone can provide support. Specifically, our exclusion of any physician education or training component limited a few key studies (62–65). We excluded these studies because physician-directed interventions may individually improve outcomes, and hypertension is routinely managed in time-restricted primary care clinic visits along with multiple concerns and health maintenance (66, 67). Secondly, as health systems may or may not be involved in community-level screenings but are typically held accountable for hypertension outcomes in their patient populations, we limited community-level screening studies to those reporting hypertension outcomes. Third, high heterogeneity was noted with diverse intervention components and intensity variations but planned meta-regression and subgroup analysis to explain the variation could not be done due to limited number of eligible studies; nevertheless, the increasing dose–response gradient with increasing intervention intensity supports directionality of the intervention effects. Literature syntheses can make sense of this heterogeneity if studies also report contextual factors affecting individual intervention component acceptability and efficacy.

4.3 Implications for future research

Our review has strong implications for future research. Reporting of most and least efficacious components of multicomponent interventions to tailor stepped upscaling of lay advisor interventions is needed. Studies mainly included adults representing the working population's age where stepped-care models may be important to reducing intervention burden and balancing healthcare resource allocations. Tailoring lay advisor services within health systems that serve diverse patient populations has been understudied as most studies targeted socially disadvantaged population groups. Pragmatic trial designs such as hybrid effectiveness implementation trials may be helpful to evaluate not only how the intervention works but also how to successfully implement the interventions in diverse settings. Qualitative assessments of why and how the lay advisor interventions reach the targeted population, improve outcomes, and can be maintained are areas for future research. Future mixed methods assessments need to contribute to understanding the facilitators and barriers to engaging patients in the interventions, retaining a lay advisor workforce, and sustainability of the intervention at an individual and organizational level.

5 Conclusion

Add-on and high intensity lay advisor interventions may improve blood pressure outcomes in socially disadvantaged populations, but studied interventions are heterogeneous. Future studies need to identify the intervention's most efficacious components and include assessments of stepped upscaling. Future research should focus on mixed methods assessments to identify explanatory processes for effectiveness and engagement at the individual, lay advisor, and setting levels to inform the real-world implementation of these interventions.

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

SP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. VB: Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. YY: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. LB: Data curation, Validation, Writing – original draft. E-OU: Data curation, Validation, Writing – original draft. IT: Data curation, Validation, Writing – original draft. RS: Supervision, Writing – review & editing. KS: Methodology, Supervision, Writing – review & editing. SB: Methodology, Supervision, Visualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Source of funding and support statement: Patil was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number KL2 TR002346. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. No financial disclosures were reported by remaining authors of this paper. No other sources of support reported by remaining authors of this paper.

Acknowledgments

We acknowledge librarians Gwendolyn Wilson (University of Missouri) and Mary Schleicher (Cleveland Clinic) for their help with the database searches, removing of duplicates, and exporting citations in Rayyan and Covidence software.

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/fmed.2024.1305190/full#supplementary-material

References

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke Statistics-2021 update: a report from the American Heart Association. *Circulation*. (2021) 143:e254–743. doi: 10.1161/CIR.0000000000000950

2. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. (2020) 16:223–37. doi: 10.1038/s41581-019-0244-2

3. Sigmund CD, Carey RM, Appel LJ, Arnett DK, Bosworth HB, Cushman WC, et al. Report of the National Heart, Lung, and Blood Institute working group on hypertension: barriers to translation. *Hypertension*. (2020) 75:902–17. doi: 10.1161/HYPERTENSIONAHA.119.13887

4. Chattopadhyay SK, Jacob V, Mercer SL, Hopkins DP, Elder RW, Jones CD. Community guide cardiovascular disease economic reviews: tailoring methods to ensure utility of findings. *Am J Prev Med*. (2017) 53:S155–63. doi: 10.1016/j.amepre.2017.06.012

5. Derington CG, King JB, Bryant KB, McGee BT, Moran AE, Weintraub WS, et al. Cost-effectiveness and challenges of implementing intensive blood pressure goals and team-based care. *Curr Hypertens Rep*. (2019) 21:91. doi: 10.1007/s11906-019-0996-x

6. Mbuthia GW, Magutah K, Pellowski J. Approaches and outcomes of community health worker's interventions for hypertension management and control in low-income and middle-income countries: systematic review. *BMJ Open*. (2022) 12:e053455. doi: 10.1136/bmjopen-2021-053455

7. *Cardiovascular disease: interventions engaging community health workers: systematic review Atlanta, GA: The Community Guide* (2015). Available at: https://www.thecommunityguide.org/findings/heart-disease-stroke-prevention-interventions-engaging-community-health-workers.html.

8. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM planning and evaluation framework: adapting to new science and practice with a 20-year review. *Front Public Health*. (2019) 7:7. doi: 10.3389/fpubh.2019.00064

9. 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. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

10. Barnett ML, Lau AS, Miranda J. Lay health worker involvement in evidence-based treatment delivery: a conceptual model to address disparities in care. *Annu Rev Clin Psychol*. (2018) 14:185–208. doi: 10.1146/annurev-clinpsy-050817-084825

11. Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies In: JPT Higgins and S Green, editors. *Cochrane handbook for systematic reviews of interventions. Version 5.1.0*. Oxford: Cochrane Collaboration (2011)

12. Kessler RS, Purcell EP, Glasgow RE, Klesges LM, Benkeser RM, Peek CJ. What does it mean to "employ" the RE-AIM model? *Eval Health Prof*. (2013) 36:44–66. doi: 10.1177/0163278712446066

13. Higgins JPT, Deeks JJ, Altman DG. Approximate analyses of cluster-randomized trials for a meta-analysis: effective sample sizes In: JPT Higgins and S Green, editors. *Cochrane handbook for systematic reviews of interventions. Version 5.1.0*. Oxford: Cochrane Collaboration (2011)

14. Deeks JJ, Higgins JPT, Altman DG. Identifying and measuring heterogeneity In: JPT Higgins and S Green, editors. *Cochrane handbook for systematic reviews of interventions. Version 5.1.0*. Oxford: Cochrane Collaboration (2011)

15. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

16. Balcazar HG, Byrd TL, Ortiz M, Tondapu SR, Chavez M. A randomized community intervention to improve hypertension control among Mexican Americans: using the promotoras de salud community outreach model. *J Health Care Poor Underserved*. (2009) 20:1079–94. doi: 10.1353/hpu.0.0209

17. Dye CJ, Williams JE, Evatt JH. Activating patients for sustained chronic disease self-management: thinking beyond clinical outcomes. *J Prim Care Community Health*. (2016) 7:107–12. doi: 10.1177/2150131915626562

18. Gamage DG, Riddell MA, Joshi R, Thankappan KR, Chow CK, Oldenburg B, et al. Effectiveness of a scalable group-based education and monitoring program, delivered by health workers, to improve control of hypertension in rural India: a cluster randomised controlled trial. *PLoS Med*. (2020) 17:e1002997. doi: 10.1371/journal.pmed.1002997

19. Goudge J, Chirwa T, Eldridge S, Gómez-Olivé FXF, Kabudula C, Limbani F, et al. Can lay health workers support the management of hypertension? Findings of a cluster randomised trial in South Africa. *BMJ Glob Health*. (2018) 3:e000577. doi: 10.1136/bmjgh-2017-000577

20. Joshi R, Agrawal T, Fathima F, Usha T, Thomas T, Misquith D, et al. Cardiovascular risk factor reduction by community health workers in rural India: a cluster randomized trial. *Am Heart J*. (2019) 216:9–19. doi: 10.1016/j.ahj.2019.06.007

21. Margolius D, Bodenheimer T, Bennett H, Wong J, Ngo V, Padilla G, et al. Health coaching to improve hypertension treatment in a low-income, minority population. *Ann Fam Med*. (2012) 10:199–205. doi: 10.1370/afm.1369

22. Ojji DB, Baldridge AS, Ojji AI, Shedul LG, Ojji OI, Egenti NB, et al. Feasibility and effect of community health worker support and home monitoring for blood pressure control in Nigeria: a randomised pilot trial. *Cardiovasc J Afr*. (2020) 31:51–3. doi: 10.5830/CVJA-2019-066

23. Poggio R, Melendi SE, Beratarrechea A, Gibbons L, Mills KT, Chen CS, et al. Cluster randomized trial for hypertension control: effect on lifestyles and body weight. *Am J Prev Med*. (2019) 57:438–46. doi: 10.1016/j.amepre.2019.05.011

24. Ursua RA, Aguilar DE, Wyatt LC, Trinh-Shevrin C, Gamboa L, Valdellon P, et al. A community health worker intervention to improve blood pressure among Filipino Americans with hypertension: a randomized controlled trial. *Prev Med Rep*. (2018) 11:42–8. doi: 10.1016/j.pmedr.2018.05.002

25. Neupane D, McLachlan CS, Mishra SR, Olsen MH, Perry HB, Karki A, et al. Effectiveness of a lifestyle intervention led by female community health volunteers versus usual care in blood pressure reduction (COBIN): an open-label, cluster-randomised trial. *Lancet Glob Health*. (2018) 6:e66–73. doi: 10.1016/S2214-109X(17)30411-4

26. Johnson W, Ezeugwu C, Monroe D, Breunig IM, Shaya F. A pilot study evaluating a community-based intervention focused on the ISHIB IMPACT cardiovascular risk reduction toolkit in African American patients with uncontrolled hypertension. *Ethn Dis*. (2015) 25:162–7.

27. Victor RG, Ravenell JE, Freeman A, Leonard D, Bhat DG, Shafiq M, et al. Effectiveness of a barber-based intervention for improving hypertension control in black men: the BARBER-1 study: a cluster randomized trial. *Arch Intern Med*. (2011) 171:342–50. doi: 10.1001/archinternmed.2010.390

28. Khetan A, Zullo M, Rani A, Gupta R, Purushothaman R, Bajaj NS, et al. Effect of a community health worker-based approach to integrated cardiovascular risk factor control in India: a cluster randomized controlled trial. *Glob Heart*. (2019) 14:355–65. doi: 10.1016/j.gheart.2019.08.003

29. Krieger J, Collier C, Song L, Martin D. Linking community-based blood pressure measurement to clinical care: a randomized controlled trial of outreach and tracking by community health workers. *Am J Public Health*. (1999) 89:856–61. doi: 10.2105/AJPH.89.6.856

30. Levine DM, Bone LR, Hill MN, Stallings R, Gelber AC, Barker A, et al. The effectiveness of a community/academic health center partnership in decreasing the level of blood pressure in an urban African-American population. *Ethn Dis*. (2003) 13:354–61.

31. Morisky DE, Lees NB, Sharif BA, Liu KY, Ward HJ. Reducing disparities in hypertension control: a community-based hypertension control project (CHIP) for an ethnically diverse population. *Health Promot Pract*. (2002) 3:264–75. doi: 10.1177/152483990200300221

32. Jafar TH, Hatcher J, Poulter N, Islam M, Hashmi S, Qadri Z, et al. Community-based interventions to promote blood pressure control in a developing country: a cluster randomized trial. *Ann Intern Med*. (2009) 151:593–601. doi: 10.7326/0003-4819-151-9-200911030-00004

33. Safford MM, Cummings DM, Halladay J, Shikany JM, Richman J, Oparil S, et al. The design and rationale of a multicenter real-world trial: the southeastern collaboration to improve blood pressure control in the US Black Belt – addressing the triple threat. *Contemp Clin Trials*. (2023) 129:107183. doi: 10.1016/j.cct.2023.107183

34. Suseela RP, Ambika RB, Mohandas S, Menon JC, Numpelil M, Vasudevan BK, et al. Effectiveness of a community-based education and peer support led by women's self-help groups in improving the control of hypertension in urban slums of Kerala, India: a cluster randomised controlled pragmatic trial. *BMJ Glob Health*. (2022) 7:e010296. doi: 10.1136/bmjgh-2022-010296

35. Islam NS, Wyatt LC, Ali SH, Zanowiak JM, Mohaimin S, Goldfeld K, et al. Integrating community health workers into community-based primary care practice settings to improve blood pressure control among south Asian immigrants in new York City: results from a randomized control trial. *Circ Cardiovasc Qual Outcomes*. (2023) 16:e009321. doi: 10.1161/CIRCOUTCOMES.122.009321

36. Nelson KM, Taylor L, Williams JL, Rao M, Gray KE, Kramer CB, et al. Effect of a peer health coaching intervention on clinical outcomes among US veterans with cardiovascular risks: the vet-COACH randomized clinical trial. *JAMA Netw Open*. (2023) 6:e2317046. doi: 10.1001/jamanetworkopen.2023.17046

37. Islam NS, Wyatt LC, Taher MD, Riley L, Tandon SD, Tanner M, et al. A culturally tailored community health worker intervention leads to improvement in patient-centered outcomes for immigrant patients with type 2 diabetes. *Clin Diabetes*. (2018) 36:100–11. doi: 10.2337/cd17-0068

38. Dye CJ, Williams JE, Evatt JH. Improving hypertension self-management with community health coaches. *Health Promot Pract*. (2015) 16:271–81. doi: 10.1177/1524839914533797

39. Hayes A, Morzinski J, Ertl K, Wurm C, Patterson L, Wilke N, et al. Preliminary description of the feasibility of using peer leaders to encourage hypertension self-management. *WMJ*. (2010) 109:85–90.

40. Hovell MF, Geary DC, Black DR, Kamachi K, Kirk R. The effects of lay counseling on medication adherence and blood pressure: adjunctive treatment for hypertension. *Patient Educ Couns*. (1984) 6:91–4. doi: 10.1016/0738-3991(84)90040-5

41. Woods SS, Costanzo CL. Community lay worker guided home-based monitoring program for hypertension control. *J Dr Nurs Pract*. (2016) 9:249–56. doi: 10.1891/2380-9418.9.2.249

42. Isiguzo GC, Santo K, Panda R, Mbau L, Mishra SR, Ugwu CN, et al. Adherence clubs to improve hypertension Management in Nigeria: Clubmeds, a feasibility study. *Glob Heart*. (2022) 17:1–13. doi: 10.5334/gh.1109

43. Sánchez V, Cacari Stone L, Moffett ML, Nguyen P, Muhammad M, Bruna-Lewis S, et al. Process evaluation of a promotora de salud intervention for improving hypertension outcomes for Latinos living in a rural U.S.-Mexico border region. *Health Promot Pract*. (2014) 15:356–64. doi: 10.1177/1524839913516343

44. Truncali A, Dumanovsky T, Stollman H, Angell SY. Keep on track: a volunteer-run community-based intervention to lower blood pressure in older adults. *J Am Geriatr Soc*. (2010) 58:1177–83. doi: 10.1111/j.1532-5415.2010.02874.x

45. Reininger BM, Mitchell-Bennett LA, Lee M, Yeh PG, Davé AC, Park SK, et al. Scaling a community-wide campaign intervention to manage hypertension and weight loss. *Front Med (Lausanne)*. (2021) 8:661353. doi: 10.3389/fmed.2021.661353

46. Schwalm J-D, McCready T, Lear SA, Lamelas P, Garis L, Musa H, et al. Exploring new models for cardiovascular risk reduction: the heart outcomes prevention and evaluation 4 (HOPE 4) Canada pilot study. *CJC Open*. (2021) 3:267–75. doi: 10.1016/j.cjco.2020.10.006

47. Samuel-Hodge CD, Gizlice Z, Allgood SD, Bunton AJ, Erskine A, Leeman J, et al. A hybrid implementation-effectiveness study of a community health worker-delivered intervention to reduce cardiovascular disease risk in a rural, underserved non-Hispanic Black population: the CHANGE study. *Am J Health Promot*. (2022) 36:948–58. doi: 10.1177/08901171221078272

48. Hess PL, Reingold JS, Jones J, Fellman MA, Knowles P, Ravenell JE, et al. Barbershops as hypertension detection, referral, and follow-up centers for black men. *Hypertension*. (2007) 49:1040–6. doi: 10.1161/HYPERTENSIONAHA.106.080432

49. Yi SS, Wyatt LC, Patel S, Choy C, Dhar R, Zanowiak JM, et al. A faith-based intervention to reduce blood pressure in underserved metropolitan New York immigrant communities. *Prev Chronic Dis*. (2019) 16:E106. doi: 10.5888/pcd16.180618

50. Ursua RA, Aguilar DE, Wyatt LC, Katigbak C, Islam NS, Tandon SD, et al. A community health worker intervention to improve management of hypertension among Filipino Americans in New York and New Jersey: a pilot study. *Ethn Dis*. (2014) 24:67–76.

51. Thomas N, Ewart C, Lewinson Roberts D, Brown A. "You can change the world with a haircut": evaluating the feasibility of a barber-led intervention for men of Black and ethnic minority heritage to manage high blood pressure. *J Prim Care Community Health*. (2023) 14:215013192311683. doi: 10.1177/21501319231168336

52. Bush K, Patrick C, Elliott K, Morris M, Tiruneh Y, McGaha P. Unsung heroes in health education and promotion: how community health workers contribute to hypertension management. *Front Public Health*. (2023) 11:11. doi: 10.3389/fpubh.2023.1088236

53. Brewer LC, Jones C, Slusser JP, Pasha M, Lalika M, Chacon M, et al. mHealth intervention for promoting hypertension self-management among African American patients receiving Care at a Community Health Center: formative evaluation of the FAITH! Hypertension app. *J Med Internet Res*. (2023) 7:e45061. doi: 10.2196/45061

54. Kisigo GA, Mgeta F, Mcharo O, Okello E, Wajanga B, Kalokola F, et al. Peer counselor intervention for reducing mortality and/or hospitalization in adults with hypertensive urgency in Tanzania: a pilot study. *Am J Hypertens*. (2023) 36:446–54. doi: 10.1093/ajh/hpad037

55. Rimawi A, Shah A, Louis H, Scales D, Kheiran JA, Jawabreh N, et al. Community health worker program outcomes for diabetes and hypertension control in West Bank refugee camps: a retrospective matched cohort study. *Glob Health Sci Pract*. (2022) 10:e2200168. doi: 10.9745/GHSP-D-22-00168

56. Manavalan P, Madut DB, Wanda L, Msasu A, Mmbaga BT, Thielman NM, et al. A community health worker delivered intervention to address hypertension among adults engaged in HIV care in northern Tanzania: outcomes from a pilot feasibility study. *J Clin Hypertens (Greenwich)*. (2022) 24:1095–104. doi: 10.1111/jch.14518

57. Shikany JM, Safford MM, Cherrington AL, Halladay JR, Anabtawi M, Richman EL, et al. Recruitment and retention of primary care practices in the southeastern collaboration to improve blood pressure control. *Contemp Clin Trials Commun*. (2023) 32:101059. doi: 10.1016/j.conctc.2023.101059

58. Thorogood M, Goudge J, Bertram M, Chirwa T, Eldridge S, Gómez-Olivé FX, et al. The Nkateko health service trial to improve hypertension management in rural South Africa: study protocol for a randomised controlled trial. *Trials*. (2014) 15:435. doi: 10.1186/1745-6215-15-435

59. Riddell MA, Mini GK, Joshi R, Thrift AG, Guggilla RK, Evans RG, et al. ASHA-led Community-based groups to support control of hypertension in rural India are feasible and potentially scalable. *Front Med*. (2021) 8:8. doi: 10.3389/fmed.2021.771822

60. Beasley JM, Shah M, Wyatt LC, Zanowiak J, Trinh-Shevrin C, Islam NS. A community health worker–led intervention to improve blood pressure control in an immigrant community with comorbid diabetes: data from two randomized, controlled trials conducted in 2011–2019. *Am J Public Health*. (2021) 111:1040–4. doi: 10.2105/AJPH.2021.306216

61. Zhang D, Wang G, Joo H. A systematic review of economic evidence on community hypertension interventions. *Am J Prev Med*. (2017) 53:S121–30. doi: 10.1016/j.amepre.2017.05.008

62. He J, Irazola V, Mills KT, Poggio R, Beratarrechea A, Dolan J, et al. Effect of a community health worker-led multicomponent intervention on blood pressure control in low-income patients in Argentina: a randomized clinical trial. *JAMA*. (2017) 318:1016–25. doi: 10.1001/jama.2017.11358

63. Peiris D, Praveen D, Mogulluru K, Ameer MA, Raghu A, Li Q, et al. SMARThealth India: a stepped-wedge, cluster randomised controlled trial of a community health worker managed mobile health intervention for people assessed at high cardiovascular disease risk in rural India. *PLoS One*. (2019) 14:e0213708. doi: 10.1371/journal.pone.0213708

64. Pladevall M, Brotons C, Gabriel R, Arnau A, Suarez C, de la Figuera M, et al. Multicenter cluster-randomized trial of a multifactorial intervention to improve antihypertensive medication adherence and blood pressure control among patients at high cardiovascular risk (the COM99 study). *Circulation*. (2010) 122:1183–91. doi: 10.1161/CIRCULATIONAHA.109.892778

65. Cooper LA, Roter DL, Carson KA, Bone LR, Larson SM, Miller ER 3rd, et al. A randomized trial to improve patient-centered care and hypertension control in underserved primary care patients. *J Gen Intern Med*. (2011) 26:1297–304. doi: 10.1007/s11606-011-1794-6

66. Haverfield MC, Tierney A, Schwartz R, Bass MB, Brown-Johnson C, Zionts DL, et al. Can patient-provider interpersonal interventions achieve the quadruple aim of healthcare? A systematic review. *J Gen Intern Med*. (2020) 35:2107–17. doi: 10.1007/s11606-019-05525-2

67. Caverly TJ, Hayward RA, Burke JF. Much to do with nothing: microsimulation study on time management in primary care. *BMJ*. (2018) 363:k4983. doi: 10.1136/bmj.k4983

TYPE Original Research
PUBLISHED 18 June 2024
DOI 10.3389/fcvm.2024.1388313

OPEN ACCESS

EDITED BY
Komal Marwaha,
Texas Tech University Health Sciences Center, United States

REVIEWED BY
Dario Leone,
University of Turin, Italy
Ioannis Leontsinis,
Hippokration General Hospital, Greece

*CORRESPONDENCE
Pu-Hua Zhang
18879292198@163.com

RECEIVED 19 February 2024
ACCEPTED 20 May 2024
PUBLISHED 18 June 2024

CITATION
Zhu X-Y, Zhang P-H, Huang W-Y, Huang W, Tang X-H, Yu H and Wang S-N (2024) The impact of sphygmomanometer placement and cuff placement on blood pressure measurements.
Front. Cardiovasc. Med. 11:1388313.
doi: 10.3389/fcvm.2024.1388313

The impact of sphygmomanometer placement and cuff placement on blood pressure measurements

Xiao-Yong Zhu, Pu-Hua Zhang*, Wen-Yin Huang, Wan Huang, Xin-Hu Tang, Hua Yu and Su-Nan Wang

Department of Cardiology, Jiujiang University Affiliated Hospital, Jiujiang, Jiangxi Province, China

Background: Hypertension is the most significant global risk factor for mortality and morbidity, making standardized blood pressure measurement crucial.
Objectives: To investigate whether the location of blood pressure monitors and the positioning of cuffs yield differing results in blood pressure measurements.
Methods: Patients admitted to the Affiliated Hospital of Jiujiang College between 1 January 2022 and 30 June 2023 were enrolled in this study and randomly allocated into four groups. These groups were defined based on the positioning of monitoring equipment as follows: varied placements of cuffs on automatic blood pressure monitors, different heights for mercury column blood pressure monitors, varied heights for automatic blood pressure monitors, and different orientations for the cuff airbag tubes on electrocardiogram monitors. Blood pressure was measured and recorded for each group, followed by an analysis of the variations in readings across the different setups.
Results: In the first cohort of 763 individuals, mean systolic blood pressure measured at the standard upper arm site was 128.8 ± 10.5 mmHg, compared to 125.3 ± 10.4 mmHg at the elbow fossa. The corresponding diastolic pressures were 79.2 ± 10.7 and 75.0 ± 10.6 mmHg, respectively. The difference in systolic pressure between these positions was significant at 3.48 ± 3.22 mmHg ($t_1 = 29.91$, $p_1 < 0.001$) and for diastolic pressure at 4.23 ± 1.31 mmHg ($t_2 = 88.98$, $p_2 < 0.001$). For the subsequent groups, involving 253, 312, and 225 individuals, respectively, blood pressure measurements were analyzed and compared across different methods within each group. All p-values exceeded 0.05, indicating no statistically significant differences.
Conclusions: Blood pressure values measured at the elbow fossa position using an upper arm-type automatic sphygmomanometer were found to be lower than those measured at the upper arm position, with a difference of 3.48 mmHg for systolic and 4.23 mmHg for diastolic pressures. It is therefore essential to position the cuff correctly, specifically 2–3 cm above the elbow fossa, when utilizing an upper arm-type automatic sphygmomanometer for blood pressure monitoring. Conversely, the placement of the mercury column sphygmomanometer and the automated sphygmomanometer at varying heights had no significant effect on blood pressure readings. Similarly, the orientation of the electrocardiogram's cuffed balloon tube, whether facing upward or downward, did not influence blood pressure measurement outcomes.

KEYWORDS
blood pressure, cardiovascular disease, hypertension, electronic sphygmomanometer, mercury sphygmomanometer

Introduction

Cardiovascular diseases are the leading cause of death globally (1). Hypertension is a major risk factor for mortality and disability worldwide, affecting over one billion individuals and contributing to an estimated 9.4 million deaths each year (2). Regular monitoring of blood pressure is crucial, and blood pressure can be measured by auscultation or automated oscillometric methods. Timely adjustment of antihypertensive treatment based on blood pressure levels can significantly reduce the risk of cardiovascular events (3). However, the accuracy of blood pressure measurements can be compromised by various factors, which may not reflect the patient's actual blood pressure accurately, such as the duration of rest before measurement (4), and the elasticity of the cuff during measurement (5). Inaccurate blood pressure readings could potentially lead to missed opportunities for reducing cardiovascular risk or to the unnecessary intensification of medication. As such, it is important to adhere to standardized measurement techniques to enhance the accuracy of blood pressure readings.

Methods

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Randomization and design

To investigate the effects of sphygmomanometer placement and cuff position on blood pressure measurement, we conducted a series of randomized controlled experiments divided into four groups:

Group A used the same upper arm sphygmomanometer to measure blood pressure and heart rate at the standard upper arm level and the elbow fossa position, recording the results separately. This was to explore the effects of cuff placement on the measurements obtained by electronic sphygmomanometers.

Group B positioned the zero scale level of mercury sphygmomanometers at 20 cm above, at the same level (0 cm), and 20 cm below the heart level to measure and record blood pressure readings. This group aimed to determine the impact of the mercury sphygmomanometer's placement on blood pressure readings.

Group C positioned the zero scale level of electronic sphygmomanometers at 20 cm above, at the same level (0 cm), and 20 cm below the heart level to measure and record blood pressure readings. This group aimed to determine the impact of the electronic sphygmomanometer's placement on blood pressure readings.

Group D conducted blood pressure measurements with the cuff airbag tube of the cardiac monitor facing both upward and downward, recording the results to assess whether the orientation of the airbag tube affected the blood pressure readings (refer to Figure 1).

Self-paired tests were administered, with the results categorized, registered, and subjected to statistical analysis. The Institutional Review Board of Jiujiang College Hospital approved the study protocol. All study participants provided written informed consent.

Study population

The inclusion criteria consisted of the following: patients hospitalized at the Affiliated Hospital of Jiujiang College, age 18 years or older, an upper arm circumference between 22 and 34 cm, stable vital signs, and ability to cooperate with the blood pressure measurement process.

Participants were primarily excluded based on conditions that could affect blood pressure measurements, including the following: rash, edema, paralysis, open ulcers or wounds, or arteriovenous shunts in both arms; atrial fibrillation, cardiac arrhythmia, or hemodynamic instability; recent phlebotomy; cognitive disorders; pregnancy; and Hb levels below 60 g/L.

Data collection

Collected data included age, gender, height, weight, body mass index (BMI), measured systolic and diastolic blood pressures, and heart rate levels of the individuals.

Blood pressure measurements

Three types of devices were utilized: (1) a standard mercury sphygmomanometer (reference device: Yuwell sphygmomanometer), also referred to as an "auscultation device" (Jiangsu Yuyue Medical Equipment Co., Ltd., Jiangsu, China); (2) an Omron oscillometric device (HEM-7121; Omron Healthcare, Kyoto, Japan); and (3) a Philips cardiac monitor (SureSigns VM6; Royal Philips, Amsterdam, Netherlands). The sphygmomanometers were verified to be in good condition and working order. Before measurement, the devices were sent to the hospital's medical engineering department for testing and calibration, with each component's function being checked and approved.

The measurement technique for each device adhered to the standard recommendations for blood pressure measurements and each manufacturer's instructions, as well as the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Hypertension Guidelines (6). Participants were required to refrain from strenuous activities and avoid consuming coffee or alcohol for 30 min before blood pressure measurement. After emptying their bladders, they sat quietly for 5–10 min. Each participant remained comfortably seated with their back supported by the chair, did not talk during the measurement, and fully exposed their right upper arm. The center of the cuff was aligned with the level of the patient's right atrium (at the midpoint of the sternum) (6). Blood pressure was measured at intervals of 1–2 min, with three consecutive measurements taken;

FIGURE 1
Four different sets of methods to perform blood pressure measurements. (A) Used the same upper arm sphygmomanometer to measure blood pressure and heart rate at the standard upper arm level and the elbow fossa position; (B) Positioned the zero scale level of mercury sphygmomanometers at 20 cm above, at the same level (0 cm), and 20 cm below the heart level to measure and record blood pressure readings; (C) Positioned the zero scale level of electronic sphygmomanometers at 20 cm above, at the same level (0 cm), and 20 cm below the heart level to measure and record blood pressure readings; (D) Conducted blood pressure measurements with the cuff airbag tube of the cardiac monitor facing both upward and downward.

the average of these three measurements was recorded. If the difference between any two systolic or diastolic measurements exceeded 5 mmHg, a fourth measurement was taken, and the average of the four measurements was recorded.

Statistical analysis

Data were processed and analyzed using Excel 2019 and SPSS version 27.0 software. The normality of the distribution was assessed using the Shapiro–Wilk test. Measurement data conforming to a normal distribution were expressed as the mean ± standard deviation ($\bar{x} \pm s$). Comparisons between two groups were made using the paired-sample t-test. Count data were expressed as the number of instances (%) and agreement was analyzed using the Bland–Altman method. A difference of $p < 0.05$ was considered statistically significant.

Results

The first experimental group consisted of 763 individuals with a mean age of 57.5 ± 10.1 years (446 men, 58.5%); their mean height was 167.6 ± 8.3 cm, weight was 62.1 ± 10.5 kg, and BMI was 22.0 ± 2.8 kg/m^2.

Table 1 presents the blood pressure and heart rate values measured by the participants in the upper arm and elbow fossa positions. The mean systolic and diastolic blood pressure readings in the upper arm position were higher than those in the elbow fossa position for all individuals (both $p < 0.001$). The mean difference in systolic blood pressure between the upper arm and the elbow fossa positions was 3.48 ± 3.2 mmHg, and the mean difference in diastolic blood pressure was 4.23 ± 1.31 mmHg. There was no significant difference in heart rate between the upper arm and the elbow fossa positions ($p = 0.147$).

Figure 2 displays the Bland–Altman analysis of systolic and diastolic blood pressure measurements taken with an electronic blood pressure monitor in the standard upper arm and elbow fossa positions ($n = 763$).

The second experimental group included 253 participants with a mean age of 58.4 ± 9.3 years (156 men, 61.7%); their mean height was 169.1 ± 5.9 cm, weight was 64.3 ± 8.5 kg, and BMI was 23.0 ± 2.7 kg/m^2.

Table 2 shows the blood pressure readings of the participants measured by a mercury sphygmomanometer at three different

TABLE 1 Blood pressure measurements x at upper arm and elbow fossa positions $\bar{x} \pm s$ (a paired-sample *t*-test was used).

Population	Number of cases	Measurement site	SBP (mmHg)	DBP (mmHg)	Heart rate (beats/min)
All	763	Upper arm position	128.8 ± 10.5	79.2 ± 10.7	72.8 ± 9.1
		Elbow fossa position	125.3 ± 10.4	75.0 ± 10.6	73.0 ± 8.2
		Difference	3.48 ± 3.22	4.23 ± 1.31	−0.20 ± 3.77
		95% CI	3.26–3.71	4.13–4.32	−0.47 to 0.07
		t	29.91	88.98	−1.46
		p	<0.001	<0.001	0.147

The difference is the ratio of upper arm position to elbow fossa position, *t*-value is the ratio of upper arm position to elbow fossa position, and *p*-value is the ratio of upper arm position to elbow socket position.

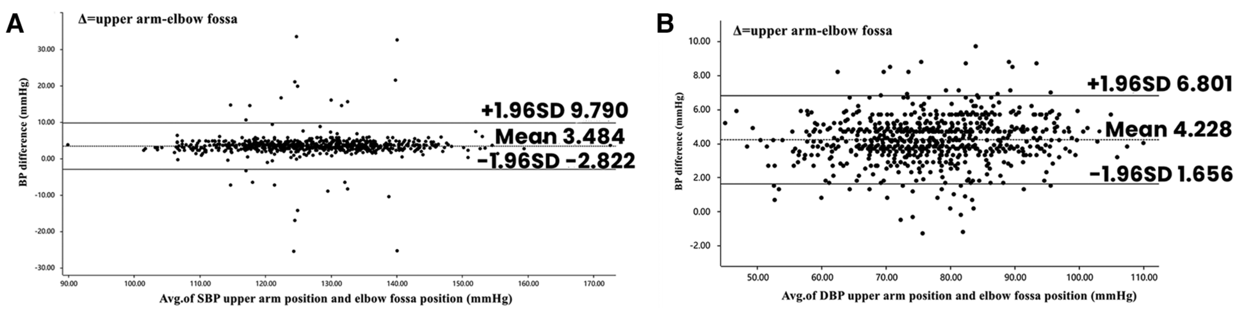


FIGURE 2
Bland–Altman plots depicting the degree of BP differences across the range of BP between elbow fossa position and upper arm position. (A) The difference in systolic BP between upper arm position and elbow fossa position in electronic sphygmomanometer. (B) The difference in diastolic BP between upper arm position and elbow fossa position in electronic sphygmomanometer. BP, blood pressure.

TABLE 2 Blood pressure measurements of mercury sphygmomanometer in high, horizontal, and low positions $\bar{x} \pm s$, using a paired samples *t*-test.

Population	Number of cases	Measurement site	SBP (mmHg)	DBP (mmHg)
All	253	High positions	124.89 ± 12.78	72.30 ± 12.01
		Horizontal positions	124.79 ± 12.31	72.66 ± 11.16
		Low positions	124.73 ± 12.42	72.58 ± 11.53
		Difference 1	−0.11 ± 2.85	0.35 ± 5.38
		Difference 2	0.06 ± 2.84	0.08 ± 2.73
		95% CI 1	−0.46 to 0.25	−0.31 to 1.02
		95% CI 2	−0.29 to 0.41	−0.26 to 0.42
		*t*1	−0.588	1.045
		*t*2	0.327	0.464
		^*P*	NS	NS
		#*P*	NS	NS

Difference 1, difference in blood pressure between horizontal and high position; Difference 2, difference in blood pressure between horizontal and low position; 95% CI 1, confidence interval for the difference between horizontal and high position; 95% CI 2, confidence interval for the difference between horizontal and low position; *t*1, horizontal compared to high position; *t*2, horizontal compared to low position; ^P, horizontal compared to high position; #P, horizontal compared to low position.

sites. There were no significant differences in systolic ($p = 0.557$) and diastolic ($p = 0.297$) blood pressure between the horizontal and high positions for all participants. Similarly, there were no significant differences in systolic ($p = 0.744$) and diastolic ($p = 0.643$) blood pressure between the horizontal and low positions for all participants. Figure 3 depicts the Bland–Altman analysis of systolic and diastolic blood pressure measurements taken with the mercury sphygmomanometer in different positions ($n = 253$).

The third experimental group comprised 312 participants with a mean age of 65.68 ± 11.4 years (167 men, 53.5%); their mean height was 166.0 ± 6.9 cm, weight was 61.6 ± 9.2 kg, and BMI was 22.3 ± 2.4 kg/m^2.

Table 3 indicates the blood pressure readings of the participants measured by an electronic sphygmomanometer at three different sites. There were no significant differences in systolic ($p = 0.362$) and diastolic ($p = 0.174$) blood pressures between the horizontal and high positions for all participants. Furthermore, there were no significant differences in systolic ($p = 0.222$) and diastolic ($p = 0.271$) blood pressures between the horizontal and low positions for all participants. No significant differences were observed in heart rate ($p = 0.445$) between the horizontal and high positions for all participants; there was no significant difference between horizontal ($p = 0.313$).

10.3389/fcvm.2024.1388313

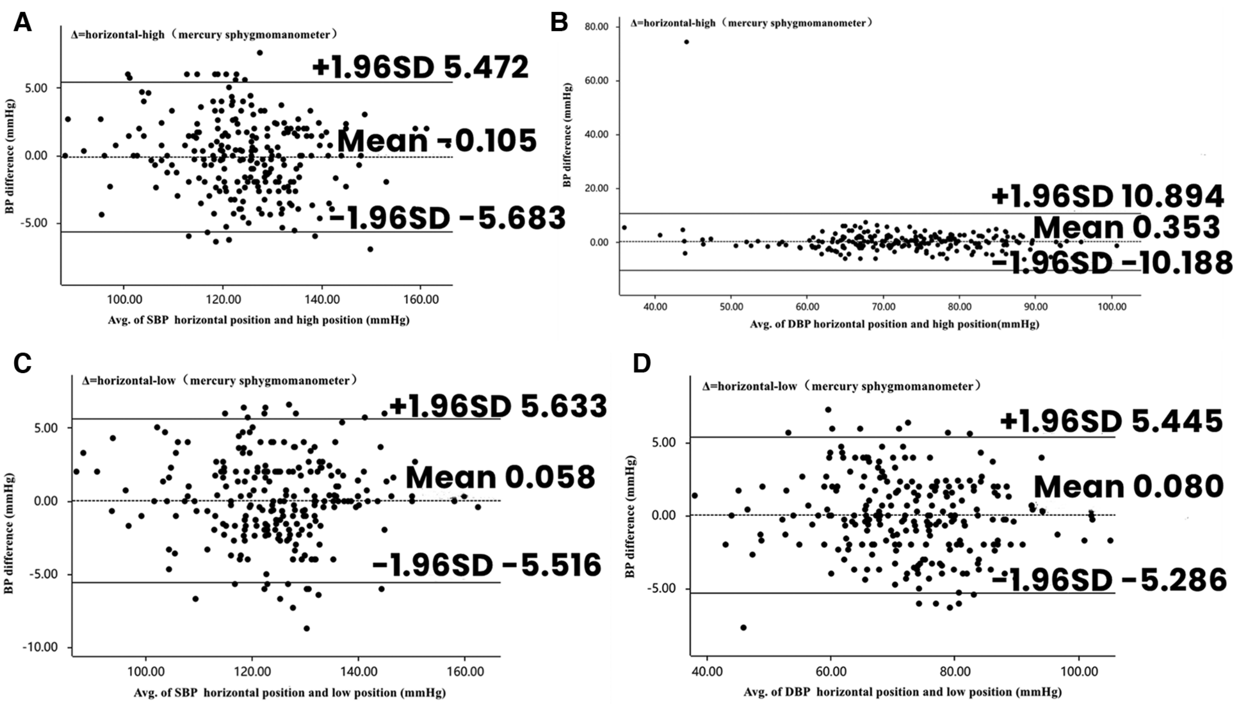


FIGURE 3
Bland–Altman plots depicting the degree of BP differences across the range of BP in placement of mercury sphygmomanometers in different positions. (A) The difference in SBP between horizontal and high positions in mercury sphygmomanometers. (B) The difference in DBP between horizontal and high positions in mercury sphygmomanometers. (C) The difference in SBP between horizontal and low positions in mercury sphygmomanometers. (D) The difference in DBP between horizontal and low positions in mercury sphygmomanometers. BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 3 Blood pressure measurements of electronic sphygmomanometers in high, horizontal, and low positions $\bar{x} \pm s$, using a paired samples *t*-test.

Population	Number of cases	Measurement site	SBP (mmHg)	DBP (mmHg)	Heart rate (beats/min)
All	312	High positions	122.47 ± 14.94	73.80 ± 10.27	75.05 ± 7.61
		Horizontal positions	122.61 ± 14.69	73.60 ± 9.92	74.89 ± 6.70
		Low positions	122.78 ± 14.70	73.45 ± 10.21	75.03 ± 7.08
		Difference 1	0.13 ± 2.56	−0.20 ± 2.56	−0.16 ± 3.78
		Difference 2	−0.18 ± 2.57	0.16 ± 2.54	−0.14 ± 2.52
		95% CI 1	−0.15 to 0.42	−0.48 to 0.09	−0.58 to 0.26
		95% CI 2	−0.46 to 0.11	−0.12 to 0.44	−0.43 to 0.14
		*t*1	0.913	−1.363	0.765
		*t*2	−1.223	1.102	−1.010
		^P	NS	NS	NS
		#P	NS	NS	NS

Difference 1, difference in blood pressure between horizontal and high position; Difference 2, difference in blood pressure between horizontal and low position; 95% CI 1, confidence interval for the difference between horizontal and high position; 95% CI 2, confidence interval for the difference between horizontal and low position; *t*1, horizontal compared to high position; *t*2, horizontal compared to low position; ^P, horizontal compared to high position; #P, horizontal compared to low position.

Figure 4 illustrates the Bland–Altman analysis of systolic and diastolic blood pressure measurements taken with the electronic sphygmomanometer in different positions ($n = 312$).

The fourth experimental group included 225 participants with a mean age of 62.2 ± 8.5 years (132 men, 58.7%); their mean height was 166.8 ± 6.7 cm, weight was 63.9 ± 10.1 kg, and BMI was 22.9 ± 2.6 kg/m^2.

Table 4 demonstrates the blood pressure and heart rate values measured by the sphygmomanometers when the participants had the cardiac monitor cuff with the balloon tubes facing down and up. There were no significant differences in systolic ($p = 0.435$) or diastolic ($p = 0.645$) blood pressures between all participants with the balloon tubes facing down and up. Similarly, there were no significant differences in heart rates ($p = 0.184$). Figure 5 presents the Bland–Altman analyses of systolic and diastolic blood pressures measured by the cardiac monitor cuff with the balloon tubes facing down and up ($n = 225$).

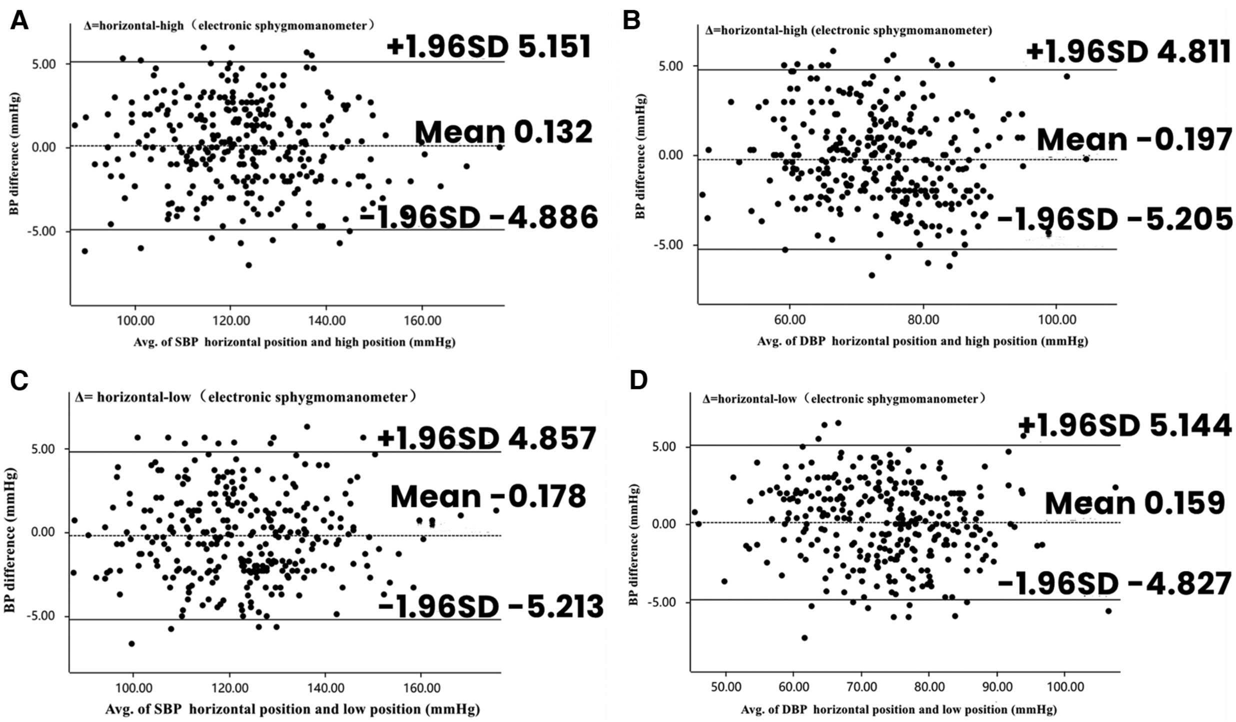


FIGURE 4
Bland–Altman plots depicting the degree of BP differences across the range of BP in placement of electronic sphygmomanometers in different positions. (A) The difference in SBP between horizontal and high positions in electronic sphygmomanometers. (B) The difference in DBP between horizontal and high positions in electronic sphygmomanometers. (C) The difference in SBP between horizontal and low positions in electronic sphygmomanometers. (D) The difference in DBP between horizontal and low positions in electronic sphygmomanometers. BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 4 Blood pressure measurements with cardiac monitor cuffed balloon tubes facing downward and upward $\bar{x} \pm s$, using a paired samples *t*-test.

Population	Number of cases	Measurement site	SBP (mmHg)	DBP (mmHg)	Heart rate (beats/min)
All	225	Tube facing downward	121.91 ± 11.94	74.94 ± 9.86	75.05 ± 9.48
		Tube facing upward	122.04 ± 12.23	74.86 ± 10.37	74.81 ± 9.53
		Difference	−0.13 ± 2.56	0.08 ± 2.73	0.24 ± 2.65
		95% CI	−0.47 to 0.20	−0.2847 to 0.44	−0.1147 to 0.58
		t	−0.783	0.461	1.33
		p	0.435	0.645	0.184

Difference is the difference between blood pressure in the downward-facing position and the upward-facing position, *t*-value is the ratio of the downward-facing position to the upward-facing position, and *p*-value is the ratio of the downward-facing position to the upward-facing position.

Table 5 summarizes the measurement characteristics of four different populations, including sample size, age, height, weight, and BMI.

Discussion

The precise measurement of blood pressure is fundamental to the diagnosis and treatment of hypertension (7). Currently, blood pressure is gauged through direct and indirect methods, with the former being less commonly employed due to its invasive nature. Indirect measurements involve occluding the brachial artery using a cuff and include methods such as mercury sphygmomanometers, which are based on the principle of Korotkoff sounds, and oscillometric sphygmomanometers, which rely on the principle of pulse wave detection (8). However, mercury sphygmomanometers are problematic due to issues such as environmental pollution and their relatively complex operation, leading to oscillometric sphygmomanometers being recommended as the preferred method for measuring blood pressure (9).

Blood pressure can be measured in various settings, including at clinics, in hospitals, at home, and through ambulatory monitoring. Nonetheless, irregularities in measurement techniques can lead to inaccuracies, potentially causing an overestimation of blood pressure, which can result in overdiagnosis and overtreatment, or an underestimation of blood pressure, which can delay necessary treatment (10, 11).

Many studies have examined the influence of different blood pressure measurement techniques on the results. Factors such as cuff length and width, the tightness of the cuff, rest time before

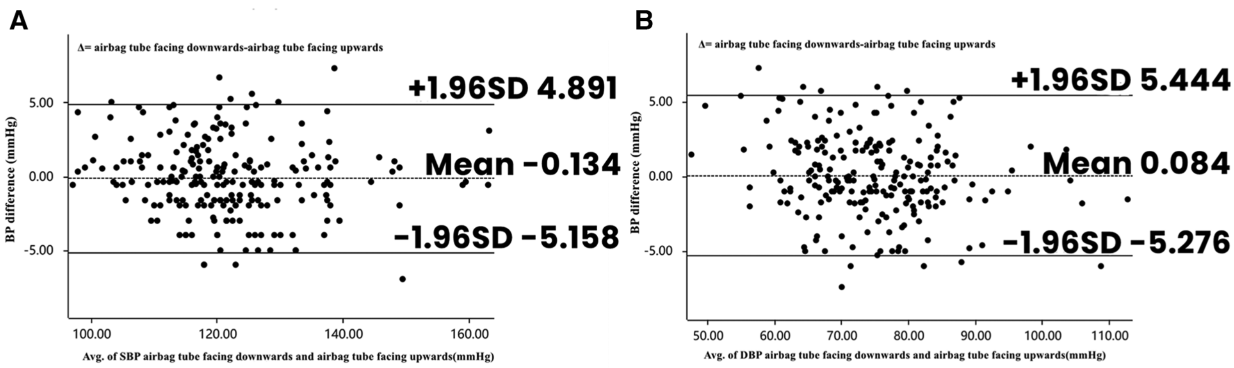


FIGURE 5
Bland–Altman plots depicting the degree of BP differences across the range of BP with the cuff airbag tube facing downward and upward. (A) The difference in SBP between ECG monitor cuff airbag tube facing downward and facing upward. (B) The difference in DBP between ECG monitor cuff airbag tube facing downward and facing upward. BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 5 Comparison of the anthropometric characteristics of the four groups.

Group	Number	Age	Male sex	Height	Weight	BMI
A	763	57.5 ± 10.1	446 (58.5%)	167.6 ± 8.3	62.1 ± 10.5	22.0 ± 2.8
B	253	58.4 ± 9.3	156 (61.7%)	169.1 ± 5.9	64.3 ± 8.5	23.0 ± 2.7
C	312	65.7 ± 11.4	167 (53.5%)	166.0 ± 6.9	61.6 ± 9.2	22.3 ± 2.4
D	225	62.2 ± 8.5	132 (58.7%)	166.8 ± 6.7	63.9 ± 10.1	22.9 ± 2.6

measurement, sitting position, and the auscultation site of the stethoscope are well-established variables that can impact the accuracy of blood pressure readings (12–14).

Adhering to the 2017 ACC/AHA Hypertension Guidelines for Blood Pressure Measurement, the cuff's midpoint should be level with the right atrium (the midpoint of the sternum) during blood pressure assessment. Alternatively, the lower edge of the cuff should be located about 2–3 cm above the elbow crease. Despite this recommendation, previous studies have shown that only one-third of the population correctly positions their blood pressure cuffs (15). This is especially true for obese patients, who may find it difficult to place the cuff 2–3 cm above the elbow joint. With the prevalence of obesity rising globally, this challenge is magnified. In addition, in colder weather, particularly during winter, patients tend to wear excessive clothing. Rather than removing these layers to fully expose the upper arm, many roll up their sleeves, which can lead to incorrect cuff placement due to the difficulty of rolling up sleeves to the upper arm. This contributes to the common occurrence of misplacement of the cuff (16). Furthermore, individuals with thicker arms might only be able to measure their blood pressure at a lower position and may not realize that a larger cuff is required to ensure accurate readings (17).

In 1897, Hill and Barnard recognized the need for standardization in cuff positioning during blood pressure measurements, observing that blood pressure readings varied with changes in the cuff's distance from the level of the heart. They proposed that the expected change in blood pressure (Δbp) could be quantified by the formula $\Delta bp = dv \cdot SG_b/SG_m$ (12), where Δbp is the change in blood pressure as measured by the cuff in mmHg, dv is the vertical distance from the cuff to the right atrium in millimeters, SG_b is the specific gravity of blood (1.05 at 37°C), and SGm is the specific gravity of mercury (approximately 13.6). This relationship is thus simplified to Δbp = (distance in millimeters/13.6 × 1.05) (18). According to this formula, for every 1 cm decrease in the distance between the cuff and the heart level, intra-arterial blood pressure is expected to increase by 0.8 mmHg, considering the specific gravities of blood and mercury. Given that the right atrium is located roughly at the level of the midpoint of the sternum (6), a cuff positioned closer to the feet will yield a lower blood pressure reading below the midpoint of the sternum, while a cuff closer to the head will yield a lower reading above this midpoint. These differences in blood pressure measurements are clinically significant, especially when considering the effects of antihypertensive medications (3).

The influence of cuff distance from the right atrium on blood pressure readings extends beyond theoretical concerns. Literature review has revealed at least two pertinent studies that confirm this effect (19, 20). These studies have specifically illustrated the impact of arm positioning on blood pressure by adjusting the arm's elevation, thus altering the distance from the cuff to the atria. In one study conducted by Mourad et al., hypertensive patients were randomly assigned to groups during ambulatory blood pressure monitoring. The experimental group had their blood pressure measured with their arm perpendicular to the torso, while the control group's measurements were taken with the arm parallel to the torso. The findings revealed that systolic blood pressure was 8.8 mmHg lower and diastolic blood pressure was 10.1 mmHg lower when the arm was perpendicular rather than parallel to the trunk. This study underscored the potential for significant variation in blood pressure readings based on arm position during measurement (19).

Mourad et al. also measured blood pressure using mercury and electronic sphygmomanometers. Individuals were initially positioned with their arms horizontally on a table, and then measurements were repeated with their arms parallel to the torso. This change in arm position led to an increase in mean blood pressure by 8/7 mmHg in normotensive participants and by 23/10 mmHg in hypertensive participants while sitting. These results were consistent with the proposed effects of arm positioning on blood pressure readings and highlighted the importance of proper cuff placement during the measurement process (19).

Kammila et al. observed that some patients experienced a significant nocturnal drop in blood pressure when ambulatory blood pressure monitoring data were analyzed. Upon further investigation, it was discovered that these patients had been sleeping with the hand being monitored on a pillow to muffle the sound of the ambulatory device and to increase comfort. Once this issue was identified, the patients were instructed to avoid using pillows for their arms at night and to keep their arms parallel to the bed. Following these instructions, the proportion of patients exhibiting a significant decrease in nocturnal systolic blood pressure dropped from 17.4% to 8.8%, and diastolic blood pressure from 37.0% to 24.4%. Conversely, the percentage of patients with an insignificant nocturnal decrease in blood pressure rose from 33.7% to 45.6% for systolic readings and from 13.0% to 31.6% for diastolic readings (20).

From the aforementioned findings, we can infer that the blood pressure readings obtained from a sphygmomanometer cuff vary depending on the position of the cuff, with readings being lower the further they are taken from the level of the heart.

Mercury sphygmomanometers, once the "gold standard" for in-office blood pressure measurements, have largely been replaced by automated sphygmomanometers. This shift occurred because mercury is recognized as a hazardous material. However, it is crucial for clinicians to be cognizant of the limitations presented by electronic sphygmomanometers in clinical settings. These devices may provide inaccurate readings in patients with cardiac arrhythmias, and not all electronic devices are reliable, effective, or suitable for every patient (21, 22). The mercury column sphygmomanometer operates on the principle that blood produces a Korotkoff sound as it flows through a constricted vascular space, creating a vortex. It comprises three main components: an inflatable cuff, a pressure gauge tube, and a mercury manometer. In the mercury manometer, the applied pressure acts directly on the brachial artery beneath the cuff. As the cuff deflates, the pressure on the brachial artery decreases, allowing blood flow to resume gradually. When the cuff pressure falls below the systolic pressure of the heart, blood flow is momentarily obstructed, creating a vortex and a detectable Korotkoff sound with a stethoscope. The reading on the sphygmomanometer at the moment this sound is first heard indicates the systolic blood pressure. The cuff is then slowly deflated further until the pressure equals the diastolic pressure of the heart, at which point the blood flow in the brachial artery becomes smooth, and the Korotkoff sound ceases. The sphygmomanometer reading at this moment represents the diastolic pressure (22, 23).

Some nursing textbooks in China state that the sphygmomanometer should be placed at the same height as the heart to ensure accurate blood pressure measurements. Is this truly necessary? Clinical experience from doctors and nurses shows that in situations where the patient cannot cooperate or where conditions are suboptimal or there is insufficient manpower, it is not easy for one person to maintain both the sphygmomanometer cuff and the device at the heart's level while also taking blood pressure readings. It would be convenient if the sphygmomanometer could be placed in any position, and in fact, the position of the sphygmomanometer has no effect on the measurement results. Both practice and theory can prove this point. When the sphygmomanometer cuff, the heart, and the mercury column zero point of the sphygmomanometer are at the same level, the pressure difference between the three is zero. However, if the mercury column zero point is higher or lower than the level of the cuff and the heart, there will be a pressure difference. Since the pressure between the cuff and the mercury column is transmitted by the air in the rubber tube connecting the cuff and the sphygmomanometer, the hydrostatic pressure formula, $P = \rho gh$ (where ρ is the fluid density, g is the acceleration of gravity, and h is the fluid height or depth), applies. This formula suggests that the hydrostatic pressure is only related to the fluid height or depth for a given fluid medium, with density and gravitational acceleration being constants. Many assume that the height of the sphygmomanometer affects blood pressure values based on this principle. While the correctness of the formula is not in dispute, the conditions for its application have been overlooked; that is, it only applies to a fluid medium that is identical and continuous. The sphygmomanometer's cuff, when placed at the same level as the heart, is correct because the brachial artery is connected to the heart and contains blood, which meets the condition of the formula's sameness and continuity, leading to a correct conclusion. However, the construction of the sphygmomanometer involves three different fluids (blood, air, and mercury), which means the conditions of sameness and continuity for the formula are not met. The cuff is separated from the body, and the sphygmomanometer's mercury column interacts with air and mercury, breaking the continuity. Therefore, the perspective that the height of the sphygmomanometer affects brachial artery blood pressure readings is theoretically invalid. The correct approach is to apply the hydrostatic pressure formula in segments: P (brachial artery blood pressure) $= \rho$ (mercury density) gh (height of the mercury column) $\pm \rho$ (air density) gh (height of the air column). With mercury having a density of 13,600 kg m^{-3} and air having a density of 1.29 kg m^{-3}, it can be calculated that a change in the height of the sphygmomanometer (with the heart level as the zero point) by 1.054 m results in only a 1 mmHg change in the mercury column. This change is less than the error margin of two consecutive blood pressure measurements, indicating that a slight variation in the height of the sphygmomanometer has an imperceptible impact on blood pressure readings. In other words, the mercury sphygmomanometer can be placed at any height when measuring blood pressure.

The cuff of the electronic sphygmomanometer is placed in the same position and arm position as that of the mercury sphygmomanometer. By inflating and deflating the cuff, the blood flow in the brachial artery is altered to estimate the systolic and diastolic blood pressures. Human blood pressure varies with the time of day, with the maximum value being the systolic pressure and the minimum value being the diastolic pressure. The electronic sphygmomanometer measures these values—systolic and diastolic blood pressures (24). During the blood pressure measurement process, the cuff becomes pressurized, squeezing the blood vessels and causing an increase in blood pressure. This pressure peaks after deflation and the release of the cuff. As the cuff's pressure is continuously decreased, the blood vessels are gradually released, and the blood pressure lowers until it returns to normal. Throughout this process, the electronic sphygmomanometer cuff detects multiple small pulses generated by the blood vessel wall. The device's built-in program connects these pulses to form a curve known as the envelope. The device then analyzes and processes the envelope to automatically determine the diastolic and systolic blood pressures. Simultaneously, the shape of the envelope changes with the actual blood pressure, a principle known as the oscillometric method of blood pressure measurement (25). The oscillometric method relies on an oscillometric curve, making it less susceptible to interference from external noise, electrocautery, or other electronic surgical instruments. It transmits pressure through the gas in the cuff's tube, and the blood pressure measured is independent of the sphygmomanometer's placement; in other words, the sphygmomanometer can be placed at any height during the measurement.

In the fourth group of experiments, which is not mentioned in textbooks and guidelines, a certain cuff-tying method is suitable when the monitor is placed above the patient's head or on the bedside table. When the cuff is tied in reverse, that is, with the inflatable tube facing upward on the upper arm, it aligns straight with the monitor's blood pressure measuring tube, preventing it from bending or twisting. This reduces the risk of joint cracking and leakage, minimizes cuff wear, and ensures accurate blood pressure measurement, even when the patient bends at the elbow or moves their elbow joint. This method prevents the instrument from repeatedly inflating due to poor cuff inflation. When the patient is in a semi-recumbent position or has a flexed upper limb due to disease, the sphygmomanometer cuff can also be placed flat on the upper arm for the patient's comfort. However, clinical nurses using this method may face challenges from patients, peers, or be mistakenly perceived as performing irregular practices. It is hoped that the data from this clinical study will support the efficacy of this technique in actual clinical work.

We grouped the cardiac monitor cuffs with the balloon tubes facing different directions and performed blood pressure measurements, finding no significant differences in the measured values regardless of whether the cuffs had the balloon tubes facing up or down. For participants recruited from the cardiology department, the difference in mean blood pressure between cuffs with balloon tubes in the upward-facing position and in the standard cuff position was within 1.0 mmHg. Furthermore, blood pressure measured in the upward-facing position correlated positively with that in the standard position, and blood pressure concordance was good for all participants. On this basis, we conclude that the difference in mean blood pressure with the cuff's balloon tubing in both the upward and downward positions is within 1.0 mmHg, and that the differences in the measured outcomes are clinically acceptable. Similarly, since blood pressure measurements on cardiac monitors are made by the transfer of pressure through the gas in the cuff tube, the orientation of the cuff tube has a negligible effect on these measurements.

It is particularly important to emphasize that blood pressure is a variable hemodynamic phenomenon influenced by many factors (26). When we perform continuous blood pressure monitoring, the values are not completely consistent, and there are fluctuations known as blood pressure variability. This natural variation in blood pressure measurements is due to the patient's own status (26). Blood pressure variability increases when the patient is in an unstable state, thus enhancing the natural variation. A review of previous clinical studies showed that the natural variability of systolic blood pressure was in the range of 4–61 mmHg, and that of diastolic blood pressure was 2–39 mmHg (27). This suggests that the effects of changes in sphygmomanometer placement, cuff orientation, and balloon tube direction during blood pressure measurements are much smaller than those of natural variability and have a negligible impact on blood pressure measurements.

Perspectives

This study contributes to the growing body of evidence that blood pressure measured by electronic sphygmomanometer cuffs placed in different positions varies, and that the farther away from the heart level, the lower the measured blood pressure value. Blood pressure measured at the elbow fossa position of upper-arm sphygmomanometers was lower than that at the standard upper-arm position by 3.48 mmHg systolic and 4.23 mmHg diastolic. Blood pressure readings from electronic and mercury sphygmomanometers are independent of the sphygmomanometer's position, and blood pressure readings from electronic sphygmomanometers are also independent of the orientation of the cuff and balloon tubing. Standardized blood pressure measurement can more accurately reflect a patient's actual blood pressure, aiding in active diagnosis and treatment, and significantly reducing the incidence of adverse cardiovascular events.

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 Medical Ethics Committee of Jiujiang University Affiliated 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. 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

X-YZ: Data curation, Investigation, Writing – original draft, Writing – review & editing. P-HZ: Data curation, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. W-YH: Data curation, Investigation, Writing – original draft. X-HT: Data curation, Investigation, Writing – original draft. HY: Data curation, Investigation, Writing – original draft.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article.

This work was supported by a grant from the National Natural Science Foundation of China (reference 82260147 and 82360626).

Acknowledgments

Thank you to Nuo Nan Li for their contributions in blood pressure measurement and data collection.

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.

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. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. (2016) 387:957–67. doi: 10.1016/s0140-6736(15)01225-8

3. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the subcommittee of professional and public education of the American Heart Association Council on High Blood Pressure Research. *Hypertension*. (2005) 45:142–61. doi: 10.1161/01.HYP.0000150859.47929.8e

4. Tobe SW, Dubrofsky L, Nasser DI, Rajasingham R, Myers MG. Randomized controlled trial comparing automated office blood pressure readings after zero or five minutes of rest. *Hypertension*. (2021) 78:353–9. doi: 10.1161/hypertensionaha.121.17319

5. Bui TV, Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, et al. Accuracy of cuff blood pressure and systolic blood pressure amplification. *Hypertens Res*. (2023) 46:1961–9. doi: 10.1038/s41440-023-01311-0

6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. (2018) 71:2199–269. doi: 10.1016/j.jacc.2017.11.005

7. Richter D, Guasti L, Walker D, Lambrinou E, Lionis C, Abreu A, et al. Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPCCS). *Eur J Prev Cardiol*. (2022) 29:216–27. doi: 10.1093/eurjpc/zwaa167

8. O'Brien E, Fitzgerald D. The history of blood pressure measurement. *J Hum Hypertens*. (1994) 8:73–84.

9. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens*. (2023) 41(12):1874–2071. doi: 10.1097/hjh.0000000000003480

10. Stergiou GS, Kyriakoulis KG, Kollias A. Office blood pressure measurement types: different methodology-different clinical conclusions. *J Clin Hypertens (Greenwich)*. (2018) 20:1683–5. doi: 10.1111/jch.13420

11. Guo QH, Cheng YB, Zhang DY, Wang Y, Huang QF, Sheng CS, et al. Comparison between home and ambulatory morning blood pressure and morning hypertension in their reproducibility and associations with vascular injury. *Hypertension*. (2019) 74:137–44. doi: 10.1161/hypertensionaha.119.12955

12. Mitchell PL, Parlin RW, Blackburn H. Effect of vertical displacement of the arm on indirect blood-pressure measurement. *N Engl J Med*. (1964) 271:72–4. doi: 10.1056/nejm196407092710204

13. Cushman WC, Cooper KM, Horne RA, Meydrech EF. Effect of back support and stethoscope head on seated blood pressure determinations. *Am J Hypertens*. (1990) 3:240–1. doi: 10.1093/ajh/3.3.240

14. Mengden T, Hernandez Medina RM, Beltran B, Alvarez E, Kraft K, Vetter H. Reliability of reporting self-measured blood pressure values by hypertensive patients. *Am J Hypertens*. (1998) 11:1413–7. doi: 10.1016/s0895-7061(98)00241-6

15. Stryker T, Wilson M, Wilson TW. Accuracy of home blood pressure readings: monitors and operators. *Blood Press Monit*. (2004) 9:143–7. doi: 10.1097/01.mbp.0000130224.18777.ce

16. Graves JW, Bailey KR, Sheps SG. The changing distribution of arm circumferences in NHANES III and NHANES 2000 and its impact on the utility of the "standard adult" blood pressure cuff. *Blood Press Monit*. (2003) 8:223–7. doi: 10.1097/00126097-200312000-00001

17. Wiliński J, Kusiak A, Wiliński B, Smolik P, Klima Ł, Chmielewska J, et al. Selection and maintenance of the blood pressure monitor for self-blood pressure monitoring (SBPM). *Prz Lek*. (2013) 70:900–3.

18. Trudnowski RJ, Rico RC. Specific gravity of blood and plasma at 4 and 37 degrees C. *Clin Chem*. (1974) 20:615–6. doi: 10.1093/clinchem/20.5.615

19. Mourad A, Carney S, Gillies A, Jones B, Nanra R, Trevillian P. Arm position and blood pressure: a risk factor for hypertension? *J Hum Hypertens*. (2003) 17:389–95. doi: 10.1038/sj.jhh.1001563

20. Kammila S, Campbell NR, Brant R, deJong R, Culleton B. Systematic error in the determination of nocturnal blood pressure dipping status by ambulatory blood pressure monitoring. *Blood Press Monit*. (2002) 7:131–4. doi: 10.1097/00126097-200204000-00007

21. Ogedegbe G, Pickering T. Principles and techniques of blood pressure measurement. *Cardiol Clin*. (2010) 28:571–86. doi: 10.1016/j.ccl.2010.07.006

22. Valler-Jones T, Wedgbury K. Measuring blood pressure using the mercury sphygmomanometer. *Br J Nurs*. (2005) 14:145–50. doi: 10.12968/bjon.2005.14.3.17519

23. Muniyandi M, Sellappan S, Chellaswamy V, Ravi K, Karthikeyan S, Thiruvengadam K, et al. Diagnostic accuracy of mercurial versus digital blood pressure measurement devices: a systematic review and meta-analysis. *Sci Rep*. (2022) 12:3363. doi: 10.1038/s41598-022-07315-z

24. Chandrasekhar A, Yavarimanesh M, Hahn JO, Sung SH, Chen CH, Cheng HM, et al. Formulas to explain popular oscillometric blood pressure estimation algorithms. *Front Physiol*. (2019) 10:1415. doi: 10.3389/fphys.2019.01415

25. Forouzanfar M, Dajani HR, Groza VZ, Bolic M, Rajan S, Batkin I. Oscillometric blood pressure estimation: past, present, and future. *IEEE Rev Biomed Eng*. (2015) 8:44–63. doi: 10.1109/rbme.2015.2434215

26. Schutte AE, Kollias A, Stergiou GS. Blood pressure and its variability: classic and novel measurement techniques. *Nat Rev Cardiol*. (2022) 19:643–54. doi: 10.1038/s41569-022-00690-0

27. Li Y, Li F, Li Y, Cui X, Li J, Zhi H, et al. Effect of cuff positioning on the accuracy of blood pressure measurement with automated electronic blood pressure monitors. *J Clin Hypertens (Greenwich)*. (2020) 22:1163–72. doi: 10.1111/jch.13902

frontiers | Frontiers in Medicine

TYPE Hypothesis and Theory
PUBLISHED 16 August 2024
DOI 10.3389/fmed.2024.1380632

EDITED BY
Komal Marwaha,
Texas Tech University Health Sciences Center,
United States

REVIEWED BY
Eleuterio Toro,
University of Trento, Italy
Emanuele Micaglio,
IRCCS San Donato Polyclinic, Italy

*CORRESPONDENCE
William Thomas Phillips
✉ phillips@uthscsa.edu

RECEIVED 01 February 2024
ACCEPTED 07 August 2024
PUBLISHED 16 August 2024

CITATION
Phillips WT and Schwartz JG (2024) Nasal turbinate lymphatic obstruction: a proposed new paradigm in the etiology of essential hypertension.
Front. Med. 11:1380632.
doi: 10.3389/fmed.2024.1380632

Nasal turbinate lymphatic obstruction: a proposed new paradigm in the etiology of essential hypertension

William Thomas Phillips[1]* and Joyce Gensberg Schwartz[2]

[1]Department of Radiology, UT-Health San Antonio, San Antonio, TX, United States, [2]Department of Pathology, Methodist Hospital, San Antonio, TX, United States

Hypertension affects an estimated 1.3 billion people worldwide and is considered the number one contributor to mortality via stroke, heart failure, renal failure, and dementia. Although the physiologic mechanisms leading to the development of essential hypertension are poorly understood, the regulation of cerebral perfusion has been proposed as a primary cause. This article proposes a novel etiology for essential hypertension. Our hypothesis developed from a review of nuclear medicine scans, where the authors observed a significantly abnormal increase in nasal turbinate vasodilation in hypertensive patients using quantitative region of interest analysis. The authors propose that nasal turbinate vasodilation and resultant blood pooling obstruct the flow of cerebrospinal fluid passing through nasal turbinate lymphatics, thereby increasing intracranial pressure. The authors discuss the glymphatic/lymphatic clearance system which is impaired with age, and at which time hypertension also develops. The increased intracranial pressure leads to compensatory hypertension via Cushing's mechanism, i.e., the selfish brain hypothesis. The nasal turbinate vasodilation, due to increased *parasympathetic* activity, occurs simultaneously along with the well-established increased *sympathetic* activity of the cardiovascular system. The increased parasympathetic activity is likely due to an autonomic imbalance secondary to the increase in worldwide consumption of processed food. This hypothesis explains the rapid worldwide rise in essential hypertension in the last 50years and offers a novel mechanism and a new paradigm for the etiology of essential hypertension. This new paradigm offers compelling evidence for the modulation of parasympathetic nervous system activity as a novel treatment strategy, specifically targeting nasal turbinate regulation, to treat diseases such as hypertension, idiopathic intracranial hypertension, and degenerative brain diseases. The proposed mechanism of essential hypertension presented in this paper is a working hypothesis and confirmatory studies will be needed.

KEYWORDS

hypertension, intracranial pressure, Cushing's mechanism, glymphatics, sympathetic activity, parasympathetic activity, brain self-protection, brain blood flow resistance

Summary

Hypertension affects an estimated 1.3 billion people worldwide and is considered the number one contributor to mortality via stroke, heart failure, renal failure, and dementia. Although the physiologic mechanisms leading to the development of essential hypertension are poorly understood, the regulation of cerebral perfusion has been proposed as a primary cause.

Our hypothesis regarding the etiology of hypertension developed from a retrospective review of 200 nuclear medicine scans, where the authors observed a significant increase in nasal turbinate vasodilation in hypertensive patients. The authors propose that the nasal turbinate vasodilation and subsequent increased blood pooling obstruct the flow of cerebrospinal fluid passing through nasal turbinate lymphatics, thereby increasing intracranial pressure. The increased intracranial pressure leads to compensatory arterial hypertension via Cushing's mechanism. This hypothesis offers a novel mechanism and a new paradigm for the etiology of essential hypertension related to nasal turbinate obstruction of brain lymphatics and suggests possible new treatments for hypertension and degenerative brain diseases. Treating hypertension by methods that focus on nasal turbinate obstruction and/or increasing cerebrospinal fluid lymphatic flow through the nasal turbinates may offer a therapeutic benefit not only to hypertensive patients but to patients with neurodegenerative pathologies as well.

1 Introduction

Essential hypertension, also known as primary hypertension, affects an estimated 1.3 billion people worldwide and is considered the number one contributor to mortality via stroke, heart failure, renal failure, and dementia. It is the largest single contributor to global mortality (1). Each year approximately 10 million people worldwide die of hypertension-related disease. The prevalence of essential hypertension is increasing. Between 1990 and 2019, the number of people aged 30–79 years with hypertension doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019 (2, 3). The number of individuals with essential hypertension has steadily increased over the past few decades, likely associated with the large increase in overweight and obese individuals in the world (4, 5). In the United States, the lifetime risk of hypertension surpasses 80% (6). Currently, half of all adults in the United States have hypertension, and the disease is responsible for the highest percentage of all doctor visits (6).

Today nearly 70 percent of what individuals eat in the United States is ultra-processed food. These foodstuffs include packaged chips, energy drinks, and ready-to-heat-and-eat meals. They are thought to be an important driver of the obesity epidemic, in part because they seem to make us eat more (7). This obesity epidemic occurring in the United States has also been noted in other developed and developing countries throughout the world.

Changes in dietary patterns in China, with increased consumption of refined grains and highly processed, high-sugar, and high-fat foods, continue to increase while physical activity levels in all major domains have decreased (5). In China, the number of processed foods available was four times higher in 2013 than in 1999 for a 22.4% annual growth over the 15 years. Over half of the packaged foods sold in China's markets are processed foods. Overweight, obesity, hypertension, and metabolic syndrome in the Chinese population have become serious public health problems. In 2015, China had the highest number of overweight and obese children globally (5). The increased rate of obesity and hypertension in China likely explains the fact that stroke is now the number one cause of death in that country (8).

Essential hypertension or primary hypertension is not equally distributed in populations worldwide. In the United States, essential hypertension accelerates more rapidly in non-Hispanic Black individuals (NHB) than in non-Hispanic White individuals (NHW) and is often more severe with higher mortality (9). In 2020, age-adjusted hypertension-related NHB adult death rates were approximately twice that of NHW adults (325.3 thousand for NHB men compared with 175.7 thousand for NHW men and 216.1 for NHB women compared with 127.9 for NHW women) (9).

In current medical practice, lifestyle changes are often mentioned as a first line of therapy for patients with hypertension. Alterations or modifications in diet, such as the Dietary Approaches to Stop Hypertension (DASH) (10) are encouraged, as are increased exercise, and restriction of sodium intake. Lowering salt intake moderately reduces blood pressure. An updated systematic review of studies where sodium intake was reduced from 2,200 mg/day to 500 mg/day for 1 week found that the median within-individual change in mean arterial blood pressure between high and low sodium diets was 4 mmHg (11). A newer, more invasive therapeutic technique to control high blood pressure involves renal nerve ablation which reduces sympathetic nervous system activity in the kidney (12).

Today, the most commonly prescribed antihypertensive drugs according to the latest guidelines are combination drug therapies that block the renin-angiotensin system and increase sodium excretion (6). With the rise of renin-angiotensin-targeted drugs, therapies that specifically target only the sympathetic nervous system have significantly decreased in use, even though one of the most verified findings in essential hypertension is that increased sympathetic nervous system activity is associated with the onset of hypertension (12–16). The etiology of this increased sympathetic activity, however, remains controversial as discussed in a recent review of autonomic dysfunction in essential hypertension (13).

Although many different theories about the cause of essential hypertension have been proposed, including excessive salt intake, renal mechanisms, and stress, for most adults there is no clearly identifiable cause with many investigators ascribing the mechanisms of hypertension to multiple factors including interactions between diet and lifestyle, an individual's gut microbiome (17), neuroimmune modulation (18), and genetic (17) and epigenetic factors (19).

It is well known that hypertension is found in families and that there is a hereditary predisposition to developing hypertension with over 100 single nucleotide polymorphisms associated with the disease (17). *Secondary hypertension*, as differentiated from primary or essential hypertension, has a higher prevalence in children (50% of cases) and young adults less the 30 years of age. Hormonal and primary kidney disease are the main causes of secondary hypertension. Genetic predisposition interacting with environmental influences is a significant contributor to the development of hypertension with the clearest genetic linkages being evident in endocrine hypertension, a form of secondary hypertension (20). Endocrine hypertension has well-defined phenotypes that have allowed patient stratification into homogeneous cohorts. These cohorts can be linked to different genetic variants which have important implications concerning patient therapy (21). Primary aldosteronism is the most frequent form of endocrine hypertension accounting for 5–10% of all hypertensive patients. Several different genetic defects have been linked to primary aldosteronism including autosomal dominant forms and somatic mutations (20).

Although genetic predisposition plays a role in *essential primary hypertension*, the genetic linkages are more complex. In addition, there are significant environmental influences making identification of specific genetic linkages less clear. Although the genetic linkages are less clear, genetic heritability is estimated to account for 40% of blood pressure variance in essential hypertension while environmental influences such as dietary and lifestyle habits can explain the majority of the remaining genetic variance (21). A promising application in the field of hypertension is the use of genetic testing to personalize medical therapy by predicting which anti-hypertensive drugs are most likely to have the greatest effect or cause adverse reactions in an individual patient (22).

Most researchers continue to state that the primary cause of non-endocrine essential hypertension is not well understood (14, 23). This is likely related to the fact that essential hypertension is a multifactorial disease that is considered to be genetically complex with significant interactions with diet and epigenetic factors.

A lack of understanding of the mechanism of essential hypertension contributes to the fact that an estimated 10–30% of patients have resistant hypertension defined as blood pressure that remains above guideline-directed targets despite the use of three anti-hypertensives (including a diuretic) at optimal or maximally tolerated doses (24). Other studies report that the global control rate of blood pressure among people with hypertension was approximately 20% in 2019 (2). A possible explanation for this overall lack of blood pressure control is that the underlying basic pathophysiology leading to the development of essential hypertension is not being addressed. Hence, there is a need to develop new paradigms for understanding essential hypertension with the potential to develop new approaches to therapy.

The objective of this paper is to focus on areas not previously considered as the pathogenesis of hypertension. The authors hypothesize that there is an increase in *parasympathetic* activity in the nasal turbinates that relates to hypertension by causing obstruction of nasal lymphatic drainage, thereby increasing intracranial pressure. The increased intracranial pressure leads to compensatory hypertension via Cushing's mechanism, also known as the selfish brain. This increased parasympathetic activity of the nasal turbinates occurs simultaneously with the well-established increase in sympathetic nervous activity of the cardiovascular system in hypertension. The increased nasal turbinate vasodilation has been previously described in patients with essential hypertension and other metabolic syndrome features in a recent article by the authors (25). This increased parasympathetic activity results not only in nasal turbinate vasodilation, but also in increased gastrointestinal motility, as observed in hypertensive patients and other patients with metabolic syndrome (26–29).

2 Regulation of cerebral perfusion

A less frequently discussed proposed cause of essential hypertension is related to homeostatic processes for the regulation of cerebral perfusion (14, 30). Physiologic processes that impair blood flow to the brain have the potential to lead to increased sympathetic activity and elevated systemic blood pressure to maintain normal blood flow to the brain. The theory has been proposed as the "selfish brain hypothesis of essential hypertension" or "Cushing's mechanism" (14, 30). Decreased blood flow to the brain and subsequent development of hypertension via the Cushing mechanism has been previously reported to be associated with the narrowing of the vessels supplying the brain (31).

This paper proposes another potential mechanism for the decreased blood flow to the brain that leads to systemic hypertension. It focuses on clinical findings by the authors of increased nasal turbinate vasodilation and resultant nasal blood pooling that causes a restriction of lymphatic flow, or drainage, of cerebrospinal fluid (CSF) from the brain (25). The obstruction of drainage leads to increased intracranial pressure, resulting in increased systemic blood pressure via Cushing's mechanism (14, 30).

The objective of this paper is to review the literature regarding the above-described physiological mechanisms of hypertension—noting the potential influence of the *parasympathetic* nervous system on increased intracranial pressure—and to propose a novel etiology for this increasingly prevalent disease.

3 Increased intracranial pressure and Cushing's mechanism

3.1 Hypertension and increased intracranial pressure

Increased intracranial pressure is present in patients with essential hypertension (32). In 2023, da Costa et al. (32) studied 391 consecutive patients with long-term essential hypertension in an attempt to evaluate intracranial pressure waveforms using a non-invasive device, brain4care. Their study revealed 77.7% of the patients had abnormal measurements of intracranial pressure. The da Costa et al. (32) article was the first to evaluate intracranial pressure behavior in patients with essential hypertension. In addition to their findings, the authors commented that very little is known on the subject of intracranial pressure in patients with hypertension and that they were hoping to "shed some light on the dark side of human history."

This increased intracranial pressure in hypertensive patients is consistent with the authors' research showing increased nasal turbinate vasodilation in these same patients. We hypothesize that inappropriately increased nasal turbinate vasodilation with blood pooling in the nasal turbinates is obstructing the normal lymphatic drainage through the nasal turbinates, resulting in increased intracranial pressure.

The authors can find no instances in the medical literature in which invasive lumbar puncture CSF pressure measurements have been performed to study intracranial pressure in patients with essential hypertension. Performing this type of study would be fairly extensive since it is likely the elevations of CSF pressure in many patients would be mild, although significant, in relation to its potential association with essential hypertension.

3.2 Cushing's mechanism

The regulation of cerebral perfusion has been proposed as a cause of essential hypertension with cerebral perfusion pressure being preserved by an increase in systemic blood pressure secondary to increased sympathetic activity (14, 33–36). As early as 1901, Dr. Harvey Cushing proposed the idea of a "Cushing reflex" which he described as a physiological nervous system response to acute elevations of intracranial pressure (ICP) (37, 38). The response consisted of a triad of signs which included widened pulse pressure (increasing systolic, decreasing diastolic), bradycardia, and irregular respirations. He believed that the dramatic increase in blood pressure was a reflex to brainstem ischemia seen in patients with increasing ICP from causes such as intracranial hemorrhage, a mass effect from a tumor, cerebral edema, and other causes. In these studies, Cushing showed that a temporary reduction in cerebral blood flow secondary to increased ICP was associated with a compensatory increase in systemic blood pressure in animals (38). This increase in systemic blood pressure was part of a regulatory process to maintain normal cerebral blood flow.

The human brain is in a tight space, limited by the rigid skull, which makes for a unique situation as it relates to blood and lymphatic flow rates and the strict requirement of the brain to maintain adequate cerebral blood perfusion. Cerebral perfusion pressure is the pressure that pushes the blood through the cerebrovascular network. Cerebral perfusion pressure is a clinical surrogate for the adequacy of cerebral blood perfusion. Cerebral perfusion pressure (CPP) is equal to the mean arterial pressure (MAP) minus the intracranial pressure (ICP) in the following equation (39).

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP}$$

MAP can be estimated as the systolic blood pressure (SBP) plus two times the diastolic blood pressure (DBP) divided by 3.

$$\frac{\mathrm{MAP} = \mathrm{SBP} + 2\mathrm{X}\ \mathrm{DBP}}{3}$$

As intracranial pressure increases, the cerebral perfusion pressure (CPP) decreases unless there is a compensatory increase in mean arterial blood pressure (14, 33, 34). With increased ICP, MAP must also increase to maintain adequate blood flow in the brain or CPP. This relationship between ICP and CPP was originally shown by Cushing (37). The authors believe nasal turbinate vasodilatation and subsequent blood pooling obstruct the normal drainage of cerebrospinal fluid from the brain. This obstruction results in increased intracranial pressure (ICP), requiring a compensatory increase in mean arterial pressure (MAP) to maintain cerebral perfusion pressure (CPP). How and where the brain senses its blood flow and is then able to maintain a normal blood flow by increasing systemic blood pressure via the increased sympathetic activity of the heart and vasculature is still a matter of debate.

3.3 Cerebral blood flow resistance and hypertension

As early as 1948, Kety et al. (34) reported that patients with essential hypertension had increased cerebral vascular resistance. Their article states that "there is at least some evidence to favor the hypothesis that in essential hypertension there may be a primary cerebrovascular constriction accompanied by a secondary and compensatory hypertension which maintains a normal cerebral blood flow."

Other researchers (40, 41) confirmed the findings of Kety et al. (34) that cerebrovascular resistance is increased in hypertension and that increased cerebral vascular resistance is the best predictor of the future development of hypertension.

Increased cerebrovascular resistance and increased intracranial pressure have been linked to increased sympathetic activity. In 2018, Schmidt et al. (42) showed that small increases in intracranial pressure would induce a significant increase in sympathetic activity in mice and in humans. In their study in human patients, a 7 mmHg rise in intracranial pressure increased sympathetic muscle activity by 17% as measured by microneurography. This increased sympathetic activity was associated with an elevation in blood pressure.

4 Hypertension: a mechanism for self-protection of the brain

Various authors have proposed that hypertension may provide self-protection for the brain by maintaining normal cerebral blood flow as suggested in the selfish brain hypothesis (14, 43).

In 1990, Dickinson (33) wrote an article reappraising the importance of the Cushing reflex for blood pressure stabilization. In this article, he stated that a restriction of blood flow to the brain can produce sustained hypertension. Dickinson also stressed the fact that the Cushing response begins when intracranial pressure begins to rise and is still within the physiological range. He described the Cushing reflex as the most powerful neural blood pressure stabilizing system involving self-protection of the brain.

Paton et al. (30) revisited the idea of self-protection of the brain in 2009, stating specifically that brainstem hypoperfusion could cause the onset of sympathetic hyperactivity and hypertension. They called this the "Cushing's mechanism," which was later termed "the selfish brain hypothesis" in an article by Hart (14). Warnert et al. (43) wrote an article that asked the question "Is high blood pressure self-protection for the brain?." In support of the increase in brain blood flow resistance as a cause of essential hypertension, Hart suggested that congenital vertebral artery hypoplasia is a risk factor for essential hypertension (14). Further studies by her group found that vertebral artery hypoplasia plus an incomplete circle of Willis was associated with lower cerebral blood flow in young adults with hypertension ($p = 0.0172$) (44). This anatomical variant was predictive of hypertension in young adults.

Although this work provides support for the selfish brain hypothesis for subjects with vertebral artery hypoplasia, it would not appear to explain the common and worldwide occurrence of essential hypertension and its near doubling in the number of affected individuals over the last 20 years (2). Instead, the rapidly increasing incidence of hypertension is more consistent with environmental changes likely related to decreased physical activity and diet.

5 The autonomic nervous system

5.1 The parasympathetic nervous system vs. the sympathetic nervous system

The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems. The sympathetic nervous system controls "flight-or-fight" responses. It prepares the body for strenuous physical activity by increasing the heart rate, elevating blood pressure, heightening awareness, and elevating the respiratory rate. The parasympathetic nervous system carries signals to relax those systems and bring about a state of calm in the body. Parasympathetic responses include an increase of digestive enzymes and more rapid gastric emptying (45), dilation of nasal turbinate blood vessels (46), and decreased heart rate (47).

5.2 The paradox of increased sympathetic activity and concurrent increased parasympathetic activity

Perhaps the most verified and agreed upon finding in essential hypertension is increased *sympathetic* nerve activity (14, 36, 48–50). Sympathetic nerve activity, measured by direct microneurography, was found to be increased in hypertension, providing evidence of the involvement of increased sympathetic activity in the development of essential hypertension. Wallin et al. (51) were the first to measure sympathetic nerve activity of the peritoneal nerve and showed that sympathetic nerve activity was increased in hypertensive patients as compared to normotensive patients. Subsequently, the increased sympathetic activity of the cardiovascular system has been confirmed by many investigators (14, 36, 48, 52, 53).

Increased sympathetic activity clearly affects the *cardiovascular system*. How increased sympathetic activity affects *other organ systems* is less well understood, although it has generally been assumed that other organ systems in patients with hypertension experience increased sympathetic activity. As support for the increased sympathetic activity in many organ systems, one article cites a decrease in salivary flow associated with hypertension (54) and suggests that there is a *down-regulation* of *parasympathetic* activity in all organ systems. However, our group reported nuclear imaging-based findings in hypertensive patients that are consistent with *increased parasympathetic activity* in several non-cardiovascular systems (25, 26). Increased *vasodilation* of the nasal turbinates and parotid glands in hypertensive patients, recently reported by our group (25), is consistent with *increased parasympathetic* activity affecting the vasculature of the nasal turbinates, as *increased sympathetic* activity is well known to be associated with nasal turbinate and parotid vascular *constriction*. Abnormally *rapid gastric emptying* in hypertensive patients, as previously reported by our group, is consistent with *increased parasympathetic* activity (26), as increased *sympathetic activity* would have the opposite effect, and *inhibit* gastrointestinal motility. In our study, following ingestion of a liquid carbohydrate meal, hypertensive patients had an average of 41% more rapid gastric emptying compared to non-hypertensive patients ($p = 0.02$), and the rate of gastric emptying correlated significantly with the postprandial glucose level at 30 min (Spearman rank correlation coefficient rs = 0.64, $p = 0.0428$). Our group has also reported that abnormally rapid gastric emptying occurs in spontaneously hypertensive rats (SHR) (55). This rapid gastric emptying observed in humans and in rat models with hypertension is consistent with increased parasympathetic activity of the gastrointestinal system.

As far as the authors know, this paradox of increased sympathetic activity in one region (cardiovascular) while there is simultaneously increased parasympathetic activity in another region has not been previously described (25). This paradox is important for the pathology we will be discussing related to the potential lymphatic obstruction from the brain.

6 New glucose set points

The upregulation, or increase in parasympathetic activity, affecting both the gastrointestinal system and nasal turbinate vasodilation that we have observed in our clinical patients, may be related to glucose homeostasis. The authors hypothesize that the increased parasympathetic activity observed in hypertensive patients is due to a resetting of the body's glucose level. The elevated blood glucose level, or elevated glucose set point, causes a triggering mechanism for an increase in parasympathetically controlled gastric emptying as a means to sustain the elevated glucose levels. Prior studies have shown that an increased gastric emptying rate is an important mechanism for maintaining blood glucose levels (56–58). The increased rate of gastric emptying occurs due to signaling from the hypothalamus via the vagus nerve (59, 60). With a higher glucose set point level, food empties more rapidly from the stomach for absorption into the intestine to elevate and maintain blood glucose levels.

Although the mechanism by which glucose set points become elevated is not clearly understood, the authors hypothesize they become gradually elevated due to the continual increased intake of processed foods. The modern diet, consisting of ultra-processed products, sucrose, and refined grains combined with reduced consumption of fiber, fruits, and vegetables, results in elevated postprandial glucose levels and an upward resetting of the glucose set point. This elevated glucose set point hypothesis is consistent with the significant increase in obesity which has nearly tripled in prevalence since 1960, and the nearly doubling of the number of patients with hypertension over the last 20 years (2).

Our group was the first to report that a gastrointestinal hormone, cholecystokinin (CCK-8), which delays the rate of gastric emptying in patients, had the potential to treat diabetes by lowering postprandial glucose levels (61). We reported that many patients with type 2 diabetes have abnormally accelerated gastric emptying and that infusion of CCK-8 significantly reduced the rate of gastric emptying, which lowered postprandial glucose levels (61). The clinically approved intestinal hormone, glucagon-like peptide 1 (GLP-1), has been widely successful in the treatment of diabetes and obesity. GLP-1 also delays gastric emptying and decreases postprandial glucose levels. Based on the results of our previous studies, GLP-1 would therefore lead to a lowering of the glucose set point. This hypothesis is consistent with the recent findings that GLP-1 agents have been shown to decrease the incidence of cardiovascular disease and stroke in patients with obesity and without diabetes (62). Importantly, GLP-1 drugs have also been shown to result in a modest (5–7 mmHg) lowering of blood pressure that is greater than would be expected from weight loss alone (63–65).

7 Nasal turbinate vasodilation and blood pooling

If increased intracranial pressure is indeed a frequent etiology for hypertension, how is it possible, much less probable, that millions of individuals with hypertension have preexisting increased intracranial pressure? The authors believe that increased parasympathetic activity leads to vasodilation of the erectile tissue of the nasal turbinates. These nasal turbinates contain important lymphatic vessels that carry spinal fluid moving through the cribriform plate along the olfactory nerves. We hypothesize that this nasal turbinate vasodilation and blood pooling obstruct the lymphatic cerebrospinal fluid (CSF) drainage leading to increased intracranial pressure.

In a retrospective study of 200 patients referred for a routine bone scan, the authors observed that hypertensive patients have significant nasal blood pooling, i.e., increased nasal turbinate vasodilation, as compared to patients without hypertension (25). This increased nasal vasodilation in patients with hypertension is illustrated in Figure 1. The methodology used for obtaining the nuclear scan and the whole-body blood pool imaging is described in the following section.

8 Scintigraphic imaging

Scintigraphic imaging of the nasal blood activity in comparison with the cardiac blood activity was determined during the 7-min interval immediately following injection of a bone avid radiopharmaceutical, technetium-99m methylene diphosphonate (^{99m}Tc-MDP), when the radioactivity was in the blood, and before it had time to begin accumulating in the bone. The same scintigraphic imaging technique was used for all 200 patients in this retrospective analysis of whole-body blood pool scanning. Each scan was obtained beginning 2–3 min after injection of the bone avid radiopharmaceutical and took a total of 6–7 min to scan from head to feet. The early images of the bone avid radiopharmaceutical, within the first few minutes after injection, are considered to be markers of the patient's blood pool, as the radiopharmaceutical requires approximately 3 h for bone deposition and clearance of activity from the soft tissues. Images were obtained with a dual-headed gamma camera (GE Infinia Hawkeye 4, Boston, MA) using low-energy, high-resolution collimators with an energy window set at 140 keV and with a 20% window moving at a rate of 36 cm/min (25). With scintigraphic imaging, it is possible to determine the distribution and activity of blood in the nasal region as compared to the cardiac region.

9 Measurement of nose/heart ratios

Nose/heart ratios were determined by placing a square region of interest box over the area of the nose on the nuclear scan. The activity in the maximum pixel was determined in each box, and a ratio of the maximum pixel in the nose was divided by the maximum pixel in the heart. Using the maximum pixel activity is very similar in technique to analyzing the maximum standard uptake value (MaxSUV) as determined in PET imaging for monitoring cancer metabolism. The use of a box and maximum pixel activity decreases the subjectivity incurred with drawing an outline around the whole organ. In our retrospective study of 200 patients, those patients with hypertension had an average nose-to-heart max ratio of 0.93 versus 0.85 in non-hypertensive patients ($p = 0.0123$ using the Wilcoxon rank-sum test) (25). Figure 1 demonstrates a normal-weight non-hypertensive control subject (A) compared to a normal-weight hypertensive patient with increased nasal pooling (B).

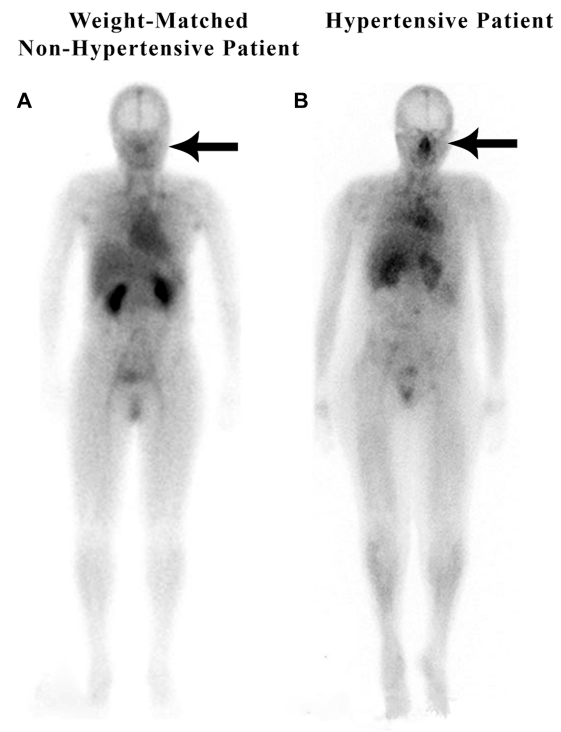


FIGURE 1
Weight-matched, non-hypertensive **(A)** vs. hypertensive patient **(B)**, both with normal BMIs.

10 Nasal blood pooling observations on nuclear medicine scan

10.1 Increased nasal blood pooling in a normal weight-matched, hypertensive patient vs. a non-hypertensive patient

10.1.1 Increased nasal blood pooling in weight-matched, obese, hypertensive vs. non-hypertensive patients

Figure 2 illustrates the nuclear medicine scan of weight-matched patients, both with an elevated body mass index (BMI). Patient A is a normal control and Patient B has hypertension and hyperlipidemia, but not diabetes or sleep apnea. There is increased nasal blood pooling in the overweight hypertensive patient compared to the overweight non-hypertensive control subject.

Both non-hypertensive patients in Figures 1, 2 have very minimal blood activity in their nasal turbinates while both patients with hypertension have very significant activity in the nasal turbinate region. These whole-body blood pool imaging studies have provided insights to the investigators which have led to their proposal of a working hypothesis described in this paper regarding a new causation paradigm for essential hypertension. Confirmation of these findings

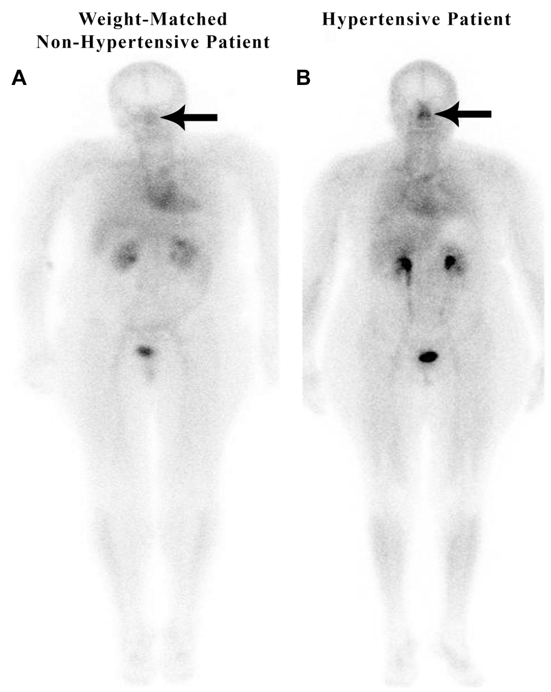


FIGURE 2
Weight-matched, non-hypertensive **(A)** vs. hypertensive patient **(B)**, both with elevated BMIs.

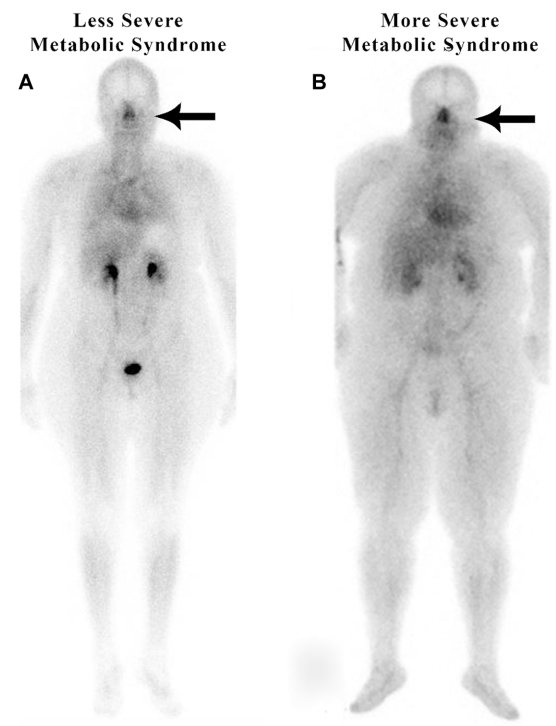


FIGURE 3
Nuclear medicine scans of patients with metabolic syndrome.

will be important. Potential methods to confirm these findings will be addressed in section 19.

10.2 Increased blood pooling in erectile tissue of the nasal turbinates

Studies of computed tomography (CT) (66) and magnetic resonance imaging (MRI) (67) have shown that the erectile tissue in the nose is located in (1) the whole of the inferior turbinate (anterior, middle, and posterior), (2) the middle turbinate (more prominent at the middle and posterior turbinate), and (3) the anterior portion of the nasal septum.

The rapidity in which these turbinates can dilate and contract has led two different investigators, Cole et al. (66) and Ng et al. (67), to conclude that nasal turbinate dilation is due to an increase in blood volume in the nasal turbinates and not due to an increase in edema or interstitial fluid. This purported increase in nasal blood pool volume is consistent with our findings of high nasal blood activity in the turbinate region observed on nuclear imaging.

The vasodilation associated with increased nasal turbinate *parasympathetic* activity is the opposite of the vasoconstrictive effect of *sympathetic* activity on the nasal turbinates and the well-known vasoconstrictive effect of sympathomimetic decongestants.

The parasympathetic innervation of the nasal turbinates is delivered through nerve fibers that reach the nasal turbinates through the posterior nasal nerve which crosses the sphenopalatine foramen and distributes to the mucosa following the branches of the sphenopalatine vessels (68). The result is vasodilation of erectile tissue in the nasal turbinates obstructing CSF lymphatic drainage.

10.3 Increased nasal blood pooling in patients with metabolic syndrome

The authors recently published an article that described subjects with metabolic syndrome, including hypertension, increased BMI, diabetes, and sleep apnea, exhibiting significantly increased nasal blood volume (2–3-fold greater), also referred to as blood pooling, as compared with subjects without metabolic syndrome as determined by whole-body nuclear imaging (25). This unique phenomenon of nasal pooling has been observed by the author using scintigraphic whole-body imaging in patients with metabolic syndrome, regardless of their body habitus (Figure 3).

Figure 3 shows increased nasal blood pooling in both patients with metabolic syndrome, including essential hypertension. Patient A, a 59-year-old female with a BMI of 32.5, has less severe metabolic syndrome. She has hypertension and hyperlipidemia with high triglycerides and is being treated with 1 anti-hypertensive and 1 anti-hyperlipidemic medication. Patient B has more severe metabolic syndrome with a BMI of 43.3. The patient is a 55-year-old female with hypertension, diabetes, sleep apnea, and hyperlipidemia, and is being treated with 3 anti-hypertensive, 1 anti-hyperlipidemic, and 1 anti-hyperglycemic medication.

As in patients with hypertension and without complete metabolic syndrome, we hypothesize that those patients with metabolic syndrome have an increase in blood volume in their nasal region significantly decreasing the normal lymphatic transport or drainage through the nasal turbinates resulting in increased intracranial pressure. The increased intracranial pressure causes the increased systemic blood pressure as part of Cushing's mechanism, i.e., the selfish brain's attempt to maintain cerebral blood flow. Patient A, the patient on the left in Figure 3, has a less severe form of metabolic syndrome (without diabetes). She, however, has three of the five criteria of metabolic syndrome, including triglycerides over 150, a high waist circumference, and high blood pressure. Nonetheless, she has a high nose/heart ratio.

11 Controversy over which comes first, essential hypertension or increased brain blood flow resistance

There continues to be controversy in this area with most researchers believing that it is the development of essential hypertension from a mechanism *not related to the brain* that occurs first and leads to increased resistance to brain blood flow. Far fewer researchers believe that the brain is involved in the initiation of hypertension as proposed by Jennings et al. (69, 70), or that an initial increase in resistance of brain blood flow leads to the development of essential hypertension as proposed by Dickinson and Thomason (71), Paton et al. (30), and Hart (14).

To understand the relationship between decreased nasal drainage, increased intracranial pressure, and hypertension, one must first be familiar with the normal nasal cycle.

12 CSF lymphatics and the normal nasal cycle

The nasal cycle is the alternating of airflow between nostrils that shifts between the left and right sides over time (72). The physical mechanism causing the nasal cycle is due to an asymmetry in blood flow leading to the engorgement of erectile tissue in the inferior turbinate and the anterior part of the nasal septum in one nostril more than the other. This normal asymmetrical enlargement of a nasal turbinate on one side blocks the passage of air. The autonomic nervous system mechanism is important in controlling the nasal cycle with sympathetic dominance associated with vasoconstriction and decongestion in one nostril while simultaneous parasympathetic vasodilation and congestion occur in the other nostril (72).

The purpose of the nasal cycle has been debated. Some studies suggest that the nasal cycle is a method of air conditioning and for removing entrapped contaminants (73). Eccles has proposed that the nasal cycle is a mechanism of respiratory defense against infection with respiratory viruses (74). Others have proposed that the nasal cycle could be a way to squeeze interstitial fluid out of the nasal turbinates during the constriction phase of the nasal cycle.

Although it has not been proposed that the nasal cycle serves as a pump to move lymphatic fluid from the CSF into the head and neck lymphatics, the authors believe that this could be one of the most important functions of the nasal cycle.

A malfunction of this normal cycle, with near-permanent vasodilation of the nasal erectile tissue, would result in a blockage of lymphatic outflow from the brain. In this regard, it is interesting that the nasal cycle was found to be diminished with age (75, 76). In one study, 50% of patients over the age of 70 showed no evidence of a nasal cycle (76). Following thorough research, the authors were unable to find any current studies examining the effect of hypertension and metabolic syndrome on the nasal cycle. In our nuclear imaging studies of the blood pool, we did not visualize any asymmetry in the distribution of blood in the region of the nasal turbinates. Patients with hypertension in our whole-body blood pool imaging study, who also had a CT scan of the head, demonstrated symmetrically dilated right and left nasal turbinates without evidence of a nasal cycle (unpublished observation).

It is important to understand how CSF lymphatics are cleared from the brain.

13 Clearance of CSF from the brain

There has been considerable controversy regarding the most important pathway of clearance of CSF from the brain. For many years, the most accepted theory was that CSF was absorbed by the arachnoid granulations directly into the venous system. This theory has been significantly challenged over the last 40 years as many investigators have shown the importance of lymphatic clearance of CSF, primarily through the cribriform plate into the nasal region. In addition, a recent study using magnetic resonance imaging (MRI) provided evidence that a portion of the CSF is cleared by the parenchymal venous system (77) with only minimal contribution of the arachnoid granulations in CSF clearance. Further studies are required to provide a better understanding of the contribution of CSF lymphatics, the parenchymal venous system, and arachnoid granulation to overall CSF clearance, however, there has been increasing evidence for the importance of nasal lymphatics in CSF clearance (78–84).

14 Evidence for significant clearance of CSF through nasal lymphatics

A major proponent of this idea was Johnston et al. (78, 82, 85) whose work contradicted the most accepted theory that the majority of CSF is cleared by the arachnoid granulations. As pointed out by Johnston and Papaiconomou (79), there has been very limited evidence to support the idea that the arachnoid granulations are the primary site of CSF clearance from the brain; however, there has been significant research supporting clearance of CSF through the cribriform plate into the nasal turbinate region. In one study, Johnston's group found that 30 min after injection of radiolabeled human serum albumin into the CSF, the tissue that contained the highest activity was the middle nasal turbinate which had approximately 6 times more activity than the blood (82). In another study, Johnston et al. (86) reported that approximately one-half of a protein tracer was transported from the CSF to the blood via extracranial lymphatic vessels. In another study by this group, when CSF transport was blocked through the cribriform plate, resting intracranial pressure doubled from 9.2 cmH_2O to 18.0 cm H_2O (87). A recent review of the importance of nasal lymphatics in CSF clearance has been published and is titled, "The brain-nose interface: a potential cerebrospinal fluid clearance site in humans" (80).

Since an original report by Schwalbe (88) in 1869, a large body of work in many different species has indicated a role for lymphatic vessels draining CSF in both cranial and spinal regions. However, only recently published anatomical and quantitative studies have shown that connections between the CSF and the extracranial lymphatic system represent a significant route for CSF drainage (83, 84, 89, 90).

A PET imaging study by de Leon et al. (89) showed tracer activity in the nasal turbinates suggesting CSF movement through the cribriform plate and into the nasal turbinate lymphatics. In a recent study by Zhou et al. (83), 92 patients clearly showed activity in the inferior nasal turbinates following intrathecal infusion of an MRI contrast agent. Another recent 2023 study in rats using high-resolution imaging was strongly supportive of lymphatic movement along olfactory nerves. The study concluded that the olfactory nerve pathway into nasal turbinate lymphatics is the major route of CSF clearance from the brain (90).

In another animal model study, infusion of Ringer's lactate with blue dye into the cisterna magna to increase the intracranial pressure caused a 3-fold increase in cervical lymph node flow and an increase in blue-colored nasal discharge that appeared 48 min after the beginning of the infusion (91). The nasal discharge increased from negligible, before the cisternal infusion, to 11.4 mL/h following the infusion. These studies support the clearance of CSF in cervical lymphatics and nasal fluid.

Ma et al. (92) found that lymphatic vessels were the major outflow pathway of CSF for both large and small molecular tracers in mice. They also found a significant decline in CSF lymphatic outflow in aged compared to young mice suggesting that the lymphatic system may represent a target for age-associated neurological conditions. In another recent study by Yoon et al. (84), a nasopharyngeal lymphatic plexus was found to be a hub for CSF drainage to the deep cervical lymph nodes. This plexus was suggested as a possible target for the treatment of age-related neurological conditions which are known to be associated with decreased CSF transport to deep cervical lymph nodes.

Meningeal lymphatic vessels located along the dural sinuses have been shown to drain into the cervical lymph nodes (93), and are coupled with, and receive drainage from, the recently described glymphatic system within the brain (94) that was first described by Iliff et al. (95) in 2012 and which will be discussed in the next section.

15 The glymphatic/lymphatic system

15.1 The glymphatic system

The glymphatic system consists of specialized low-resistance spaces known as Virchow–Robin paravascular spaces that permit CSF inflow deep into the neural parenchyma. A detailed review of this glymphatic system has recently been published by the author (WP) and colleagues (96). The glymphatic system runs in the same direction as blood flow which is propelled by pulsations from the arterial vascular wall. This system can deliver protective molecules, such as melatonin, deep into the brain along the periarterial spaces. It also transports protein waste products, such as amyloid and tau degradation products, from the brain via the paravenous spaces (97). The fluid in the paravenous space eventually moves into the subarachnoid space on the surface of the brain where the fluid and any waste material are absorbed into meningeal lymphatic vessels as reported by Aspelund et al. (98) and Louveau et al. (99) in 2015. This network of meningeal lymphatics serves the same purpose as classical lymphatic drainage and is essential for maintaining neurophysiological homeostasis. The fluid in the meningeal lymphatics is then transported out of the brain and moves into cervical lymphatics. Although the precise anatomic pathway taken by this CSF/lymphatic fluid out of the cranial cavity remains to be clearly defined, the greatest evidence supports its movement along the cranial and spinal nerves, with the olfactory nerve thought to be the most predominant (78, 82). Drainage from these meningeal and cervical lymphatics is relatively fast as tracers injected into the brain or CSF accumulate in the cervical lymph nodes within minutes after injection into the brain or CSF (100). The discovery of this glymphatic/lymphatic clearance system has clearly shown that CSF and interstitial fluid are directionally transported within the CNS.

Interestingly, it has been shown that this glymphatic/lymphatic clearance system is impaired with age at which time hypertension also develops (101). Because the glymphatic/lymphatic system plays a key role in the clearance of amyloid-beta and tau proteins, this system has been suggested to represent a new target to combat neurodegenerative disease (102). There is a recent MRI tracer imaging study supporting this theory which showed that impaired peri-olfactory cerebrospinal fluid clearance through the inferior turbinate was associated with aging, cognitive decline, and decreased sleep quality (83).

15.2 Importance of lymphatic nasal drainage for brain fluid homeostasis

Abnormally increased parasympathetic-induced nasal turbinate vasodilation and resultant blood pooling that interferes with the normal nasal cycle would be expected to obstruct lymphatic flow from the brain. In a rat model, nasal turbinate lymphatics were shown to be important for the clearance of CNS fluid when intracranial pressure was artificially increased (85). An increase in intracranial pressure by infusion of plasma into the lateral ventricle resulted in elevated pressure in the deep cervical lymph nodes which receive lymphatic drainage from the nasal turbinates. Very recently reported research in a rat model has also shown that CSF moves through the cribriform plate along the olfactory nerve to join lymphatics in the nasal mucosa which then are carried to a nasopharyngeal lymphatic plexus. CSF then drains to cervical lymph nodes through medial deep cervical lymphatics. These medial deep cervical lymphatics carry a significantly greater volume of CSF as compared to the lateral deep cervical lymphatics (84).

16 Increased intracranial pressure consistent with arterial wall thickening

In previous studies, narrowing and thickening of the cervical arteries feeding the brain were cited as evidence of the selfish brain hypothesis of hypertension. The theory is that the vessel narrowing, caused either congenitally or due to atheroma formation, causes an elevation of blood pressure as the brain ensures that it has sufficient blood flow through these narrowed arteries acting via Cushing's mechanism (14, 30, 31). Vertebral artery thickening has been shown to occur in spontaneously hypertensive rats (SHR) before the development of systemic hypertension (30) supporting the selfish brain theory.

We believe another possible explanation for the thickened vessel walls is that increased intracranial pressure causes a back pressure in the arteries feeding the brain which leads to thickening of the cervical arteries. We hypothesize that lymphatic obstruction of CSF outflow through the nasal turbinates causes increased intracranial pressure and it is this increased intracranial pressure that leads to vessel wall thickening and increased systemic blood pressure as part of the selfish brain hypothesis, i.e., Cushing's mechanism.

Evidence compatible with increased vascular thickening due to lymphatic obstruction has recently been published in the case of lymphedema of the arms in which brachial arteries feeding the lymphedema arm have significantly greater thickening of the arterial walls compared to the non-lymphedematous arm (103). The significantly increased wall thickness was principally due to increased intima-media thickening resulting in 0.38 mm in the lymphedema arm versus 0.31 mm in the normal arm ($p = 0.0008$).

17 Glymphatic/lymphatic obstruction of CSF leads to increased intracranial pressure and hypertension

The obstruction of CSF lymphatic clearance from the brain at the level of the nasal turbinate due to abnormal turbinate vasodilation and blood pooling would result in decreased clearance of lymphatic fluid from the brain. The decrease in lymphatic fluid drainage would also decrease glymphatic function and the clearance of CSF waste proteins from the brain. Evidence of fluid obstruction in the glymphatic space is provided by MRI imaging in which the perivascular space has been noted to be enlarged in patients with hypertension (104). Evidence of the coupling of the glymphatic system to meningeal lymphatics was first described by Louveau et al. (99) using fluorescent markers. Evidence has also been found for the coupling of these two systems in humans using MRI imaging (94). Prior studies by Johnston (78) and recent PET and MRI imaging studies have shown that significant CSF clearance passes through the nasal turbinates (83, 89). The decreased clearance of fluid from brain lymphatics and the glymphatic system due to nasal turbinate lymphatic obstruction would lead to increased intracranial pressure and a subsequent increase in the systemic blood pressure required to maintain normal blood flow to the brain via Cushing's mechanism (Figure 4).

Mildly increased intracranial pressure due to lymphatic obstruction would also explain the significant correlation our group observed with increased nasal blood pooling and headaches (unpublished observations to be submitted soon). Similarly, the vasodilation of nasal erectile tissue caused by sildenafil, a drug commonly used to treat erectile dysfunction, causes symptomatic nasal obstruction and headaches (105). Sildenafil is one of the most common causes of drug-induced headaches (106).

18 Sleep disturbances

18.1 The importance of sleep for adequate CSF lymphatic drainage

Numerous associations have been documented between sleep disturbances and the failure to clear waste products from the brain (107). Sleep disturbances are associated with increased CSF metabolite concentrations (e.g., amyloid-beta, orexin, tau proteins), and increased CSF volumes or pressure (108). Recent studies have suggested that glymphatic dysfunction is a common underlying etiology of sleep disorders and headache pain (109). The glymphatic system is particularly active during sleep whereby potentially toxic neural waste substances that accumulate during wakefulness are cleared via the

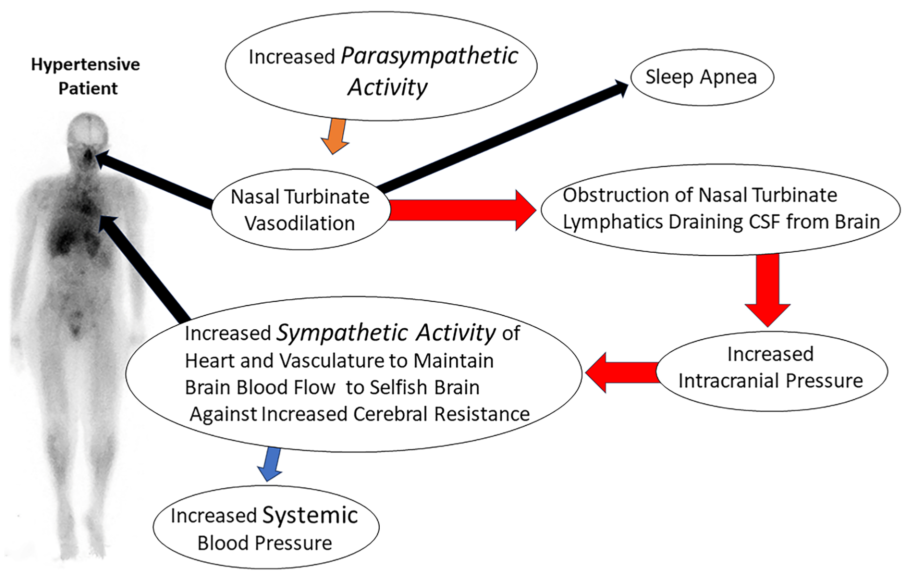


FIGURE 4
Illustration of consequences of nasal turbinate obstruction leading to increased intracranial pressure and resultant essential hypertension.

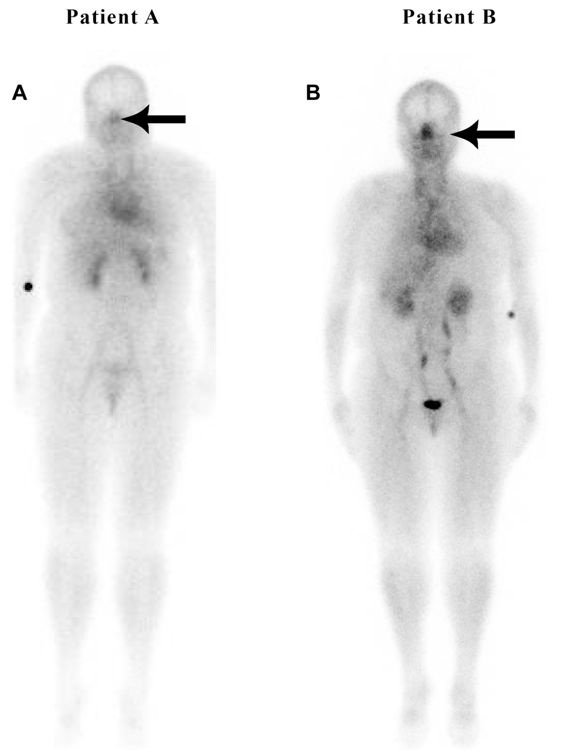


FIGURE 5
Patients without **(A)** and with **(B)** sleep apnea.

glymphatic system (108, 110). It is thought that the brain cell volume decreases during sleep, expanding the size of the paravascular space, and facilitating the influx of CSF into the peritubular space for material exchange and metabolic waste removal (111). Animal experiments using intravital 2-photon microscopy in mice showed that glymphatic clearance is decreased by 90% during wakefulness, while protein clearance in the intima of the brain doubles during sleep (97, 112).

Short sleep duration has also been associated with essential hypertension in many epidemiologic studies (113), although there has been no clear pathophysiologic connection found between the two. It is the authors' hypothesis that decreased CSF clearance due to short sleep and obstructed nasal lymphatics is related to the development of hypertension.

18.2 Sleep apnea and hypertension

Obstructive sleep apnea (OSA), another common disorder, is strongly associated with the development of hypertension (114–116) and recent evidence suggests that it may also be linked with cognitive decline and dementia. Sleep apnea may be the common pathway linking hypertension and the development of dementia (117).

The authors have found significantly increased nasal turbinate blood pooling in patients with OSA. In our review of 200 patients, sleep apnea patients had an average nose-to-heart max ratio of 0.99 versus 0.86 in patients without sleep apnea ($p = 0.0002$) using the Wilcoxon rank-sum test (25). An example image of a patient with sleep apnea is shown in Figure 5. Subjects with OSA have also been shown to have increased sympathetic activity and sleep apnea has been linked to resistant hypertension (118). Although not yet investigated, based on our findings of increased nasal turbinate vasodilation in patients with OSA, it is likely that these sleep apnea patients also have increased nasal parasympathetic activity. In this regard, a recently published Phase 2 study has shown that a drug that reduces the activity of the parasympathetic system significantly improves OSA (119). This drug, taken before bedtime, significantly reduced the apnea-hypopnea index in OSA patients.

A prior study in sleep apnea patients used CT-acquired nasal turbinate measurements to find a significantly positive correlation between the size of the inferior nasal turbinates in obese patients with sleep apnea (120). This prior study did not include patients without sleep apnea so there were no direct comparisons of nasal turbinate size between sleep apnea patients and normal subjects; however, future studies using this CT methodology could be performed to investigate the correlation of nasal turbinate dimensions with hypertension and sleep apnea in the future.

Figure 5 is a nuclear scan of a 49-year-old female (Patient A) without sleep apnea, hypertension, hyperlipidemia, or diabetes, with a nose/heart max ratio of 0.67. Patient B is a 52-year-old female with sleep apnea but without hypertension or diabetes at the time of the study, with a nose/heart max ratio of 1.16. A CT scan at the time of the nuclear study showed dilated nasal turbinates. A 3-year follow-up scan of Patient B showed an increased nose/heart max ratio of 1.28. The patient had developed Stage 1 hypertension and pre-diabetes.

Increased intracranial pressure has been associated with sleep apnea (121, 122), a known risk factor for hypertension (123). Treatment of sleep apnea has been suggested as a method to prevent hypertension (124). The increased intracranial pressure associated with sleep apnea and obesity has even been reported to cause thinning of the skull with an increased likelihood of producing a CSF leak (122). Our findings of nasal vasodilation in patients with hypertension and sleep apnea suggest the possibility that obstruction of the CSF lymphatic clearance from the brain through nasal turbinate lymphatics is responsible for the increased intracranial pressure and the resultant sleep apnea and hypertension. Obstruction of nasal turbinate lymphatic flow as described in this article could also be related to the development of idiopathic intracranial hypertension (IIH). The most common occurrence of IIH is in obese women of childbearing age who are also more likely to have essential hypertension and metabolic syndrome. Sleep apnea has also been associated with both essential hypertension and IIH (116, 125).

19 Future confirmatory studies

The proposed mechanism of essential hypertension presented in this paper is a working hypothesis and confirmatory studies will be needed. There is a potential for prospective studies to complement the retrospective studies in patients with hypertension as discussed in this paper. Studies could be performed using nuclear blood pool imaging to assess nasal turbinates as in our retrospective studies. An advantage of the nuclear imaging technique is that dynamic imaging, viewing changes in the nasal blood pool over 8 h, could be performed by simply placing a standard gamma camera over the upper body of the patient. This would allow studies to be performed during sleep or during other medical or physical interventions that affect the nasal turbinates. The gamma camera could be placed several inches away from the patient, resulting in minimal disturbance. To perform prolonged studies, a blood pool imaging agent such as labeled red blood cells could be utilized to permit dynamic imaging for 8–12 h. Technetium-99 m labeled red blood cells are standard blood pool nuclear imaging agents most commonly used for locating the site of gastrointestinal bleeding, diagnosing hepatic hemangiomas, and determining left ventricular ejection fractions (126). Other imaging studies to assess nasal turbinate vasodilation in hypertension could be performed with MRI or CT, such as those previously reported by Rodrigues et al. (120), stating that obese patients had inferior turbinate hypertrophy.

Other studies could be performed with MRI contrast agents, investigating the lymphatic drainage of cerebrospinal fluid through nasal turbinates and its association with hypertension. Studies could also be performed to further assess the absence or presence of the nasal cycle in patients with hypertension as compared to controls.

20 Potential novel therapeutic approaches targeting the nasal turbinates

Based on the evidence in this paper, the nasal turbinates are potential targets for the treatment of hypertension. One possible treatment would be to block the increased parasympathetic activity of the nasal turbinates by blocking the sphenopalatine ganglion that carries parasympathetic activity to the nasal turbinates. The sphenopalatine ganglion is the largest extracranial parasympathetic ganglion of the head (127). Sphenopalatine ganglion blockage has been used to treat migraine headaches (127) and a recent study has shown that blocking the sphenopalatine ganglion can modestly lower blood pressure (128). However, completely blocking parasympathetic activity to the nose may not be the best approach for treating hypertension as it would adversely affect the nasal cycle which is dependent on alternating sympathetic and parasympathetic activity to the nasal turbinates (72) which may be important for the clearance of CSF fluid from the brain.

Future therapeutic approaches could be aimed at increasing the volume of CSF flowing through the nasal lymphatics. These therapies' goal would be to restore the nasal cycle or to use other physical approaches to increase the movement of CSF through and out of the brain. Decreasing intracranial pressure through therapy targeted at the nasal turbinates could lead to significantly improved blood pressure control and a more effective treatment for sleep apnea.

21 Conclusion

Finding more effective treatments for essential hypertension offers the possibility of better blood pressure control resulting in a decrease in the incidence of myocardial infarction, stroke, renal failure, dementia, and overall mortality currently associated with hypertension. Considering that accumulation of amyloid and tau proteins in the brain are involved in the pathogenesis of neurodegenerative diseases, the potential of treating hypertension by methods that focus on nasal turbinate obstruction and/or increasing cerebrospinal fluid lymphatic flow may also offer a therapeutic benefit for neurodegenerative pathologies in addition to its potential to treat hypertension.

Data availability statement

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

Author contributions

WP: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. JS: Conceptualization, Methodology, 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.

Acknowledgments

The authors thank Jonathan Sumner for his contribution to the medical illustration (Figure 4).

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

References

1. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. (2020) 396:1223–49. doi: 10.1016/S0140-6736(20)30752-2

2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. (2021) 398:957–80. doi: 10.1016/S0140-6736(21)01330-1

3. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. (2020) 16:223–37. doi: 10.1038/s41581-019-0244-2

4. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight, obesity, and extreme obesity among adults: United States, 1960–1962 through 2011–2012. Hyattsville, Maryland, USA: National Center for Health Statistics (2014).

5. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. *Lancet Diabetes Endocrinol*. (2021) 9:373–92. doi: 10.1016/S2213-8587(21)00045-0

6. Bludorn J, Railey K. Hypertension guidelines and interventions. *Prim Care*. (2024) 51:41–52. doi: 10.1016/j.pop.2023.07.002

7. Ouyang H. Bariatric surgery at 16. *N Y Times Mag*. (2023):24–33.

8. Tu WJ, Zhao Z, Yin P, Cao L, Zeng J, Chen H, et al. Estimated burden of stroke in China in 2020. *JAMA Netw Open*. (2023) 6:e231455. doi: 10.1001/jamanetworkopen.2023.1455

9. Ferdinand KC, Charbonnet RM, Laurent J, Villavaso CD. Eliminating hypertension disparities in U.S. non-Hispanic black adults: current and emerging interventions. *Curr Opin Cardiol*. (2023) 38:304–10. doi: 10.1097/HCO.0000000000001040

10. Onwuzo C, Olukorode JO, Omokore OA, Odunaike OS, Omiko R, Osaghae OW, et al. DASH diet: a review of its scientifically proven hypertension reduction and health benefits. *Cureus*. (2023) 15:e44692. doi: 10.7759/cureus.44692

11. Gupta DK, Lewis CE, Varady KA, Su YR, Madhur MS, Lackland DT, et al. Effect of dietary sodium on blood pressure: a crossover trial. *JAMA*. (2023) 330:2258–66. doi: 10.1001/jama.2023.23651

12. Grassi G. Sympathetic modulation as a goal of antihypertensive treatment: from drugs to devices. *J Hypertens*. (2023) 41:1688–95. doi: 10.1097/HJH.0000000000003538

13. Carthy ER. Autonomic dysfunction in essential hypertension: a systematic review. *Ann Med Surg*. (2014) 3:2–7. doi: 10.1016/j.amsu.2013.11.002

14. Hart EC. Human hypertension, sympathetic activity and the selfish brain. *Exp Physiol*. (2016) 101:1451–62. doi: 10.1113/EP085775

15. Grassi G, Dell'Oro R, Quarti-Trevano F, Vanoli J, Oparil S. Sympathetic neural mechanisms in hypertension: recent insights. *Curr Hypertens Rep*. (2023) 25:263–70. doi: 10.1007/s11906-023-01254-4

16. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res*. (2014) 114:1804–14. doi: 10.1161/CIRCRESAHA.114.302524

17. Louca P, Menni C, Padmanabhan S. Genomic determinants of hypertension with a focus on metabolomics and the gut microbiome. *Am J Hypertens*. (2020) 33:473–81. doi: 10.1093/ajh/hpaa022

18. Calvillo L, Gironacci MM, Crotti L, Meroni PL, Parati G. Neuroimmune crosstalk in the pathophysiology of hypertension. *Nat Rev Cardiol*. (2019) 16:476–90. doi: 10.1038/s41569-019-0178-1

19. Arif M, Sadayappan S, Becker RC, Martin LJ, Urbina EM. Epigenetic modification: a regulatory mechanism in essential hypertension. *Hypertens Res*. (2019) 42:1099–113. doi: 10.1038/s41440-019-0248-0

20. Fernandes-Rosa FL, Boulkroun S, Fedlaoui B, Hureaux M, Travers-Allard S, Drossart T, et al. New advances in endocrine hypertension: from genes to biomarkers. *Kidney Int*. (2023) 103:485–500. doi: 10.1016/j.kint.2022.12.021

21. Rossi GP, Ceolotto G, Caroccia B, Lenzini L. Genetic screening in arterial hypertension. *Nat Rev Endocrinol*. (2017) 13:289–98. doi: 10.1038/nrendo.2016.196

22. Micaglio E, Locati ET, Monasky MM, Romani F, Heilbron F, Pappone C. Role of pharmacogenetics in adverse drug reactions: an update towards personalized medicine. *Front Pharmacol*. (2021) 12:651720. doi: 10.3389/fphar.2021.651720

23. Luft FC. Did you know? Why is essential hypertension essential-or is it? *Acta Physiol*. (2020) 229:e13469. doi: 10.1111/apha.13469

24. Chan RJ, Helmeczi W, Hiremath SS. Revisiting resistant hypertension: a comprehensive review. *Intern Med J*. (2023) 53:1739–51. doi: 10.1111/imj.16189

25. Phillips WT, Issa NJ, Elhalwagi SB, Draeger HT, Schwartz JG, Gelfond JA. Nasal and parotid blood pool activity is significantly correlated with metabolic syndrome components and sleep apnea. *Metab Syndr Relat Disord*. (2022) 20:395–404. doi: 10.1089/met.2022.0015

26. Phillips WT, Salman UA, McMahan CA, Schwartz JG. Accelerated gastric emptying in hypertensive subjects. *J Nucl Med*. (1997) 38:207–11.

27. Phillips WT, Schwartz JG, McMahan CA. Rapid gastric emptying in patients with early non-insulin-dependent diabetes mellitus. *N Engl J Med*. (1991) 324:130–1. doi: 10.1056/nejm199101103240217

28. Schwartz JG, Green GM, Guan D, McMahan CA, Phillips WT. Rapid gastric emptying of a solid pancake meal in type II diabetic patients. *Diabetes Care*. (1996) 19:468–71. doi: 10.2337/diacare.19.5.468

29. Schwartz JG, McMahan CA, Green GM, Phillips WT. Gastric emptying in Mexican Americans compared to non-Hispanic whites. *Dig Dis Sci*. (1995) 40:624–30. doi: 10.1007/bf02064382

30. Paton JF, Dickinson CJ, Mitchell G. Harvey Cushing and the regulation of blood pressure in giraffe, rat and man: introducing 'Cushing's mechanism'. *Exp Physiol*. (2009) 94:11–7. doi: 10.1113/expphysiol.2008.043455

31. Dickinson CJ, Thomson AD. A post mortem study of the main cerebral arteries with special reference to their possible role in blood pressure regulation. *Clin Sci*. (1960) 19:513–38.

32. da Costa MM, Sousa ALL, Correia MC, Inuzuka S, Costa TO, Vitorino PVO, et al. Intracranial pressure waveform in patients with essential hypertension. *Front Cardiovasc Med*. (2023) 10:1288080. doi: 10.3389/fcvm.2023.1288080

33. Dickinson CJ. Reappraisal of the Cushing reflex: the most powerful neural blood pressure stabilizing system. *Clin Sci*. (1990) 79:543–50. doi: 10.1042/cs0790543

34. Kety SS, Hafkenschiel JH, Jeffers WA, Leopold IH, Shenkin HA. The blood flow, vascular resistance, and oxygen consumption of the brain in essential hypertension. *J Clin Invest*. (1948) 27:511–4. doi: 10.1172/jci101998

35. Paton JF, Raizada MK. Neurogenic hypertension. *Exp Physiol*. (2010) 95:569–71. doi: 10.1113/expphysiol.2009.047282

36. Fisher JP, Paton JF. The sympathetic nervous system and blood pressure in humans: implications for hypertension. *J Hum Hypertens*. (2012) 26:463–75. doi: 10.1038/jhh.2011.66

37. Cushing H. Concerning a definitive regulatory mechanism of the vasomotor centre which controls blood pressure during cerebral compression. *Bull Johns Hopk Hosp*. (1901):290–2.

38. Cushing H. Some experimental and clinical observations concerning states of increased intracranial tension. *Am J Med Sci*. (1902) 124:375–400. doi: 10.1097/00000441-190209000-00001

39. Smith ER, Madsen JR. Cerebral pathophysiology and critical care neurology: basic hemodynamic principles, cerebral perfusion, and intracranial pressure. *Semin Pediatr Neurol*. (2004) 11:89–104. doi: 10.1016/j.spen.2004.04.001

40. Nobili F, Rodriguez G, Marenco S, De Carli F, Gambaro M, Castello C, et al. Regional cerebral blood flow in chronic hypertension. A correlative study. *Stroke*. (1993) 24:1148–53. doi: 10.1161/01.str.24.8.1148

41. Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res*. (1990) 66:8–17. doi: 10.1161/01.res.66.1.8

42. Schmidt EA, Despas F, Pavy-Le Traon A, Czosnyka Z, Pickard JD, Rahmouni K, et al. Intracranial pressure is a determinant of sympathetic activity. *Front Physiol*. (2018) 9:11. doi: 10.3389/fphys.2018.00011

43. Warnert EA, Rodrigues JC, Burchell AE, Neumann S, Ratcliffe LE, Manghat NE, et al. Is high blood pressure self-protection for the brain? *Circ Res*. (2016) 119:e140–51. doi: 10.1161/CIRCRESAHA.116.309493

44. Manghat NE, Robinson E, Mitrousi K, Rodrigues JCL, Hinton T, Paton JFR, et al. Cerebrovascular variants and the role of the selfish brain in young-onset hypertension. *Hypertension*. (2022) 79:1265–74. doi: 10.1161/HYPERTENSIONAHA.121.18612

45. Bhatia V, Tandon RK. Stress and the gastrointestinal tract. *J Gastroenterol Hepatol*. (2005) 20:332–9. doi: 10.1111/j.1440-1746.2004.03508.x

46. Baraniuk JN, Merck SJ. New concepts of neural regulation in human nasal mucosa. *Acta Clin Croat*. (2009) 48:65–73. doi: 10.1111/j.1749-6632.2009.04481.x

47. Armstrong R, Wheen P, Brandon L, Maree A, Kenny RA. Heart rate: control mechanisms, pathophysiology and assessment of the neurocardiac system in health and disease. *QJM*. (2022) 115:806–12. doi: 10.1093/qjmed/hcab016

48. Esler M. The sympathetic nervous system in hypertension: back to the future? *Curr Hypertens Rep*. (2015) 17:11. doi: 10.1007/s11906-014-0519-8

49. Grassi G, Biffi A, Dell'Oro R, Quarti Trevano F, Seravalle G, Corrao G, et al. Sympathetic neural abnormalities in type 1 and type 2 diabetes: a systematic review and meta-analysis. *J Hypertens*. (2020) 38:1436–42. doi: 10.1097/HJH.0000000000002431

50. Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Relationship between central sympathetic activity and stages of human hypertension. *Am J Hypertens*. (2004) 17:217–22. doi: 10.1016/j.amjhyper.2003.10.010

51. Wallin BG, Delius W, Hagbarth KE. Comparison of sympathetic nerve activity in normotensive and hypertensive subjects. *Circ Res*. (1973) 33:9–21. doi: 10.1161/01.res.33.1.9

52. Seravalle G, Grassi G. Sympathetic nervous system and hypertension: new evidences. *Auton Neurosci*. (2022) 238:102954. doi: 10.1016/j.autneu.2022.102954

53. Morise T, Horita M, Kitagawa I, Shinzato R, Hoshiba Y, Masuya H, et al. The potent role of increased sympathetic tone in pathogenesis of essential hypertension with neurovascular compression. *J Hum Hypertens*. (2000) 14:807–11. doi: 10.1038/sj.jhh.1001114

54. Böhm R, van Baak M, van Hooff M, Moy J, Rahn KH. Salivary flow in borderline hypertension. *Klin Wochenschr*. (1985) 63:154–6.

55. Salman UA, Schwartz JG, McMahan CA, Michalek JE, Phillips WT. Rapid gastric emptying in spontaneously hypertensive rats. *J Hypertens*. (2023) 42:572–8. doi: 10.1097/HJH.0000000000003640

56. De Fano M, Porcellati F, Fanelli CG, Corio S, Mazzieri A, Lucidi P, et al. The role of gastric emptying in glucose homeostasis and defense against hypoglycemia: innocent bystander or partner in crime? *Diabetes Res Clin Pract*. (2023) 203:110828. doi: 10.1016/j.diabres.2023.110828

57. Murthy TA, Grivell J, Hatzinikolas S, Chapple LS, Chapman MJ, Stevens JE, et al. Acceleration of gastric emptying by insulin-induced hypoglycemia is dependent on the degree of hypoglycemia. *J Clin Endocrinol Metab*. (2021) 106:364–71. doi: 10.1210/clinem/dgaa854

58. Schvarcz E, Palmér M, Aman J, Berne C. Hypoglycemia increases the gastric emptying rate in healthy subjects. *Diabetes Care*. (1995) 18:674–6. doi: 10.2337/diacare.18.5.674

59. Lopez-Gambero AJ, Martinez F, Salazar K, Cifuentes M, Nualart F. Brain glucose-sensing mechanism and energy homeostasis. *Mol Neurobiol*. (2019) 56:769–96. doi: 10.1007/s12035-018-1099-4

60. Shi M, Jones AR, Niedringhaus MS, Pearson RJ, Biehl AM, Ferreira M Jr, et al. Glucose acts in the CNS to regulate gastric motility during hypoglycemia. *Am J Physiol Regul Integr Comp Physiol*. (2003) 285:R1192–202. doi: 10.1152/ajpregu.00179.2003

61. Phillips WT, Schwartz JG, McMahan CA. Reduced postprandial blood glucose levels in recently diagnosed non-insulin-dependent diabetics secondary to pharmacologically induced delayed gastric emptying. *Dig Dis Sci*. (1993) 38:51–8. doi: 10.1007/BF01296773

62. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. (2023) 389:2221–32. doi: 10.1056/NEJMoa2307563

63. Lovshin JA, Zinman B. Blood pressure-lowering effects of incretin-based diabetes therapies. *Can J Diabetes*. (2014) 38:364–71. doi: 10.1016/j.jcjd.2014.05.001

64. Wang B, Zhong J, Lin H, Zhao Z, Yan Z, He H, et al. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obes Metab*. (2013) 15:737–49. doi: 10.1111/dom.12085

65. Li QX, Gao H, Guo YX, Wang BY, Hua RX, Gao L, et al. GLP-1 and underlying beneficial actions in Alzheimer's disease, hypertension, and NASH. *Front Endocrinol*. (2021) 12:721198. doi: 10.3389/fendo.2021.721198

66. Cole P, Haight JS, Cooper PW, Kassel EE. A computed tomographic study of nasal mucosa: effects of vasoactive substances. *J Otolaryngol*. (1983) 12:58–60.

67. Ng BA, Ramsey RG, Corey JP. The distribution of nasal erectile mucosa as visualized by magnetic resonance imaging. *Ear Nose Throat J*. (1999) 78:159–6. doi: 10.1177/014556139907800309

68. Cassano M, Russo L, Del Giudice AM, Gelardi M. Cytologic alterations in nasal mucosa after sphenopalatine artery ligation in patients with vasomotor rhinitis. *Am J Rhinol Allergy*. (2012) 26:49–54. doi: 10.2500/ajra.2012.26.3683

69. Jennings JR, Muldoon MF, Sved AF. Is the brain an early or late component of essential hypertension? *Am J Hypertens*. (2020) 33:482–90. doi: 10.1093/ajh/hpaa038

70. Jennings JR, Zanstra Y. Is the brain the essential in hypertension? *NeuroImage*. (2009) 47:914–21. doi: 10.1016/j.neuroimage.2009.04.072

71. Dickinson CJ, Thomason AD. Vertebral and internal carotid arteries in relation to hypertension and cerebrovascular disease. *Lancet*. (1959) 2:46–8. doi: 10.1016/s0140-6736(59)90494-5

72. Kahana-Zweig R, Geva-Sagiv M, Weissbrod A, Secundo L, Soroker N, Sobel N. Measuring and characterizing the human nasal cycle. *PLoS One*. (2016) 11:e0162918. doi: 10.1371/journal.pone.0162918

73. Soane RJ, Carney AS, Jones NS, Frier M, Perkins AC, Davis SS, et al. The effect of the nasal cycle on mucociliary clearance. *Clin Otolaryngol Allied Sci*. (2001) 26:9–15. doi: 10.1046/j.1365-2273.2001.00423.x

74. Eccles R. The role of nasal congestion as a defence against respiratory viruses. *Clin Otolaryngol*. (2021) 46:4–8. doi: 10.1111/coa.13658

75. Mirza N, Kroger H, Doty RL. Influence of age on the 'nasal cycle'. *Laryngoscope*. (1997) 107:62–6. doi: 10.1097/00005537-199701000-00014

76. Williams MR, Eccles R. The nasal cycle and age. *Acta Otolaryngol*. (2015) 135:831–4. doi: 10.3109/00016489.2015.1028592

77. Hu J, Shen Y, Fahmy LM, Krishnamurthy S, Li J, Zhang L, et al. The role of the parenchymal vascular system in cerebrospinal fluid tracer clearance. *Eur Radiol*. (2023) 33:656–65. doi: 10.1007/s00330-022-09022-9

78. Johnston M. The importance of lymphatics in cerebrospinal fluid transport. *Lymphat Res Biol*. (2003) 1:41–5. doi: 10.1089/15396850360495682

79. Johnston M, Papaiconomou C. Cerebrospinal fluid transport: a lymphatic perspective. *News Physiol Sci*. (2002) 17:227–30. doi: 10.1152/nips.01400.2002

80. Mehta NH, Sherbansky J, Kamer AR, Carare RO, Butler T, Rusinek H, et al. The brain-nose interface: a potential cerebrospinal fluid clearance site in humans. *Front Physiol*. (2021) 12:769948. doi: 10.3389/fphys.2021.769948

81. Chae J, Choi M, Choi J, Yoo SJ. The nasal lymphatic route of CSF outflow: implications for neurodegenerative disease diagnosis and monitoring. *Anim Cells Syst*. (2024) 28:45–54. doi: 10.1080/19768354.2024.2307559

82. Nagra G, Koh L, Zakharov A, Armstrong D, Johnston M. Quantification of cerebrospinal fluid transport across the cribriform plate into lymphatics in rats. *Am J Physiol Regul Integr Comp Physiol*. (2006) 291:R1383–9. doi: 10.1152/ajpregu.00235.2006

83. Zhou Y, Ran W, Luo Z, Wang J, Fang M, Wei K, et al. Impaired peri-olfactory cerebrospinal fluid clearance is associated with ageing, cognitive decline and dyssomnia. *EBioMedicine*. (2022) 86:104381. doi: 10.1016/j.ebiom.2022.104381

84. Yoon JH, Jin H, Kim HJ, Hong SP, Yang MJ, Ahn JH, et al. Nasopharyngeal lymphatic plexus is a hub for cerebrospinal fluid drainage. *Nature*. (2024) 625:768–77. doi: 10.1038/s41586-023-06899-4

85. Koh L, Nagra G, Johnston M. Properties of the lymphatic cerebrospinal fluid transport system in the rat: impact of elevated intracranial pressure. *J Vasc Res*. (2007) 44:423–32. doi: 10.1159/000104255

86. Boulton M, Flessner M, Armstrong D, Hay J, Johnston M. Lymphatic drainage of the CNS: effects of lymphatic diversion/ligation on CSF protein transport to plasma. *Am J Phys*. (1997) 272:R1613–9. doi: 10.1152/ajpregu.1997.272.5.R1613

87. Mollanji R, Bozanovic-Sosic R, Zakharov A, Makarian L, Johnston MG. Blocking cerebrospinal fluid absorption through the cribriform plate increases resting intracranial pressure. *Am J Physiol Regul Integr Comp Physiol*. (2002) 282:R1593–9. doi: 10.1152/ajpregu.00695.2001

88. Schwalbe G. Die Arachnoidalraum ein Lymphraum und sein Zusammenhang mit den Perichorioidalraum. [the arachnoidal space as a lymphatic space with connection to the perichoroidal compartment]. *Zbl Med Wiss*. (1869) 7:4650467.

89. de Leon MJ, Li Y, Okamura N, Tsui WH, Saint-Louis LA, Glodzik L, et al. Cerebrospinal fluid clearance in Alzheimer disease measured with dynamic PET. *J Nucl Med*. (2017) 58:1471–6. doi: 10.2967/jnumed.116.187211

90. Spera I, Cousin N, Ries M, Kedracka A, Castillo A, Aleandri S, et al. Open pathways for cerebrospinal fluid outflow at the cribriform plate along the olfactory nerves. *EBioMedicine*. (2023) 91:104558. doi: 10.1016/j.ebiom.2023.104558

91. Leeds SE, Kong AK, Wise BL. Alternative pathways for drainage of cerebrospinal fluid in the canine brain. *Lymphology*. (1989) 22:144–6.

92. Ma Q, Ineichen BV, Detmar M, Proulx ST. Outflow of cerebrospinal fluid is predominantly through lymphatic vessels and is reduced in aged mice. *Nat Commun*. (2017) 8:1434. doi: 10.1038/s41467-017-01484-6

93. Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature*. (2018) 560:185–91. doi: 10.1038/s41586-018-0368-8

94. Ringstad G, Eide PK. Glymphatic-lymphatic coupling: assessment of the evidence from magnetic resonance imaging of humans. *Cell Mol Life Sci*. (2024) 81:131. doi: 10.1007/s00018-024-05141-2

95. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med*. (2012) 4:147ra111. doi: 10.1126/scitranslmed.3003748

96. Reiter RJ, Sharma R, Rosales-Corral S, de Mange J, Phillips WT, Tan DX, et al. Melatonin in ventricular and subarachnoid cerebrospinal fluid: its function in the neural glymphatic network and biological significance for neurocognitive health. *Biochem Biophys Res Commun*. (2022) 605:70–81. doi: 10.1016/j.bbrc.2022.03.025

97. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science*. (2020) 370:50–6. doi: 10.1126/science.abb8739

98. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. (2015) 212:991–9. doi: 10.1084/jem.20142290

99. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. (2015) 523:337–41. doi: 10.1038/nature14432

100. Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, et al. Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. *J Neurosci*. (2015) 35:518–26. doi: 10.1523/JNEUROSCI.3742-14.2015

101. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, et al. Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol*. (2014) 76:845–61. doi: 10.1002/ana.24271

102. Mestre H, Mori Y, Nedergaard M. The brain's glymphatic system: current controversies. *Trends Neurosci*. (2020) 43:458–66. doi: 10.1016/j.tins.2020.04.003

103. Klusch V, Boyle EC, Rustum S, Franz M, Park-Simon TW, Haverich A, et al. Chronic unilateral arm lymphedema correlates with increased intima-media thickness in the brachial artery. *Vasa*. (2022) 51:19–23. doi: 10.1024/0301-1526/a000982

104. Shulyatnikova T, Hayden MR. Why are perivascular spaces important? *Medicina*. (2023) 59:917. doi: 10.3390/medicina59050917

105. Kiroglu AF, Bayrakli H, Yuca K, Cankaya H, Kiris M. Nasal obstruction as a common side-effect of sildenafil citrate. *Tohoku J Exp Med*. (2006) 208:251–4. doi: 10.1620/tjem.208.251

106. Young WB. Drug-induced headache. *Neurol Clin*. (2004) 22:173–84. doi: 10.1016/s0733-8619(03)00090-2

107. Komaroff AL. Does sleep flush wastes from the brain? *JAMA*. (2021) 325:2153–5. doi: 10.1001/jama.2021.5631

108. Chong PLH, Garic D, Shen MD, Lundgaard I, Schwichtenberg AJ. Sleep, cerebrospinal fluid, and the glymphatic system: a systematic review. *Sleep Med Rev*. (2022) 61:101572. doi: 10.1016/j.smrv.2021.101572

109. Yi T, Gao P, Zhu T, Yin H, Jin S. Glymphatic system dysfunction: a novel mediator of sleep disorders and headaches. *Front Neurol*. (2022) 13:885020. doi: 10.3389/fneur.2022.885020

110. Rasmussen MK, Mestre H, Nedergaard M. Fluid transport in the brain. *Physiol Rev*. (2022) 102:1025–151. doi: 10.1152/physrev.00031.2020

111. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. *Science*. (2013) 342:373–7. doi: 10.1126/science.1241224

112. Miyakoshi LM, Staeger FF, Li Q, Pan C, Xie L, Kang H, et al. The state of brain activity modulates cerebrospinal fluid transport. *Prog Neurobiol*. (2023) 229:102512:102512. doi: 10.1016/j.pneurobio.2023.102512

113. Killick R, Stranks L, Hoyos CM. Sleep deficiency and cardiometabolic disease. *Sleep Med Clin*. (2023) 18:331–47. doi: 10.1016/j.jsmc.2023.05.012

114. Battaglia E, Banfi P, Compalati E, Nicolini A, Diaz DETT, Gonzales M, et al. The pathogenesis of OSA-related hypertension: what are the determining factors? *Minerva Med*. (2023) 115:68–82. doi: 10.23736/s0026-4806.23.08466-5

115. Brown J, Yazdi F, Jodari-Karimi M, Owen JG, Reisin E. Obstructive sleep apnea and hypertension: updates to a critical relationship. *Curr Hypertens Rep*. (2022) 24:173–84. doi: 10.1007/s11906-022-01181-w

116. Chaudhary SC, Gupta P, Sawlani KK, Gupta KK, Singh A, Usman K, et al. Obstructive sleep apnea in hypertension. *Cureus*. (2023) 15:e38229. doi: 10.7759/cureus.38229

117. Mansukhani MP, Kolla BP, Somers VK. Hypertension and cognitive decline: implications of obstructive sleep apnea. *Front Cardiovasc Med*. (2019) 6:96. doi: 10.3389/fcvm.2019.00096

118. Ahmed AM, Nur SM, Xiaochen Y. Association between obstructive sleep apnea and resistant hypertension: systematic review and meta-analysis. *Front Med*. (2023) 10:1200952. doi: 10.3389/fmed.2023.1200952

119. Schweitzer PA, Taranto-Montemurro L, Ojile JM, Thein SG, Drake CL, Rosenberg R, et al. The combination of aroxybutynin and atomoxetine in the treatment of obstructive sleep apnea (MARIPOSA): a randomized controlled trial. *Am J Respir Crit Care Med*. (2023) 208:1316–27. doi: 10.1164/rccm.202306-1036OC

120. Rodrigues MM, Carvalho PHA, Gabrielli MFR, Lopes RN, Garcia Junior OA, Pereira Filho VA, et al. How obesity affects nasal function in obstructive sleep apnea: anatomic and volumetric parameters. *Braz J Otorhinolaryngol*. (2022) 88:296–302. doi: 10.1016/j.bjorl.2020.06.002

121. Jennum P, Borgesen SE. Intracranial pressure and obstructive sleep apnea. *Chest*. (1989) 95:279–83. doi: 10.1378/chest.95.2.279

122. Rabbani CC, Saltagi MZ, Nelson RF. The role of obesity, sleep apnea, and elevated intracranial pressure in spontaneous cerebrospinal fluid leaks. *Curr Opin Otolaryngol Head Neck Surg*. (2019) 27:349–55. doi: 10.1097/MOO.0000000000000562

123. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. *Curr Cardiol Rep*. (2020) 22:6. doi: 10.1007/s11886-020-1257-y

124. Zhao L, Gao Y, Xu W, Li K, Liu L, Fan L. Factors influencing new-onset hypertension in elderly patients with obstructive sleep apnea: a multicenter cohort study. *Clin Transl Sci*. (2023) 16:2507–18. doi: 10.1111/cts.13631

125. Kabanovski A, Chan A, Shapiro C, Margolin E. Obstructive sleep apnea in men with idiopathic intracranial hypertension: a prospective case-control study. *J Neuroophthalmol*. (2022) 43:531–4. doi: 10.1097/WNO.0000000000001734

126. Espinosa-Muñoz E, Ruíz-García FJ, Puentes-Zarzuela C. Simultaneous detection of lower gastrointestinal bleeding and hepatic hemangioma in a scintigraphy study with red blood cells labeled with ^{99m}Tc-stannous pyrophosphate. *Rev Gastroenterol Mex*. (2020) 85:90–1. doi: 10.1016/j.rgmx.2019.06.005

127. Khan S, Schoenen J, Ashina M. Sphenopalatine ganglion neuromodulation in migraine: what is the rationale? *Cephalalgia*. (2014) 34:382–91. doi: 10.1177/0333102413512032

128. Triantafyllidi H, Arvaniti C, Palaiodimos L, Vlachos S, Schoinas A, Batistaki C, et al. Infiltration of the sphenopalatine ganglion decreases blood pressure in newly diagnosed and never treated patients with essential hypertension. *Int J Cardiol*. (2016) 223:345–51. doi: 10.1016/j.ijcard.2016.08.230

frontiers | Frontiers in Cardiovascular Medicine

TYPE Opinion
PUBLISHED 29 August 2024
DOI 10.3389/fcvm.2024.1458089

OPEN ACCESS

EDITED BY
Ali A. Khraibi,
Khalifa University, United Arab Emirates

REVIEWED BY
Mariana Alves,
Universidade de Lisboa, Portugal

*CORRESPONDENCE
Milos Mijalkovic
m.mijalkovic84@gmail.com

RECEIVED 01 July 2024
ACCEPTED 12 August 2024
PUBLISHED 29 August 2024

CITATION
Mijalkovic M and Sacic D (2024) A new potential cause of secondary hypertension. Front. Cardiovasc. Med. 11:1458089.
doi: 10.3389/fcvm.2024.1458089

A new potential cause of secondary hypertension

Milos Mijalkovic[1]* and Dalila Sacic[2]

[1]Polyclinic Kardio Medika, Nish, Serbia, [2]Clinic for Cardiology, University Clinical Center of Serbia, Belgrade, Serbia

KEYWORDS

arterial hypertension, secondary hypertension, blood pressure, hyperinsulinemia, pancreatic insulinoma

Introduction

Arterial hypertension is a well-known and leading cause of cardiovascular diseases and premature death worldwide. In the last few decades, the prevalence of arterial hypertension has been constantly increasing in low and middle-income countries of the world, as opposed to high-income countries (1).

According to the European guidlines for the managment of hypertension from 2018 to 2023, arterial hypertension is defined when blood pressure is ≥140/90 mmHg, while the American College of Cardiology/American Heart Association (ACC/AHA) for the treatment of hypertension from 2017 redefine arterial hypertension as blood pressure values ≥130/80 mmHg. This change and redefinition of the ACC/AHA hypertension guidelines is based on the findings of numerous large prospective observational studies, as well as the results of randomized clinical trials, including the SPRINT study, which showed that intensive lowering of systolic blood pressure <120 mmHg, reduced the risk of cardiovascular death and all-cause mortality, to a greater extent than lowering systolic blood pressure ≤140 mmHg. When the new definition was applied to the general population of the United States of America, the prevalence of hypertension increased from 32% to 45.4%, while in the general population of China the increase in the prevalence of hypertension was even greater from 23.2% to 46.4% (1–4).

The global increase in the prevalence of primary arterial hypertension in the world, which does not have a clear etiology, requires greater attention and care, and a more detailed search for the possible causes of secondary hypertension. Secondary hypertension is significantly less common than primary arterial hypertension, its true prevalence is not precisely known, but it is assumed to be about 5%–15% of all hypertensive cases, and often remains unrecognized. Secondary forms of hypertension require specific diagnostic procedures, which allow to discover their specific causes, and to choose an effective drug treatment or an appropriate interventional treatment that controls or treats elevated blood pressure (3). Secondary hypertension can lead to target organ damage, independent of the effect of blood pressure itself, which can be remedied with appropriate treatment. Discovering the potential cause of secondary hypertension can lead to successful intervention, with the potential to improve quality of life, and reduce cardiovascular morbidity and mortality (5). Screening all hypertensive patients for secondary hypertension is not feasible or cost-effective, but there are some general clinical characteristics of patients that suggest they are more likely to have secondary hypertension and in whom screening should be considered after confirmation of elevated blood pressure by ambulatory blood pressure monitoring (4). Severe or resistant hypertension, the appearance of hypertension in persons under 30 years of age, malignant or accelerated hypertension, an acute rise in blood pressure from previously stable readings, a sudden increase in blood pressure in the elderly, should certainly arouse the suspicion of the existence of secondary hypertension (5). As is well known, the more common causes of secondary hypertension include obstructive sleep apnea, renal parenchymal disease, renovascular hypertension (atherosclerotic renovascular disease, fibromuscular dysplasia), primary hyperaldosteronism. Less common causes of secondary hypertension include pheochromocytoma, paraganglioma, acromegaly, Cushing's syndrome, hyperthyroidism, hypothyroidism, hyperparathyroidism, coarctation of the aorta, effects of alcohol and some drugs, chemotherapy agents, rare genetic causes of secondary hypertension, etc (3–5).

Pancreatic insulinomas are rare, mostly benign, small neuroendocrine tumors with an estimated incidence of 1–4 cases per million population annualy. They can be can be classified symptomatically into secreting and non-secreting (silent) tumors. The average age of patients is around 47 years, and they are more common in women than in men (1,4:1). Over the past few decades, the incidence of neuroendocrine tumors has been increasing, compared to the overall incidence of carcinomas (6).

Pancreatic insulinomas are characterized by chronic sustained hyperinsulinemia leading to recurrent hypoglycemia. There is evidence suggesting that hyperinsulinemia and insulin resistance may be the initial events in the genesis of secondary hypertension. The hypothesized relationship between hyperinsulinemia and hypertension occurs more frequently in white people than in black. There are several possible mechanisms of secondary hypertension caused by pancreatic insulinoma. Firstly, severe hypoglycemia due to insulinoma can trigger the release of catecholamines, leading to paroxysmal hypertension via activation of the sympathoadrenal system. Secondly, insulin can increase sodium retention in the kidneys, primarily in the distal nephron, as well as induce changes in the vascular system, contributing to an increase in blood pressure (6).

Only a few small studies have been done that are older and were published in the 90 s, which investigated the relationship between insulinoma of the pancreas and hypertension (7–9). The most significant is the long-term cohort study at the Mayo Clinic published in 1993, in which a solid cause-and-effect relationship between pancreatic insulinoma and significant hypertension was not proven, but the possibility of its existence was also not completely excluded (10).

However, it should be emphasized that the number of data and case reports showing a relationship between pancreatic insulinoma and significant hypertension is increasing.

Kaul et al. reported a 10-year-old girl with hypoglycemia with high insulin levels, distal symmetric motor-sensory axonal neuropathy, and hypertension, with normal urinary catecholamines (11). Ko Harada et al. described a case of a 65-year-old woman with pancreatic insulinoma, hypoglycemia and paroxysmal hypertension and elevated plasma and urinary catecholamines (12). Mijalkovic M. et al. presented a case of a 61-year-old man with pancreatic insulinoma, sleep apnea, hypoglycemia, and significant hypertension (6).

In conclusion, further research is needed to establish a definitive causal relationship between pancreatic insulinoma and secondary hypertension.

Author contributions

MM: Formal Analysis, Investigation, Software, Validation, Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization. DS: Investigation, Software, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Resources, 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

References

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol.* (2020) 16(4):223–37. doi: 10.1038/s41581-019-0244-2

2. Vemu PL, Yang E, Ebinger J. 2023 ESH hypertension guideline update: bringing us closer together across the pond. *JACC* (2024) 83(5).

3. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension. *J Hypertens.* (2023) 41(12):1874–2071. doi: 10.1097/HJH.0000000000003480

4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J.* (2018) 39(33):3021–104. doi: 10.1093/eurheartj/ehy339

5. Sarathy H, Salman LA, Lee C, Cohen JB. Evaluation and management of secondary hypertension. *Med Clin North Am.* (2022) 106(2):269–83. doi: 10.1016/j.mcna.2021.11.004

6. Mijalkovic M, Sacic D, Pajovic S. A rare case of pancreatic insulinoma, sleep apnea, and hypertension. *Cardiol Res Cardio Vasc Med.* (2024) 9:243. doi: 10.29011/2575-7083.100243

7. Tsutsu N, Nunoi K, Kodama T, Nomiyama R, Iwase M, Fujishima M. Lack of association between blood pressure and insulin in patients with insulinoma. *J Hypertens*. (1990) 8:479–82. doi: 10.1097/00004872-199005000-00014

8. Sawicki PT, Heinemann L, Starke A, Berger M. Hyperinsulinaemia is not linked with blood pressure elevation in patients with insulinoma. *Diabetologia*. (1992) 35:649–52. doi: 10.1007/BF00400257

9. Fujita N, Baba T, Tomiyama T, Kodama T, Kako N. Hyperinsulinaemia and blood pressure in patients with insulinoma. *Br Med J*. (1992) 304:1157. doi: 10.1136/bmj.304.6835.1157

10. O'Brien T, Young WF, Palumbo PJ, O'Brien PC, Service FJ. Hypertension and dyslipidemia in patients with insulinoma. *Mayo Clin Proc*. (1993) 68(2):141–6. doi: 10.1016/S0025-6196(12)60161-X

11. Kaul B, Kaur P, Tripathi M, Khadgawat R, Ammini AC, Agarwala S, et al. An unusual cause of reversible axonal neuropathy and hypertension in a 10-year-old girl. *J Clin Neurosci*. (2012) 19(8):1196–7. doi: 10.1016/j.jocn.2011.10.018

12. Harada K, Hanayama Y, Hasegawa K, Iwamuro M, Hagiya H, Yoshida R, et al. Paroxysmal hypertension induced by an insulinoma. *Intern Med*. (2017) 56(4):413–7. doi: 10.2169/internalmedicine.56.7758

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
PUBLISHED 22 October 2024
DOI 10.3389/fcvm.2024.1346265

Check for updates

OPEN ACCESS

EDITED BY
Guido Iaccarino,
Federico II University Hospital, Italy

REVIEWED BY
David John Vigerust,
Vanderbilt University, United States
Jens Djurhuus,
Aarhus University, Denmark

*CORRESPONDENCE
Abdullah Nadeem
✉ iam.abduln@outlook.com

RECEIVED 29 November 2023
ACCEPTED 27 September 2024
PUBLISHED 22 October 2024

CITATION
Nadeem A, Rais T, Aamir M, Habte A, Siddiqui T, Karamat RI, Munsab R and Habib A (2024) Acetylsalicylic acid dosed at bedtime vs. dosed in the morning for circadian rhythm of blood pressure- a systematic review and meta-analysis.
Front. Cardiovasc. Med. 11:1346265.
doi: 10.3389/fcvm.2024.1346265

Acetylsalicylic acid dosed at bedtime vs. dosed in the morning for circadian rhythm of blood pressure- a systematic review and meta-analysis

Abdullah Nadeem[1*], Taruba Rais[1], Minahil Aamir[2], Alexander Habte[3], Tasmiyah Siddiqui[1], Riyan Imtiaz Karamat[4], Rabbia Munsab[1] and Ashna Habib[1]

[1]Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan, [2]Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan, [3]Department of Surgery, Assab Military Hospital, Assab, Eritrea, [4]Department of Medicine, Rahbar Medical and Dental College, Lahore, Pakistan

Introduction: Cardiovascular disease (CVD) is a leading global cause of morbidity and mortality, with high systolic blood pressure (SBP) identified as a major risk factor. Aspirin (Acetylsalicylic acid—ASA) has been considered for CVD prevention, prompting questions about its optimal use in primary and secondary prevention and the ideal dosing time to maximize its impact on circadian blood pressure rhythms. Previous research suggests a potential benefit of bedtime aspirin dosing in reducing blood pressure, attributed to its effects on the renin-angiotensin-aldosterone system and nitric oxide production. This systematic review and meta-analysis aim to further explore the circadian effects of aspirin on blood pressure, focusing on the timing of administration.

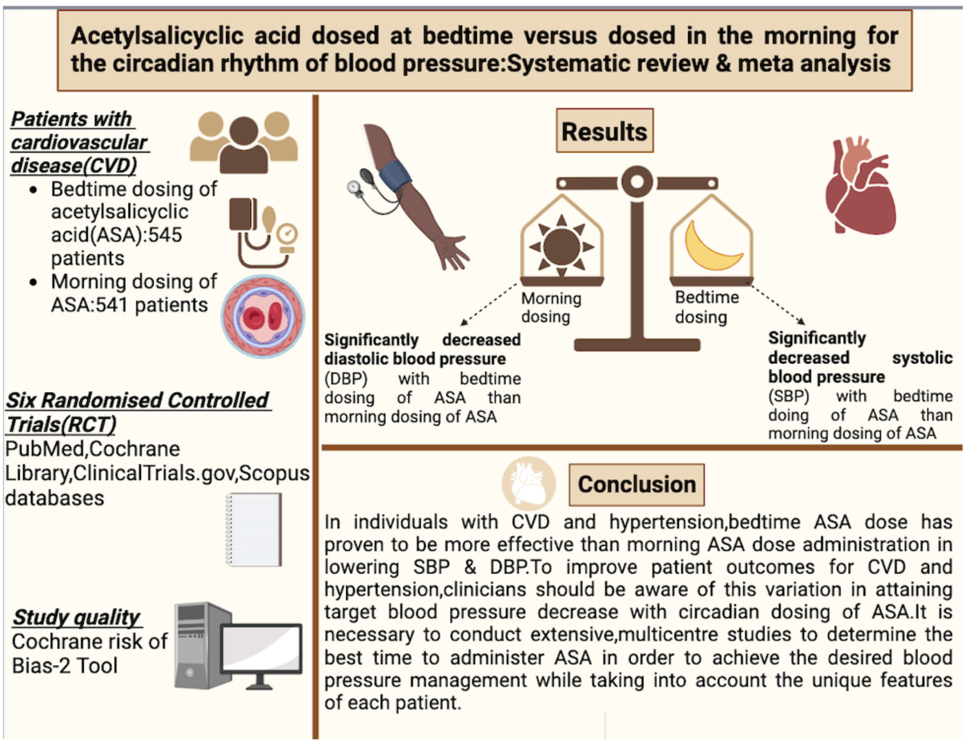
Methods: Adhering to PRISMA guidelines, a comprehensive search of PubMed, Cochrane Library, and clinicaltrials.gov was conducted. Randomized controlled trials (RCTs) involving patients aged >18 with cardiovascular history and hypertension were included. The primary objective was to assess the impact of bedtime-dosed and morning-dosed aspirin on systolic and diastolic blood pressure. Low-dose aspirin was administered for primary or secondary prevention. The Cochrane Risk of Bias tool evaluated study quality. Meta-analyses were conducted using RevMan 5.3, with mean deviations and 95% confidence intervals employed for outcomes.

Results: Initial searches yielded 1,181 articles, with six studies meeting the inclusion criteria. These RCTs involved 1,470 patients, with 1,086 completing follow-up. Bedtime aspirin dosing demonstrated a significant reduction in both systolic and diastolic blood pressure compared to morning dosing ($p < 0.05$). Meta-analysis results for systolic blood pressure revealed a weighted mean difference of approximately 3.65 mmHg in favour of bedtime dosing, with low heterogeneity ($I^2 = 0\%$). For diastolic blood pressure, the weighted mean difference was 1.92, again favouring bedtime dosing, with 3% heterogeneity.

Conclusion: This meta-analysis, involving over 1,300 cardiovascular/hypertensive patients, supports the effectiveness of bedtime aspirin in reducing systolic and diastolic blood pressure compared to morning dosing. The results align with previous findings but distinguish themselves by incorporating a more diverse patient population and addressing moderate heterogeneity. While the study's outcomes are promising, further research, including larger sample sizes and longer durations, is warranted for comprehensive clinical implementation. As the study exclusively focused on aspirin timing, future investigations should explore sustained blood pressure effects in patients with clinical indications for aspirin alongside other hypertensive medications.

KEYWORDS

cardiovascular disease, aspirin, systolic blood pressure, diastolic blood pressure, hypertension, circadian rhythm, bedtime dosing



GRAPHICAL ABSTRACT

1 Introduction

Several diseases contribute to the makeup of the term cardiovascular disease (CVD). CVD is a major cause of death, morbidity, and healthcare resource expenditure in the world (1). CVD has a number of prognosis-determining modifiable risk factors. High systolic blood pressure (SBP) is attributed to be the leading risk factor for premature cardiovascular deaths. Globally in 2021, high SBP accounted for 10.8 million CVD-related deaths and 11.3 million overall. It is a particularly strong precipitator of ischemic heart disease, stroke, and intracerebral hemorrhage-related deaths (2). In the United States alone during the 2017–2020 period, 58.4% of adult non-Hispanic Black females had high blood pressure (HBP), the highest prevalence of all race and sex categories. The lowest prevalence is in Hispanic females at 35.3%. Of the HBP mortality population in 2020, 51.3% were females and 48.7% were males (3). Logically, HBP or High SBP tend to be impactful targets for the primary and secondary prevention of cardiovascular and cerebrovascular events in at-risk hypertensive patients. Aspirin or Acetylsalicylic acid (ASA) is one such drug attempting prophylaxis in this regard. Two questions arise for optimal aspirin clinical use. Firstly, whether it is more suited for primary or secondary prevention of CVD and secondly the ideal dose swallow time to cause the greatest beneficial impact on circadian rhythms of blood pressure in humans.

A previous meta-analysis answering the first question indicated that using aspirin for secondary prevention of CVD-related events yielded a greater absolute reduction in serious vascular events (6·7% aspirin vs. 8·2% control per year, $p < 0.0001$) as compared to the primary prevention group (0·51% vs. 0·57% per year, $p = 0{\cdot}0001$). Additionally, there were increased major gastrointestinal and extracranial bleeds (0·10% vs. 0·07% per year, $p < 0{\cdot}0001$) in the primary prevention patients on aspirin administration (4). Hence, for primary prevention patient populations the increased chance of bleeding events makes any rationale to use aspirin prophylactically questionable (4, 5).

Several factors such as serum nitric oxide, prostaglandin, angiotensin II, angiotensin-converting enzyme, renin-angiotensin-aldosterone system (RAAS) activity, expression of pro-inflammatory cytokines, and leukocyte adhesives contribute to HBP (6). Many of these influencers of HBP are known to be under the control of circadian clocks (7–9). The HBP-lowering effect of aspirin in the evening can be explained by the effect of inhibiting the otherwise increasing RAAS system activity, as well as production of the vasodilatory nitric oxide (10).

Normal individuals have a 10%–20% decrease in Blood Pressure (BP) at night. Non-dipping individuals with less than 10% dips in BP are linked to activation of the RAAS system (11) and at greater risk of CVD events (12, 13). This suggests the assumption that the night dipping phenomenon may neutralize the relatively higher blood pressures present in the day which are attributed to greater sympathetic system activity unmasking the full extent of aspirin BP lowering effects (14). It is also known that the antiplatelet action of aspirin is suboptimal during the morning while a significant reduction in platelet aggregation was obtained in a relevant randomized trial (15, 16). The multifactorial usefulness of aspirin in lowering BP via its effects on vascular endothelium, inhibiting thromboxane A2 mediated platelet aggregation paired with optimal bedtime administration deals a significant blow to HBP and as a result reoccurrences of CVD events such as Myocardial Infarction (MI) and stroke. Several clinical trials and previous meta-analyses support this evening/bedtime/night BP lowering hypothesis in CVD patients (15–17).

An issue with previous trials and meta-analyses on this subject is that the majority of the data was from populations of Chinese origin. Our updated meta-analysis includes RCTs conducted on populations other than Chinese origin. Additionally, we analyze only high-level evidence from RCTs, as reflected by our exclusion criteria.

This present analysis is intended to further establish the benefits of nocturnally dosed aspirin in countering the major modifiable risk factor of CVD, namely BP. If this quick fact-turning bedtime hypothesis keeping in mind individual patient BP circadian rhythms in mind is adopted widely enough the overall incidence of CVD and many of its various causative factors may visibly reduce worldwide.

2 Methods

2.1 Data sources and search strategy

This comprehensive review adheres to the meticulous reporting standards outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines 2019 (18) discern studies meeting the criteria for inclusion, we methodically searched three databases, including PubMed, Cochrane Library, and clinicaltrials.gov. These searches were carried out autonomously by two of our study investigators and culminated on August 31, 2020. Our search keywords encompassed terms like "Aspirin," "ASA," "acetylsalicylic acid," "Time," "Morning," "Night," "Before Sleeping," "Chronotherapy," "Circadian rhythms," "Cardiovascular," "Hypertension," combined with study-type identifiers such as "RCT," "Randomized-Controlled trials," and "trial." Further details of our search strategy can be found in the Additional file (Supplementary Table S1).

2.2 Inclusion and exclusion criteria

(a) The study design included Randomized Control Trials (RCTs).
(b) The targeted population was patients aged >18 years with a history of cardiovascular and hypertension.
(c) The primary objective of our investigation was to evaluate the impact of bedtime-dosed and morning-dosed aspirin as an intervention and control, respectively, on systolic and diastolic blood pressure.
(d) Low-dose aspirin was administered for primary or secondary cardiovascular event prevention, either as a sole antiplatelet therapy or in combination with non-antiplatelet drugs, such as antihypertensive medications.
(e) Our study excluded abstracts, unpublished materials, reviews, book chapters, non-RCT studies, and studies published in languages other than English, as well as studies lacking clear reporting of primary and secondary outcomes.

2.3 Quality assessment and risk of bias in studies

The Cochrane Risk of Bias tool (19) was employed to evaluate the quality of the included RCTs. This assessment encompassed factors such as sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, handling of incomplete outcome data, selective outcome reporting, and other potential sources of bias. Each study was categorized as having a low, high, or unclear risk of bias for each of these factors. If a study was deemed to have a "high risk" of bias in any one category, it was classified as having an overall "high risk of bias". Two independent assessors conducted the quality assessment, and any discrepancies were resolved through consensus or by consulting a third researcher.

2.4 Data extraction

Two investigators independently collected all pertinent data from the 7 included studies. This information, including general study characteristics (such as first authors, publication years, study type, and sample size), demographic details (covering age and gender), intervention and control specifics (including treatment frequency and duration), and outcome-related features (comprising outcome categories, definitions, and follow-up details), was systematically entered in Google sheets.

2.5 Data analysis

We conducted meta-analyses utilizing Cochrane's Review Manager (RevMan) version 5.3. Mean deviations with 95% confidence intervals (CIs) were employed to assess clinical outcomes, systolic and diastolic blood pressure, in patients with cardiovascular disease and hypertension who were undergoing Aspirin treatment at Morning and Bedtime respectively. We applied a fixed effects model to calculate combined effect estimates for comparing outcomes between the intervention and control groups. Heterogeneity was assessed using the I^2 statistic, with a classification of significant heterogeneity ($I^2 \geq 50\%$), interpreted based on study characteristics.

2.6 Ethical consideration

No ethical approval or patient consent was necessary for this meta-analysis since we solely utilized data extracted from RCTs identified in the literature search. All patient data used was entirely anonymized, eliminating the need for ethical clearance or individual patient consent.

3 Result

3.1 Literature search result

An initial search of the 3 databases i.e., PubMed, Cochrane and clinicaltrials.gov, revealed 1,181 potentially relevant articles, of which 157 remained after excluding duplicates. After applying eligibility criteria, we selected 6 articles for inclusion in the systematic review (20–25). The Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart shown in Figure 1 summarizes the literature search for this study. All included studies were given 100 mg of aspirin except Krasińska B, (25), in which 75 mg of acetylsalicylic acid was given to the participants.

3.2 Study characteristics and quality assessment

These trials randomly assigned a total of 1,470 patients, out of which 1,086 completed the follow-up with 545 in the intervention group (bedtime dose) and 541 in the control group (morning dose). Follow-up duration ranged from 12 weeks to 3 months. The baseline characteristics of all trials are summarized in Table 1.

All studies were of considerably high methodological quality as shown in Figures 2a,b. A detailed quality assessment of each study is given in Table 2.

3.3 Change in blood pressure in response to ASA chronotherapy

Seven distinct studies examined the impact of aspirin on blood pressure at various time intervals. The findings indicated that the administration of 75–100 mg of aspirin before bedtime resulted in a noteworthy reduction in both systolic and diastolic blood pressure when compared to morning dosing (both $p < 0.05$), signifying a significant difference in the outcomes.

3.3.1 Meta-analysis results for systolic blood pressure

Systolic blood pressure represents the maximum force exerted by blood against arterial walls during each cardiac cycle, particularly during the heart's left ventricular contraction. Aspirin's anti-inflammatory properties enhance blood vessel flexibility, reducing resistance to blood flow, while its antiplatelet effects prevent clot formation, promoting improved circulation. These factors collectively contribute to a modest reduction in blood pressure, specifically systolic values.

The analysis, depicted in Figure 3, underscores a more pronounced decrease in systolic blood pressure when aspirin is administered before bedtime. The data reveals a weighted mean difference (WMD) of approximately 3.65 (95 per cent confidence interval, 2.58–4.73) relative to morning dosing. Within the seven studies analyzed, a moderate level of heterogeneity at 0 per cent was observed, with a highly significant p-value of less than 0.00001, indicating substantial and statistically significant diversity in the results. Consequently, these findings substantiate the association between bedtime aspirin administration and a mean systolic blood pressure reduction of 3.65 mmHg in randomized controlled trials.

3.3.2 Meta-analysis results for diastolic blood pressure

Diastolic blood pressure, representing arterial pressure during the heart's resting phase, is influenced by aspirin's antiplatelet and anti-inflammatory properties, potentially enhancing blood vessel function. A comparative analysis illustrated in Figure 4 indicates a weighted mean difference of 1.92 (95 per cent confidence interval: 1.41–2.71) between individuals taking aspirin at bedtime and those taking it in the morning. This suggests a modest reduction in diastolic blood pressure for bedtime aspirin

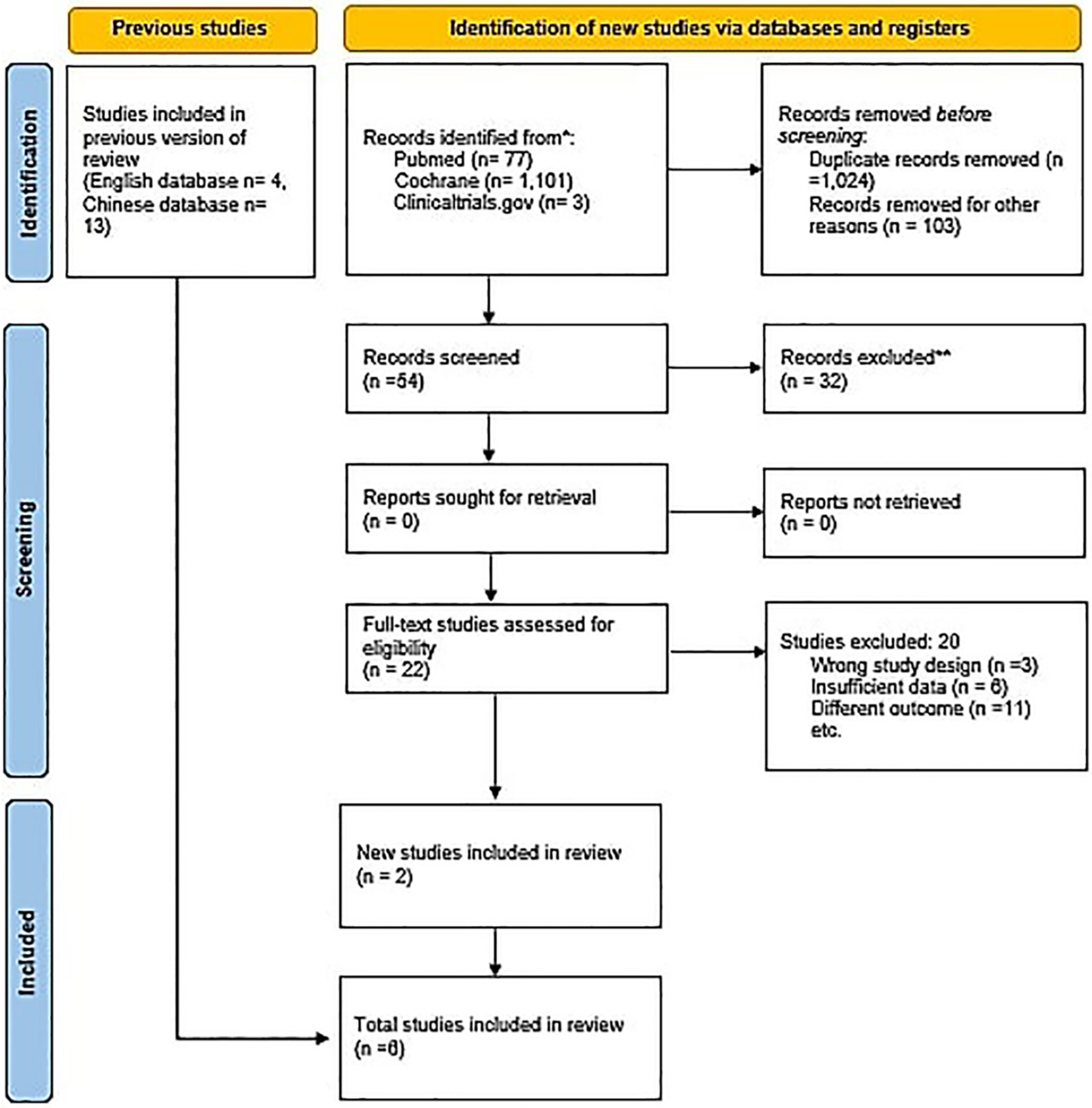


FIGURE 1
PRISMA flowchart. The PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened, and the full texts retrieved.

users. The observed 3 per cent heterogeneity, along with a remarkably low p-value of 0.00001, signifies statistically significant diversity in the studied populations, emphasizing the need for further exploration in this context.

4 Discussion

Our pooled analysis of six RCTs involving more than 1300 cardiovascular/hypertensive patient populations assessed the effects of different chronotherapy of aspirins over blood pressure and demonstrated that administration of aminosalicylic acid before bedtime resulted in a statistically significant reduction in systolic as well as diastolic blood pressure in comparison to the administration of same dosage of aspirin in the morning (Figures 3,4).

It is particularly noteworthy because this is the only meta-analysis that combined the results of RCTs with relatively moderate heterogeneity in contrast to other studies that reported their results with substantial heterogeneity (17) The findings of our study are consistent with the results reported by previous meta-analyses (17) that included 17 RCTs, however, there are many factors that make our study dissimilar from the previously published study. The prior meta-analysis consisted of 17 RCTs, out of which 13 were Chinese RCTs which could potentially create the bias of application of their reported findings only to the Chinese population. Apart from that, significantly high heterogeneity was reported in its results not only in total effect

TABLE 1 Basic characteristics of included studies.

Study	Year	Design	Population	Participants (*n*)	Sex,% female	Avg. BMI, kg/m^2	Mean age, years	Intervention time, dose
Hermida et al. (20)	2005	Prospective, randomized, open-label, blinded end point (PROBE), parallel-group trial	Grade 1 (mild) essential hypertension	328	65.55	28.73	44.6	3 months, 100 mg
Hermida* et al. (21)	2005	Prospective, randomized, open-label, blinded end point (PROBE), parallel-group trial	Grade 1 (mild) essential hypertension	257	61.86	29	44.6	3 months, 100 mg
Hermida et al. (22)	2009	A single-center prospective, randomized, open-label, parallel-group, blinded endpoint (PROBE)	Prehypertension	244	56.55	28.13	42.9	3 months, 100 mg
Ayala and Hermida (23)	2010	Prospective, open-label, parallel-group, blinded endpoint (PROBE) trial	Grade 1 (mild) essential hypertension	316	58.9	28.65	44.1	12 weeks, 100 mg
Ji et al. (24)	2016	RCT	Grade 1-2 hypertension	150	49.33	-	62.4	3 months, 100 mg
Krasińska et al. (25)	2020	RCT	Coronary heart disease and hypertension	175	33.7	29.51	59.8	3 months, 75 mg

size but also in subgroup analysis. This substantially high heterogeneity with no resolution with subgroup analysis is another factor that distinguishes our study from previous meta-analyses. Thus, our systematic review and meta-analysis could serve as a source of robust findings owing to its moderate heterogeneity and diverse patient population. Nevertheless, the core outcomes of this and previous study share the same results of reduction in systolic blood pressure and diastolic blood pressure at evening dose rather than in the morning.

While our results show promise, questions linger about its practical implications in real-world clinical settings. The modest magnitude of this reduction prompts a critical consideration of its significance in the broader context of cardiovascular risk management. Thus, our study endeavours to bridge the gap between statistical significance and clinical applicability, aiming to investigate the true impact of bedtime dosing of aspirin on long-term cardiovascular health outcomes.

The probable explanation of such findings could be provided by the study that reported a significant reduction in renin activity of plasma for 24 h when aspirin is taken at bedtime in comparison to its administration in the morning. Furthermore, cortisol, dopamine and norepinephrine were also significantly reduced with their urinary excretion over a 24 h period proving a sound biological rationale for the drop in blood pressure at bedtime dosages of aspirin (26). Similarly, one of the multiple studies conducted by Hermida et al. on Chrono pharmacological effects of aspirin demonstrated the decline in blood pressure at bedtime based on the reason that bedtime-associated use of aspirin induces the nocturnal release of NO, reduces nocturnal peak of plasma renin activity, produced a favorable effect on vascular endothelial cells and blocks alpha- and beta-adrenergic receptors. However patient population (e.g., without co-morbidities) included in this study was very different from those that came for consulting in nephrology and cardiology (22). Although this study is strictly based on the established reporting specification of meta-analysis, we do not claim it to be implemented in clinical practice. While we observed significant outcomes, it is crucial to acknowledge the presence of moderate heterogeneity across the studies. This heterogeneity was effectively addressed through a sensitivity analysis, revealing that the study conducted by Maria V. Ruiz in 2019 was the primary source of maximum heterogeneity in both systolic and diastolic blood pressure. The rationale behind this heightened heterogeneity lies in the fact that the study encompassed a total of 20 primary centres. The intention-to-treat analyses were methodically conducted, comparing outcomes between bedtime and daytime intake periods. The analysis included adjustments for baseline values at the start of each period, utilizing mixed effects repeated measures analysis of covariance models.

Furthermore, the authors of the study extended their analytical models to account for potential confounding or modifying variables. This encompassed adjustments for changes in medication, age, sex, unhealthy habits, risk factors, comorbidities, and the time of study enrollment. This level of comprehensive adjustment was not reported in other trials, contributing to the observed heterogeneity.

In the vast field of medical research, our study stands out for its methodological rigour and clinical insight on aspirin chronotherapy. Although our results align with the previous meta-analysis, they are distinguished by their methodological refinement and the inclusion of diverse patient populations. It is within this context that our study gains significance and offers a nuanced exploration of the timing dynamics of aspirin administration in addition to a synthesis of existing evidence. Our pursuit represents a scholarly contribution aimed at adding valuable insights to the ongoing discussion on managing hypertension.

It is important to note that this meta-analysis has certain limitations. Firstly, the number of randomized controlled trials (RCTs) and the size of the study population were relatively small, which may limit the ability to draw consistent findings.

10.3389/fcvm.2024.1346265

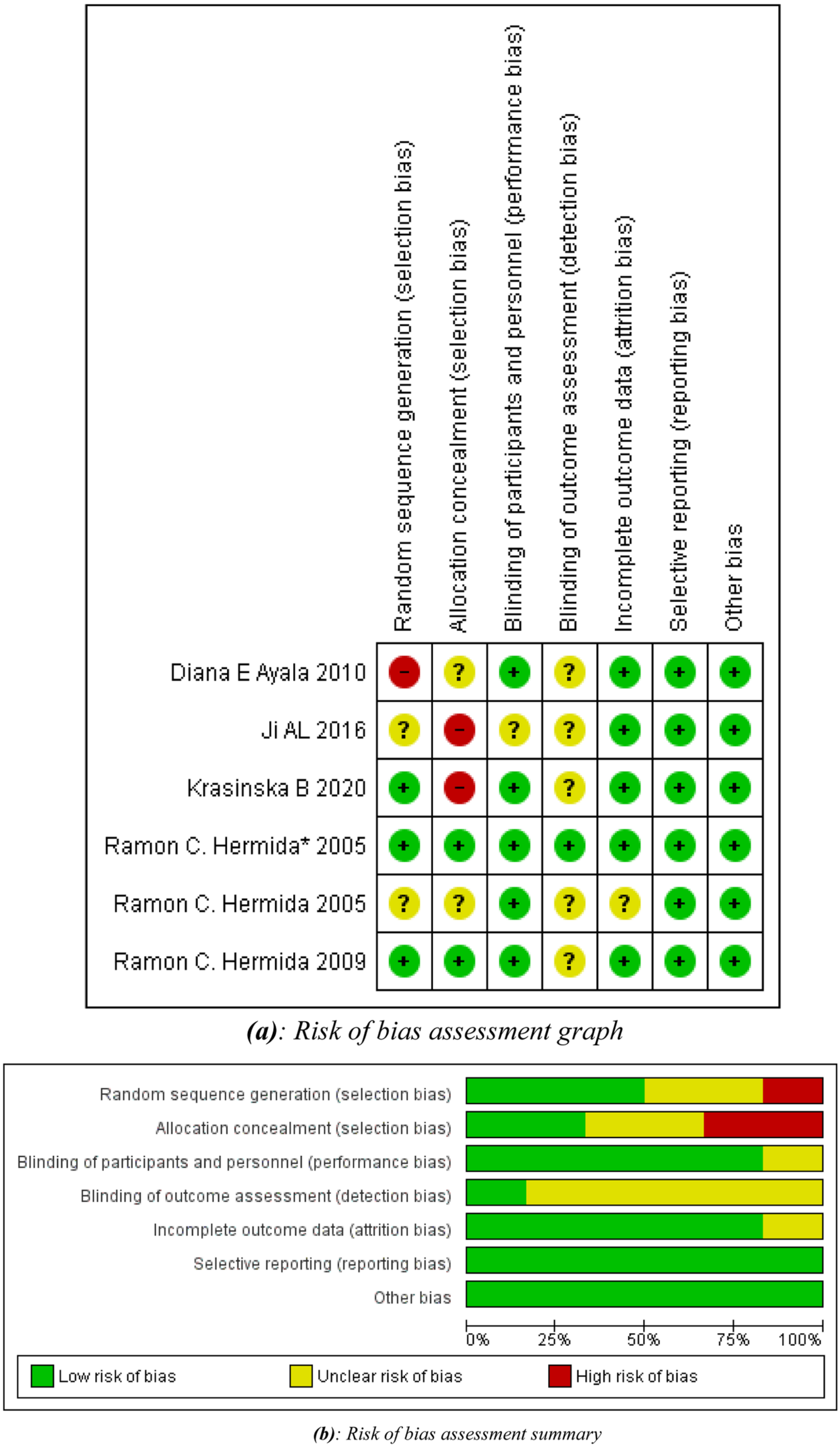


FIGURE 2
(a) Risk of bias assessment graph. (b) Risk of bias assessment summary.

TABLE 2 Quality assessment of included trials.

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Other bias
Hermida et al. (22)	Low	Low	Low	Unclear	Low	Low
Hermida et al. (20)	Unclear	Unclear	Low	Unclear	Unclear	Low
Hermida et al. (21)*	Low	Low	Low	Low	Low	Low
Ayala and Hermida (23)	High	Unclear	Low	unclear	Low	Low
Ji et al. (24)	Unclear	High	Unclear	Unclear	Low	Low
Krasińska et al. (25)	Low	High	Low	Unclear	Low	Low

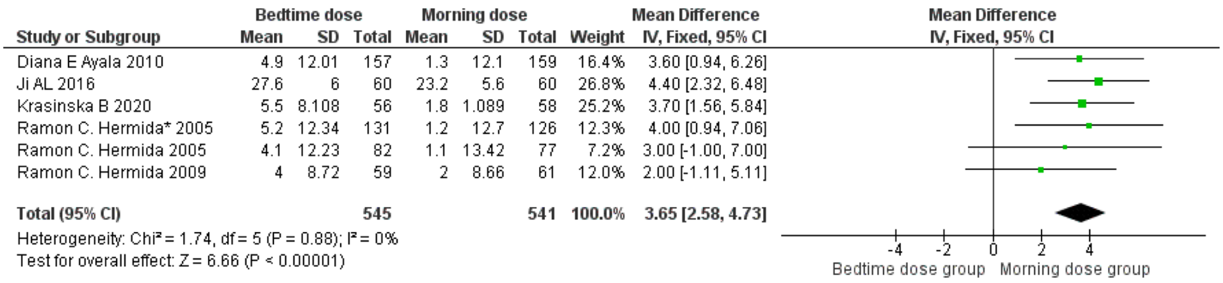


FIGURE 3
Bedtime vs. Morning dose of ASA on Systolic Blood Pressure (SBP). The diamond indicates the overall MD with an associated 95% CI. SD, standard deviation; IV, inverse variance; CI, confidence interval.

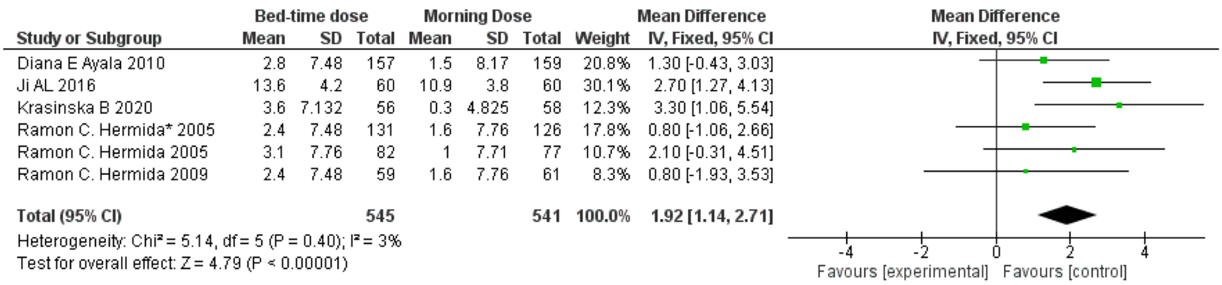


FIGURE 4
Bedtime vs. Morning dose of ASA on Diastolic Blood Pressure (DBP). The diamond indicates the overall MD with an associated 95% CI. SD, standard deviation; IV, inverse variance; CI, confidence interval.

Additionally, the total duration of dose administration was relatively short, which could potentially influence the accuracy of the results.

Certain studies included in this analysis exhibited some moderate bias, which should be taken into consideration when interpreting the results. This study exclusively compared data between individuals taking medicine in the morning and at bedtime, with no data available for those taking medicine in the morning and a placebo. Therefore, it is difficult to conclusively determine whether taking aspirin in the morning can effectively reduce blood pressure.

Before implementation of these findings in clinical practice, there's a need to conduct studies in future to evaluate the sustainability of blood pressure-reducing effects of bedtime aspirin in patients who carry clinical indications for intake of aspirin as they are on many other hypertensive medications as well which can likely dilute or interfere with the time-dependent impact of aspirin on blood pressure. However, if further, large and dedicated trials are conducted to explore the effects of dosage timing of aspirin on blood pressure keeping all the above-mentioned factors together, it could prove to be the most convenient way of improving control of blood pressure in patients who are already under the effect of so many therapeutic interventions since just a shift in the schedule of intake from morning to bedtime would be required to bring fine change in blood pressure in already debilitated patients, preventing the needs of further medicines and without effecting compliance of patients. In conclusion, further research is imperative to extract meaningful insights for clinical implementation. Additional studies with larger sample sizes, longer durations, and a more comprehensive approach are necessary in future to provide a more robust understanding of the effects of aspirin on blood pressure.

5 Conclusion

In conclusion, our systematic review and meta-analysis provide valuable insights into the impact of aspirin chronotherapy on blood pressure in cardiovascular and hypertensive patients. The analysis, based on high-quality randomized controlled trials (RCTs) with diverse populations, reveals a statistically significant reduction in both systolic and diastolic blood pressure when aspirin is administered at bedtime compared to morning dosing. This finding is consistent with previous studies but contributes unique strengths such as moderate heterogeneity and a more varied patient population.

The observed reduction in blood pressure is of clinical significance, considering the crucial role of elevated blood pressure as a major modifiable risk factor for cardiovascular diseases. The bedtime administration of aspirin demonstrates a potential strategy for optimizing the therapeutic effects of aspirin in countering hypertension, thereby reducing the risk of cardiovascular events. The underlying biological mechanisms, including the impact on plasma renin activity, cortisol, dopamine, and norepinephrine, offer a plausible rationale for the observed blood pressure-lowering effects during nighttime dosing.

However, it is essential to acknowledge the limitations of our analysis. The relatively small number of RCTs and study populations, along with the short duration of dose administration, warrant a cautious interpretation of the findings. Additionally, certain studies included in the analysis exhibited moderate bias, emphasizing the need for further dedicated trials.

Future research should focus on assessing the sustainability of bedtime aspirin's blood pressure-reducing effects, particularly in patients with clinical indications for aspirin who are concurrently on other hypertensive medications. Large-scale, long-term studies with a comprehensive approach are crucial for validating and extending the clinical implications of our findings. Before widespread implementation in clinical practice, further investigation is necessary to establish the optimal timing of aspirin administration for blood pressure control, considering patient compliance and potential interactions with other therapeutic interventions.

Data availability statement

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

Author contributions

AN: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Formal Analysis, Conceptualization. TR: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal Analysis, Data curation. MA: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Formal Analysis. AH: Writing – review & editing, Writing – original draft, Methodology, Formal Analysis, Data curation. TS: Writing – review & editing, Writing – original draft. RK: Writing – review & editing. RM: Writing – review & editing. AH: 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1346265/full#supplementary-material

References

1. Iqbal J, Iqbal A, Mukhtar H, Jahangir K, Mashkoor Y, Zeeshan MH, et al. Cardioprotective effects of nanoparticles in cardiovascular diseases: a state-of-the-art review. *Curr Problems Cardiol.* (2023) 48(8):101713. doi: 10.1016/j.cpcardiol.2023.101713

2. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk. *J Am College Cardiol.* (2022) 80(25):2361–71. doi: 10.1016/j.jacc.2022.11.005

3. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart disease and stroke statistics—2023 update: a report from the American Heart Association. *Circulation.* (2023) 147(8):e93–e621. doi: 10.1161/CIR.0000000000001123

4. Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from

randomised trials. *Lancet*. (2009) 373(9678):1849–60. doi: 10.1016/S0140-6736(09)60503-1

5. Liu S, Eckstein J, Lam A, Cheema AN. Acetylsalicylic acid (Aspirin) for primary prevention of cardiovascularevents in patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. *Curr Vasc Pharmacol*. (2023) 21(2):111–9. doi: 10.2174/1570161121666230131120544

6. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, et al. Hypertension. *Nat Rev Dis Primers*. (2018) 4(1):18014. doi: 10.1038/nrdp.2018.14

7. Felip-Benach À, Sobrino-Martínez J. Cronoterapia en hipertensión arterial. *Med Clín*. (2006) 126(10):18–9. doi: 10.1157/13086056

8. Kanabrocki EL, George M, Hermida RC, Messmore HL, Ryan MD, Ayala DE, et al. Day-night variations in blood levels of nitric oxide, T-TFPI, and E-selectin. *Clin Appl Thromb Hemost*. (2001) 7(4):339–45. doi: 10.1177/107602960100700417

9. Cermakian N, Westfall S, Kiessling S. Circadian clocks and inflammation: reciprocal regulation and shared mediators. *Arch Immunol Ther Exp*. (2014) 62(4):303–18. doi: 10.1007/s00005-014-0286-x

10. Gordon RD, Wolfe LK, Island DP, Liddle GW. A diurnal rhythm in plasma renin activity in man. *J Clin Invest*. (1966) 45(10):1587–92. doi: 10.1172/JCI105464

11. Pati P, Fulton DJR, Bagi Z, Chen F, Wang Y, Kitchens J, et al. Low-salt diet and circadian dysfunction synergize to induce angiotensin II–dependent hypertension in mice. *Hypertension*. (2016) 67(3):661–8. doi: 10.1161/HYPERTENSIONAHA.115.06194

12. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure. *J Hypertens*. (2002) 20(11):2183–9. doi: 10.1097/00004872-200211000-00017

13. Liu M. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. *Nephrol Dial Transplant*. (2003) 18(3):563–9. doi: 10.1093/ndt/18.3.563

14. Sayk F, Becker C, Teckentrup C, Fehm HL, Struck J, Wellhoener JP, et al. To dip or not to dip. *Hypertension*. (2007) 49(5):1070–6. doi: 10.1161/HYPERTENSIONAHA.106.084343

15. Racca C, van Diemen JJK, Fuijkschot WW, Spit K, Bonten TN, Numans ME, et al. Aspirin intake in the morning is associated with suboptimal platelet inhibition, as measured by serum thromboxane B_2, during infarct-prone early-morning hours. *Platelets*. (2019) 30(7):871–7. doi: 10.1080/09537104.2018.1528347

16. Krasińska B, Paluszkiewicz L, Miciak-Lawicka E, Krasiński M, Rzymski P, Tykarski A, et al. The effect of acetylsalicylic acid dosed at bedtime on the anti-aggregation effect in patients with coronary heart disease and arterial hypertension: a randomized, controlled trial. *Cardiol J*. (2020) 26(6):727–35. doi: 10.5603/CJ.a2018.0142

17. Zhou B, Wang Q, Zhao Z, Feng X. A systematic review of the efficacy and safety of aspirin when delivered at different medication times for the primary and secondary prevention of cardiovascular and cerebrovascular diseases. *Ther Innov Regul Sci*. (2020) 54(6):1339–48. doi: 10.1007/s43441-020-00156-w

18. Moher D, Liberati A, Tetzlaff J, Altman DG, Antes G, Atkins D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097

19. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst Rev*. (2019) 2019(10):ED000142. doi: 10.1002/14651858.ED000142

20. Hermida RC, Ayala DE, Calvo C, López JE. Aspirin administered at bedtime, but not on awakening, has an effect on ambulatory blood pressure in hypertensive patients. *J Am Coll Cardiol*. (2005) 46(6):975–83. doi: 10.1016/j.jacc.2004.08.071

21. Hermida RC, Ayala DE, Calvo C, López JE, Mojón A, Rodríguez M, et al. Differing administration time-dependent effects of aspirin on blood pressure in dipper and non-dipper hypertensives. *Hypertension*. (2005) 46(4):1060–8. doi: 10.1161/01.HYP.0000172623.36098.4e

22. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Ambulatory blood pressure control with bedtime aspirin administration in subjects with prehypertension. *Am J Hypertens*. (2009) 22(8):896–903. doi: 10.1038/ajh.2009.83

23. Ayala DE, Hermida RC. Sex differences in the administration-time-dependent effects of low-dose aspirin on ambulatory blood pressure in hypertensive subjects. *Chronobiol Int*. (2010) 27(2):345–62. doi: 10.3109/07420521003624662

24. Ji AL, Chen WW, Huang WJ. Clinical study on influences of enteric coated aspirin on blood pressure and blood pressure variability. *Eur Rev Med Pharmacol Sci*. (2016) 20(23):5017–20.

25. Krasińska B, Paluszkiewicz L, Miciak-Ławicka E, Krasinski M, Rzymski P, Tykarski A, et al. The impact of acetylsalicylic acid dosed at bedtime on circadian rhythms of blood pressure in the high-risk group of cardiovascular patients—a randomized, controlled trial. *Eur J Clin Pharmacol*. (2021) 77(1):35–43. doi: 10.1007/s00228-020-02997-8

26. Snoep JD, Hovens MMC, Pasha SM, Frölich M, Pijl H, Tamsma JT, et al. Time-dependent effects of low-dose aspirin on plasma renin activity, aldosterone, cortisol, and catecholamines. *Hypertension*. (2009) 54(5):1136–42. doi: 10.1161/HYPERTENSIONAHA.109.134825

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 12 December 2024
DOI 10.3389/fcvm.2024.1426953

OPEN ACCESS

EDITED BY
Komal Marwaha,
Texas Tech University Health Sciences Center, United States

REVIEWED BY
Yaman Walid Kassab,
National University of Science and Technology, Oman
Shuang Liang,
People's Liberation Army General Hospital, China

*CORRESPONDENCE
Bo Wu
✉ wujinbobo@163.com
Lanlan Qiu
✉ 1959169437@qq.com

[†]These authors have contributed equally to this work

RECEIVED 02 May 2024
ACCEPTED 02 December 2024
PUBLISHED 12 December 2024

CITATION
Qiu L and Wu B (2024) The relationship between the age of onset of hypertension and chronic kidney disease: a cross-sectional study of the American population.
Front. Cardiovasc. Med. 11:1426953.
doi: 10.3389/fcvm.2024.1426953

The relationship between the age of onset of hypertension and chronic kidney disease: a cross-sectional study of the American population

Lanlan Qiu[1*†] and Bo Wu[2*†]

[1]Department of Cardiology, Longyan People's Hospital, Longyan, Fujian, China, [2]Department of Cardiology, Longyan First Affiliated Hospital of Fujian Medical University, Longyan, Fujian, China

Background: Hypertension can damage multiple target organs. The younger the age of onset of hypertension is, the greater the risk of cardiovascular disease (CVD) and cardiovascular death. Chronic kidney disease (CKD) is a complication of hypertension, but few studies have investigated the relationship between the age of onset of hypertension and CKD.

Objective: We investigated the relationship between the age of onset of hypertension and CKD.

Method: We analyzed data from the National Health and Nutrition Examination Survey (NHANES) 2007–2018. A total of 30,613 participants were assigned to one of four groups. Group 1, no hypertension ($n = 19{,}516$); Group 2, age of onset <35 years ($n = 2{,}180$); Group 3, 35≤ age of onset <45 years ($n = 2{,}128$); and Group 4, age of onset ≥45 years ($n = 6{,}789$). Logistic regression analysis was used to evaluate the relationship between the age of onset of hypertension and CKD.

Results: After adjusting for potential confounders, a younger age at onset of hypertension was associated with a greater risk of developing CKD compared with the absence of hypertension (Group 2 OR: 2.52, 95% CI: 1.53–4.14, $P < 0.001$; Group 3 OR: 1.59, 95% CI: 1.01–2.51, $P = 0.048$; Group 4 OR: 1.54, 95% CI: 1.00–2.38, $P = 0.050$).

Conclusions: There was a strong association between the age of onset of hypertension and CKD. The younger the age of onset of hypertension is, the greater the risk of CKD.

KEYWORDS

hypertension, onset age, early-onset hypertension, CKD, NHANES

Introduction

Hypertension can damage the heart, brain, kidney, and other target organs (1), and it has a heavy global disease burden (2). Notably, epidemiological findings show that the hypertension population is becoming younger and that the proportion of patients with early-onset hypertension is increasing (3). Compared with patients with late-onset hypertension, those with early-onset hypertension appear to be at greater risk for a poor prognosis.

Available evidence suggests that patients with early-onset hypertension are at increased risk for ventricular remodeling and coronary artery calcification (4). In addition, patients with a younger age of onset of hypertension had a greater risk of nonfatal cardiovascular disease (CVD) events and CVD mortality than patients with an older age of onset (5, 6). However, most studies on the age of onset of hypertension and the risk of poor prognosis are limited to CVD, and the dangers of early-onset hypertension are far from well understood (7). The relationship between the age of onset of hypertension and other clinical outcomes needs further study (8).

CKD is a common complication of hypertension (9). Approximately 20% of hypertensive patients progress to CKD each year (10). The prevalence of CKD has been increasing over the past 20 years, with one of the causes being the increasing prevalence of hypertension (11). The main cause of death in CKD patients is usually not CKD itself but CVD complications due to CKD (12). Recently, the American Heart Association (AHA) proposed the concept of cardiovascular–kidney–metabolic (CKM) syndrome (13). In the United States, nearly 60% of adults are in CKM stage 2 (additional metabolic risk factors or moderate- or high-risk CKD) or higher (13). This further confirms the strong association between CKD and CVD incidence. Therefore, CKD cannot be overlooked when exploring the harms of early-onset hypertension.

Exploring the influence of early-onset hypertension on CKD will be beneficial for the clinical management of cardiorenal diseases. Our aim was to explore the relationship between the age of onset of hypertension and CKD and to provide references for identifying hypertensive patients with a high risk of CKD.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES) includes data on the health and nutritional status of adults and children in the United States beginning in the early 1960s. It is an annual self-report survey of different populations and health topics in a nationally representative sample of approximately 5,000 people located in counties throughout the country. Data on the age of onset of hypertension were available from participants from 2007 to 2018. In the NHANES 2007–2018, 34,770 participants were over the age of 20 years. A total of 46 patients lacked hypertension data, 278 lacked information on the age of onset, and 3,499 lacked the estimated glomerular filtration rate (eGFR) data, randomized urinary albumin/creatinine ratio (UACR) data, or data needed to diagnose CKD. Additionally, 334 pregnant women were excluded. The remaining 30,613 people were included in the study (Figure 1).

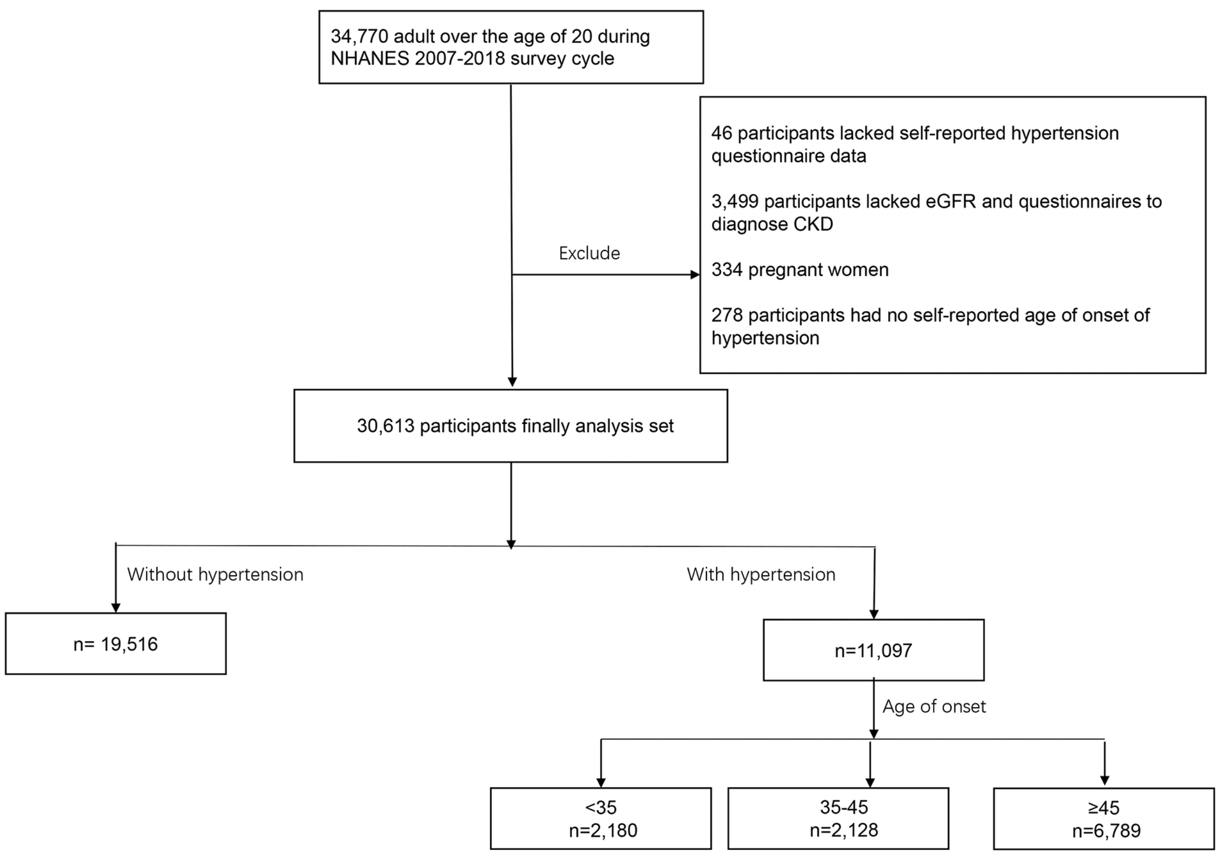


FIGURE 1
Flowchart of the study design.

Definitions, primary outcomes, and patient characteristics

Participants who answered "yes" to the NHANES questionnaire item that asked "Has a doctor ever told you that you have hypertension?" were considered hypertensive. The age of onset was also self-reported as the answer to the question "How old were you when your doctor first told you that you had high blood pressure?" In addition, the duration of exposure to hypertension was obtained by subtracting the age of onset from the current age.

The primary outcome was CKD. Participants with an eGFR of <60 ml/min/1.73 m^2 and/or a UACR of >30 mg/g were considered to have CKD (14).

The participant characteristics that were variables of interest were age, sex, ethnicity, body mass index (BMI), smoking status, education level, poverty income ratio (PIR), smoking status, and alcohol use. The diagnosis of comorbidities was assigned in the case of an affirmative response to the question "Has a doctor or other health professional ever told you that you had diabetes mellitus (DM), CVD including coronary heart disease, congestive heart failure, heart attack, stroke, or angina?" Systolic blood pressure (SBP) was the mean pressure measured at the mobile examination center and at home via a mercury sphygmomanometer. Laboratory measurements, such as creatinine (Cr), triglyceride (TG) and total cholesterol (TC) levels, were assayed with automated hematological analysis equipment. eGFR was determined via the CKD-EPI-SCr 2009 equation (15). The detailed procedures for obtaining laboratory measurements are described on the website of the National Center for Health Statistics (https://wwwn.cdc.gov/Nchs/Nhanes/).

Population grouping method

Participants without hypertension composed the reference group (Group 1). Hypertensive patients were divided into three groups according to their self-reported age of onset: <35 years (Group 2), <35 years and <45 years (Group 3), and ≥45 years (Group 4). The grouping method was the same as that used in previous studies (16).

Statistical analysis

The weights recommended by the NHANES were used for complex sampling analysis for all the statistical analyses. To reflect the representativeness of the sample, continuous variables are reported as the means (standard errors), and categorical variables are reported as numbers (percentages). Baseline characteristics were compared via analysis of variance or *t*-tests for continuous variables and chi-square tests for categorical variables. We used logistic regression analysis to evaluate the association between the age of onset of hypertension and CKD. Both estimates and probabilities were based on values recommended by the NHANES. Model 1 was adjusted for age. Model 2 was adjusted for age, sex, and ethnicity. Model 3 was adjusted for all potential confounders. To reduce retrospective bias because of current age, we stratified the data by current age. We also stratified patients by sex and the presence of DM. To investigate the possibility of a nonlinear relationship between age at the onset of hypertension and CKD, a regression cubic spline (RCS) analysis was performed.

The statistical analysis was performed via the survey package in R statistics (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). Two-sided *p*-values <0.05 indicated significance for all analyses.

Results

Participant characteristics

There were 30,613 participants, 11,097 with hypertension and 19,516 without hypertension. Those with hypertension were older, had higher lipid levels, included higher proportions of smokers and drinkers, were more likely to have CVD and CKD, and had lower levels of education and income compared with those without hypertension (Table 1). Hypertensive patients were grouped by age of onset. Group 2 (age of onset <35 years) included 2,180 participants, Group 3 (age of onset ≥35 years and <45 years) included 2,128 participants, and Group 4 (age of onset ≥45 years) included 6,789 participants. Patients with older-onset hypertension were currently older and more likely to be female. Participants with an older age at hypertension onset had higher levels of education and income and were less likely to drink. In addition, the older the age of onset of hypertension is, the greater the prevalence of DM and CVD. There were no significant differences in blood lipid levels among the age groups. The results are shown in Table 2.

Relationship between the age of hypertension onset and CKD

There were 2,129 CKD patients (8.9%) without hypertension and 3,681 (27.9%) with hypertension. In models adjusted only for current age, a younger age at onset of hypertension was associated with a greater risk of developing CKD compared with the absence of hypertension (Group 2 OR: 3.17, 95% CI: 2.70–3.72, $p < 0.001$; Group 3 OR: 2.08, 95% CI: 1.79–2.42, $p < 0.001$; and Group 4: OR: 1.91, 95% CI: 1.75–2.08, $p < 0.001$). After full adjustment for potential confounders (age, sex, race/ethnicity, education, PIR, smoking, alcohol use, BMI, TG, TC, LDL-C, DM, CVD, duration of exposure to hypertension), the association between age of onset of hypertension and CKD remained significant (Group 2 OR: 2.52, 95% CI: 1.53–4.14, $P < 0.001$; Group 3 OR: 1.59, 95% CI: 1.01–2.51, $P = 0.048$; Group 4 OR: 1.54, 95% CI: 1.00–2.38, $P = 0.050$) (Table 3).

TABLE 1 Baseline characteristics of the study population (weighted).

	Non-HTN (*n* = 19,516)	HTN (*n* = 11,097)	*P*-value
Age, mean (SE), years	43.0 (0.2)	57.7 (0.2)	<0.001
Male, *n* (%)	9,643 (48.9)	5,390 (48.7)	0.716
Ethnicity, *n* (%)			<0.001
Mexican American	3,353 (10.0)	1,318 (5.7)	
Non-Hispanic Black	3,407 (9.4)	2,921 (13.5)	
Non-Hispanic White	7,884 (65.5)	4,726 (69.1)	
Other Hispanic	2,169 (6.5)	1,062 (4.7)	
Other	2,703 (8.6)	1,070 (7.0)	
Education level			<0.001
<High school	4,499 (14.7)	3,013 (17.9)	
High school	4,266 (22.0)	2,701 (25.0)	
Collage or above	1,0735 (63.3)	5,370 (57.0)	
PIR	3.0 (0.0)	2.9 (0.0)	0.012
SBP, mean (SE), mmHg	117.8 (0.2)	130.9 (0.3)	<0.001
BMI, mean (SE), kg/m^2	28.0 (0.1)	31.4 (0.1)	<0.001
TG, mean (SE), mg/dl	114.70 (1.28)	142.27 (2.41)	<0.001
TC, mean (SE), mg/dl	193.11 (0.52)	193.13 (0.71)	0.984
LDL-C, mean (SE), mg/dl	114.59 (0.50)	111.91 (0.66)	<0.001
Smoking, *n* (%)	8,045 (41.6)	5,507 (50.3)	<0.001
Alcohol[a], *n* (%)	12,770 (71.3)	6,157 (63.3)	<0.001
DM, *n* (%)	2,112 (7.8)	3,845 (28.8)	<0.001
Duration of hypertension, *n* (%)			<0.001
<1 years	19,516 (100.0)	597 (5.6)	
1–4.9 years	0 (0.0)	2,698 (25.3)	
5–9.9 years	0 (0.0)	2,264 (22.3)	
≥10 years	0 (0.0)	5,538 (46.8)	
CVD, *n* (%)	885 (3.8)	2,513 (19.6)	<0.001
CKD, *n* (%)	2,129 (8.9)	3,681 (27.9)	<0.001

PIR, poverty income ratio; SBP, systolic blood pressure; BMI, body mass index; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease.
[a]The average number of drinks consumed per day over the past 12 months.

TABLE 2 Baseline characteristics of participants at different ages of onset (weighted).

	<35 (*n* = 2,180)	35–45 (*n* = 2,128)	≥45 (*n* = 6,789)	*P*-value
Age, mean (SE), years	42.5 (0.5)	51.6 (0.3)	65.7 (0.2)	<0.001
Male, *n* (%)	1,081 (54.9)	1,072 (52.8)	3,237 (44.8)	<0.001
Ethnicity, *n* (%)				<0.001
Mexican American	228 (7.4)	242 (6.3)	848 (4.8)	
Non-Hispanic Black	716 (18.4)	665 (16.4)	1,540 (10.6)	
Non-Hispanic White	837 (61.6)	810 (64.8)	3,079 (73.5)	
Other Hispanic	189 (5.4)	198 (5.2)	675 (4.2)	
Other	210 (7.2)	213 (7.2)	647 (6.8)	
Education levels, *n* (%)				0.004
<High school	463 (15.8)	519 (16.9)	2,031 (19.1)	
High school	564 (24.9)	497 (22.9)	1,640 (25.9)	
Collage or above	1,152 (59.3)	1,112 (60.2)	3,106 (55.0)	
PIR	2.7 (0.1)	3.1 (0.1)	3.0 (0.0)	<0.001
SBP, mean (SE), mmHg	128.6 (0.4)	129.5 (0.6)	132.4 (0.4)	<0.001
BMI, mean (SE), kg/m^2	32.8 (0.2)	32.4 (0.2)	30.4 (0.1)	<0.001
TG, mean (SE), mg/dl	148.58 (4.80)	143.99 (3.70)	139.24 (3.03)	0.185
TC, mean (SE), mg/dl	191.36 (1.16)	195.19 (1.54)	193.05 (0.79)	0.104
LDL-C, mean (SE), mg/dl	111.58 (1.55)	114.38 (1.47)	111.08 (0.87)	0.153
Smoking, *n* (%)	1,076 (49.2)	1,005 (48.6)	3,426 (51.3)	0.275
Alcohol[a], *n* (%)	1,378 (70.2)	1,248 (65.3)	3,531 (60.0)	<0.001
DM, *n* (%)	570 (20.3)	726 (28.9)	2,549 (32.1)	<0.001
Duration of hypertension, *n* (%)				<0.001
<1 years	76 (3.8)	80 (3.7)	441 (7.0)	
1–4.9 years	419 (21.7)	509 (25.7)	1,770 (26.6)	
5–9.9 years	359 (19.1)	365 (20.6)	1,540 (24.1)	
≥10 years	1,326 (55.4)	1,174 (50.0)	3,038 (42.4)	
CVD, *n* (%)	384 (13.8)	422 (16.5)	1,707 (22.9)	<0.001
CKD, *n* (%)	561 (21.1)	556 (20.9)	2,564 (33.0)	<0.001

PIR, poverty income ratio; SBP, systolic blood pressure; BMI, body mass index; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease.
[a]The average number of drinks consumed per day over the past 12 months.

Subgroup analysis

After the participants were stratified by current age, and sex status, the association between the age of onset of hypertension and CKD did not change. Compared with patients without hypertension, those with a younger age of hypertension onset have a greater risk of developing CKD (Figure 2). In the analysis stratified by diabetes status, an interaction was observed between DM and the age of onset for hypertension. Among patients with DM, Although the risk of CKD was lower in the group with the later onset of hypertension, this was not statistically significant. For those with an onset age of <35 years: OR = 2.93 (95% CI: 1.79–4.81); For those with an onset age between 35 and 45 years: OR = 1.35 (95% CI: 0.48–2.16); For those with an onset age of ≥45 years: OR = 1.17 (95% CI: 0.80–1.71).

Regression cubic splines

In hypertension patients, RCS revealed a U-shaped relationship between the age of onset of hypertension and CKD (Figure 3A). The risk of developing CKD in participants who developed hypertension before 49 years of age decreased with increasing age of onset. In participants who became hypertensive after age 49, the risk of developing CKD increased with age of onset. When stratified according to the current age of the hypertensive patients. In hypertensive patients younger than 65 years of age (Figures 3B,C), the earlier the onset of hypertension is, the greater the risk of CKD. When the current age of hypertensive patients was greater than 65 years (Figure 3D), there was a U-shaped association between the age of hypertension onset and the risk of CKD.

Discussion

This large cross-sectional study revealed that the age at onset of hypertension was strongly associated with the risk of developing CKD. The younger the age of onset is, the greater the risk of CKD. The relationship between age at onset of

TABLE 3 The association between the age of onset of hypertension and CKD (weighted).

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Non-HTN	Ref		Ref		Ref	
Onset age						
<35 years	3.17 (2.70,3.72)	<0.001	3.13 (2.66,3.67)	<0.001	2.52 (1.53,4.14)	<0.001
≥35 and <45 years	2.08 (1.79,2.42)	<0.001	2.05 (1.76,2.38)	<0.001	1.59 (1.01,2.51)	0.048
≥45 years	1.91 (1.75,2.08)	<0.001	1.87 (1.72,2.05)	<0.001	1.54 (1.00,2.38)	0.050

Model 1: Adjusted by age.
Model 2: Adjusted by age, sex, and race/ethnicity.
Model 3: Adjusted for age, sex, race/ethnicity, education, PIR, smoking status, alcohol status, BMI, TG, TC, LDL-C, duration of hypertension, DM, and CVD.

hypertension and CKD did not change after stratification by current age and sex.

Many studies have investigated the relationship between the age of onset of hypertension and poor prognosis in hypertensive patients. They reported that a younger age of onset was associated with an increased risk of ventricular remodeling and coronary artery calcification compared with those without hypertension (4). In addition, a lower age of onset of hypertension was found to be a risk factor for nonfatal cardiovascular events, including myocardial infarction, ischemic stroke, and hemorrhagic stroke; cardiovascular death; and all-cause death (5, 6, 17). These findings indicate that the age at hypertension onset is a non-negligible factor in the stratification of hypertension prognosis. However, the age at onset is not included in risk assessment in existing hypertension guidelines (18, 19). A review by Suvila et al. noted that the complications of hypertension are not limited to cardiovascular disease and death and that more evidence is needed to include age at onset of hypertension in the assessment of risk and to translate it into clinical practice (8).

CKD is a major complication of hypertension (20), and its increasing prevalence worldwide (21) adds to the global medical economic burden. In the United States alone, the annual cost of treating CKD increased from $28 billion 10 years ago to $50 billion at the time of writing (22, 23). Current evidence shows that the increase in the prevalence of hypertension is an important reason for the increase in the prevalence of CKD (11). Consequently, it is necessary to extend the study of the age of onset of hypertension to CKD. In our study, the results revealed that patients who developed hypertension at a younger age had a greater risk of developing CKD than did those who developed hypertension at an older age. After stratification by sex and DM, the relationship between age at onset of hypertension and CKD did not change. Notably, patients who developed hypertension later in life were actually older. As this was a retrospective study, it was difficult to avoid. To minimize bias, patients were stratified by age into groups of <55 years and 55–65 years of age for subgroup analysis, the results of which were consistent with the main results. The younger the age of onset of hypertension is, the greater the risk of CKD. Although a U-shaped association was found in people ≥65 years of age, the 95% CI was not statistically significant.

In exploring the possibility of a nonlinear relationship between age at onset of hypertension and CKD, the RCS indicated a U-shaped relationship between age at onset of hypertension and CKD. However, the relationship disappeared after the patients were stratified by their current age. As described above, patients with late-onset hypertension in this retrospective analysis were also older. Current age, as a risk factor for CKD (24, 25), may mask the linear relationship between the age of onset of hypertension and CKD. After controlling for the effect of current age in a stratified analysis, a younger age of onset remained associated with a greater risk of developing CKD. Therefore, our results are still reliable.

Additionally, it is necessary to note that the duration of exposure to hypertension is also an important factor for the occurrence of CKD in patients with hypertension. Therefore, the negative correlation between the age of onset of hypertension and CKD may be because patients who develop hypertension later in life have a shorter exposure time to high blood pressure. However, in Model 3 of this study, the exposure time to hypertension was also included in the regression model for analysis. The results still hold statistical significance. This finding indicates that the negative correlation between the age of onset of hypertension and CKD is independent of the duration of exposure to hypertension.

In the stratification based on DM status, it was observed that among diabetic patients, only those with hypertension onset at age <35 years have a higher risk of developing CKD. For individuals who have both DM and hypertension, the primary cause of CKD may stem from DM rather than hypertension. The speed at which DM patients progress to CKD is often more rapid than that of hypertension patients (26, 27). Therefore, the significance of the onset age of hypertension may be overshadowed by DM.

However, the reason why patients with early-onset hypertension are more likely to develop CKD may not be due only to substandard treatment for hypertension. Several studies have suggested that there is a genetic risk of early-onset hypertension; people whose parents have early-onset hypertension are more than three times as likely to develop high blood pressure as those whose parents do not (17). There is evidence that the M235T angiotensinogen gene variant is associated with familial early-onset hypertension (28). Numerous studies have reported a strong correlation between M235T and CKD (29–31).

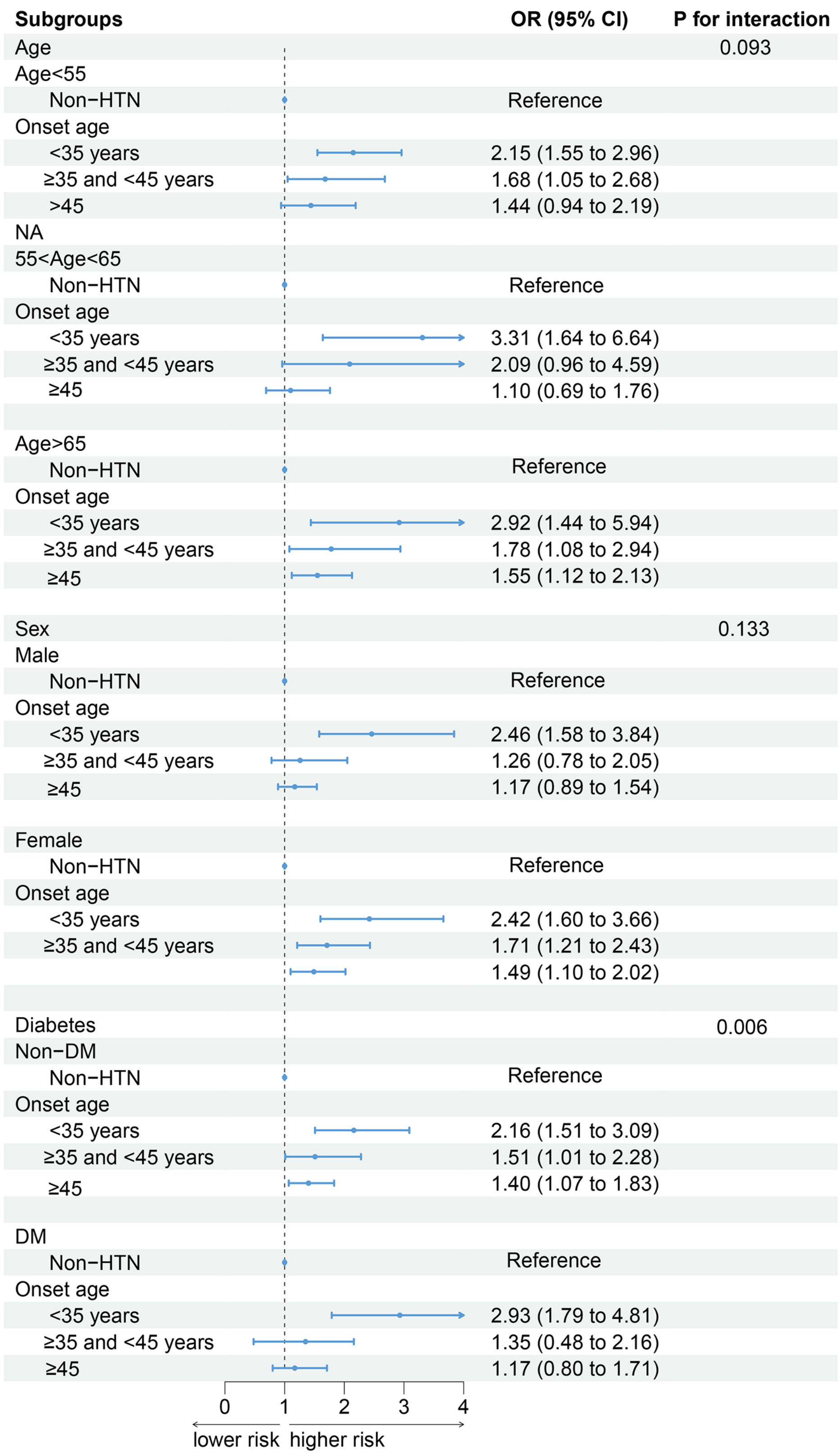


FIGURE 2
The associations between the age of onset of hypertension and the incidence of CKD in different subgroups (weighted). Adjusted for age, sex, race/ethnicity, education, PIR, smoking, alcohol use, BMI, TG, TC, LDL-C, DM, CVD, duration of exposure to hypertension.

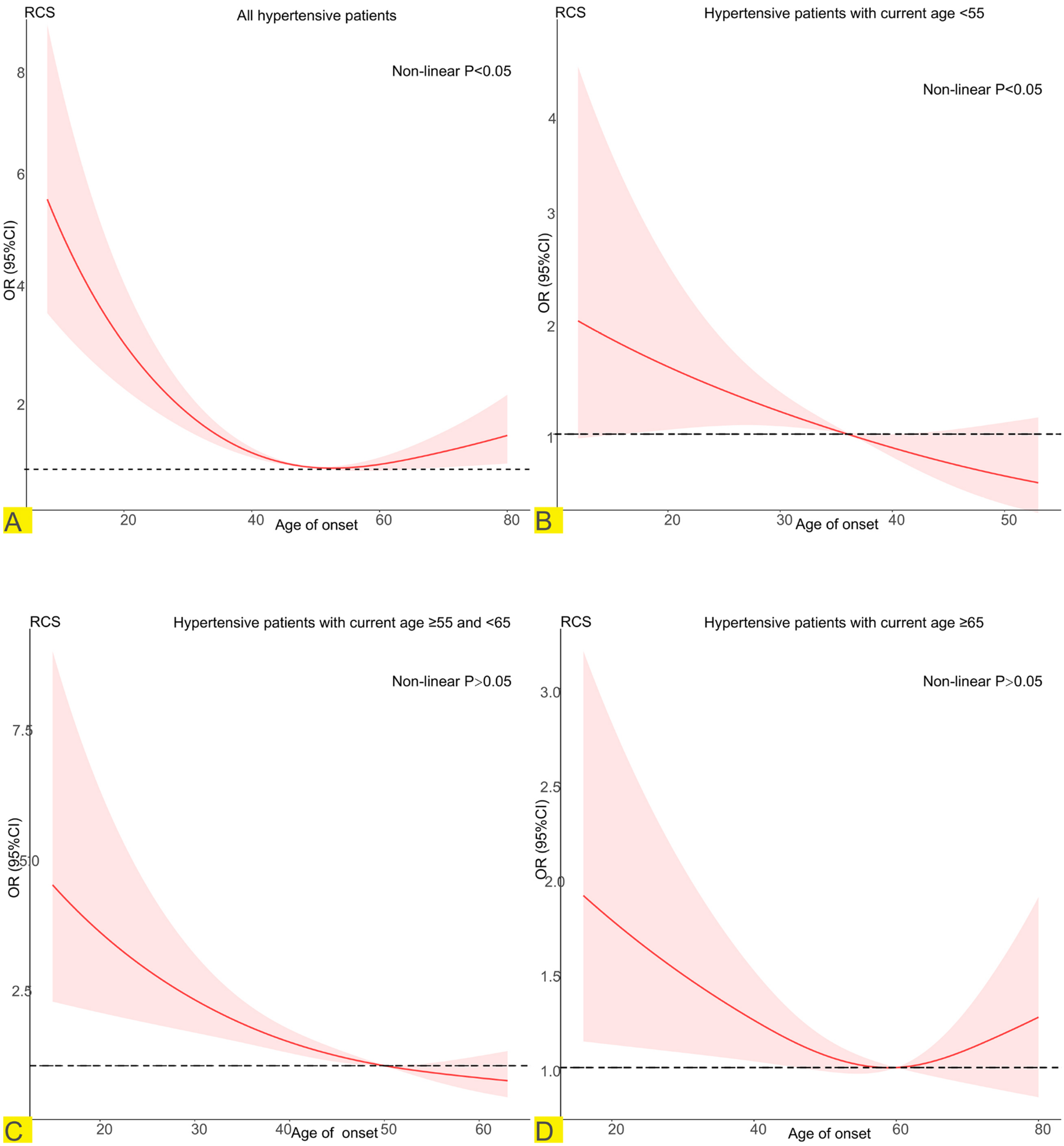


FIGURE 3
Potential nonlinear relationship between age at onset of hypertension and CKD (weighted). Adjusted for age, sex, race/ethnicity, education, PIR, smoking, alcohol use, BMI, TG, TC, LDL-C, DM, CVD, duration of exposure to hypertension. **(A)** Relationship between age of onset of hypertension and CKD in all hypertensive patients. **(B)** Relationship between age of onset of hypertension and CKD in hypertensive patients with current age <55. **(C)** Relationship between age of onset of hypertension and CKD in hypertensive patients with current age ≥55 and <65. **(D)** Relationship between age of onset of hypertension and CKD in hypertensive patients with current age ≥55.

In addition, Yoshiji et al. reported that the MOB3C-TMOD4, COL6A3 and COL6A5 gene loci are associated with the occurrence of early-onset hypertension and CKD (32). We suspect that patients with early-onset hypertension may be genetically more likely to develop CKD than those with late-onset hypertension. Given that these findings cannot be verified by a retrospective study, prospective studies are needed to verify this hypothesis.

In this cross-sectional study, the sample size was large enough to be powered to represent 252,462,687 people in the United States, making our results more reliable. Our study revealed that the age of onset of hypertension was associated not only with cardiovascular disease risk, all-cause mortality, and cardiovascular death in hypertensive patients but also with CKD in hypertensive patients. This finding fills a gap in age-related studies on hypertension and provides more evidence for stratifying the prognosis of hypertensive patients. Although current hypertension management guidelines do not include age of onset when assessing the prognosis of hypertensive patients, considering the correlation between early-onset hypertension and CKD as well as CVD, incorporating age of onset into clinical guidelines could enhance risk stratification. This would enable health care providers to more effectively identify high-risk patients. For example, younger patients with early-onset hypertension may benefit from more aggressive monitoring and management strategies to reduce the risk of CKD and other complications. Therefore, early identification of the harms associated with early-onset hypertension and its integration into clinical practice for the treatment and management of hypertensive patients is highly important.

Limitations

There were several study limitations. First, it was subject to the limitations inherent in a retrospective analysis. The relationship between the age of onset of hypertension and CKD could be interpreted only as a correlation rather than as a causal relationship. Second, whether hypertension was the cause of a diagnosis of CKD could not be determined. Third, the age of onset was self-reported by patients, which may be different from the actual age of hypertension. However, previous studies have demonstrated consistency among self-reported age groups with hypertension as defined by objective age groups, and our results are still reliable (16).

Conclusions

Our results indicated a strong association between age at onset of hypertension and CKD. The younger the age of onset of hypertension is, the greater the risk of CKD. For patients with early-onset hypertension, early intervention should be prioritized.

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 requirement of ethical approval was waived by National Center for Health Statistics (NCHS) for the studies involving humans because National Center for Health Statistics (NCHS). 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

LQ: Writing – review & editing. BW: Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded and supported by the Longyan City Science and Technology Plan Project (grant numbers: 2022LYF17026 and 2022LYF17084).

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

References

1. Rubattu S, Pagliaro B, Pierelli G, Santolamazza C, Castro SD, Mennuni S, et al. Pathogenesis of target organ damage in hypertension: role of mitochondrial oxidative stress. *Int J Mol Sci*. (2014) 16:823–39. doi: 10.3390/ijms16010823

2. Bairey Merz CN, Alberts MJ, Balady GJ, Ballantyne CM, Berra K, Black HR, et al. ACCF/AHA/ACP 2009 competence and training statement: a curriculum on prevention of cardiovascular disease: a report of the American College of Cardiology foundation/American Heart Association/American college of physicians task force on competence and training (writing committee to develop a competence and training statement on prevention of cardiovascular disease): developed in collaboration with the American academy of neurology; American association of cardiovascular and pulmonary rehabilitation; American college of preventive medicine; American college of sports medicine; American diabetes association; American society of hypertension; association of black cardiologists; centers for disease control and prevention; national heart, lung, and blood institute; national lipid association; and preventive cardiovascular nurses association. *Circulation*. (2009) 120:e100–26. doi: 10.1161/CIRCULATIONAHA.109.192640

3. De Venecia T, Lu M, Figueredo VM. Hypertension in young adults. *Postgrad Med*. (2016) 128:201–7. doi: 10.1080/00325481.2016.1147927

4. Suvila K, McCabe EL, Lehtonen A, Ebinger JE, Lima JAC, Cheng S, et al. Early onset hypertension is associated with hypertensive end-organ damage already by MidLife. *Hypertension*. (2019) 74:305–12. doi: 10.1161/HYPERTENSIONAHA.119.13069

5. Buck C, Baker P, Bass M, Donner A. The prognosis of hypertension according to age at onset. *Hypertension*. (1987) 9:204–8. doi: 10.1161/01.hyp.9.2.204

6. Wang C, Yuan Y, Zheng M, Pan A, Wang M, Zhao M, et al. Association of age of onset of hypertension with cardiovascular diseases and mortality. *J Am Coll Cardiol*. (2020) 75:2921–30. doi: 10.1016/j.jacc.2020.04.038

7. Niiranen TJ, Suvila K, Cheng S. Early-onset hypertension: under-recognized, under-treated, and under-estimated in risk. *J Am Coll Cardiol*. (2020) 75:2931–3. doi: 10.1016/j.jacc.2020.04.059

8. Suvila K, Langén V, Cheng S, Niiranen TJ. Age of hypertension onset: overview of research and how to apply in practice. *Curr Hypertens Rep*. (2020) 22:68. doi: 10.1007/s11906-020-01071-z

9. Korzh O, Titkova A, Fylenko Y, Lavrova Y. Evaluation of health-promoting self-care behaviors in hypertensive patients with concomitant chronic kidney disease in primary care. *Prim Health Care Res Dev*. (2022) 23:e48. doi: 10.1017/S1463423622000299

10. Darshi M, Van Espen B, Sharma K. Metabolomics in diabetic kidney disease: unraveling the biochemistry of a silent killer. *Am J Nephrol*. (2016) 44:92–103. doi: 10.1159/000447954

11. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet Lond Engl*. (2013) 382:260–72. doi: 10.1016/S0140-6736(13)60687-X

12. Kobo O, Abramov D, Davies S, Ahmed SB, Sun LY, Mieres JH, et al. CKD-associated cardiovascular mortality in the United States: temporal trends from 1999 to 2020. *Kidney Med*. (2023) 5:100597. doi: 10.1016/j.xkme.2022.100597

13. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. (2023) 148:1606–35. doi: 10.1161/CIR.0000000000001184

14. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. (2021) 100:S1–276. doi: 10.1016/j.kint.2021.05.004

15. Bernier-Jean A, Beaubien-Souligny W, Goupil R, Madore F, Paquette F, Troyanov S, et al. Diagnosis and outcomes of acute kidney injury using surrogate and imputation methods for missing preadmission creatinine values. *BMC Nephrol*. (2017) 18:141. doi: 10.1186/s12882-017-0552-3

16. Suvila K, McCabe EL, Lima JAC, Aittokallio J, Yano Y, Cheng S, et al. Self-reported age of hypertension onset and hypertension-mediated organ damage in middle-aged individuals. *Am J Hypertens*. (2020) 33:644–51. doi: 10.1093/ajh/hpaa055

17. Niiranen TJ, McCabe EL, Larson MG, Henglin M, Lakdawala NK, Vasan RS, et al. Heritability and risks associated with early onset hypertension: multigenerational, prospective analysis in the Framingham heart study. *Br Med J*. (2017) 357:j1949. doi: 10.1136/bmj.j1949

18. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. (2018) 71:1269–324. doi: 10.1161/HYP.0000000000000066

19. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. (2018) 39:3021–104. doi: 10.1093/eurheartj/ehy339

20. Wang J, Wang B, Liang M, Wang G, Li J, Zhang Y, et al. Independent and combined effect of bilirubin and smoking on the progression of chronic kidney disease. *Clin Epidemiol*. (2018) 10:121–32. doi: 10.2147/CLEP.S150687

21. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. (2002) 39:S1–266. doi: 10.1053/ajkd.2002.29865

22. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet Lond Engl*. (2005) 365:331–40. doi: 10.1016/S0140-6736(05)17789-7

23. Swee ML, Sanders ML, Phisitkul K, Bailey G, Thumann A, Neuzil N, et al. Development and implementation of a telenephrology dashboard for active surveillance of kidney disease: a quality improvement project. *BMC Nephrol*. (2020) 21:424. doi: 10.1186/s12882-020-02077-0

24. Chia YC, Ching SM. Hypertension and the development of new onset chronic kidney disease over a 10 year period: a retrospective cohort study in a primary care setting in Malaysia. *BMC Nephrol*. (2012) 13:173. doi: 10.1186/1471-2369-13-173

25. Chronic Hepatitis B Infection Is Significantly Associated with Chronic Kidney Disease: a Population-based, Matched Case-control Study—PubMed. Available online at: https://pubmed.ncbi.nlm.nih.gov/30310365 (accessed November 12, 2024)

26. Gupta S, Dominguez M, Golestaneh L. Diabetic kidney disease: an update. *Med Clin North Am*. (2023) 107:689–705. doi: 10.1016/j.mcna.2023.03.004

27. Thomas G. Hypertension management in chronic kidney disease and diabetes: lessons from the systolic blood pressure intervention trial. *Cardiol Clin*. (2019) 37:307–17. doi: 10.1016/j.ccl.2019.04.006

28. Schmidt S, Sharma AM, Zilch O, Beige J, Walla-Friedel M, Ganten D, et al. Association of M235T variant of the angiotensinogen gene with familial hypertension of early onset. *Nephrol Dial Transplant*. (1995) 10:1145–8.

29. Su S-L, Chen W-T, Hsiao P-J, Lu K-C, Lin Y-F, Lin C, et al. Angiotensin II receptor type 1 A1166C modifies the association between angiotensinogen M235T and chronic kidney disease. *Oncotarget*. (2017) 8:107833–43. doi: 10.18632/oncotarget.22121

30. Analysis of polymorphism in renin angiotensin system and other related genes in South Indian chronic kidney disease patients—PubMed. Available online at: https://pubmed.ncbi.nlm.nih.gov/19520069/ (accessed November 12, 2024)

31. Prasad P, Tiwari AK, Kumar KMP, Ammini AC, Gupta A, Gupta R, et al. Chronic renal insufficiency among Asian Indians with type 2 diabetes: I. Role of RAAS gene polymorphisms. *BMC Med Genet*. (2006) 7:42. doi: 10.1186/1471-2350-7-42

32. Yamada Y, Kato K, Oguri M, Horibe H, Fujimaki T, Yasukochi Y, et al. Identification of 13 novel susceptibility loci for early-onset myocardial infarction, hypertension, or chronic kidney disease. *Int J Mol Med*. (2018) 42:2415–36. doi: 10.3892/ijmm.2018.3852

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 24 December 2024
DOI 10.3389/fcvm.2024.1409212

OPEN ACCESS

EDITED BY
Komal Marwaha,
Texas Tech University Health Sciences Center, United States

REVIEWED BY
Rade Babic,
University of Belgrade, Serbia
Pao-Hwa Lin,
Duke University, United States

*CORRESPONDENCE
Abate Wondesen Tsige
✉ Abatewondesen@dbu.edu.et

RECEIVED 29 March 2024
ACCEPTED 04 December 2024
PUBLISHED 24 December 2024

CITATION
Tsige AW and Ayele SG (2024) Malignant hypertension: current challenges, prevention strategies, and future perspectives.
Front. Cardiovasc. Med. 11:1409212.
doi: 10.3389/fcvm.2024.1409212

Malignant hypertension: current challenges, prevention strategies, and future perspectives

Abate Wondesen Tsige[1]* and Siraye Genzeb Ayele[2]

[1]School of Pharmacy, College of Health Sciences, Debre Berhan University, Debre Berhan, Ethiopia, [2]Department of Midwifery, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Introduction: Based on office blood pressure (BP) values, hypertension is categorized into three stages: stage 1 (140–159/90–99 mmHg), stage 2 (160–179/100–109 mmHg), and stage 3 (≥180/≥110 mmHg). Malignant hypertension (MHT) is characterized by extreme BP elevation (systolic blood pressure above 200 mmHg and diastolic blood pressure above 130 mmHg) and acute microvascular damage affecting various organs, particularly the retinas, brain, and kidneys.
Objectives: The pathogenesis, predisposing variables, therapy, and preventive strategies for MHT were examined in this review.
Conclusions and recommendations: Malignant hypertension requires prompt and efficient treatment because it is the most severe kind of hypertension that affects target organs. At the same time, there are a number of alternatives available for treating MHT. The International Society of Hypertension 2020 and European Society of Cardiology/European Society of Hypertension 2018 recommendations suggest using labetalol and nicardipine as the first-line choice, with urapidil and nitroprusside serving as alternative medications. Elevated risk of MHT has been linked to many socio-demographic and genetic factors.

KEYWORDS
malignant hypertension, risk factors, complication, treatment, prevention strategies

1 Introduction

According to the 2023 European Society of Hypertension (ESH) guideline, hypertension (HTN) is defined as a recurrent office systolic blood pressure (SBP) value of 140 mmHg and diastolic blood pressure (DBP) value of 90 mmHg. Based on office blood pressure (BP) values, HTN is categorized into three stages: stage 1 (140–159/90–99 mmHg), stage 2 (160–179/100–109 mmHg), and stage 3 (≥180/≥110 mmHg) (1).

Malignant hypertension (MHT) is characterized by extreme BP elevation (SBP above 200 mmHg and DBP above 130 mmHg) and acute microvascular damage affecting various organs, particularly the retinas, brain, and kidneys (2–4).

The 2018 European Society of Cardiology (ESC)/ESH guideline differentiates MHT from "hypertension urgencies and emergencies" through the severity of damage to the organs, which is referred to as hypertension-multi-organ damage (retinopathy, microangiopathy, disseminated intravascular coagulation, encephalopathy, abrupt heart failure, or acute deterioration in renal function). It is a medical emergency with a poor prognosis if left untreated (5).

MHT requires emergency medical attention to limit organ damage and other complications related to severely high blood pressure (6). Vascular injury is mainly caused by the loss of autoregulation of blood flow, which typically occurs in individuals with uncontrolled and chronic hypertension (3, 7, 8).

TABLE 1 Agreements and disagreements regarding the definition of malignant hypertension in current guideline/consensus documents (3).

Guidelines	Definition	Agreement and disagreement
2023 ESH Guidelines (1)	This guideline does not define MHT but it does categorize HTN into three grades. Grade 3 HTN (≥180/≥110 BP) with the presence of CVD or CKD stage 4 or 5.	
BIHS position document (9)	Diastolic blood pressure has a value greater than 120 mmHg, and the Keith and Wagner classification needs concurrent symmetrical grade 3 (flame or dot-shaped hemorrhages, cotton wool spots, hard exudates, and microaneurysms) or grade 4 hypertensive retinopathy of the eyes (bilateral papilledema) to make a clinical diagnosis.	The authors agreed that more research is required in this area and that there is a lack of consensus statements regarding the exact rate of BP lowering.
ISH 2020 (10)	Severe symmetrical retinopathy with a large increase in arterial blood pressure (which is frequently >200/120 mmHg) with bleeding, cotton wool spots, and papilledema.	Although a significant increase in blood pressure is required, no particular threshold has been verified. MHT can be detected in this situation when significant retinopathy due to hypertension is present. This is agreed upon. It is debatable if it is necessary when there is heart, kidney, brain, or thrombotic microangiopathy damage, or when there is bilateral retinal involvement or papilledema. Severe hypertensive retinopathy may also be accompanied by isolated dry exudates, cotton wool patches, and hemorrhages.
NICE 2019 (11)	Blood pressure increases quickly to 180/120 mmHg or above (and typically >220/120 mmHg), together with symptoms of retinal bleeding and/or papilledema (optic nerve enlargement). Typically connected with new or newly developing major organ harm.	The committee concluded that more investigation was required. Neither published evidence nor pertinent clinical studies were found during the review process.
ESC/ESH 2018 (5)	Malignant hypertension is a hypertensive emergency characterized by the presence of severe BP elevation (usually >200/120 mmHg) and advanced retinopathy, defined as the bilateral presence of flame-shaped hemorrhages, cotton wool spots, or papilledema.	The authors claimed that when estimating the severity of organ injury, the degree and magnitude of BP increases can be as significant as absolute BP level.
European Consensus 2018 (8)	The presence of severe retinopathy (defined by the bilateral presence of flame-shaped hemorrhages, cotton wool patches, or papilledema), acute renal failure, thrombotic microangiopathy, and acute hypertensive microangiopathy could be an alternative term with elevated blood pressure (typically 200/120 mmHg).	In support of a larger definition, it is argued that retinal lesions may not always be present in individuals who have had acute microvascular damage to the kidney, heart, or brain. This is due to evidence gaps and the disease's pathophysiology.
AHA 2017 (6)	Not brought up in the discussion.	The absence of malignant hypertension in the section on emergencies with hypertension reflects how the medical community overlooked MHT.
AHA 2024 Scientific Statement (12)	Does not define MHT as a distinct category in hypertension emergencies.	
2024 ESC Guidelines (13)	MHT is a hypertensive emergency characterized by extreme BP elevations and acute microvascular damage affecting various organs, particularly the retinas, brain, and kidneys.	The authors recommended safe BP reduction to prevent further complications.

BIHS, British and Irish Hypertension Society; AHA, American Heart Association.

There is limited data on MHT so the diagnostic and therapeutic guidelines are primarily based on consensus. The different definitions of MHT in the guidelines are listed in Table 1.

2 Epidemiology of malignant hypertension

Although the prevalence and incidence data for MHT are scarce, a study conducted in Amsterdam (Netherlands) and Birmingham (United Kingdom) revealed an incident rate of 2/100,000 new cases per year, with up to fourfold higher rates among patients of Black African/Afro-Caribbean ethnicities (14). In the Afro-American population, 7.3/100,000 new cases per year were reported. A worse disease prognosis and greater disease predisposition were also observed (15).

3 Predisposing factors of malignant hypertension

Malignant hypertension mainly occurs in individuals with a history of uncontrolled high blood pressure and those who missed or discontinued their antihypertensive medications (16, 17). In addition, patients with stroke, structural heart disease, thyroid disorders, brain bleeding, renal artery disease, traumatic brain injury, Conn's syndrome, Cushing's syndrome, pheochromocytoma, and substance and medication withdrawal may experience MHT (17). In addition, pregnancy is another known precipitating factor of MHT (3, 18).

The study conducted in Birmingham included 460 patients diagnosed with MHT from 1958 to May 2016 and indicated that the study participants' ethnic differences, advanced age, prior use of antihypertensive medication, duration of hypertension, and presence of proteinuria were strong predictors of MHT outcomes (19). There are more pronounced abnormalities in macrovascular and microvascular function in patients with MHT (which seem to be both endothelium-dependent and endothelium-independent) compared with patients with hypertension and healthy controls (20).

3.1 Socio-demographic factors

According to a study conducted on the Birmingham registry of patients with MHT, white Caucasian patients were more likely than

African-Caribbean and South Asian patients to experience papilledema-related ocular problems (19). A study in Nigeria indicated patients with MHT had stressful lifestyles, were members of lower socio-economic groups, were older, had higher body mass indexes (BMI), had high BP, and had shorter in-time diagnoses of MHT (21).

Patients who had higher serum creatinine levels, who were current smokers, and who had no medical insurance had a significant association with MHT complications (22). A study conducted by Hertz et al. using the National Health and Nutrition Examination Survey (NHANES) 1999–2002 data indicated higher prevalence rates of hypertension in Black people compared to white people and a growing disparity in BP control among those treated using pharmacological agents (23).

3.2 Genetic factors

According to a study conducted using the Bordeaux, Birmingham, and Amsterdam MHT registries, ethnic minorities had a higher risk of MHT (15). Black patients had a higher incidence and more complications than white patients (22). In the USA, non-Hispanic Black patients had poor BP control compared to non-Hispanic white patients, and a higher prevalence of HTN was observed among non-Hispanic Black patients (24, 25).

Kalinowski et al. reported that Black patients' endothelial cells had an increased release of both oxygen-free radicals and peroxynitrite and a reduced release of biologically active nitric oxide (NO). The study implied that there are differences in vascular function among patients of different races (26).

Another factor contributing to racial/ethnic pathophysiological differences in the mechanisms of HTN was BMI. The BMI of non-Hispanic Black patients was higher compared to non-Hispanic white patients and Chinese and Asian patients, resulting in a high prevalence of HTN (27).

Seven single-nucleotide polymorphisms (G589S, R597H, T594M, R624C, G442V, E632G, and V434M) were identified in the β subunit of the epithelial sodium channel (ENaC) (*SCNN1β* gene). The threonine-to-methionine point one mutation has only shown an association with HTN at position 594 (T594M). Persons of African origin have approximately 6% of the T594M allele, which is associated with elevated HTN risk in the African-American population, but this has not been found in any white patients (28).

4 Pathophysiology of malignant hypertension

There are various factors associated with the pathogenesis of MHT, although the underlying mechanism leading to MHT is not fully understood. Fibrinoid arteriolar necrosis in vascular tissue beds is the hallmark pathophysiological marker of MHT (9). Appropriate tissue blood perfusion is maintained by the auto-regulatory arterial and arteriolar processes which prevent the increase in pressure from being transmitted to the smaller, more distal vessels. During severe HTN, this autoregulation eventually fails and the vascular wall of arterioles and capillaries becomes damaged due to the rise in BP. The vascular endothelium then allows plasma constituents (including fibrinoid material) to enter the vascular wall, thereby narrowing or obliterating the vascular lumen (29).

Macrovascular and microvascular endothelium dysfunction is one of the abnormalities found in MHT patients (20). Thrombotic microangiopathies have resulted from the activation of the renin–angiotensin–aldosterone system (RAAS) and impairment of the intravascular prothrombotic state (agglutination/coagulation) along with excessive endothelial injury (20, 30) (Figure 1).

Significant activation of the RAAS is evident in patients with MHT and may also contribute to the development of fibrinoid necrosis (31). In patients with MHT, there is evidence that irrespective of the impact of BP elevation on plasma renin activity, angiotensin 2-dependent aldosterone secretion was more profound than in patients with severe HTN (32, 33).

The basic pathophysiology of MHT is summarized in Figure 1.

4.1 Symptoms of malignant hypertension

In many cases, there are no symptoms associated with high blood pressure. However, this is not the case with MHT (16). During the MHT phase, a visual disturbance is one of the MHT symptoms. Retinopathy secondary to MHT is divided into grades A and B. Grade A retinopathy includes arteriolar narrowing and focal constriction of the retina and it corresponds to non-MHT changes. Grade B retinopathy corresponding to MHT includes linear flame-shaped hemorrhages, exudates, and/or cotton wool spot changes with or without papilledema (34).

Furthermore, sudden onset of headache, nausea, vomiting, visual disturbances, and visual field loss [in some cases, the symptoms depend on the damaged organ (e.g., brain) and include restlessness, confusion, seizures, and coma] are the signs and symptoms of MHT encephalopathy (35, 36).

MHT also results from acute renal failure (37). Malignant hypertensive patients have been shown to have severe renal dysfunction and a good cardiovascular risk profile compared to patients with controlled HTN (38). A long follow-up period and close BP control are required to preserve renal function (32, 39).

Clinically, thrombotic microangiopathy (TMA) is defined as microangiopathic hemolytic anemia, thrombocytopenia, and increased serum lactate dehydrogenase (LDH), all of which are frequently seen in patients with MHT (30).

Pulmonary edema has also been associated with MHT (38).

5 Complications of malignant hypertension

Macrovascular and microvascular function abnormalities are one of the major complications of MHT (20, 40). Malignant

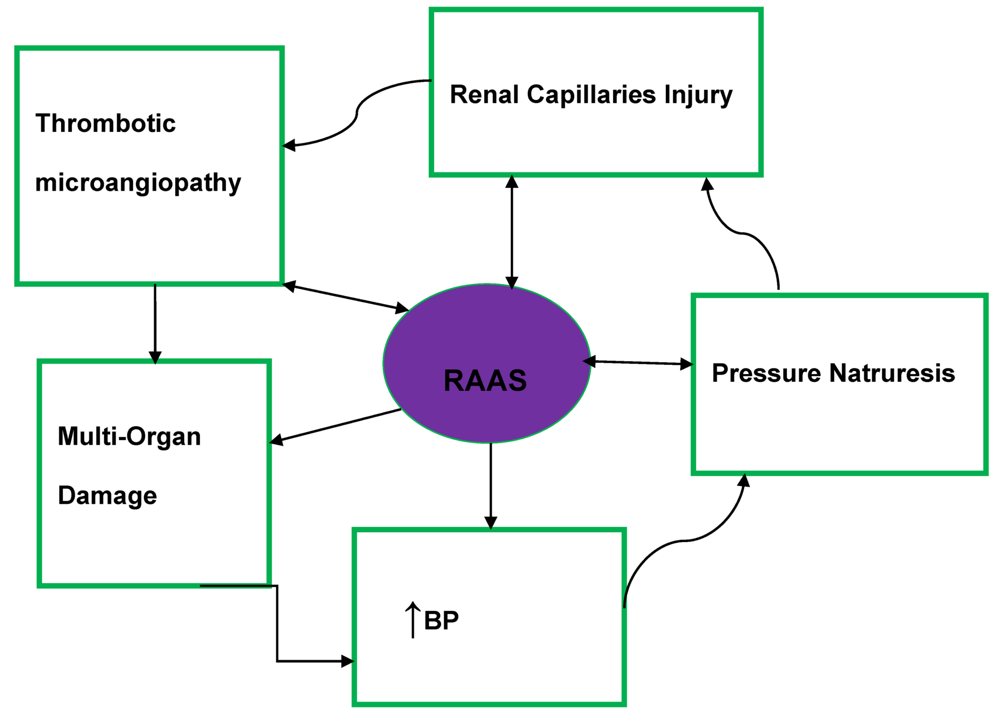


FIGURE 1
Malignant hypertension pathophysiology diagram. RAAS, renin–angiotensin–aldosterone system; BP, blood pressure.

TABLE 2 Target organs damaged by MHT.

Target organs	Complication due to MHT
Heart	Heart attack, aortic dissection, chest pain (angina), and arrhythmias (irregular heartbeat)
Brain	Reversible encephalopathy syndrome
Kidneys	Proteinuria
Eyes	Retinopathy (serous retinal detachment)
Blood vessels	Fibrinoid necrosis

hypertension can also lead to stroke and encephalopathy (20, 41), heart damage (angina, heart attack, and arrhythmia), kidney failure, vision damage (permanent blindness), and pulmonary edema (16, 17, 20, 40, 42, 43) (Table 2).

A single-center retrospective study conducted by Mishima et al. indicated that patients with MHT had a wide range of distribution patterns in the brainstem and 60% of the patients had posterior reversible encephalopathy syndrome (PRES) (44) (Table 2).

6 Prognostic factors of malignant hypertension

The prognosis is typically favorable for those who obtain an early diagnosis and suitable antihypertensive medication. Due to the disease's tendency to advance quickly and produce irreversible end organ damage, the interval between diagnosis and therapy is crucial (3). The death rate for untreated MHT is 80% within 2 years. MHT can be fatal even with treatment; one study found that across 25 US hospitals, the hospital death rate was close to 7% and the readmission rate was 37% within 90 days (15).

7 Assessment of malignant hypertension

7.1 Diagnosis of malignant hypertension

In many patients, the initial diagnosis of MHT is frequently missed which results in the diagnosis only being established when target organ damage occurs (14).

Some evidence suggests that a diagnosis of MHT can be made when a patient presents with acutely and quickly raised BP in cardiovascular disease (CVD) and chronic kidney disease (CKD) stages 4 and 5, respectively (1).To differentiate between a hypertensive urgency, emergency, or MHT, healthcare providers must perform a comprehensive assessment. A patient's symptoms will determine the kinds of investigation tests they undergo, which could include an electrocardiogram (EKG), a chest x-ray, an eye exam to check for signs of bleeding or damage to the eyes, a neurological exam to assess brain function, a physical examination, a toxicology serum drug level study, a urinalysis, liver function tests, and renal function tests (17).

Malignant hypertension is diagnosed clinically when there is evidence of organ damage from a fundoscopic eye examination, a chest x-ray, urine analysis, blood tests, and high blood pressure (taken using both arms) at or above 180/120 mmHg (1, 2, 45).

In addition, one of several possible presentations is also hypertension-mediated multi-organ damage (2, 5). Typically, concurrent bilateral grade 3 (flame or dot-shaped hemorrhages, cotton wool spots, hard exudates, and microaneurysms) or grade 4 hypertensive retinopathy (bilateral papilledema), as defined by Keith and Wagner's classification, is required for a clinical diagnosis of MHT (9).

8 Malignant hypertension treatment and prevention methods

There are limited therapeutic options specifically indicated for MHT (3, 46), and its treatment depends on expert decision-making (11). According to the National Institute for Health and Care Excellence (NICE) guideline, there is no consensus on the BP targets, BP reduction frequency, or type of drugs to administer to patients when treating MHT. However, the goal of therapy for MHT is to rapidly lower the mean arterial pressure by approximately 10%–15% in the first hour, and by no more than 25% compared with baseline by the end of the first day of treatment (47) (Table 3).

According to the British and Irish Hypertension Society regarding the speed of BP reduction and BP targets in uncomplicated MHT (eye changes alone), BP is to be lowered within days, aiming for a gradual reduction to reach the target BP within weeks. For example, within 24 h, BP should be lowered to <200/120 mmHg, within a week to <160/100 mmHg, and then to <140/90 mmHg within 6–12 weeks (9) (Table 3).

The latest hypertension guidelines provide a BP goal and the rate of BP reduction during treatment. Large and sudden reductions in BP must be avoided in patients with MHT as this can exacerbate ischemic lesions. The gradual increase in BP control allowed gradual healing of necrotizing vascular lesions (8) (Table 3).

Since MHT constitutes a hypertensive emergency, the ESC position document on the management of hypertensive emergencies advises using intravenous BP-lowering medicines in patients with acute presentations. Because there are no randomized controlled trials on various treatment approaches, the position paper does recognize that any recommendations are based on clinical experience and consensus (8, 42) (Table 3).

Parenteral antihypertensive drugs are used for the treatment of MHT (46, 48–51) (Table 4).

Once the target BP range is achieved in patients with MHT, oral antihypertensive treatment is progressively introduced at the clinician's discretion (46, 50) (Table 4).

Based on the reviewed works in the literature above and using the latest hypertension guidelines, the current treatment protocol for MHT is depicted in Figure 2 (5, 8, 46, 52, 53). A retrospective cohort study conducted by Endo et al. reported that in individuals experiencing hypertensive emergencies, early administration of renin-angiotensin system (RAS) inhibitors aids in the recovery of renal function following an abrupt decrease in estimated glomerular filtration rate (eGFR). In addition, compared to calcium channel blockers (CCB), renin-angiotensin system inhibitor (RASi) has a stronger positive impact on 2-year renal survival (54).

Non-pharmacological prevention modalities can also prevent MHT. Dr. Walter Kempner began using "The Rice Diet," named

TABLE 3 Agreement and disagreement in latest hypertension guidelines regarding BP reduction rate and BP target in malignant hypertension.

Guidelines	BP reduction rate and BP goal	Drug choice	Agreement and disagreement
2023 ESH (1)	The target blood pressure range for adults is below 130/80 mmHg for those 18–64 years old, below 140/80 mmHg for those 65–79 years old, and 140–150/80 mmHg for those 80 years and above.	Labetalol and nicardipine are the first-line treatment. Nitroprusside and urapidil are the alternatives.	There seems to be agreement with the ESC/ESH 2018 and ISH 2020 guidelines. There is disagreement with the AHA/ACC 2017 and NICE 2019 guidelines.
ISH 2020 (10)	Reduce mean arterial pressure (MAP) by 20%–25% over several hours.	Labetalol and nicardipine are the first-line treatment while nitroprusside and urapidil are the alternatives.	There seems to be agreement with the ESC/ESH 2018 and 2023 ESH guidelines. There seems to be disagreement with the AHA/ACC 2017 and NICE 2019 guidelines.
NICE 2019 (11)	There are no BP targets, BP reduction rate, or specific medications for patients with MHT.	No specific antihypertension medications.	It seems to be in disagreement with the ESC/ESH 2018, ISH 2020, and 2023 ESH guidelines. There seems to be agreement with the AHA/ACC 2017 guideline.
ESC/ESH 2018 (5)	Reduce MAP by 20%–25% over several hours.	Labetalol and nicardipine are the first-line treatment. Nitroprusside and urapidil are the alternatives.	There seems to be agreement with the ISH 2020 and 2023 ESH guidelines. It appears that the AHA/ACC 2017 and NICE 2019 guidelines disagree with this guideline.
AHA/ACC 2017 (6)	Not clearly stated.	No specific antihypertension medications.	There seems to be disagreement with the ESC/ESH 2018, ISH 2020, 2023 ESH, and BIHS guidelines. However, there seems to be agreement with the NICE 2019 guideline.
BIHS position document (9)	For uncomplicated MHT, target BP <135/85 mmHg at home) within days to weeks (6–12 weeks). For complicated MHT, does not necessarily favor certain rates of BP lowering.	For uncomplicated MHT (eye changes only), 25 mg oral atenolol, 5 mg oral amlodipine/30 mg long-acting oral nifedipine. For complicated MHT, no specific antihypertension medications.	There is no full agreement with ESC/ESH 2018, ISH 2020, and 2023 ESH guidelines. There seems to be disagreement with the AHA/ACC 2017 and NICE 2019 guidelines.

AHA, American Heart Association; ACC, American Collage of Cardiology; BIHS, British and Irish Hypertension Society.

TABLE 4 Parenteral antihypertensive drugs used for the treatment of MHT.

Drugs	Dosage and administration
Clevidipine	Use 1–2 mg/h in an IV infusion with rapid titration to 4–6 mg/h and a maximum dose of 16 mg/h or less. Its duration of action is 5–15 min.
Enalaprilat	Administer 1.25–5 mg QID IV and the duration of action is approximately 6 h to more than 12 h.
Fenoldopam	Administer 0.1 µg/kg min in an IV with a maximum dose of 1.6 µg/kg/min. It has a 30–60 min duration.
Nicardipine	Uses 5–15 mg per hour in an IV infusion and the maximum dose we use is 30 mg/h. The duration of action is approximately 1.5 h to more than or equal to 4 h.
Nitroglycerin	Administer 5–100 µg/min in an IV infusion. It has a 5–10 min duration of action.
Nitroprusside	Administer 0.25–10 µg/kg per minute in an IV infusion. The cyanide toxicity is minimized by administering a short infusion and not exceeding 2 µg/kg/min. Its duration of action is 1–10 min. To avoid cyanide toxicity, patients who receive higher doses (i.e., >500 µg/kg at a rate exceeding 2 µg/kg/min) should receive a sodium thiosulfate infusion.
Esmolol	Use a 250–500 µg/kg loading dose over 1 min and then initiate an IV infusion at 25–50 µg/kg/min, using a maximum dose of 300 µg/kg min. Its duration of action is 10–30 min.
Labetalol	Administer a bolus dose of 20 mg followed by a 20–80 mg IV infusion every 10 min (maximum 300 mg). Its duration of action is 2–4 h.
Metoprolol	Administer 1.25–5 mg followed by a 2.5–15 mg IV infusion every 3–6 h. The duration of action is 5–8 h
Urapidil	Administer 10–50 mg with a slow IV injection every 5 min based on the patient's BP record.

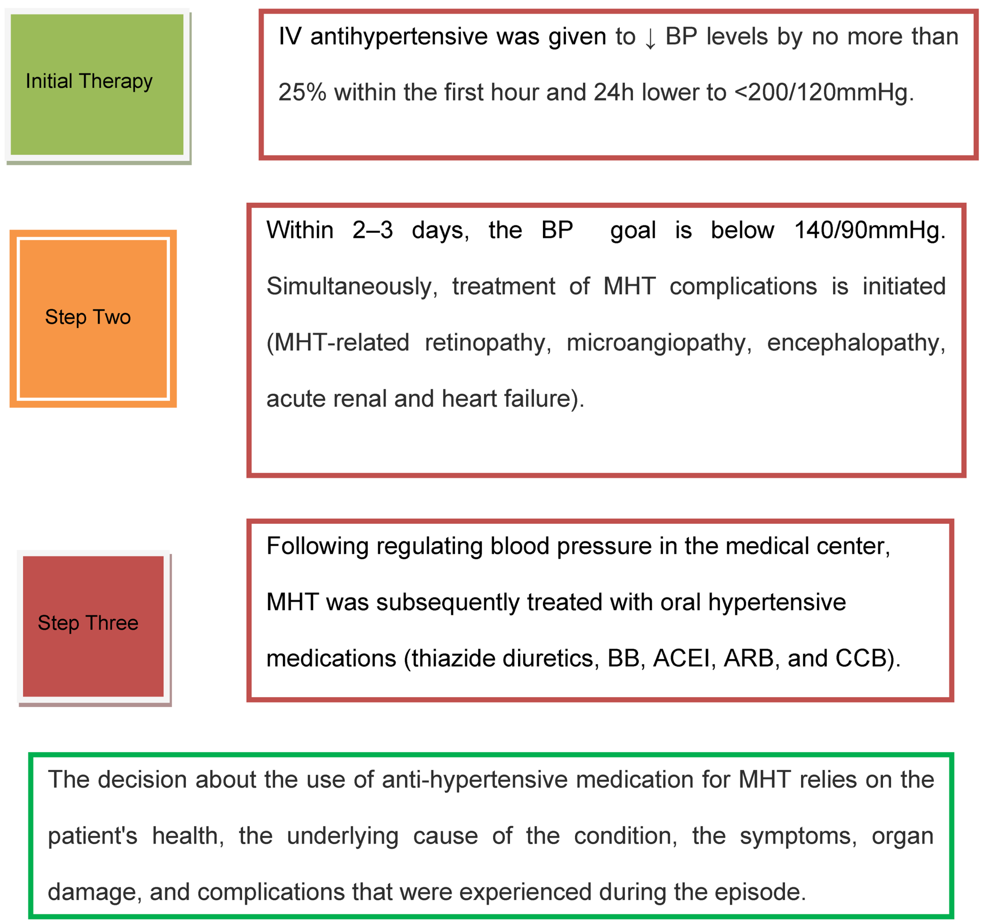


FIGURE 2
Malignant hypertension treatment protocol. IV, intravenous; MHT, malignant hypertension; BP, blood pressure; BB, beta-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

thus because the patients consumed a bowl of white rice with every meal, to treat patients with kidney disease and MHT in 1934 while he was a physician at Duke Hospital. At the time, there was no other treatment for these conditions. Dr. Kempner realized that the best way to avoid and treat these disorders would be to follow a diet low in added salt and fat (55).

Therefore, it is advisable that patients with MHT frequently check their blood pressure, take their medicine as directed, eat a nutritious diet low in saturated fat and salt, stop smoking if they already do, and maintain a healthy weight (16).

Clinically, a significant risk factor for MHT is the self-discontinuation of antihypertensive medication by patients who have previously experienced MHT. Thus, long-term continuous follow-up is very important for prevention of MHT.

9 Conclusion and future perspectives

Malignant hypertension requires prompt and efficient treatment because it is the most severe kind of hypertension that affects target organs. There are a number of alternatives available for treating MHT, with the International Society of Hypertension (ISH) 2020 and ESC/ESH 2018 recommendations suggesting the use of labetalol and nicardipine as the first-line choice, with urapidil and nitroprusside serving as alternative medications.

An elevated risk of MHT has been linked to many socio-demographic factors and genetic factors. The international scientific community and governmental and non-governmental organizations, particularly those involved in hypertension research, should examine the new international MHT studies and conduct additional MHT research.

Author contributions

AT: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SA: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, 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.

References

1. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension. *J Hypertens*. (2023) 41(12):1874–2071. doi: 10.1097/HJH.0000000000003480

2. Cremer A, Amraoui F, Lip GY, Morales E, Rubin S, Segura J. From malignant hypertension to hypertension-MOD: a modern definition for an old but still dangerous emergency. *J Hum Hypertens*. (2016) 30(8):463–6. doi: 10.1038/jhh.2015.112

3. Boulestreau R, van den Born BJH, Lip GY, Gupta A. Malignant hypertension: current perspectives and challenges. *J Am Heart Assoc*. (2022) 11(7):e023397. doi: 10.1161/JAHA.121.023397

4. European Society of Cardiology. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. (2024). https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Elevated-Blood-Pressure-and-Hypertension (cited November 16, 2024)

5. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. (2018) 39(33):3021–104. doi: 10.1093/eurheartj/ehy339

6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. (2018) 71(6):1269–324. doi: 10.1161/HYP.0000000000000066

7. Rubin S, Cremer A, Boulestreau R, Rigothier C, Kuntz S, Gosse P. Malignant hypertension: diagnosis, treatment and prognosis with experience from the Bordeaux cohort. *J Hypertens*. (2019) 37(2):316–24. doi: 10.1097/HJH.0000000000001913

8. van den Born BH, Lip GYH, Brguljan-Hitij J, Cremer A, Segura J, Morales E, et al. ESC council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother*. (2019) 5(1):37–46. doi: 10.1093/ehjcvp/pvy032

9. Kulkarni S, Glover M, Kapil V, Abrams SML, Partridge S, McCormack T, et al. Management of hypertensive crisis: British and Irish hypertension society position document. *J Hum Hypertens*. (2022) 37(10):863–79. doi: 10.1038/s41371-022-00776-9

10. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 international society of hypertension global hypertension practice guidelines. *Hypertension*. (2020) 75(6):1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026

11. The National Institute for Health and Care Excellence. *Hypertension in Adults: Diagnosis and Management*. NICE guidelines (2019). Available online at: https://www.nice.org.uk/guidance/ng136/resources/hypertension-in-adults-diagnosis-and-management-pdf-66141722710213 (cited May 23, 2023)

12. Bress AP, Anderson TS, Flack JM, Ghazi L, Hall ME, Laffer CL, et al. The management of elevated blood pressure in the acute care setting: a scientific statement from the American Heart Association. *Hypertension*. (2024) 81(8): e94–e106. doi: 10.1161/HYP.0000000000000238

13. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. (2024) 45(38):3912–4018. doi: 10.1093/eurheartj/ehae178

14. Shantsila A, Lip GY. Malignant hypertension revisited—does this still exist? *Am J Hypertens*. (2017) 30(6):543–9. doi: 10.1093/ajh/hpx008

15. Domek M, Gumprecht J, Lip GYH, Shantsila A. Malignant hypertension: does this still exist? *J Hum Hypertens*. (2020) 34(1):1–4. doi: 10.1038/s41371-019-0267-y

16. Prestige ER. *Malignant Hypertension—Causes, Symptoms, Complications*. Texas: Prestige ER (2021). Available online at: https://prestigeer.org/2021/03/19/malignant-hypertension-causes-symptoms-complications/ (cited March 31, 2023)

17. Cleveland Clinic. *Malignant Hypertension*. Cleveland Clinic (2023). Available online at: https://my.clevelandclinic.org/health/diseases/22285-malignant-hypertension (cited March 31, 2023)

18. Agrawal A, Wenger NK. Hypertension during pregnancy. *Curr Hypertens Rep*. (2020) 22(9):64. doi: 10.1007/s11906-020-01070-0

19. Shantsila A, Shantsila E, Beevers DG, Lip GYH. Predictors of 5-year outcomes in malignant phase hypertension. *J Hypertens*. (2017) 35(11):2310–4. doi: 10.1097/HJH.0000000000001446

20. Shantsila A, Dwivedi G, Shantsila E, Butt M, Beevers DG, Lip GY. Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension*. (2011) 57(3):490–6. doi: 10.1161/HYPERTENSIONAHA.110.166314

21. Kadiri S, Olutade BO, Osobamiro O. Factors influencing the development of malignant hypertension in Nigeria. *J Hum Hypertens*. (2000) 14(3):171–4. doi: 10.1038/sj.jhh.1000963

22. van den Born BJ, Koopmans RP, Groeneveld JO, van Montfrans GA. Ethnic disparities in the incidence, presentation, and complications of malignant hypertension. *J Hypertens*. (2006) 24(11):2299–304. doi: 10.1097/01.hjh.0000249710.21146.38

23. Hertz RP, Unger AN, Cornell JA, Saunders E. Racial disparities in hypertension prevalence, awareness, and management. *Arch Intern Med*. (2005) 165(18):2098–104. doi: 10.1001/archinte.165.18.2098

24. Balfour PC, Rodriguez CJ, Ferdinand KC. The role of hypertension in race-ethnic disparities in cardiovascular disease. *Curr Cardiovasc Risk Rep*. (2015) 9(4):18. doi: 10.1007/s12170-015-0446-5

25. Saeed A, Dixon D, Yang E. Racial disparities in hypertension prevalence and management: a crisis control? *Am Coll Cardiol*. (2020) 2021. doi: 10.1001/archinte.165.18.2098

26. Kalinowski L, Dobrucki IT, Malinski T. Race-specific differences in endothelial function. *Circulation*. (2004) 109(21):2511–7. doi: 10.1161/01.CIR.0000129087.81352.7A

27. Stevens J, Truesdale KP, Katz EG, Cai J. Impact of body mass index on incident hypertension and diabetes in Chinese Asians, American whites, and American blacks: the people's republic of China study and the atherosclerosis risk in communities study. *Am J Epidemiol*. (2008) 167(11):1365–74. doi: 10.1093/aje/kwn060

28. Nesbitt S, Victor RG. Pathogenesis of hypertension in African Americans. *Congest Heart Fail*. (2004) 10(1):24–9. doi: 10.1111/j.1527-5299.2004.02021.x

29. Pickering GW. The pathogenesis of malignant hypertension. *Circulation*. (1952) 6(4):599–612. doi: 10.1161/01.CIR.6.4.599

30. Akimoto T, Muto S, Ito C, Takahashi H, Takeda S, Ando Y, et al. Clinical features of malignant hypertension with thrombotic microangiopathy. *Clin Exp Hypertens*. (2011) 33(2):77–83. doi: 10.3109/10641963.2010.503303

31. González R, Morales E, Segura J, Ruilope LM, Praga M. Long-term renal survival in malignant hypertension. *Nephrol Dial Transplant*. (2010) 25(10):3266–72. doi: 10.1093/ndt/gfq143

32. Amraoui F, Bos S, Vogt L, van den Born BJ. Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study. *BMC Nephrol*. (2012) 13:71. doi: 10.1186/1471-2369-13-71

33. van den Born BJ, Koopmans RP, van Montfrans GA. The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. *Am J Hypertens*. (2007) 20(8):900–6. doi: 10.1016/j.amjhyper.2007.02.018

34. Tajunisah I, Patel DK. Malignant hypertension with papilledema. *J Emerg Med*. (2013) 44(1):164–5. doi: 10.1016/j.jemermed.2011.05.042

35. Krieglsteiner S, Nussbaumer K, Haring H, Aichner F. Hypertensive emergencies. *Lancet*. (2000) 356(9239):1443. doi: 10.1016/S0140-6736(05)74085-X

36. Acelajado MC, Calhoun DA. Resistant hypertension, secondary hypertension, and hypertensive crises: diagnostic evaluation and treatment. *Cardiol Clin*. (2010) 28(4):639–54. doi: 10.1016/j.ccl.2010.07.002

37. Gassanov N, Pollok M, Er F. Acute renal failure associated with malignant hypertension. *Dtsch Med Wochenschr*. (2009) 134(44):2224–7. doi: 10.1055/s-0029-1241930

38. Amraoui F, Van Der Hoeven NV, Van Valkengoed IG, Vogt L, Van Den Born BJ. Mortality and cardiovascular risk in patients with a history of malignant hypertension: a case-control study. *J Clin Hypertens*. (2014) 16(2):122–6. doi: 10.1111/jch.12243

39. van der Merwe W, van der Merwe V. Malignant hypertension: a preventable emergency. *N Z Med J*. (2013) 126(1380):39–45.

40. Boulestreau R, Śpiewak M, Januszewicz A, Kreutz R, Guzik TJ, Januszewicz M, et al. Malignant hypertension: a systemic cardiovascular disease. *J Am Coll Cardiol*. (2024) 83(17):1688–701. doi: 10.1016/j.jacc.2024.02.037

41. Polgreen LA, Suneja M, Tang F, Carter BL, Polgreen PM. Increasing trend in admissions for malignant hypertension and hypertensive encephalopathy in the United States. *Hypertension*. (2015) 65(5):1002–7. doi: 10.1161/HYPERTENSIONAHA.115.05241

42. Shantsila A, Lip GYH. Malignant hypertension: not quite an obsolete diagnosis yet. *J Hypertens*. (2019) 37(2):282–3. doi: 10.1097/HJH.0000000000001974

43. Saito T, Hasebe N. Malignant hypertension and multiorgan damage: mechanisms to be elucidated and countermeasures. *Hypertens Res*. (2021) 44(1):122–3. doi: 10.1038/s41440-020-00555-4

44. Mishima E, Funayama Y, Suzuki T, Mishima F, Nitta F, Toyohara T, et al. Concurrent analogous organ damage in the brain, eyes, and kidneys in malignant hypertension: reversible encephalopathy, serous retinal detachment, and proteinuria. *Hypertens Res*. (2021) 44(1):88–97. doi: 10.1038/s41440-020-0521-2

45. Gosse P, Coulon P, Papaioannou G, Litalien J, Lemetayer P. Impact of malignant arterial hypertension on the heart. *J Hypertens*. (2011) 29(4):798–802. doi: 10.1097/HJH.0b013e3283430b12

46. Lewek J, Bielecka-Dąbrowa A, Maciejewski M, Banach M. Pharmacological management of malignant hypertension. *Expert Opin Pharmacother*. (2020) 21(10):1189–92. doi: 10.1080/14656566.2020.1732923

47. Kaplan NM, Victor RG, Flynn JT. *Kaplan's Clinical Hypertension*. 11th ed. Philadelphia: Wolters Kluwer (2015).

48. Varon J. Treatment of Acute Severe Hypertension. *Drugs*. (2008) 68(3):283–97. doi: 10.2165/00003495-200868030-00003

49. Marik PE, Varon J. Hypertensive Crises. *Chest*. (2007) 131(6):1949–62. doi: 10.1378/chest.06-2490

50. Gosse P, Boulestreau R, Brockers C, Puel C, Rubin S, Cremer A. The pharmacological management of malignant hypertension. *J Hypertens*. (2020) 38(11):2325–30. doi: 10.1097/HJH.0000000000002547

51. Prodan G, Leucuța D-C, Marc G, Simu H, Nastasă C, Oniga O. The Impact of urapidil use in hypertension prehospital emergency intervention. *Farmacia J*. (2017) 65(6):896–99.

52. Aronow WS. Treatment of hypertensive emergencies. *Ann Transl Med*. (2017) 5(Suppl 1):S5. doi: 10.21037/atm.2017.03.34

53. Chakraborty DS, Lahiry S, Choudhury S. Hypertension clinical practice guidelines (ISH, 2020): what is new? *Med Princ Pract*. (2022) 30(6):579–84. doi: 10.1159/000518812

54. Endo K, Hayashi K, Hara Y, Miyake A, Takano K, Horikawa T, et al. Impact of early initiation of renin-angiotensin blockade on renal function and clinical outcomes in patients with hypertensive emergency: a retrospective cohort study. *BMC Nephrol*. (2023) 24(1):68. doi: 10.1186/s12882-023-03117-1

55. Rosati KG. *The New Rice Diet Program for Reversing Heart Disease through Nutrition, Exercise, and Spiritual Renewal*. Urayasu, Japan: Turner Publishing Company (2008).

TYPE Original Research
PUBLISHED 09 January 2025
DOI 10.3389/fcvm.2024.1429112

Check for updates

OPEN ACCESS

EDITED BY
Guido Iaccarino,
Federico II University Hospital, Italy

REVIEWED BY
Santiago J. Ballaz,
Yachay Tech University, Ecuador
Chengchun Tang,
Southeast University, China

*CORRESPONDENCE
Xiong Min
✉ 12124975@qq.com

†These authors have contributed equally to this work

RECEIVED 07 May 2024
ACCEPTED 23 December 2024
PUBLISHED 09 January 2025

CITATION
Hongyu L, Ga L, Yiqian Z, Qiuyu X, Kemin L, Maiyongcuo Q and Min X (2025) Impact of high hemoglobin levels on carotid artery intima–media thickness and its predictive value for hypertension in high-altitude areas: a real-world study.
Front. Cardiovasc. Med. 11:1429112.
doi: 10.3389/fcvm.2024.1429112

Impact of high hemoglobin levels on carotid artery intima–media thickness and its predictive value for hypertension in high-altitude areas: a real-world study

Long Hongyu[1†], Long Ga[2†], Zhang Yiqian[1], Xu Qiuyu[3], Li Kemin[4], Qing Maiyongcuo[2] and Xiong Min[1*]

[1]Hyperbaric Oxygen, Chengdu First People's Hospital, Chengdu, Sichuan, China, [2]Internal Medicine Department, Dege County People's Hospital of Ganzi Prefecture, GanZi, Sichuan, China, [3]Internal Medicine Department, The Second People's Hospital of Jiangyang District, Luzhou City, Sichuan, China, [4]The Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China

Background and purpose: The hemoglobin levels in the peripheral blood of individuals living at high altitudes are significantly higher than normal levels. These levels are closely associated with atherosclerosis and cardiovascular events. This study aimed to investigate the correlation between hemoglobin levels in the peripheral blood and hypertension in high-altitude regions, providing a basis for preventing and treating primary hypertension in these regions.
Materials and methods: From May 2020 to May 2021, patients diagnosed with primary hypertension in plateau regions of China were selected as participants. The clinical data, including lifestyle habits and blood biochemical indicators, were collected from the clinical case database for patients meeting the inclusion criteria. The logistic regression analysis was performed to identify factors influencing carotid intima–media thickness in patients with primary hypertension in plateau regions. The ROC curve was plotted to analyze the impact of peripheral blood hemoglobin levels on hypertension, determine the hemoglobin threshold for predicting hypertension in plateau areas, and evaluate the predictive value of hemoglobin level for hypertension.
Results: A total of 200 patients (105 men with an average age of 64.8 ± 12.75 years and 95 women with an average age of 69.5 ± 11.54 years) were enrolled in this study. Logistic regression analysis revealed that age, CO_2-CP, ALT, APOB, CRP, and HGB were independent risk factors for increased carotid artery intima–media thickness ($P < 0.05$). The hemoglobin threshold for predicting hypertension in high-altitude areas was 131 g/L. The area under the ROC curve for predicting hypertension with elevated hemoglobin level was 0.799 (0.719–0.880).
Conclusion: Elevated hemoglobin levels contribute to the thickening of the carotid artery intima–media layer and hold predictive value for high-altitude hypertension.

KEYWORDS
carotid intima-media thickness, hemoglobin, hypertension, plateau region, predictive value, real-world study

Abbreviations
BMI, body mass index; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CO2-CP, carbondioxide combining power; CREA, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma glutamyl transpeptidase; TG, triglycerides; TCHO, total cholestero; HDL-C, high density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, blood platelet; ESR, erythrocyte sedimentation rate.

Highlights

- Hemoglobin levels effect carotid artery intima–media thickness
- High hemoglobin predictive value for hypertension in plateau regions

1 Introduction

Hypertension is one of the most common cardiovascular diseases globally, posing a significant risk of conditions such as stroke, coronary heart disease, and heart failure, leading to mortality among humans. According to the largest hypertension research report globally, the number of adults with hypertension, aged 30–79 years, increased from 650 million to 1.28 billion between 1990 and 2019 (1).

The primary pathological feature of hypertension is arteriosclerosis, which affects both large and small arteries. The thickness of the carotid artery intima-media (CIMT) serves as a marker for vascular structural abnormalities, such as atherosclerosis, and is of significant importance for the prevention and treatment of hypertension. Hypertension acts as a catalyst for the thickening of the carotid intima-media. Prolonged hypertension can alter hemodynamics, damage endothelial cells, and mediate the adhesion of lipids and platelets to the vascular wall, gradually resulting in increased CIMT. Hypertension and CIMT thickening influence each other; sustained high blood pressure accelerates the thickening process, increasing the risk of cardiovascular and cerebrovascular diseases. Conversely, increased CIMT can elevate blood pressure, creating a vicious cycle. Studies have shown a close correlation between IMT thickening and the onset and progression of hypertension, reflecting pathological changes in the vascular wall and its response to hemodynamic factors. By monitoring carotid IMT, cardiovascular risks in hypertensive patients can be identified early, guiding clinical interventions that help reduce the incidence of cardiovascular events (2–4). Therefore, carotid IMT plays an increasingly important role in the early diagnosis and management of hypertension, and exploring the factors influencing intima-media thickening is crucial for the prevention and treatment of hypertension.

The global plateau region is vast, with a permanent population of 140 million (2). The unique environmental factors of the plateau region may affect the occurrence and development of hypertension. Studies indicate that the prevalence of hypertension is significantly higher in plateau regions than in plain areas. Moreover, the incidence of hypertension also significantly increases with the increase in altitude (5, 6). Therefore, investigating the risk factors associated with primary hypertension in plateau regions is essential for its prevention, diagnosis, and treatment.

Previous studies have indicated a correlation between hemoglobin levels and hypertension, with an increase in hemoglobin typically thought to promote elevated blood pressure through its effects on blood viscosity and hemodynamics (7–10). In high-altitude regions, where oxygen levels are lower, individuals often experience a significant increase in hemoglobin to adapt to the hypoxic environment. While this adaptation enhances oxygen transport, it may also raise the risk of hypertension. However, the relationship between elevated hemoglobin levels and increased blood pressure in high-altitude populations has not been thoroughly investigated. Some studies have observed lower blood pressure levels among residents of high-altitude areas; however, the underlying mechanisms may involve complex environmental factors, genetic backgrounds, and individual physiological characteristics. Additionally, previous research often lacked large sample sizes and longitudinal data, failing to adequately consider the impact of lifestyle and other comorbidities on hypertension. Therefore, further exploration of the relationship between hemoglobin levels and blood pressure in high-altitude populations is crucial for providing a more comprehensive understanding and clinical guidance, highlighting its research significance.

This study examined the predictive significance of different hemoglobin levels for hypertension among populations residing in high-altitude regions, using CIMT as an early indicator of arterial sclerosis. The study further explored the impact of hemoglobin levels on hypertension in this population, offering insights for the development of hypertension prevention and management strategies tailored to high-altitude areas.

2 Materials and methods

2.1 Research objectives

This retrospective study, conducted in real-world settings, enrolled patients diagnosed with primary hypertension in plateau regions from May 2020 to May 2021. All patients came from Dege County People's Hospital of Ganzi Prefecture, GanZi, Sichuan, China. The diagnostic criteria for hypertension included blood pressure measurements taken three times on different days without antihypertensive medication, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. The diagnosis of carotid atherosclerosis relied on carotid ultrasound examination, with thickening of the intima–media layer defined as a maximum intima–media thickness (IMT) of the common carotid artery ≥1.0 mm, or maximum IMT of the carotid sinus ≥1.2 mm, and carotid plaque defined as IMT ≥1.5 mm (7). Patients with malignant hypertension, secondary hypertension, and those with conditions such as diabetes affecting CIMT were excluded from the study. Patients with diseases that affect hemoglobin levels, such as hematological malignancies and unexplained anemia, were also excluded. This study received ethical approval from Chengdu Hospital of Integrated Traditional Chinese and Western Medicine and was exempted from informed consent.

2.2 Data collection

Patient data were retrospectively collected from the clinical medical records database, encompassing information such as age, sex, ethnicity, body mass index (BMI), waist circumference, lifestyle habits (diet and sleep), and underlying diseases, as well as blood routine, full blood lipids (fasting venous blood), fasting blood sugar, uric acid, myocardial enzymes, procalcitonin, and other blood biochemical indicators. Additionally, routine urine tests (morning midstream urine tests) were included in the dataset.

2.3 CIMT measurement

Ultrasound examinations were conducted using a color Doppler ultrasound detector (American GEe9, equipped with a 10-MHz linear array probe). During the procedure, the patient lay supine with their head slightly turned to the opposite side. Longitudinal and transverse scans were performed along the carotid artery, covering both sides, the carotid artery bifurcation, and the internal and external carotid arteries from various planes and angles. The CIMT and plaque status in the blood vessels were observed. In the ultrasound images, the carotid artery vessel wall appeared as two slightly bright parallel linear echoes, with the outer line representing the vessel's outer membrane and the inner line representing the vessel's intima. The vertical distance between these two lines indicated the thickness of the carotid artery intima. Measurements of the carotid artery intima–media thickness were obtained at three specific locations: the far end near the bifurcation of both carotid arteries, 1 cm above the bifurcation, and 1 cm above the start of the internal carotid artery on the back wall. The average of these measurements was calculated to determine the CIMT.

2.4 Statistical analysis

Statistical analysis was conducted using SAS 9.4 statistical software. Descriptive statistical analysis was initially performed on various indicators. The Shapiro-Wilk test was used to test for normality of distribution, and the Levene's test was used to test for the stability of variance. Quantitative data that conforms to a normal distribution were presented as mean (standard deviation) to indicate central tendency and dispersion, whereas qualitative data were expressed as rates or percentages. Logistic regression analysis was used to identify factors influencing intima–media thickness of the carotid artery. A P value <0.05 indicated a statistically significant difference. Furthermore, an ROC curve was plotted to predict hypertension using hemoglobin levels. The cutoff value for predicting hypertension and the area under the ROC curve for hemoglobin levels were calculated. We will use the Youden index to select the cutoff value. The Youden index is a statistical measure used to evaluate the effectiveness of diagnostic tests. It is particularly useful for determining the optimal threshold that distinguishes between two groups, typically those with and without a specific disease. The index is defined as the maximum vertical distance between the receiver operating characteristic (ROC) curve and the no-discrimination diagonal, which represents random guessing. This index helps assess the balance between the sensitivity and specificity of the test.

3 Results

3.1 Basic characteristics of the participants

The study enrolled 200 patients, including 105 men with an average age of 64.8 ± 12.8 years and 95 women with an average age of 69.5 ± 11.5 years. The majority of the study participants were Tibetan (99.5%), with farmers and herders constituting 86% of the occupations. More than 90% of the patients reported no history of smoking or alcohol consumption. Additionally, 31% of the patients were classified as obese. The basic characteristics of the study participants are summarized in Tables 1, 2.

3.2 Factors influencing the CIMT in logistic regression analysis

Age, sex, BMI, smoking history, alcohol history, waist circumference, blood test results, and so forth were the probable influencing factors in the logistic regression analysis (Table 1). The results indicated that age, CO_2-CP, ALT, APOB, CRP, and HGB were the probable influencing factors for the thickening of carotid intima–media ($P < 0.05$), with odds ratio (OR) and 95% confidence interval (CI) of 1.692 (1.059–2.704), 0.475 (0.290–0.777), 0.211 (0.091–0.489), 2.012 (1.131–3.579), 6.945 (1.177–40.972), and 0.540 (0.307–0.949), respectively. Conversely, the following factors raise the risk: CRP (up to seven times) and ApoB (it doubles). Further details of the logistic regression analysis are depicted in Table 3.

3.3 Predictive value of peripheral blood hemoglobin for high-altitude hypertension

The ROC curve depicting the predictive ability of peripheral blood hemoglobin for high blood pressure in high-altitude areas is shown in Figure 1. The threshold for HGB predicting high blood pressure in high-altitude regions is determined to be 131 g/L. Based on this threshold, the study participants were categorized into high-hemoglobin and low-hemoglobin groups. When peripheral blood hemoglobin levels were ≥131 g/L, the area under the ROC curve for predicting high blood pressure in high-altitude regions was 0.799, with its 95% CI = 0.719–0.880.

4 Discussion

Several studies have indicated a correlation between elevated hemoglobin levels and hypertension (11, 12). Huang Jianyu (12) and others explored the association between peripheral hemoglobin and arteriosclerosis. Their study involved 419 randomly selected hypertensive patients, and multiple logistic regression analysis identified hemoglobin as an independent risk factor for severe (OR = 1.025, 95% CI: 1.003–1.045, $P < 0.05$) and moderate (OR = 1.035, 95% CI: 1.008–1.056, $P < 0.05$)

TABLE 1 Basic characteristics of participants (part 1).

Variables	*n* (%)/Mean ± STD
Gender	
Male	105 (52.5%)
Female	95 (47.5%)
Age	67.0 ± 12.4
Weight	70.4 ± 13.7
Height	164.5 ± 7.8
Nationality	
Tibetan	199 (99.5%)
Han nationality	1 (0.5%)
Profession	
Employees of enterprises and institutions	21 (10.5%)
Self-employed/employed	7 (3.5%)
Farmer	145 (72.5%)
Herdsmen	27 (13.5%)
Smoking history	
No	188 (94.0%)
Yes	12 (6.0%)
Drinking history	
No	189 (94.5%)
Yes	11 (5.5%)
Diet situation	
Mainly rice	23 (11.5%)
Mainly highland barley	168 (84.0%)
Ainly rice + highland barley	7 (3.5%)
Mainly rice + highland barley + pasta	2 (1.0%)
Love food	
Meat-based	7 (3.5%)
Meats, vegetables and fruits	4 (2.0%)
Meats, vegetables, fruits, eggs, soy products	188 (94.0%)
Vegetarian diet	1 (0.5%)
Sleep time per day	
<6 h	10 (5.0%)
6–8 h	103 (51.5%)
9–12 h	86 (43.0%)
>12 h	1 (0.5%)
BMI	
<18.5	5 (2.5%)
18.5–23.9	66 (33.0%)
24–27.9	67 (33.5%)
≥28	62 (31.0%)
Waistline	
Abdominal obesity in men	76 (72.4%)
Abdominal obesity in women	71 (74.7%)
Family history	
No	194 (97.0%)
Hypertension	2 (1.0%)
Diabetes	1 (0.5%)
Unknown	3 (1.5%)

TABLE 2 Basic characteristics of participants (part 2).

Variables	*n* (%)/Mean ± STD
Admission blood pressure	
Diastolic blood pressure	95.9 ± 18.6
Systolic blood pressure	149.6 ± 28.6
Hypertension	140 (70.0%)
Normal blood pressure	54 (27.0%)
Unknown	6 (3.0%)
CIMT	
Left	1.0 ± 0.3
Right	1.0 ± 0.2
Thicken	132 (66.0%)
Norman	68 (34.0%)
Hemoglobin	150.0 ± 31.9
Abnormal (−)	19 (9.5%)
Normal	68 (34.0%)
Abnormal (+)	88 (44.0%)
Unknown	25 (12.5%)
Carotid atherosclerotic plaque formation	
Yes	154 (77.0%)
No	46 (23.0%)
Number of hardened plaques	
<2↑	128 (64.0%)
≥2↑	72 (36.0%)

CIMT, carotid intima-media thickness; STD, standard deviation; +, indicates greater than normal threshold; −, indicates less than the normal threshold.

arteriosclerosis in patients with hypertension. Furthermore, multifactor analysis in this study revealed a positive correlation between hemoglobin levels and CIMT, suggesting that higher hemoglobin levels increase the risk of hypertension development and hold the potential as a predictor of hypertension.

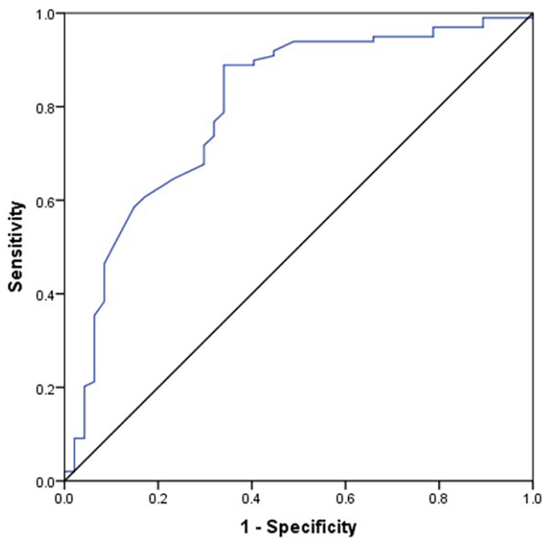
The mechanism by which increased hemoglobin levels increase the risk of hypertension remains unclear. Existing research suggests several potential mechanisms: (1) Activation of renin–angiotensin–aldosterone system (RAAS): Activation of RAAS leads to the conversion of renin into angiotensin II, which promotes vasoconstriction. Additionally, other tissues may produce angiotensin II and stimulate the production of erythropoietin. (2) Damage of endothelial cells: Endothelial cell damage may affect both blood pressure regulation and hemoglobin concentration. (3) Increased levels of growth factor: Elevated growth factor levels may promote endothelial cell damage, and these levels are positively correlated with hemoglobin levels. Additionally, studies have shown a positive correlation between serum hepatocyte growth factor levels and hypertension, potentially increasing the risk of hypertension.

In high-altitude regions, environmental changes such as increased altitude lead to hypoxia, resulting in elevated hemoglobin levels in the population. High hemoglobin levels not only contribute to atherosclerosis but also promote hypertension (8). Studies have indicated that elevated blood hemoglobin levels may increase the risk of hypertension in high-altitude populations (8). This study analyzed the risk factors for the thickening of carotid artery intima–media in patients with hypertension using multifactorial logistics regression analysis. The findings revealed that hemoglobin was a high-risk factor for carotid artery intima–media thickening in patients with hypertension, with a threshold of 131 g/L, which holds promise for predicting high-altitude hypertension. Simultaneously measuring hemoglobin levels and blood pressure can effectively predict the occurrence of hypertension. Studies have shown that elevated hemoglobin levels are often associated with an increased

TABLE 3 Logistic regression analysis of influencing factors of carotid artery intima-media thickness.

Variables	DF	PE	STD ERR	Chi-square value	*P*	OR	OR 95%CI	
Gender	1	0.366	0.302	1.470	0.225	1.442	0.798	2.606
Age	1	0.526	0.239	4.839	0.028	1.692	1.059	2.704
Smoking history	1	−0.975	0.817	1.424	0.233	0.377	0.076	1.871
Drinking history	1	0.287	1.068	0.072	0.789	1.332	0.164	10.811
Diet situation	1	0.010	0.013	0.559	0.455	0.010	−0.016	0.036
Love food	1	−0.298	0.357	0.698	0.404	0.742	0.369	1.494
Weight	1	−0.006	0.011	0.264	0.608	0.994	0.973	1.016
Height	1	−0.009	0.019	0.207	0.649	0.991	0.955	1.029
BMI	1	−0.056	0.180	0.098	0.754	0.945	0.665	1.344
Waistline	1	0.246	0.339	0.526	0.468	1.279	0.658	2.486
ALP	1	0.687	0.445	2.356	0.125	1.979	0.828	4.730
LDH	1	−0.099	0.279	0.125	0.724	0.906	0.524	1.566
CO2-CP	1	−0.744	0.251	8.792	0.003	0.475	0.290	0.777
CREA	1	0.625	0.337	3.445	0.064	1.869	0.966	3.616
ALT	1	−1.554	0.428	13.175	0.000	0.211	0.091	0.489
AST	1	−0.782	0.537	2.118	0.146	0.457	0.160	1.312
γ-GT	1	−0.151	0.310	0.236	0.628	0.860	0.469	1.580
TG	1	0.009	0.412	0.001	0.983	1.009	0.450	2.264
TCHO	1	0.242	0.334	0.522	0.470	1.273	0.661	2.453
HDL-C	1	0.338	0.261	1.670	0.196	1.402	0.840	2.340
ApoA1	1	−0.205	0.288	0.507	0.477	0.814	0.463	1.433
ApoB	1	0.699	0.294	5.651	0.017	2.012	1.131	3.579
LDL-C	1	0.541	0.318	2.902	0.089	1.718	0.922	3.203
CRP	1	1.938	0.906	4.580	0.032	6.945	1.177	40.972
WBC	1	−0.056	0.390	0.021	0.886	0.946	0.441	2.029
RBC	1	−0.401	0.304	1.749	0.186	0.669	0.369	1.214
HGB	1	−0.617	0.288	4.595	0.032	0.540	0.307	0.949
PLT	1	−0.070	0.398	0.031	0.861	0.933	0.428	2.034
ESR	1	0.629	0.531	1.406	0.236	1.876	0.663	5.306

PE, parameter estimation; DF, degree of freedom.



AUC(95%CI)	SD	P	Cut-off
0.799 (0.719, 0.880)	0.041	0.0001	131.00

FIGURE 1
The ROC curve depicting the predictive ability of peripheral blood hemoglobin for high blood pressure in high-altitude areas. AUC, area under curve; ROC, receiver operating characteristic.

risk of hypertension. By integrating these two important indicators, it becomes easier to identify potential hypertensive patients, thereby providing a basis for early intervention. Regular monitoring of hemoglobin and blood pressure not only aids in assessing cardiovascular health but also guides personalized treatment in clinical practice, enhancing the effectiveness of hypertension management. This underscored the potential value of peripheral blood hemoglobin detection in the early identification and prevention of hypertension in high-altitude populations.

The average hemoglobin (HGB) level among hypertensive individuals in China typically ranges from 120 to 140 g/L, with men generally exhibiting higher HGB levels than women. Studies indicate that in high-altitude areas, the HGB levels of residents are significantly higher than those of individuals living in flatland regions due to the effects of a hypoxic environment. Elevated HGB levels reflect the body's ability to adapt to low oxygen conditions, making it particularly important to maintain appropriate HGB levels in these areas. Normal HGB levels not only facilitate effective oxygen transport but also reduce the risk of carotid intima-media thickening, consequently decreasing the incidence of hypertension and its associated cardiovascular diseases. In high-altitude regions, sustaining optimal HGB levels is crucial for lowering the risk of carotid intima-media thickening, thereby improving overall cardiovascular health. Therefore, enhancing the monitoring and intervention of HGB levels in hypertensive populations will provide a solid foundation for preventing cardiovascular events.

In conclusion, this real-world study investigated the correlation between elevated peripheral blood hemoglobin levels and hypertension, as well as CIMT, in high-altitude populations. High hemoglobin levels can predict hypertension in these populations. However, given the limitations of this being a single-center, small-sample study, further validation from large-sample, high-quality studies is warranted.

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 Medical Ethics Committee of Chengdu First People's Hospital. 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 because exempt from signing informed consent by Medical Ethics Committee.

Author contributions

LH: Methodology, Writing – original draft, Conceptualization, Project administration. LG: Formal Analysis, Methodology, Resources, Writing – original draft. ZY: Data curation, Formal Analysis, Project administration, Resources, Writing – original draft. XQ: Conceptualization, Formal Analysis, Methodology, Writing – original draft. LK: Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. QM: Data curation, Formal Analysis, Methodology, Validation, Writing – original draft. XM: Conceptualization, Formal Analysis, Investigation, Supervision, Writing – review & editing, Writing – original draft.

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

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. (2021) 398(10304):957–80. doi: 10.1016/S0140-6736(21)01330-1

2. Portilla-Fernández E, Hwang SJ, Wilson R, Maddock J, Hill WD, Teumer A, et al. Meta-analysis of epigenome-wide association studies of carotid intima-media thickness. *Eur J Epidemiol*. (2021) 36(11):1143–55. doi: 10.1007/s10654-021-00759-z

3. Byrkjeland R, Stensæth KH, Anderssen S, Njerve IU, Arnesen H, Seljeflot I, et al. Effects of exercise training on carotid intima-media thickness in patients with type 2 diabetes and coronary artery disease. Influence of carotid plaques. *Cardiovasc Diabetol*. (2016) 15:13. doi: 10.1186/s12933-016-0336-2

4. Shimoda S, Kitamura A, Imano H, Cui R, Muraki I, Yamagism K, et al. Associations of carotid intima-media thickness and plaque heterogeneity with the risks of stroke subtypes and coronary artery disease in the Japanese general population: the circulatory risk in communities study. *J Am Heart Assoc*. (2020) 9(19):e017020. doi: 10.1161/JAHA.120.017020

5. Zhang Y, Yang Y, Wu X, Han B, Mao A, Gu D, et al. The association between altitude and the pre valence of hypertension among permanent highlanders. *Hypertens Res*. (2022) 45(11):1754–62. doi: 10.1038/s41440-022-00985-2

6. Peng W, Li K, Yan AF, Shi Z, Zhang J, Cheskin L, et al. Prevalence, management, and associated factor s of obesity, hypertension, and diabetes in Tibetan population compared with China overall. *Int J Environ Res Public Health*. (2022) 19(14):8787. doi: 10.3390/ijerph19148787

7. Yan Y, Mao Z, Jia Q, Zhao X, Yang S. Changes in blood pressure, oxygen saturation, hemoglobin concentration, and heart rate among low-altitude migrants living at high altitude (5380 m) for 360 days. *Am J Hum Biol*. (2023) 35(9):e23913. doi: 10.1002/ajhb.23913

8. Liu X, Yang C, Zhang X, Te R, Li X, Zhang Z, et al. Association between hemoglobin concentration and hypertension risk in native Tibetans at high altitude. *J Clin Hypertens*. (2024) 26(1):17–23. doi: 10.1111/jch.14726

9. Webb KL, Joyner MJ, Wiggins CC, Secomb TW, Roy TK. The dependence of maximum oxygen uptake and utilization (v˙O2 max) on hemoglobin-oxygen affinity and altitude. *Physiol Rep*. (2023) 11(17):e15806. doi: 10.14814/phy2.15806

10. Luo B, Feng L, Bi Q, Shi R, Cao H, Zhang Y. Fasting plasma glucose and glycated hemoglobin levels as risk factors for the development of hypertension: a retrospective cohort study. *Diabetes Metab Syndr Obes*. (2023) 16:1791–8. doi: 10.2147/DMSO.S410670

11. Ling L. Effect of glycosylated hemoglobin on ambulatory blood pressure and heart rate in patients with essential hypertension. *Syst Med*. (2023) 8(2):103–6.

12. Jianyu H, Jun M, Yan G, Wang Y, Zhang Q, Zhang J, et al. Peripheral blood albumin level in significantly correlated with the severity of atherosclerosis in hypertensive patients. *J South Med Univ*. (2020) 40(2):240–5. doi: 10.12122/j.issn.1673-4254.2020.02.16

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 13 January 2025
DOI 10.3389/fpubh.2024.1378561

Check for updates

OPEN ACCESS

EDITED BY
Xiaozhen Lai,
Peking University, China

REVIEWED BY
Victoria Ramos Gonzalez,
Carlos III Health Institute (ISCIII), Spain
Huan-Keat Chan,
Ministry of Health, Malaysia

*CORRESPONDENCE
Ahmad Homoud Al-Hazmi
ahhazmi@ju.edu.sa

†PRESENT ADDRESS
Nasser Saleh Alriwely,
Department of Health Support Services,
Ministry of Health, Riyadh, Saudi Arabia

RECEIVED 29 January 2024
ACCEPTED 30 December 2024
PUBLISHED 13 January 2025

CITATION
Al-Hazmi AH, Alanazi ADM, Thirunavukkarasu A, Alriwely NS, Alrais MMF, Alruwaili ABS, Alnosairi MS and Alsirhani AI (2025) Evaluation of hypertension knowledge and its association with medication adherence among hypertensive patients attending primary health centers: a cross-sectional study from eastern Saudi Arabia.
Front. Public Health 12:1378561.
doi: 10.3389/fpubh.2024.1378561

Evaluation of hypertension knowledge and its association with medication adherence among hypertensive patients attending primary health centers: a cross-sectional study from eastern Saudi Arabia

Ahmad Homoud Al-Hazmi[1]*, Abdullah Dhoimi Mureed Alanazi[1], Ashokkumar Thirunavukkarasu[1], Nasser Saleh Alriwely[2†], Mmdoh Mohammad F. Alrais[3], Alreem Barghash S. Alruwaili[3], Mona Saleh Alnosairi[3] and Amnah Ibrahim Alsirhani[4]

[1]Department of Family and Community Medicine, College of Medicine Jouf University, Sakaka, Saudi Arabia, [2]Department of Compliance, Ministry of Health, Arar, Saudi Arabia, [3]College of Medicine Jouf University, Sakaka, Saudi Arabia, [4]Family Medicine Resident, Ministry of Health, Tabuk, Saudi Arabia

Background and aim: The global healthcare system acknowledged the crucial role of disease knowledge in health outcomes and improving quality of life among patients with chronic disease. A lack of adequate knowledge and understanding of hypertension, its symptoms, and available treatments can lead to poor treatment outcomes. The present study aimed to determine the level of hypertension knowledge and associated factors among hypertensive patients. Furthermore, we evaluated the correlation between levels of knowledge and medication adherence among them.

Methods: The present study was carried out among 406 hypertensive patients attending different primary health centers in Hafr Al Batin, Saudi Arabia. Participants' hypertension-related knowledge was evaluated using the validated hypertension knowledge–level scale, and adherence practice was evaluated using the medication adherence and refill scale. We categorized the knowledge score into low, medium, and high, according to Bloom's criteria. We applied Spearman's correlation test to find the strength and direction of the correlation between hypertension-related knowledge and medication adherence. Furthermore, we used binomial logistic regression analysis to find the associated factors of the low hypertension-related knowledge among the patients.

Results: Of the studied patients, only 10.3% demonstrated a high level of knowledge, and the highest knowledge levels were observed in the domains of complications ($\overline{x}$ = 4.39, standard deviation [SD] = 1.20) and lifestyle ($\overline{x}$ = 3.13, SD = 0.69), while knowledge about drug compliance ($\overline{x}$ = 0.62, SD = 0.98) was the lowest. A statistically significant positive correlation was observed between knowledge and adherence regarding hypertension (rho = 0.268, p = 0.001) among study participants. We observed that marital status (p = 0.032), income (p = 0.042), and absence of chronic diseases (p = 0.001) are associated factors for low hypertension-related knowledge.

Conclusion: The study findings highlight a moderate level of knowledge about hypertension among patients, with significant gaps in drug compliance understanding. The positive correlation between knowledge and medication adherence underscores the need for better hypertension education at primary health centers. Furthermore, it is recommended that future prospective studies be conducted within various cultural contexts.

KEYWORDS

hypertension, knowledge, adherence, health center, complications, Saudi Arabia

1 Introduction

Hypertension is a chronic medical condition characterized by elevated blood pressure. The World Health Organization (WHO) has estimated that about 1.3 billion people suffer from hypertension worldwide, and nearly half of them are not aware of their hypertension status (1). Hence, it is increasingly emerging as a worldwide public health concern, encompassing a significant portion of public health financial allocations (2, 3). The prevalence of hypertension exhibits variation across different countries, with a notable upward trend observed in developing nations (4, 5). People with uncontrolled hypertension are at high risk of experiencing heart failure, renal failure, atherosclerosis, and stroke (6, 7). Hypertension, however, is preventable, treatable, and can be managed through medication (2, 8).

A higher risk of negative consequences, such as hospitalization and higher healthcare expenses due to problems, is seen in individuals with poor adherence to antihypertensive drugs compared to those with strong adherence. So, medication adherence is necessary to achieve blood pressure control. Medication adherence refers to the percentage of patients who take their prescribed medications as their treating physician recommends (9, 10). Peacock and Krousel-Wood report that only 50% of people with "chronic diseases medication," for instance, hypertensive patients, adhere to their medication regimen as prescribed (11). Another research conducted in 2022 among hypertensive adult patients (18+ years) attending primary health centers (PHC) in the Kingdom of Saudi Arabia (KSA) shows that only 36% of the hypertensive patients had high adherence to the treatment (12). In contrast, a comprehensive survey conducted in the United States, including an extensive sample of 24 million individuals diagnosed with hypertension, has revealed that a notable proportion, specifically about one-third, exhibited nonadherence to their prescribed drug regimen (13).

The global healthcare system acknowledges the crucial role of disease knowledge in health outcomes and improving quality of life among patients with chronic disease. Health professionals should provide patients with information about the benefits of taking their drugs and how to ensure that they are taking them as prescribed, which is essential to help patients control their blood pressure in the long term and reduce the risk of developing complications of hypertension (14, 15). An integrated approach to managing hypertension and increasing literacy levels among hypertensive patients and healthcare professionals is essential. The physicians and other healthcare practitioners must then collaborate to ensure success in helping patients avoid complications related to high blood pressure (16, 17). One way to achieve this is through a shared decision-making (SDM) model. Shared decision-making refers to a collaborative decision-making process in which all involved in the decision-making process have a stake in the outcome. The SDM model is particularly effective in managing chronic conditions like hypertension, where long-term adherence to treatment plans is crucial. By involving patients in the decision-making process, they are more likely to understand the importance of their medication regimen, lifestyle modifications, and the potential consequences of nonadherence (18, 19). Educating hypertensive patients is necessary to make them aware of the condition and the available medications so that they can make informed decisions about their care (17, 20). This collaborative approach can improve patient satisfaction, adherence to treatment, and overall health outcomes (21, 22).

A lack of adequate knowledge, awareness, and understanding of hypertension, its symptoms, and available treatments can lead to poor treatment adherence. Furthermore, a good knowledge about disease improves self-management, which is critical for patients to self-manage their situations (23). Studies have consistently shown that a lack of knowledge is a significant factor associated with poor adherence, and patients with a lack of knowledge are more likely to discontinue medications for several reasons (24, 25). Moreover, some studies have shown that knowledge regarding hypertension is generally low among hypertensive patients in KSA. Among those with some knowledge, there was a significant correlation between knowledge level, blood pressure control, and medication adherence (26, 27).

In the KSA, healthcare is delivered at four levels: PHCs, general hospitals, specialty hospitals, and medical cities. PHCs are integral to the healthcare system and provide essential services, including the diagnosis, management, and follow-up of chronic diseases such as hypertension. Continuous monitoring of epidemiological characteristics related to hypertension, such as knowledge of hypertension in terms of risk factors, complications, treatment compliance, and lifestyle factors among the patients attending PHCs, is critical to planning and implementing an intervention program to address the knowledge gap, eventually to improve the medication adherence and health of the individuals with hypertension. Furthermore, the sociocultural and demographic characteristics of each region of KSA, including Eastern Province, differ highly. Hence, there is an absolute necessity for region-specific data and evaluation. Understanding the local context and challenges in this specific region can inform tailored interventions and improve hypertension management practices in this region. Considering these factors, we aimed to assess the level of hypertension knowledge and associated factors among the patients attending different PHCs of Hafr Al Batin. Furthermore, we assessed the correlation between levels of knowledge and medication adherence among them.

2 Participants and methods

2.1 Study design

The present study was an analytical cross-sectional study that was performed from June 2023 to December 2023.

2.2 Study setting

The present survey was conducted among the patients attending different PHCs of Hafr-Al Batin. Hafr Al-Batin is in the Eastern province of KSA, with a total population of approximately about 400,000. These centers are critical in diagnosing, treating, and educating patients about hypertension, thereby playing a crucial role in mitigating its complications and improving the overall health outcomes of the patients. There are 73 PHCs in this region, and the present study selected 10 PHCs randomly to recruit hypertensive patients for the current survey. In order to recruit hypertensive patients over a period of time, we restricted five patients per day in each PHC.

2.3 Sample size estimation and sampling method

We used the World Health Organization (WHO) sample size formula ($n = z^2pq / e^2$) to estimate the required number of adults to participate in the present survey. The WHO formula uses the principles of Cochran's sample size calculation method, a commonly used method to calculate the minimum required sample size in a cross-sectional study (28). During estimation, we considered 50% of expected adequate knowledge (p), q = 1-p, 95% of the confidence interval ($z = 1.96$), and 5% of the margin of error (d). After carefully calculating the above-stated values, we concluded that 384 participants are required for the survey (rounded to 390). These required participants were selected from 10 randomly selected PHCs. In this study, we applied a non-probability consecutive sampling method, a type of convenience sampling where participants were consecutively selected based on their availability and meeting the inclusion criteria until the required sample size was achieved. Furthermore, we restricted our data collection per day to a maximum of 10 participants to ensure that the data is collected over a period of time.

2.4 Inclusion and exclusion criteria

We included all adult-confirmed hypertensive patients who were on antihypertensive medications for a minimum of 3 months and attended the outpatient clinics of the PHCs from the Hafr Al-Batin region. The 3 months duration was determined by the research team through a focus group discussion considering the guidelines of follow-up visit (29, 30). We excluded pediatric patients, pregnant women, patients from other regions, and patients who were unwilling to participate.

2.5 Data collection procedure

The present research followed the ethical principles of the Declaration of Helsinki during the entire study duration. We initiated the data collection after obtaining ethical clearance from the research committee, the Ministry of Health, Hafr Al-batin (approval no: 134), and other necessary approvals from the concerned authorities. After briefing the survey to the hypertensive patients and obtaining informed consent, we gave the participants the Arabic version of the data collection tool (Google form). This was on the day of their visit to the health center, and the data was filled in the data collectors' electronic devices. The data collection tool is a standard, pretested, and validated tool adapted from previous literature (12, 31–33). The first section inquired about participants' background and health-related aspects: age, gender, income, occupation, education, presence of other comorbidities, duration since the first diagnosis of hypertension, and the number of medications taken for hypertension. The second part asked about participants' hypertension-related knowledge using the hypertension knowledge–level scale (HK-LS) (32, 34). The HK-LS consists of 22 items to investigate participants' knowledge regarding six subscales, including definition (two items), medical treatment (four items), drug compliance (four items), lifestyle (five items), diet (two items), and complications (five items). The correct answer was given 1 point, and the wrong answer, not sure, was given zero. Participants' overall knowledge was based on summing up the correct responses to these items. Therefore, the overall knowledge scores ranged between 0 and 22. We further categorized them into low (less than 60% of total score), medium (60 to 80% of total score), and high (more than 80% of total score). The research team determined these categories according to Bloom's criteria, which is used in several studies (35–37). The final section inquired about medication adherence and refill practices among the selected participants and consisted of 10 questions (12, 31). Hypertensive patients responded with a range of answers, from never (score 4) to always (score 1). The scores of each item were summed up to get the total scores for further analysis. The higher scores indicate a higher adherence practice. Initially, we pretested the tool among 30 adult hypertensive patients. All pilot study patients were informed that the data collection tool was simple and easy to understand. The Cronbach alpha values for the knowledge and adherence sections that were obtained through pilot study were 0.79 and 0.83, respectively.

2.6 Statistical analysis

The research team downloaded the Excel sheet from Google Form and exported it to the Statistical Package for Social Sciences (SPSS) version 23.0 for data entry, coding, and analysis. We presented the descriptive data as frequency, proportion, mean/median, and standard deviation/interquartile range. The normality assumption of the data was analyzed through the Shapiro–Wilk test. The test revealed that both hypertension-related knowledge scores (statistical value = 0.971, $p < 0.001$) and medication adherence scores (statistical value = 0.982, $p < 0.001$) did not meet the normality assumption. Hence, we applied Spearnman's correlation test (non-parametric test) to find the correlation between knowledge and medication adherence practice. Furthermore, we used the binary logistic regression analysis (enter method) to find the factors for the knowledge categories. In this regression model, we calculated the odds ratio with a 95% confidence interval after adjusting with other covariables of the study. A p-value less than 0.05 will be considered a statistically significant association.

3 Results

The majority of participants were male (60.3%), residing in urban areas (80.3%), and currently married (89.2%). Nearly half of the participants belonged to the age group of 45 to 60 years, comprising 48.8% of the total respondents. Most participants had a university degree or higher (75.1%). Almost half of the participants were employed in the government sector (47.8%). The vast majority of participants had an income exceeding 7,000 SAR (82.8%). Most participants were non-smokers (84.2%). Over half of the participants had hypertension for 5 years or above (54.4%). One-third of the participants reported having chronic diseases (33.3%; Table 1).

The study participants demonstrated a relatively high awareness of fundamental aspects of hypertension, such as the importance of daily medication intake (94.3%) and the necessity of lifelong medication adherence (83.0%). However, a considerable proportion of study participants believe that high blood pressure only occurs with aging (17.5%) and that lifestyle changes can negate the need for medication (18.2%). Moreover, there were notable gaps in knowledge regarding dietary habits, as a significant number thought it was permissible for hypertensive individuals to consume salty foods (12.8%) or drink alcohol (15.8%). Furthermore, the highest levels of wrong answers were observed on the knowledge of the statements: people with high blood pressure should only take their medications when they feel tired and unwell (90.9%), people with high blood pressure can eat salty foods as long as they take their medications regularly (87.2%), and type of food intake such as frying food (86.7%). The majority of participants have a medium level of knowledge (51 to 75%), and only 10.3% demonstrate a high level of knowledge (above 75%; Tables 2, 3).

The overall mean knowledge score for hypertension among the 406 participants was 12.66 (SD = 2.41), indicating a moderate level of knowledge. Participants demonstrated the highest knowledge levels in the domains of complications ($\bar{x}$ = 4.39, SD = 1.20) and lifestyle ($\bar{x}$ = 3.13, SD = 0.69), while knowledge about drug compliance ($\bar{x}$ = 0.62, SD = 0.98) was the lowest (Table 4).

Regarding antihypertensive medication adherence, 51.5% of the patients never forget to take their medicines, and more than two-thirds (71.4%) of the patients never stopped their medicines even when their blood pressure is controlled. Similarly, about 55% of patients always refill their antihypertensive medications well in advance before they finish (Table 5).

A statistically significant positive correlation was observed between knowledge and adherence regarding hypertension (rho = 0.268, p = 0.001) among study participants (Table 6).

In the univariate analysis, several socio-demographic factors were identified as predictors of knowledge about hypertension. Participants aged 45 to 60 years (crude odds ratio [COR] = 0.339, 9% confidence interval [CI] = 0.180–0.639, p = 0.001), females (COR = 2.058, 95% CI = 1.290–3.282, p = 0.002), those residing in rural areas (COR = 4.687, 95% CI = 2.771–7.927, p = 0.001), employed in the private sector/business (COR = 2.206, 95% CI = 1.192–4.084, p = 0.012), unmarried individuals (COR = 6.245, 95% CI = 3.240–12.038, p = 0.001), those with high income, non-smokers (COR = 0.299, 95% CI = 0.124–0.716, p = 0.001), and those with 1 to 5 years of hypertension duration (COR = 0.224, 95% CI = 0.102–0.492, p = 0.001) were significantly associated with the hypertension related knowledge. After adjusting for confounding factors in the multivariate analysis, marital status (adjusted odds ratio [AOR] = 2.538, 95% CI = 1.086–5.932, p = 0.032), income (AOR = 0.364, 95% CI = 0.138–0.963, p = 0.042), and absence of chronic diseases (AOR = 0.491, 95% CI = 0.260–0.932, p = 0.001) remained significant predictors of knowledge about hypertension (Table 7).

TABLE 1 Socio-demographic characteristics of the study participants (n = 406).

Parameters	Frequency	Proportion
Gender		
Male	245	60.3
Female	161	39.7
Residence status		
Urban	326	80.3
Rural	80	19.7
Marital status		
Currently married	362	89.2
Single	44	10.6
Age groups, year		
Less than 45	105	25.9
45 to 60	198	48.8
More than 60	103	25.4
Education status		
Up to high school	101	24.9
University and above	305	5.1
Employment status		
Government sector	194	47.8
Private sector / Business	153	37.7
Unemployed	59	14.5
Income		
Less than 5,000 SAR	40	9.9
5,000 to 7,000 SAR	30	7.4
More than 7,000 SAR	336	82.8
Smoking status		
Nonsmoker	342	84.2
Smoker	64	15.8
Duration of hypertension		
Less than 1 year	30	7.4
1–5 years	155	38.2
5 years and above	221	54.4
Chronic diseases		
Yes	135	33.3
No	271	66.7

4 Discussion

Hypertension poses a significant public health burden worldwide. In KSA, its prevalence is alarming, with one in four adults estimated to have the condition (38). To effectively combat this challenge,

TABLE 2 Participants' responses to hypertension knowledge-level scale.

Items	Correct answer		Wrong answer	
	n	%	n	%
Systolic or diastolic hypertension is an indication of high blood pressure	349	86.0	57	14.0
Diastolic hypertension (number II) alone is also considered as an indicator of high blood pressure	212	52.2	194	47.8
Medications prescribed to treat high blood pressure should be taken daily	383	94.3	23	5.7
People with high blood pressure should only take their medications when they feel tired and unwell.	37	9.1	369	90.9
People with high blood pressure should take their medications throughout their lives.	337	83.0	69	17.0
People with high blood pressure should take their medications in a way that makes them feel comfortable	54	13.5	351	86.5
If medications can control high blood pressure, there is no need to change the patient's lifestyle and daily behaviors.	55	13.3	352	86.7
High blood pressure occurs with aging, so there is no need to take treatment in such a case	71	17.5	335	82.5
If a person with high blood pressure succeeds in changing his lifestyle and healthy behaviors in his daily life, then there is no need to continue taking treatment	74	18.2	332	81.8
People with high blood pressure can eat salty foods as long as they take their medications regularly.	52	12.8	354	87.2
People with high blood pressure can drink alcohol	64	15.8	342	84.2
People with high blood pressure should not smoke	382	94.6	22	5.4
People with high blood pressure should eat vegetables and fruits constantly	386	95.1	20	4.9
Frying foods is the best way to prepare meals for hypertensive patients	54	13.3	352	86.7
Boiling or grilling foods is the best way to prepare meals for hypertensive patients	384	94.6	22	5.4
The best types of meat that are suitable for hypertensive patients are white meat	362	89.2	44	10.8
The best types of meat that are suitable for hypertensive patients are red meat	101	24.9	305	75.1
If not treated, high blood pressure can cause early death.	354	87.2	52	12.8
If not treated, high blood pressure can cause cardiovascular diseases such as thrombosis.	374	92.1	32	7.9
If not treated, high blood pressure can cause strokes.	367	90.4	39	9.6
If not treated, high blood pressure can cause kidney failure.	329	81.0	77	19.0
If not treated, high blood pressure can cause eye and vision problems.	356	87.7	50	12.3

understanding the knowledge about hypertension and adherence to hypertensive medication of hypertensive individuals is crucial. The present study delves into the knowledge and medication adherence landscape among patients attending various primary health centers in Saudi Arabia, offering valuable insights for tailored interventions and improved health outcomes. The findings from this study underscore the ongoing challenge of managing hypertension in Saudi Arabia, particularly in the Eastern region.

Overall, participants' knowledge about hypertension was moderate (mean 2.66), which is similar to research conducted in Lebanon (39), Sri Lanka (24), Indonesia (25), and Pakistan (40). However, specific knowledge domains revealed notable disparities. Participants demonstrated a strong understanding of complications (mean 4.39) and lifestyle modifications (mean 3.13), aligning with the research findings of Buang NFB et al. (41) and Alshammari SA et al. (42). Conversely, a significant knowledge gap was identified in our study regarding drug compliance (mean 0.62), similar to the concerns raised in studies from India (43) and Pakistan (44). The current study highlights the persistent knowledge gaps that could contribute to suboptimal health outcomes.

The present study also reports that the participants have poor knowledge in the domains "definition and diet." This finding is similar to the study done by Al Zahrani S et al. (26) and Jankowska-Polańska B et al. (45). Low scores in understanding definitions, diet, and drug compliance may be attributed to various factors. These could include unclear communication from healthcare providers, insufficient awareness of the significance of medication adherence, or cultural beliefs influencing medication use. Exploring these contributing factors can guide the development of targeted interventions. Tailored interventions like communication training for health care providers and behavioral change communication to the community will address these root causes and empower individuals and communities for improved health outcomes. The present study found several domains related to medication adherence and proper diet. These results emphasize the importance of the SDM model, as many patients were unaware of the importance of medication adherence even if they felt well and the importance of proper dietary methods. Furthermore, as a process of SDM, healthcare professionals must provide patients with comprehensive information about the benefits of medications even if the patients are feeling well, the role of lifestyle changes in managing hypertension, and the importance of regular monitoring and follow-up. Additionally, addressing patients' concerns, preferences, and values is crucial in developing a personalized treatment plan that patients are more likely to follow (18, 46, 47).

In our study, about half of the participants responded as "always" in most of the medication adherence scale items. This aligns with recent findings by Amer M et al. (40), Lee EK et al. (48) Shi S et al. (49), and Gavrilova A et al. (50), high prevalence of nonadherence to antihypertensive medication globally with non-western countries showing even higher rates (48). These stark figures underscore the persistent challenge of medication nonadherence in chronic disease management, particularly in hypertension, affecting over 1.3 billion people globally, as highlighted by the World Health Organization in 2023 (51). This warrants further investigation into the specific factors influencing adherence patterns within low-adherence populations. Exploring modifiable factors, such as financial barriers, medication complexity, and patient-provider communication, could inform targeted interventions to improve adherence and ultimately optimize clinical outcomes, especially in the context of hypertension, where uncontrolled blood pressure can lead to devastating consequences like heart attacks and strokes. Our study provides specific insights into these gaps, such as the limited understanding of drug compliance and diet, which are crucial for effective hypertension management. These insights emphasize the need for targeted educational interventions at primary health centers to enhance patients' knowledge and adherence to treatment regimens.

Similar to the research findings by Amer M (40) and Paczkowska A et al. (52), the present study shows that knowledge about hypertension was found to have a statistically significant positive correlation with medication adherence with a coefficient of 0.268, indicating a positive association between medication adherence and knowledge about hypertension. Patients with an adequate knowledge of hypertension may better perceive the need for regular drug adherence in managing their disease, resulting in a better dedication to following prescribed treatment regimens. Furthermore, the correlation coefficient of 0.268 suggests a positive relationship between hypertension awareness and medication adherence, highlighting the importance of patient education in improving positive health behaviors. This can lead to better blood pressure control and overall health outcomes, reducing the burden on the healthcare system due to complications arising from poorly managed hypertension.

We found that the knowledge level of the participants about hypertension is influenced by factors such as education, income, marital status, and the presence of chronic conditions. Individuals who are married, have chronic illnesses, have lower incomes, and are less educated are more likely to have a lack of knowledge about hypertension. These results are consistent with studies conducted in Poland (52), Malaysia (41), Saudi Arabia (38), and Lebanon (39). These warrants targeted intervention, especially for people of lower socio-economic status, to effectively manage this significant global health problem. Hence, we can decrease the associated complications and healthcare expenditure (53, 54). In agreement with

TABLE 3 Level of Knowledge related to hypertension among participants (*n* = 406).

Variable	Frequency	Proportion
Low (<60%)	94	23.2
Medium (60 to 80%)	270	66.5
High (> 80%)	42	10.3

TABLE 4 Participants' responses to knowledge-domain wise.

Variable	All participants; *n* = 406	
	Mean	Standard deviation
Total knowledge (Domain all)	12.66	2.41
Knowledge about definition of hypertension (D1)	1.38	0.69
Knowledge about medical treatment (D2)	2.00	0.61
Knowledge about drug compliance (D3)	0.62	0.98
Knowledge about lifestyle (D4)	3.13	0.69
Knowledge about diet (D5)	1.14	0.41
Knowledge about complications (D6)	4.39	1.20

TABLE 5 Participants' responses to medication adherence scale (*n* = 406).

Variable	Never	Once in a while	Majority of the times	Always
	n (%)	n (%)	n (%)	n (%)
How often do you forget to take your medication to control blood pressure?	209 (51.5)	175 (43.1)	14 (3.4)	8 (2.0)
How frequently do you choose not to take your medication?	256 (63.1)	127 (31.3)	18 (4.4)	5 (1.2)
Do you change the medicine dose or number of tablets without physician consultation?	231(57.1)	150 (36.9)	19 (4.7)	5 (1.2)
Do you stop taking medications on the day you feel comfortable?	230 (56.7)	153 (37.7)	16 (3.9)	7 (1.7)
Have you ever stopped taking your medications without telling your doctor because of your perceived side effects?	275 (67.7)	100 (24.6)	22 (5.4)	9 (2.2)
How frequently do you forget to take medicine due to forgetfulness?	227 (55.9)	129 (31.8)	35 (8.6)	15 (3.7)
How often do you stop medicines when your blood pressure is controlled?	290 (71.4)	83 (20.4)	15 (3.7)	18 (4.4)
How frequently have you stopped taking blood pressure medicine while you are sick due to other acute illnesses such as flu?	288 (70.9)	95 (23.4)	14 (3.4)	9 (2.2)
Have you ever been annoyed by adhering to the treatment plan, as some patients feel discomfort taking it daily?	294 (72.4)	90 (22.2)	16 (3.9)	6 (1.5)
How frequently do you refill well in advance before the blood pressure medicine finishes?*	8 (2.0)	48 (11.8)	127 (31.3)	223 (54.9)

*Reverse scoring.

recommendations from previous global studies, the present study offers a road map for creating proper interventions to increase awareness of hypertension and medication adherence. Culturally tailored health promotion activities that address specific knowledge gaps and target high-risk groups and include social aspects of health are vital. These programs must actively address the fears and myths surrounding the illness in addition to merely providing information. Furthermore, integrating community-based interventions and encouraging self-management abilities can enable people to take charge of their health and enhance long-term results worldwide. Additionally, integrating regular counseling sessions during

TABLE 6 Correlation of knowledge about hypertension with adherence.

Variable	rho/ *p*-value
Knowledge–Adherence	0.268 (0.001)

TABLE 7 Univariate and multivariate regression analysis for the predictors of knowledge regarding hypertension.

Variables	Total	Univariate analysis					Multivariable analysis		
		Low; *n* = 94	Medium / High; *n* = 312	Unadjusted odds Ratio (OR)	95% CI	*p*-value	Adjusted; OR*	95% CI	*p*-value
Age (in years)									
Less than 45	105	42	63	Ref			Ref		
45 to 60	198	33	165	0.339	(0.180–0.639)	0.001	0.590	(0.239–1.458)	0.253
More than 60	103	19	84	1.131	(0.607–2.108)	0.698	0.992	(0.473–2.080)	0.983
Gender									
Male	245	44	201	Ref			Ref		
Female	161	50	111	2.058	(1.290–3.282)	0.002	1.435	(0.816–2.522)	0.210
Residence status									
Urban	326	55	271	Ref			Ref		
Rural	80	39	41	4.687	(2.771–7.927)	0.001	1.837	(0.916–3.684)	0.087
Education status									
Up to high school	101	30	71	Ref			Ref		
University and above	305	64	241	0.628	(0.378–1.045)	0.073	0.528	(0.275–1.012)	0.054
Employment status									
Government sector	194	46	148	Ref			Ref		
Private sector / Business	153	24	129	2.206	(1.192–4.084)	0.012	0.638	(0.263–1.545)	0.319
Unemployed	59	24	35	3.686	(1.871–7.260)	0.001	1.199	(0.493–2.917)	0.689
Marital status									
Currently married	362	68	294	Ref			Ref		
Single	44	26	18	6.245	(3.240–12.038)	0.001	2.538	(1.086–5.932)	0.032
Income									
Less than 5,000 SAR	40	24	16	Ref			Ref		
5,000 to 7,000 SAR	30	12	18	0.139	(0.070–0.278)	0.001	0.364	(0.138–0.963)	0.042
More than 7,000 SAR	336	58	278	0.313	(0.143–0.685)	0.004	0.519	(0.202–1.331)	0.172
Smoking status									
Nonsmoker	342	88	254	Ref			Ref		
Smokers	64	6	58	0.299	(0.124–0.716)	0.007	0.525	(0.200–1.382)	0.192
Duration of hypertension									
Less than 1 year	30	16	14	Ref			Ref		
1–5 years	155	33	122	0.224	(0.102–0.492)	0.001	0.960	(0.337–2.735)	0.939
5 years and above	221	45	176	0.945	(0.570–1.566)	0.827	1.595	(0.844–3.014)	0.151
Chronic diseases									
Yes	135	72	199	Ref			Ref		
No	271	22	113	0.538	(0.317–0.915)	0.002	0.492	(0.260–0.932)	0.001

*Enter method was applied in regression analysis. Adjusted with other covariables of the study.

follow-ups in PHCs could help reinforce the importance of medication adherence and lifestyle modifications.

We have carried out this survey with an adequate sample size and a validated Arabic questionnaire. Nonetheless, the readers should consider some of the essential constraints of this research findings. Firstly, we assessed the knowledge gap among hypertensive patients in a unique sociocultural setting. Hence, the conclusions assessed in this study may not be applicable to other regions. Secondly, the limitations of cross-sectional studies, such as the lack of ability to identify the causal association, need to be kept in mind. Next, the study faced limitations due to the non-probability consecutive sampling method, which may have introduced selection bias. Additionally, the higher proportion of male participants reflects sociocultural restrictions, affecting generalizability. Finally, some other biases, such as recall and self-report, cannot be ruled out.

5 Conclusion

We found that the majority of the participants had either low or medium knowledge of hypertension. Furthermore, a positive correlation was observed between hypertension-related knowledge and medication adherence. The results emphasize the need for better hypertension education at the primary health centers. It also emphasizes the need for culturally sensitive interventions that fill in knowledge gaps and provide people with the tools they need to take charge of their health. These issues can be effectively addressed by adopting targeted interventions for the high-risk population and the prevalence of hypertension in Saudi Arabia, enabling people to properly manage their health and enhance their quality of life. To contribute to a comprehensive understanding of this global challenge, it is recommended that future prospective studies be conducted to examine the factors influencing drug adherence, lifestyle modifications, and healthcare expenditure within a variety of cultural contexts.

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 IRB, Directorate of Health Affairs, Hafr Al Batin, Saudi Arabia. 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

AA-H: Conceptualization, Data curation, Methodology, Software, Supervision, Validation, Writing – original draft, Funding acquisition, Resources. AMA: Conceptualization, Data curation, Formal analysis, Validation, Visualization, Writing – original draft, Methodology, Resources, Software. AT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Software, Visualization, Writing – original draft, Methodology. NA: Conceptualization, Formal analysis, Funding acquisition, Methodology, Validation, Visualization, Writing – original draft, Investigation. MMA: Conceptualization, Data curation, Resources, Software, Validation, Writing – review & editing, Visualization. ASA: Conceptualization, Data curation, Methodology, Resources, Software, Validation, Writing – review & editing. MSA: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. AA: Conceptualization, Data curation, Formal analysis, Project administration, Visualization, Writing – review & editing, Resources, Software.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was funded by the Deanship of Graduate Studies and Scientific Research at Jouf University under grant no. (DGSSR-2023-01-02069).

Acknowledgments

We would like to thank the Hafr Al Batin health affairs for their immense support in data collection from the patients.

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.

References

1. WHO. Hypertension: fact sheets Geneva, Switzerland: World Health Organization. (2022). Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension (Accessed on 2023, 15 March)

2. Jaffe MG, DiPette DJ, Campbell NRC, Angell SY, Ordunez P. Developing population-based hypertension control programs. *Rev Panam Salud Publica*. (2022) 46:e153. doi: 10.26633/rpsp.2022.153

3. Lemogoum D. Challenge for hypertension prevention and control worldwide: the time for action. *J Clin Hypertens (Greenwich)*. (2014) 16:554–6. doi: 10.1111/jch.12373

4. Alenazi AM, Alqahtani BA. National and regional prevalence rates of hypertension in Saudi Arabia: a descriptive analysis using the National Survey Data. *Front Public Health*. (2023) 11:1092905. doi: 10.3389/fpubh.2023.1092905

5. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. (2020) 16:223–37. doi: 10.1038/s41581-019-0244-2

6. Mamaghani EA, Hasanpoor E, Maghsoodi E, Soleimani F. Barriers to medication adherence among hypertensive patients in deprived rural areas. *Ethiop J Health Sci*. (2020) 30:85–94. doi: 10.4314/ejhs.v30i1.11

7. Poznyak AV, Sadykhov NK, Kartuesov AG, Borisov EE, Melnichenko AA, Grechko AV, et al. Hypertension as a risk factor for atherosclerosis: cardiovascular risk assessment. *Front Cardiovasc Med*. (2022) 9:959285. doi: 10.3389/fcvm.2022.959285

8. Carey RM, Muntner P, Bosworth HB, Whelton PK. Prevention and control of hypertension: Jacc health promotion series. *J Am Coll Cardiol*. (2018) 72:1278–93. doi: 10.1016/j.jacc.2018.07.008

9. Kengne AP, Brière J-B, Zhu L, Li J, Bhatia MK, Atanasov P, et al. Impact of poor medication adherence on clinical outcomes and health resource utilization in patients with hypertension and/or dyslipidemia: systematic review. *Expert Rev Pharmacoecon Outcomes Res* (2023) 24:1–12. doi: 10.1080/14737167.2023.2266135

10. Gebreyohannes EA, Bhagavathula AS, Abebe TB, Tefera YG, Abegaz TM. Adverse effects and non-adherence to antihypertensive medications in University of Gondar Comprehensive Specialized Hospital. *Clin Hypertension*. (2019) 25:1. doi: 10.1186/s40885-018-0104-6

11. Peacock E, Krousel-Wood M. Adherence to antihypertensive therapy. *Med Clin North Am*. (2017) 101:229–45. doi: 10.1016/j.mcna.2016.08.005

12. Thirunavukkarasu A, Naser Abdullah Alshahrani A, Mazen Abdel-Salam D, Homoud Al-Hazmi A, Farhan AB, Awad Alsaidan A, et al. Medication adherence among hypertensive patients attending different primary health centers in Abha, Saudi Arabia: a cross-sectional study. *Patient Prefer Adherence*. (2022) 16:2835–44. doi: 10.2147/ppa.S388365

13. Chang TE, Ritchey MD, Park S, Chang A, Odom EC, Durthaler J, et al. National Rates of nonadherence to antihypertensive medications among insured adults with hypertension, 2015. *Hypertension*. (2019) 74:1324–32. doi: 10.1161/hypertensionaha.119.13616

14. Wieczorek M, Meier C, Vilpert S, Reinecke R, Borrat-Besson C, Maurer J, et al. Association between multiple chronic conditions and insufficient health literacy: cross-sectional evidence from a population-based sample of older adults living in Switzerland. *BMC Public Health*. (2023) 23:253. doi: 10.1186/s12889-023-15136-6

15. Liu L, Qian X, Chen Z, He T. Health literacy and its effect on chronic disease prevention: evidence from China's data. *BMC Public Health*. (2020) 20:690. doi: 10.1186/s12889-020-08804-4

16. Satriana A, Kadar KS, Saleh A. Effect of health literacy towards medication compliance on elderly with hypertension: an updated literature review. *Enferm Clin*. (2021) 31:S802–6. doi: 10.1016/j.enfcli.2021.07.034

17. Nam HJ, Yoon JY. Linking health literacy to self-Care in Hypertensive Patients with physical disabilities: a path analysis using a multi-mediation model. *Int J Environ Res Public Health*. (2021) 18:e3363. doi: 10.3390/ijerph18073363

18. Montori VM, Ruissen MM, Hargraves IG, Brito JP, Kunneman M. Shared decision-making as a method of care. *BMJ Evid Based Med*. (2023) 28:213–7. doi: 10.1136/bmjebm-2022-112068

19. Simmons L, Leavitt L, Ray A, Fosburgh B, Sepucha K. Shared decision making in common chronic conditions: impact of a resident training workshop. *Teach Learn Med*. (2016) 28:202–9. doi: 10.1080/10401334.2016.1146600

20. Kurnia AD, Melizza N, Ruhyanudin F, Masruroh NL, Prasetyo YB, Setyowati CI, et al. The effect of educational program on hypertension management toward knowledge and attitude among uncontrolled hypertension patients in rural area of Indonesia. *Community Health Equity Res Policy*. (2020) 42:181–8. doi: 10.1177/0272684X20972846

21. Hu Q, Feng Z, Zong Q, Wang J, Zheng Z, Feng D. Analysis of factors that promote the participation of patients with chronic diseases in shared decision making on medication: a cross-sectional survey in Hubei Province, China. *BMC Public Health*. (2023) 23:2440. doi: 10.1186/s12889-023-17099-0

22. Ward J, Kalsi D, Barnett N, Fulford B, Handa A. Shared decision making in chronic medication use: scenarios depicting exemplary care. *Res Soc Adm Pharm*. (2020) 16:108–10. doi: 10.1016/j.sapharm.2019.04.047

23. Centre for Health Protection, Department of Health. Hypertension - the Preventable and Treatable Silent Killer United Kingdom. (2023). Available from: https://www.chp.gov.hk/en/features/28272.html#:~:text=Hypertension%20is%20a%20chronic%20disease (Accessed on 2023, 15 June 2023)

24. Pirasath S, Sundaresan T. Descriptive cross-sectional study on knowledge, awareness and adherence to medication among hypertensive patients in a tertiary care center. *Eastern Sri Lanka SAGE Open Med*. (2021) 9:20503121211012497. doi: 10.1177/20503121211012497

25. Pristianty L, Hingis ES, Priyandani Y, Rahem A. Relationship between knowledge and adherence to hypertension treatment. *J Public Health Afr*. (2023) 14:2502. doi: 10.4081/jphia.2023.2502

26. Al Zahrani S, Eid Alosaimi M, Alamrim A, Alotaibi M, Almatar EA, Almanea BA. Association between knowledge and drug adherence in patients with hypertension in Saudi Arabia. *Arch Pharm Pract*. (2019) 10:71–6.

27. Duraihim HA, Alghamdi G, AlNemer M, Abdulaal AE, Sayyari AA. Blood pressure control, lifestyle and disease awareness of Saudi hypertensive patients. *Saudi J Kidney Dis Transpl*. (2019) 30:33–8. doi: 10.4103/1319-2442.252930

28. Cochran WG. Sampling Techniques John Wiley & Sons (1977).

29. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. (2020) 75:1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026

30. PAHO/WHO. Hearts in the Americas: Protocols and Medications - Paho/Who | Pan American Health Organization: Pan American Health Organization. (2021). Available from: https://www.paho.org/en/hearts-americas/hearts-americas-protocols-and-medications (Accessed on 2023, 15 May)

31. Alammari G, Alhazzani H, AlRajhi N, Sales I, Jamal A, Almigbal TH, et al. Validation of an Arabic version of the adherence to refills and medications scale (arms). *Healthcare (Basel)*. (2021) 9:e1430. doi: 10.3390/healthcare9111430

32. Eshah NF, Al-daken LI. Assessing publics' knowledge about hypertension in a community-dwelling sample. *J Cardiovasc Nurs*. (2016) 31:158–65. doi: 10.1097/JCN.0000000000000227

33. Alsaidan AA, Alotaibi SF, Thirunavukkarasu A. Medication adherence and its associated factors among patients with type 2 diabetes mellitus attending primary health centers of Eastern Province, Saudi Arabia. *Medicina (Kaunas)*. (2023) 59:e989. doi: 10.3390/medicina59050989

34. Erkoc SB, Isikli B, Metintas S, Kalyoncu C. Hypertension knowledge-level scale (Hk-ls): a study on development, validity and reliability. *Int J Environ Res Public Health*. (2012) 9:1018–29. doi: 10.3390/ijerph9031018

35. Thirunavukkarasu A, Alsaidan AA, Al-Ruwaili AM, Alanazi RBS, Alruwaili AMB. Knowledge, attitude, and practice towards evidence-based medicine among northern Saudi primary care physicians: a cross-sectional study. *Healthcare (Basel)*. (2022) 10:e2285. doi: 10.3390/healthcare10112285

36. Machaalani M, Fakhry B, Zwaideh M, Mendelek K, Mahmoud N, Hammoud T, et al. Knowledge, attitude, and practice toward cardiovascular diseases in the Lebanese population. *Glob Heart*. (2022) 17:47. doi: 10.5334/gh.1138

37. Yakut S, Karagülle B, Atçalı T, Öztürk Y, Açık MN, Çetinkaya B. Knowledge, attitudes, practices and some characteristic features of people recovered from Covid-19 in Turkey. *Medicina (Kaunas)*. (2021) 57:e431. doi: 10.3390/medicina57050431

38. Alshammari SA, Alshammari AS, Alshammari HS, Ahamed SS. Overview of hypertension in Saudi Arabia: a systematic review and Meta-analysis. *Saudi Med J*. (2023) 44:951–64. doi: 10.15537/smj.2023.44.10.20230178

39. Machaalani M, Seifeddine H, Ali A, Bitar H, Briman O, Chahine MN. Knowledge, attitude, and practice toward hypertension among hypertensive patients residing in Lebanon. *Vasc Health Risk Manag*. (2022) 18:541–53. doi: 10.2147/vhrm.S367187

40. Amer M, Raza A, Riaz H, Sadeeqa S, Sultana M. Hypertension-related knowledge, medication adherence and health-related quality of life (Hrqol) among hypertensive patients in Islamabad. *Pakistan Tropical J Pharmaceutical Res*. (2019) 18:1123–32. doi: 10.4314/tjpr.v18i5.30

41. Buang NFB, Rahman NAA, Haque M. Knowledge, attitude and practice regarding hypertension among residents in a housing area in Selangor. *Malaysia Med Pharm Rep*. (2019) 92:145–52. doi: 10.15386/mpr-1227

42. Alshammari SA, Alshathri AH, Alshathri AH, Aleban SA, Alabdullah DW, Abukhlaled JK, et al. Assessment of public knowledge of hypertension among the Saudi population. *Cureus*. (2023) 15:e37649. doi: 10.7759/cureus.37649

43. Shah AJ, Singh V, Patil SP, Gadkari MR, Ramchandani V, Doshi KJ. Factors affecting compliance to antihypertensive treatment among adults in a tertiary Care Hospital in Mumbai. *Indian J Community Med*. (2018) 43:53–5. doi: 10.4103/ijcm.IJCM_40_17

44. Qasim A, Qureshi MI, Kumar D, Kashif SM. Factors associated with compliance to antihypertensive therapy in patients visiting tertiary care hospital. *Professional Med J*. (2020) 27:1511–5. doi: 10.29309/TPMJ/2020.27.07.4552

45. Jankowska-Polańska B, Uchmanowicz I, Dudek K, Mazur G. Relationship between Patients' knowledge and medication adherence among patients with hypertension. *Patient Prefer Adherence*. (2016) 10:2437–47. doi: 10.2147/ppa.S117269

46. Force USPST. Collaboration and shared decision-making between patients and clinicians in preventive health care decisions and us preventive services task Force recommendations. *JAMA*. (2022) 327:1171–6. doi: 10.1001/jama.2022.3267

47. Merschel M. What is shared decision-making, and how can it help patients? United States: American Heart Association (2023).

48. Lee EKP, Poon P, Yip BHK, Bo Y, Zhu MT, Yu CP, et al. Global burden, regional differences, trends, and health consequences of medication nonadherence for hypertension during 2010 to 2020: a Meta-analysis involving 27 million patients. *J Am Heart Assoc*. (2022) 11:e026582. doi: 10.1161/jaha.122.026582

49. Shi S, Shen Z, Duan Y, Ding S, Zhong Z. Association between medication literacy and medication adherence among patients with hypertension. *Front Pharmacol*. (2019) 10:822. doi: 10.3389/fphar.2019.00822

50. Gavrilova A, Bandere D, Rutkovska I, Šmits D, Mauriņa B, Poplavska E. Urtāne AI knowledge about disease, medication therapy, and related medication adherence levels among patients with hypertension. *Medicina (Kaunas)*. (2019) 55:e715. doi: 10.3390/medicina55110715

51. WHO. First who report details devastating impact of hypertension and ways to stop it. Geneva, Switzerland: World Health Organization (2023).

52. Paczkowska A, Hoffmann K, Kus K, Kopciuch D, Zaprutko T, Ratajczak P, et al. Impact of patient knowledge on hypertension treatment adherence and efficacy: a single-Centre study in Poland. *Int J Med Sci*. (2021) 18:852–60. doi: 10.7150/ijms.48139

53. Zhang D, Wang G, Zhang P, Fang J, Ayala C. Medical expenditures associated with hypertension in the U.S., 2000-2013. *Am J Prev Med*. (2017) 53:S164–71. doi: 10.1016/j.amepre.2017.05.014

54. Kirkland EB, Heincelman M, Bishu KG, Schumann SO, Schreiner A, Axon RN, et al. Trends in healthcare expenditures among us adults with hypertension: National Estimates, 2003–2014. *J Am Heart Assoc*. (2018) 7:e008731. doi: 10.1161/JAHA.118.008731