frontiers | Research Topics

Women in hypertension

Edited by
Maria Dorobantu and Daniela Sorriento

Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-83252-126-7
DOI 10.3389/978-2-83252-126-7

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

Women in hypertension

Topic editors

Maria Dorobantu — Carol Davila University of Medicine and Pharmacy, Romania

Daniela Sorriento — University of Naples Federico II, Italy

Citation

Dorobantu, M., Sorriento, D., eds. (2023). *Women in hypertension*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83252-126-7

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 24 March 2023
DOI 10.3389/fcvm.2023.1156589

OPEN ACCESS

EDITED AND REVIEWED BY
Hendrik Tevaearai Stahel,
University Hospital of Bern, Switzerland

*CORRESPONDENCE
Daniela Sorriento
✉ daniela.sorriento@unina.it

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 01 February 2023
ACCEPTED 14 March 2023
PUBLISHED 24 March 2023

CITATION
Dorobantu M and Sorriento D (2023) Editorial: Women in hypertension.
Front. Cardiovasc. Med. 10:1156589.
doi: 10.3389/fcvm.2023.1156589

Editorial: Women in hypertension

Maria Dorobantu[1,2] and Daniela Sorriento[3,4]*

[1]Department of Cardiology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [2]The Romanian Academy, Bucharest, Romania, [3]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy, [4]CIRIAPA Interdepartmental Center for Research on Arterial Hypertension and Associated Conditions CIRIAPA, Federico II University, Naples, Italy

KEYWORDS

hypertension, women, preeclampsia, anti-hypertensive treatment, risk-prediction model, gender discrimination

Editorial on the Research Topic
Women in hypertension

Introduction

Women's history in science has always been a history of prejudice and discrimination, without equality with the opposite sex. Despite the great progresses, such discrimination is still present in the scientific world, especially in the so-called hard sciences (Mathematics, Physics, Chemistry, Biology), maybe due to old gender prejudices and stereotypes. In the academic world, female researchers currently represent more than half of all researchers, but this percentage decreases drastically as we advance in the university hierarchy, predisposing to a clear gender inequality. In the leading academic positions, gender differences are even more marked, denoting an unfair approach towards female leadership and an overall aged attitude that does not reflect the current educational status. Although history does not give much credit to female researchers, many scientific discoveries belong to women. Over time, various female personalities have made scientific history and have proven to be a source of inspiration for future generations. A famous example is Marie Curie, one of the first scientists recognized worldwide for her studies on radiation and radioactive materials (Nobel Prizes for Physics in 1903 and Chemistry in 1911). The story of Rosalind Franklin is yet another emblematic one since she created the foundations of molecular biology by providing experimental evidence of the helix structure of DNA, even though the Nobel Prize was later awarded to her male colleagues. Francoise Barre-Sinoussi was awarded the Nobel Prize for Medicine in 2008 following the discovery of the human immunodeficiency virus (HIV), essential to turn AIDS from a death sentence to a manageable disease. Rita Levi-Montalcini received the Nobel Prize for Medicine in 1986 for the identification of the nerve fiber growth factor Ngf contributing to the study of several diseases, such as tumors and Alzheimer's disease.

Several projects aimed at gender equality are currently being developed, including this specific research topic, to promote female research, encourage women to be involved in scientific projects and, eventually, disseminate their results. Nevertheless, despite the progress that we have seen in recent years, gender equality is still far from being achieved. Sensitivity towards this problem has certainly grown and several initiatives are increasingly successful in promoting the much-needed cultural change.

Contributions to the topic

The current Research Topic, entitled "Women in hypertension", promotes the work of female scientists in the field of hypertension contributing to counteracting the gender imbalance currently present in the research field. To support this purpose, both the editors and the reviewers of this Editorial are women, and only submissions headed by women (as first or last author) were considered. In this context, the editors themselves are an example of female leadership in pre-clinical and clinical research fields: the SEPHAR study, led by Prof. Maria Dorobantu, had a major impact on the actual understanding of overall cardiovascular disease (1–3); pre-clinical research, led by Prof. Sorriento, increased the knowledge of endothelial function in diseases (4–9). To further emphasize the importance of this research topic, we have ultimately selected nine scientific studies, which significantly contributed to advances in the field of hypertension, the most common modifiable risk factor for cardiovascular and other diseases (10, 11). Risk prediction and an early diagnosis of hypertension are essential for the primary prevention and management of this condition and its cardiovascular complications. Therefore, effective, and easy-to-manage hypertension risk prediction models (machine learning models) have been generated to identify individuals at high risk of developing hypertension (12, 13). Practice guidelines are available for the management of hypertension, indicating the most effective drugs, therapeutic associations, and lifestyle modifications (14–15) to prevent cardiovascular events and reduce mortality, but many patients with hypertension remain uncontrolled. This could be partly due to diagnostic and treatment initiation inertia (16) and the type of intervention and clinical approach (17). Novel therapeutic targets have been identified using pre-clinical models of hypertension but most failed in clinical trials or generated contrasting results, possibly due to defects in patient enrollment and comorbidities, as it occurs with Vitamin D supplementation (18–21). The gender difference in blood pressure levels appears during adolescence and in the elderly (22). Premenopausal women have a lower risk and incidence of hypertension compared with men of the same age, but this advantage for women gradually disappears after menopause. In this context, clinical and experimental findings emphasize the role of sex hormones, the autonomic nervous system, the renin-angiotensin-aldosterone system, and arterial stiffness in the development of chronically elevated blood pressure in women (24). A particular condition that requires special attention from physicians is preeclampsia, the leading cause of maternal and neonatal death, for which an early diagnosis and a timely initiated and well-conducted antihypertensive therapy are essential (25–27). With the sole exception of pregnancy, the current good clinical practice guidelines do not make any differences between men and women regarding the general therapeutic approach (28), even if a gender-related response to therapy has been suggested (29–31).

Conclusions

The contributions of this Research Topic from female researchers demonstrate the remarkable contribution of females in the research field, contributing to advances in knowledge of hypertension. In the future, female participation in the scientific field and their access to leading positions in academia and science should be further encouraged and supported. In a society where we are aiming at overall transparency and fairness, where our only purpose should be notable progress in medicine and science regardless of the subspecialty, discrimination based on the researcher's gender has no place. The world has no gender but only brilliant minds at the service of science!

Author contributions

MD and DS contributed to the conception and design of the study and wrote the manuscript. All authors read and approved the submitted version.

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. Cojocaru C, Vijiiac AE, Gheorghe-Fronea O, Mohaiu T, Itu L, Dorobantu M. Nine-Year trends in atrial fibrillation prevalence among Romanian adult hypertensives: a post-hoc analysis of SEPHAR II-IV surveys. *Int J Environ Res Public Health*. (2022) 19(15):9250. doi: 10.3390/ijerph19159250

2. Dorobantu M, Darabont RO, Badila E, Ghiorghe S. Prevalence, awareness, treatment, and control of hypertension in Romania: results of the SEPHAR study. *Int J Hypertens*. (2010) 2010:970694. doi: 10.4061/2010/970694

3. Dorobantu M, Tautu OF, Dimulescu D, Sinescu C, Gusbeth-Tatomir P, Arsenescu-Georgescu C. Perspectives on hypertension's prevalence, treatment and control in a high cardiovascular risk east European country: data from the SEPHAR III survey. *J Hypertens*. (2018) 36:690–700. doi: 10.1097/HJH.0000000000001572

4. Gambardella J, Sorriento D, Bova M, Rusciano M, Loffredo S, Wang X. Role of endothelial G protein-coupled receptor kinase 2 in angioedema. *Hypertension*. (2020) 76:1625–36. doi: 10.1161/HYPERTENSIONAHA.120.15130

5. Bellis A, Sorriento D, Fiordelisi A, Izzo R, Sadoshima J, Mauro C. Autocrine bradykinin release promotes ischemic preconditioning-induced cytoprotection in bovine aortic endothelial cells. *Int J Mol Sci*. (2020) 21(8):2965. doi: 10.3390/ijms21082965

6. Gambardella J, De Rosa M, Sorriento D, Prevete N, Fiordelisi A, Ciccarelli M. Parathyroid hormone causes endothelial dysfunction by inducing mitochondrial ROS and specific oxidative signal transduction modifications. *Oxid Med Cell Longev*. (2018) 2018:9582319. doi: 10.1155/2018/9582319

7. Ciccarelli M, Sorriento D, Franco A, Fusco A, Del Giudice C, Annunziata R. Endothelial G protein-coupled receptor kinase 2 regulates vascular homeostasis through the control of free radical oxygen species. *Arterioscler Thromb Vasc Biol*. (2013) 33:2415–24. doi: 10.1161/ATVBAHA.113.302262

8. Galasso G, De Rosa R, Ciccarelli M, Sorriento D, Del Giudice C, Strisciuglio T. beta2-Adrenergic receptor stimulation improves endothelial progenitor cell-mediated ischemic neoangiogenesis. *Circ Res*. (2013) 112:1026–34. doi: 10.1161/CIRCRESAHA.111.300152

9. Sorriento D, Santulli G, Del Giudice C, Anastasio A, Trimarco B, Iaccarino G. Endothelial cells are able to synthesize and release catecholamines both in vitro and in vivo. *Hypertension*. (2012) 60:129–36. doi: 10.1161/HYPERTENSIONAHA.111.189605

10. Iaccarino G. Editorial: highlights in hypertension: 2021. *Front Cardiovasc Med*. (2022) 9:926949. doi: 10.3389/fcvm.2022.926949

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

12. Kanegae H, Oikawa T, Suzuki K, Okawara Y, Kario K. Developing and validating a new precise risk-prediction model for new-onset hypertension: the jichi genki hypertension prediction model (JG model). *J Clin Hypertens (Greenwich)*. (2018) 20:880–90. doi: 10.1111/jch.13270

13. Qin L, Zhang Y, Yang X, Wang H. Development of the prediction model for hypertension in patients with idiopathic inflammatory myopathies. *J Clin Hypertens (Greenwich)*. (2021) 23:1556–66. doi: 10.1111/jch.14267

14. Emrich IE, Bohm M, Mahfoud F. The 2018 ESC/ESH guidelines for the management of arterial hypertension: a German point of view. *Eur Heart J*. (2019) 40:1830–1. doi: 10.1093/eurheartj/ehz381

15. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D. 2020 International society of hypertension global hypertension practice guidelines. *Hypertension*. (2020) 75:1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026

16. Pallares-Carratala V, Carratala-Munuera C, Lopez-Pineda A, Quesada JA, Gil-Guillen V, Orozco-Beltran D. Characterizing diagnostic inertia in arterial hypertension with a gender perspective in primary care. *Front Cardiovasc Med*. (2022) 9:874764. doi: 10.3389/fcvm.2022.874764

17. Santschi V, Wuerzner G, Pais B, Chiolero A, Schaller P, Cloutier L. Team-Based care for improving hypertension management: a pragmatic randomized controlled trial. *Front Cardiovasc Med*. (2021) 8:760662. doi: 10.3389/fcvm.2021.760662

18. Sorriento D, De Luca N, Trimarco B, Iaccarino G. The antioxidant therapy: new insights in the treatment of hypertension. *Front Physiol*. (2018) 9:258. doi: 10.3389/fphys.2018.00258

19. Vimaleswaran KS, Cavadino A, Berry DJ, LifeLines Cohort Study i, Jorde R, Dieffenbach AK. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. *Lancet Diabetes Endocrinol*. (2014) 2:719–29. doi: 10.1016/S2213-8587(14)70113-5

20. Trimarco V, Manzi MV, Mancusi C, Strisciuglio T, Fucile I, Fiordelisi A. Insulin resistance and vitamin D deficiency: a link beyond the appearances. *Front Cardiovasc Med*. (2022) 9:859793. doi: 10.3389/fcvm.2022.859793

21. Cifkova R, Bruthans J, Strilchuk L, Wohlfahrt P, Krajcoviechova A, Sulc P. Longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension in the Czech population. Are there any sex differences? *Front Cardiovasc Med*. (2022) 9:1033606. doi: 10.3389/fcvm.2022.1033606

22. Singh JN, Nguyen T, Kerndt CC, Dhamoon AS. *Physiology, blood pressure age related changes*. Treasure island, FL: StatPearls (2022).

23. Tasic T, Tadic M, Lozic M. Hypertension in women. *Front Cardiovasc Med*. (2022) 9:905504. doi: 10.3389/fcvm.2022.905504

24. Sinkey RG, Battarbee AN, Bello NA, Ives CW, Oparil S, Tita ATN. Prevention, diagnosis, and management of hypertensive disorders of pregnancy: a comparison of international guidelines. *Curr Hypertens Rep*. (2020) 22:66. doi: 10.1007/s11906-020-01082-w

25. Antihypertensive Treatment of Acute Cerebral Hemorrhage i. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med*. (2010) 38:637–48. doi: 10.1097/CCM.0b013e3181b9e1a5

26. Zhao S, Yin C, Zhai Y, Jia Z, Su S, Lu Y. Serum peptidomic screening identified circulating peptide biomarkers predictive for preeclampsia. *Front Cardiovasc Med*. (2022) 9:946433. doi: 10.3389/fcvm.2022.946433

27. Cheetham TC, Shortreed SM, Avalos LA, Reynolds K, Holt VL, Easterling TR. Identifying hypertensive disorders of pregnancy, a comparison of two epidemiologic definitions. *Front Cardiovasc Med*. (2022) 9:1006104. doi: 10.3389/fcvm.2022.1006104

28. Tadic M, Cuspidi C, Grassi G, Ivanovic B. Gender-specific therapeutic approach in arterial hypertension—challenges ahead. *Pharmacol Res*. (2019) 141:181–8. doi: 10.1016/j.phrs.2018.12.021

29. Lodi E, Carollo A, Martinotti V, Modena MG. Hypertension and pharmacological therapy in women. *High Blood Press Cardiovasc Prev*. (2018) 25:147–50. doi: 10.1007/s40292-018-0257-0

30. Canfora F, Calabria E, Pecoraro G, Leuci S, Coppola N, Mazzaccara C. Prevalence of hypertension and correlation with mental health in women with burning mouth syndrome: a case-control study. *Front Cardiovasc Med*. (2022) 9:969148. doi: 10.3389/fcvm.2022.969148

31. Wenger NK, Arnold A, Bairey Merz CN, Cooper-DeHoff RM, Ferdinand KC, Fleg JL. Hypertension across a woman's life cycle. *J Am Coll Cardiol*. (2018) 71:1797–813. doi: 10.1016/j.jacc.2018.02.033

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 25 October 2021
doi: 10.3389/fcvm.2021.760662

Team-Based Care for Improving Hypertension Management: A Pragmatic Randomized Controlled Trial

Valérie Santschi[1], Gregoire Wuerzner[2], Bruno Pais[1], Arnaud Chiolero[3,4,5], Philippe Schaller[6], Lyne Cloutier[7], Gilles Paradis[5] and Michel Burnier[2]*

[1] La Source, School of Nursing Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland, [2] Service of Nephrology and Hypertension, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland, [3] Population Health Laboratory, #PopHealthLab, University of Fribourg, Fribourg, Switzerland, [4] Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, [5] School of Population and Global Health, McGill University, Montreal, QC, Canada, [6] Cité Générations, Onex, Switzerland, [7] Département des sciences infirmières, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada

OPEN ACCESS

Edited by:
Guido Iaccarino,
University of Naples Federico II, Italy

Reviewed by:
Vincenzo De Luca,
Università degli Studi di Napoli Federico II, Italy
Jordi Piera-Jiménez,
Catalan Health Service, Spain

***Correspondence:**
Valérie Santschi
v.santschi@ecolelasource.ch

Specialty section:
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

Received: 18 August 2021
Accepted: 30 September 2021
Published: 25 October 2021

Citation:
Santschi V, Wuerzner G, Pais B, Chiolero A, Schaller P, Cloutier L, Paradis G and Burnier M (2021) Team-Based Care for Improving Hypertension Management: A Pragmatic Randomized Controlled Trial. Front. Cardiovasc. Med. 8:760662. doi: 10.3389/fcvm.2021.760662

Objective: We evaluated the effect on long term blood pressure (BP) of an interprofessional team-based care (TBC) intervention, involving nurses, pharmacists, and physicians, compared to usual care.

Methods: We conducted a pragmatic randomized controlled study in ambulatory clinics and community pharmacies in Switzerland (ClinicalTrials.gov: NCT02511093). Uncontrolled treated hypertensive patients were randomized to TBC or usual care (UC). In the TBC group, nurses and pharmacists met patients every 6 weeks to measure BP, assess lifestyle, support medication adherence, and provide health education for 6 months. After each visit, they wrote a report to the physician who could adjust antihypertensive therapy. The outcome was the intention-to-treat difference in mean daytime ambulatory blood pressure measurement (ABPM) and control (<135/85 mmHg) at 6 and 12 months.

Results: Eighty-nine patients (60 men/29 women; mean (SD) age: 61(12) year) were randomized to TBC ($n = 43$) or UC ($n = 46$). At baseline, mean (SD) BP was 144(10)/90(8) mmHg and 147(12)/87(11) mmHg in the TBC and UC groups. At 6 months, the between-groups difference in daytime systolic ABPM was−3 mmHg [95% confidence interval (CI):−10 to +4; $p = 0.45$]; at 12 months, this difference was−7 mmHg [95% CI:−13 to−2; $p = 0.01$]. At 6 months, the between-groups difference in daytime diastolic ABPM was +2 mmHg [95% CI:−1 to +6; $p = 0.20$]; at 12 months, this difference was−2 mmHg [95% CI:−5 to +2; 0.42]. Upon adjustment for baseline covariates including baseline BP, the between-groups differences at 6 and 12 months were maintained. At 6 months, there was no difference in BP control. At 12 months, the TBC group tended to have a better control in systolic BP ($p = 0.07$) but not in diastolic BP ($p = 0.33$).

Conclusion: While there was not significant effect on BP at 6 months of follow-up, the TBC intervention can help decrease long-term systolic BP among uncontrolled hypertensive patients.

Keywords: hypertension, team-based care, healthcare professionals, healthcare services research, interprofessional intervention

INTRODUCTION

Hypertension is a major risk factor for stroke and cardiovascular diseases and a major cause of mortality worldwide (1). One quarter to one third of European adults have hypertension, and this burden will increase due to the aging of the population (2). Despite effective blood pressure (BP) lowering drugs to prevent cardiovascular events and reduce mortality (3), a large proportion of patients with hypertension remain uncontrolled (4–6). In responses to these challenges, innovative models of care are needed to improve BP control, such as team-based care (TBC) approaches that include pharmacists and nurses in primary care (7, 8).

Various studies involving pharmacists or nurses in primary care have shown that they can help improve BP control (9–13). Moreover, the evidence from systematic reviews with meta-analysis supports that pharmacists—working alone or in teams (8, 14)—can improve the management of hypertension as well other cardiovascular risk factors (15, 16). Another systematic review found evidence that nurses led interventions are effective in the management of BP (17). Since 2014, the U.S Community Preventive Services Task Force recommends TBC for hypertension management (7, 18). TBC is defined as a coordinated model of care involving different healthcare professionals, such as physicians and other non-physician clinicians such as pharmacists, nurses, working in collaborative partnership, each with their own expertise, to manage hypertension, and optimize patient education. Recent guidelines on hypertension management, notably the 2017 guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) as well as the 2018 guidelines of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) recommend TBC for the first time with the involvement of pharmacists and nurses in the management of hypertension (19–21).

However, high quality evidence showing the efficacy of TBC in hypertension comes essentially from randomized controlled studies conducted in North America in outpatient clinics or by general practitioners and with a median duration of follow-up of 6 month (8). The TBC model to improve long term BP with both nurses and pharmacists need therefore to be evaluated in a European real-life primary care setting. The objective of the TBC for improving Hypertension management (TBC-HTA) randomized controlled study was to assess whether a TBC intervention, involving nurses and community pharmacists working in collaboration with physicians, improves long term daytime ambulatory BP among uncontrolled treated hypertensive patients in primary care practices under real-life conditions (22).

MATERIALS AND METHODS

Study Design, Setting and Participants

This study was a pragmatic randomized controlled trial conducted from September 2014 to December 2019 comparing a 6-month TBC interprofessional intervention among outpatients followed in ambulatory clinics and community pharmacies in Lausanne and Geneva, Switzerland (ClinicalTrials.gov: NCT02511093), which were included in the study on a voluntary basis. The details of the study protocol have been published previously (22). The ethics committees of the cantons of Vaud (CER-VD 449/13) and Geneva (CCER GE 15/281), Switzerland approved the study protocol which followed the principles of the Declaration of Helsinki.

Outpatient clinic databases built on the electronic medical records of patients followed-up in the ambulatory clinics, were used to identify patients. To be selected, patients had the following inclusion criteria: (1) uncontrolled hypertension defined as daytime ambulatory BP $\geq$ 135/85 mmHg or office BP $\geq$ 140/90 mmHg over at least two consecutive visits; (2) taking at least one antihypertensive medication; (3) aged 18 years old or more; (4) speak and understand French; (5) agree to use the service from the same pharmacy for the duration of the study. Exclusion criteria were (1) pregnancy or lactation, (2) hospitalization, (3) living in a nursing home, (4) inability to understand the study aim, (5) participation in another clinical study, or (6) daytime ambulatory BP $>$ 180/110 mmHg.

Patients meeting inclusion criteria were approached during a routine clinic visit by the physician or contacted by phone by a nurse who explained the study and ascertained patients' willingness to participate. If patients agreed to participate, and provide a written consent form, a research clinic visit was scheduled at the ambulatory clinic. Demographic data were collected at baseline, including sex, age, comorbid conditions, and the number and type of antihypertensive drugs. After completing the baseline assessment, patients were randomized *via* a computer number generated using sequentially numbered opaque sealed envelopes in an equal allocation ratio (1:1) using permuted blocks to either the 6-month TBC intervention group or the UC care group (22). Due to the nature of the intervention, patients and healthcare professionals (physicians, nurses and community pharmacists) could not be blinded to the allocation.

TBC Intervention

Each patient allocated to the TBC group received the TBC interprofessional intervention from nurses and community

pharmacists working in collaboration with physicians. Prior to the study, nurses and community pharmacists were trained during a 2-h workshop about the study requirements, TBC intervention, standardized BP measurement and hypertension care according to the ESC/ESH recommendations (22), antihypertensive medication management, and counseling about lifestyle modification (physical activity and diet). More precisely, the TBC intervention, based on specific competencies of healthcare professionals, comprises (22):

1) A structured individual intervention conducted by trained nurses and community pharmacists every 6 weeks (at baseline, 6-, 12-, 18-week) during the 6-month of follow-up.
2) At each visit, patients received structured individual interventions conducted by trained nurses and community pharmacists (BP measurement, assessment and counseling about lifestyle and medication adherence and, health education concerning treatment and disease), respectively.
3) Following each 6-week visit, a summary report (BP measures, medication adherence and lifestyle assessment) with recommendations were prepared by the nurse and the pharmacist for the physician who adjusted antihypertensive therapy accordingly.

No medication change was allowed during the first 6 weeks of follow-up. If BP was uncontrolled (≥140/90 mmHg) at the 6, 12, and 18-week sessions with the community pharmacist or the nurse, the physician was informed by phone or in face-to-face meeting. The physician then adapted the treatment as needed taking account the nurse's and the community pharmacist's recommendations on lifestyle, medication adherence, and therapy.

Usual Care

Patients allocated to UC group received routine care by their habitual physician without any specific nurse or community pharmacist intervention. They attended schedule visits at baseline, 6 and 12 months of follow-up, where ABPM was taken.

Blood Pressure Measurement

At baseline, 6- and 12-months (i.e., 6 months post-intervention), daytime ABPM, used as the main outcome, was taken in TBC and UC patients using clinically validated electronic devices, and using a standardized protocol (22) in line with the European Society of Hypertension (ESH) recommendations (23). More precisely, the ABPM device was installed on the dominant arm by the nurse who explains the procedure to the patient. Measurements were based on the auscultatory mode, relayed by the oscillometric mode in case of failure of the auscultatory mode. Measurements were made every 20-min interval during the day and every 60-min interval during the night (23). The device used was the electronic Diasys (DIASYS integra; Novacor SA, Rueil-Malmaison, France) or Boso (Bosch+Sohn, Allemagne).

If ABPM was not available at baseline, BP was based on automated office BP measurements and computed as the average of the last 3 out of 6 measurements with the patient resting alone quietly (24). In the TBC group, every 6 weeks, automated office BP was measured by the nurse and by the community pharmacist using the Microlife WatchBP home, a clinically validated oscillometric device (25).

Outcome

The primary outcome was the difference in mean systolic/diastolic daytime ABPM between TBC and UC patients and the difference in the proportion of TBC and UC patients with controlled systolic/diastolic daytime ABPM (<135/85 mmHg) at 6-month. The secondary outcome was the difference in mean systolic/diastolic daytime ABPM between TBC and UC patients and the difference in the proportion of TBC and UC patients with controlled systolic/diastolic daytime ABP (<135/85 mmHg) at 12-month (6 months post-intervention).

Other outcomes included the number, classes and daily dosages of antihypertensive drugs taken during the study that were documented using medical electronic records at 6- and 12-month (6 months post-intervention follow-up). The differences in mean number, modification, intensification and reduction of antihypertensive drugs were also assessed. Using the start and end dates of prescribed drugs, we defined antihypertensive-drug modifications as drug changes (changing one class of drug for another), or drug intensifications (adding a new drug or increasing a drug dosage), or drug reductions (stopping a drug without replacing it or decreasing a drug dosage) (26).

Sample Size and Statistical Analysis

Based on the results of the systematic review by Santschi et al. assessing the impact of pharmacist interventions on BP, a difference in systolic BP of 6 to 10 mmHg was expected between TBC and UC groups. A sample size of 46 patients per group provided 80% power to detect a 6 mmHg difference in systolic BP (SD: 10 mmHg) with a two-sided alpha of 5%. Assuming a drop-out or loss to follow-up rate of ∼15%, the targeted sample size was adjusted to 55 per group, for a total sample size of 110.

Descriptive statistics were used to present baseline characteristics of TBC and UC patients as number, percentage and means (standard deviation). For the per-protocol analysis, missing BP value at 6 or 12 months were not imputed; the analyses were conducted on patients with complete follow-up and no missing BP data. For the ITT analyses, the last observation carried forward method was used for missing data (27). We imputed missing values for measurements at 6 months of follow-up (TBC: 4 patients; UC: 4 patients) or at 12 months of follow-up (TBC: 5 patients; UC: 8 patients) of follow-up. As planned, main analyses were followed the intention-to-treat (ITT) principle (22) and used Student's two-sided *t*-test to assess the statistical significance of the ITT between-groups difference in systolic and diastolic ambulatory BP at 6- and 12-month of follow-up. The statistical significance for the ITT between-groups difference in the proportion of patients with systolic/diastolic BP control were calculated at 6- and 12-month of follow-up using a chi-squared test. Further, in addition of the main analyses and following recent recommendations for the analyses of pragmatic randomized trials (28), along first the ITT principle and second the per-protocol principle, a set of linear regression analyses were conducted to account for the potential biasing effect of differences in baseline characteristics,

especially baseline BP level, between the TBC and the UC groups on the outcomes. Hence, to assess the association of group allocation with systolic and diastolic daytime BP, respectively, three regression models of growing complexity were fitted with (1) no adjustment; (2) adjustments for age, sex, and recruitment center and (3) additional adjustments for the number of antihypertensive treatment at baseline and for BP at baseline (29). Two-sided *P*-value <0.05 was considered as statistically significant. All statistical analyses were conducted with Stata software version 16.0 (Stata Corp, College Station, TX, USA) and Microsoft Excel (version 16).

RESULTS

In total, 4,654 patients were assessed for eligibility using the ambulatory clinic database and 371 were identified as potentially eligible (**Figure 1**). As underlined in the **Figure 1**, the number of participants who did not meet all inclusion criteria or had exclusion criteria—i.e., no hypertension drug treatment, no recent BP measurement, aged <18 years old, hospitalized, living in nursing home or not followed-up by a participating physician—were documented. Eighty-nine patients (24% of potentially eligible) agreed to participate and were included in the study: 43 patients were randomly assigned to TBC and 46 patients to UC group. Of these, 81 (91%) (TBC: 39; UC: 42) completed the 6-month of follow-up, and 76 (85%) (TBC: 35; UC: 41) completed the 12-month follow-up.

Table 1 summarizes the baseline characteristics of the 89 included patients. The mean age was 60 (SD: 12) years and two thirds of patients were men. More than 50% of patients were obese and 12% were current smokers. Patients took on average 3 (SD: 2 drugs) (to treat hypertension and other conditions) daily, and more than 50% were treated with 4 drugs or more per day. A large proportion of patients had comorbidities, such as cardiovascular diseases, diabetes, dyslipidaemia, and chronic kidney disease. In the TBC group, systolic BP was slightly lower and diastolic BP slightly higher compared to the UC group. To account for a potential biasing effect of these differences on the outcomes, regression analyses adjusted for baseline BP were conducted (see below).

Blood Pressure and Antihypertensive Treatment

Table 2 summarizes information about baseline BP and antihypertensive treatment. TBC and UC patients were treated most often with angiotensin receptor blockers (55%), diuretics (44%), angiotensin converting enzyme inhibitors (30%), calcium channel blockers (30%), and beta-blockers (22%). The mean number of daily antihypertensive drugs taken was 2 (SD: 1; range: 1–4) in both groups, with 38% of patients taking one drug per day, 40% two drugs per day, and 22% three drugs or more per day. No major clinical difference was observed between TBC and UC groups regarding the baseline BP and treatment for hypertension.

Table 3 shows that systolic and diastolic BP decreased in both groups during follow-up. At 6 months, the ITT between-groups difference in daytime systolic/diastolic ABPM was−3/+2 mmHg [95% confidence interval (CI):−10 to +4/-1 to +6; $p = 0.45/0.20$] and the systolic/diastolic control was 42%/48% in the TBC group and 39%/52% in the UC group ($p = 0.63/0.45$), respectively. At 12 months, the ITT between-groups difference in daytime ABPM was−7/-2 mmHg [95% CI:−13 to−2/-5 to +2; $p = 0.01/0.42$]; the systolic/diastolic control was 44%/53% in TBC group and 26%/48%% in UC group ($p = 0.07/0.33$), respectively. Upon adjustment for covariates in a set of linear regression models of growing complexity, the between-groups difference in systolic and diastolic ABP at 6- and 12-months of follow-up was maintained allowing to exclude important biasing effect of imbalance between groups (see **Supplementary Tables S1**, **S2** in supplementary material). Of note, upon adjustment for baseline number of antihypertensive treatments and baseline BP, the ITT between-groups difference in daytime systolic/diastolic ABPM was maintained at 12 months of follow-up (i.e.,−5/-3 mmHg [95% CI:−10 to−1/-6 to 0; $p = 0.02/0.09$]. Finally, per-protocol analyses yielded similar results (see **Supplementary Table S2** in supplementary material).

Table 4 summarizes antihypertensive drug use during follow-up. In both groups, the mean number of antihypertensive drugs taken by TBC and UC patients slightly increased during follow-up. There was no difference between groups in the mean number of antihypertensive drugs at 6- and at 12-month of follow-up. The type of antihypertensive treatment taken did not change substantially during follow-up and between groups. However, patients in the TBC group tended to have experienced more frequently a switch to another class of drug as well as an increase of dosage or number of drugs. When all types of drug changes were considered, the mean number of changes per patient was greater in the TBC group compared to the UC group, at 6- and 12-months of follow-up.

Difficulties to Medications and Lifestyle and Recommendations During Follow-Up

Among TBC patients, a total of 174 difficulties in 43 patients related to medications and lifestyle (such as lack of knowledge, beliefs, difficulties to integrate drugs in daily life) were identified (132/174 (75%) by the nurses and 42/174 (24%) by the pharmacists) during the first 6-months of follow-up. Nurses reported 83 (47%) issues related to physical activity and 49 (28%) to dietary and lifestyle habits (e.g., lack of motivation or lack of time to implement the change). Pharmacists reported mostly on medication adherence (15/42; 36% e.g., too many drugs to take daily, omission to take drugs or difficulties to integrate drugs in the daily activities of the patients). Another barrier frequently reported by pharmacists (14/42; 34%) was lack of knowledge concerning hypertension. During the same period, nurses made 164 recommendations related to dietary and lifestyle habits (most often to reduce salt consumption and to increase daily physical activity). Pharmacists made 40 recommendations related to hypertension drug treatment (most often patient adherence counseling about how to improve adherence (e.g., weekly reminder, clock alarm) and education about hypertension treatment.

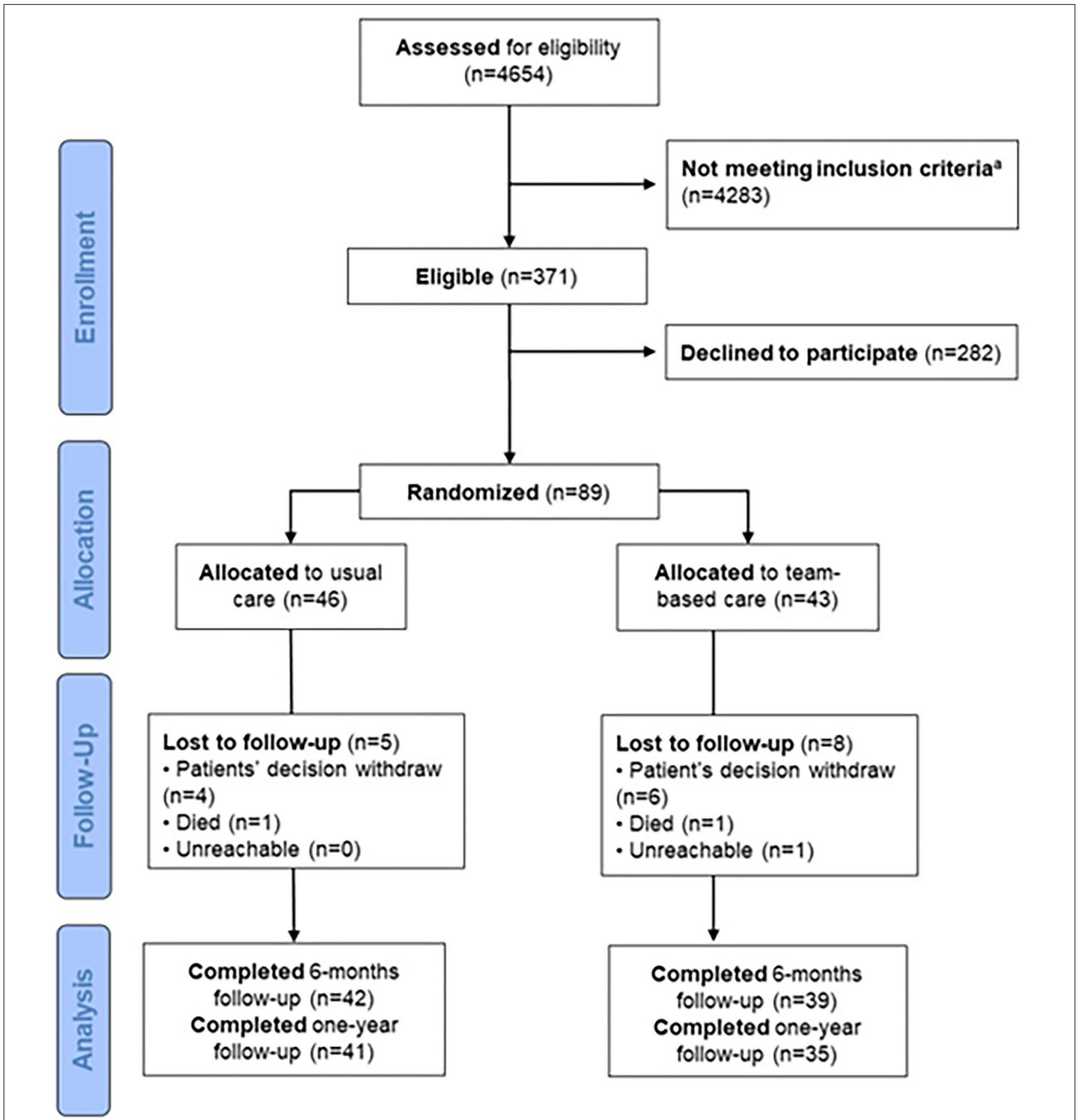


FIGURE 1 | Flow diagram of included patients. [a]Of the 4,283 who did not meet inclusion criteria, 195 have HTN drug treatment since <1 months, 1,388 did not have HTN drug treatment, 1,063 did not have recent BP measurement, 315 were aged <18 years, 486 were hospitalized or nursing home and 320 were patients not followed by participating physicians.

DISCUSSION

The TBC-HTA randomized controlled study was one of the first pragmatic attempt to evaluate the effect of a TBC intervention involving community pharmacists and nurses working in collaboration with physicians to improve long term ambulatory BP in a European primary care setting under real conditions, that is, designed accounting for local constraints, resources, and

TABLE 1 | Baseline characteristics of the patients.

	UC	TBC
Patients, *n*	46	43
Sex, (men/women), *n*	29/17	31/12
Mean age, years (SD)	61 (13)	60 (11)
Current smoker, *n* (%)	6 (13%)	5 (12%)
Mean BMI, kg/m^2 (SD)	28.0 (4.6)	30.6 (6.5)
Comorbid conditions		
Cardiovascular disease, *n* (%)	9 (20%)	9 (21%)
Diabetes mellitus, *n* (%)	7 (15%)	14 (33%)
Dyslipidemia, *n* (%)	19 (41%)	17 (40%)
Chronic kidney disease, *n* (%)	3 (7%)	4 (9%)
Mean number of all prescription drugs, *n* (SD) [min; max]	3.0 (1.8) [1; 9]	3.2 (2.0) [1; 10]
Polymedication (3 drugs or more), *n* (%)	25 (54%)	25 (58%)
Mean time since hypertension diagnosis, years (SD) [min; max]	7.5 (7.9) [0; 30]	11.7 (11.7) [0; 35]

UC, usual care; TBC, team-based care; SD, standard deviation; BMI, body mass index; smoking, current smoking ≥1 cigarette/day.

TABLE 2 | Baseline blood pressure (BP) and treatment for hypertension.

	UC *n* = 46	TBC *n* = 43
Mean systolic BP*, mmHg (SD)	147 (12)	144 (10)
Mean diastolic BP*, mmHg (SD)	87 (11)	90 (8)
Mean number of antihypertensive drugs, *n* (SD) [min; max]	1.9 (0.8) [1; 4]	1.8 (0.9) [1; 4]
Antihypertensive drugs used, *n* (%)		
Diuretics	21 (46%)	18 (42%)
ACE inhibitors	13 (28%)	14 (33%)
Ang II receptor blockers	28 (61%)	21 (49%)
Calcium antagonists	13 (28%)	14 (33%)
Beta-blockers	10 (22%)	10 (23%)
Other	0 (0%)	0 (0%)
Number of antihypertensive drugs, *n* (%)		
0	0 (0%)	0 (0%)
1	14 (30%)	20 (47%)
2	23 (50%)	13 (30%)
≥3	9 (20%)	10 (23%)

UC, usual care; TBC, team-based care; SD, standard deviation; ACE, angiotensin converting enzyme; Ang, angiotensin.
**The BP reported at baseline was mean daytime ABPM. If ABPM was not available at baseline, BP was based on automated office BP measurements and computed as the average of the last 3 out of 6 measurements with the patient resting alone quietly (24).*

expertise. While there was not significant effect on BP at 6 months of follow-up, the TBC intervention can help decrease long-term systolic BP among uncontrolled hypertensive patients.

Comparison With Other Studies

Our results are consistent with previous studies (9, 11) and systematic reviews (8) reporting that physician-pharmacist collaboration can improve BP management and control. Our results are also congruent with the much fewer studies (30, 31) with a long-term follow-up, that is, beyond 6 months. Our results are also in line with the finding of a recent systematic review with meta-analysis of more than 100 trials and 55,920 patients showing that the most effective BP-lowering strategies use multilevel and multicomponent approaches to improve hypertension control, often involving non-physician providers assessing patients, measuring BP, and titrating medications as needed (6). In this review, the effect on BP of TBC with physician titrating medication was a mean 6.2/2.5 mmHg decrease in systolic/diastolic BP, which is close to the effect size of 7/2 mmHg seen in our study at 12 months of follow-up.

As underlined, the TBC-HTA study was pragmatic notably because it used the resources available and, the intervention was conducted by healthcare professionals involved in the follow-up of patients in their local setting. These human and local resources were used to conduct the study and the intervention which was designed accounting for the existing expertise. The fact that numerous patients screened were not included does not mean that we have excluded "real-world" patients. This is largely due to the lack of structured and specific practitioner database used in the different healthcare setting involved, but not to highly selective criteria of inclusion. As a result, many participants initially screened did not have inclusion criteria and were not invited to participate. Moreover, to design our study, we did not refer a priori to a specific model of care. However, we can consider that implicitly the model of care used in our study was close to the Chronic Care Model (32), incorporating patients, providers, and system level intervention.

Strengths and Limitations of the Study

The main strengths of our pragmatic randomized controlled study are its design, the long-term follow-up, and the close interprofessional collaboration between nurses, community pharmacists, and physicians to evaluate the effects of TBC intervention on BP control among uncontrolled treated hypertensive patients in primary care practices. The use of a 24-h ambulatory BP monitoring device to measure BP at 6- and 12-month according to a standard protocol was also an asset to evaluate more precisely the effect of TBC intervention on BP control compared to office BP measurement (33). One key strength is the evaluation of the effect of the intervention at 1 year of follow-up (i.e., 6 months after ending the intervention). This is of importance because few studies evaluating this type of team-based care intervention have had follow-ups of more than 6 months (34). Nevertheless, our study suggests that the TBC intervention had almost no effect at 6 months of follow-up, i.e., at the end of the period of active intervention. This could be partly due to regression to the mean, as mean BP decreased in both groups. Another explanation could be a Hawthorne effect (35) during the first 6-months of follow-up: participants in the control group might have improved, at least initially, their dietary and lifestyle habits, as well as their drug adherence, because they knew they were part of a study. Interestingly, a similar observation was made during the first 2 months of a 12-month randomized controlled study that we had conducted

TABLE 3 | Daytime systolic/diastolic ambulatory blood pressure monitoring (ABPM) and control at 6- and 12-month of follow-up.

	6-month of follow-up				12-month of follow-up			
	UC ***n* = 42**	**TBC** ***n* = 39**	***Δ [95% CI]**	***p-value**	**UC** ***n* = 41**	**TBC** ***n* = 35**	***Δ [95% CI]**	***p-value**
Mean systolic ABPM, mmHg (SD)	140 (17)	137 (17)	−3 [-10 to +4]	0.45	141 (14)	134 (14)	−7 [-13 to−2]	0.01
Mean diastolic ABPM, mmHg (SD)	83 (8)	85 (9)	2 [-1 to +6]	0.20	84 (10)	81 (8)	−2 [-5 to +2]	0.42
Systolic ABPM <135 mmHg, *n* (%)	39%	42%		0.63	26%	44%		0.07
Diastolic ABPM <85 mmHg, *n* (%)	52%	48%		0.45	48%	53%		0.33

**The mean between group difference (Δ) and related statistical significance are computed following the intention-to-treat principle (ITT).*
UC, usual care; TBC, team-based care; SD, standard deviation; CI, confidence interval.

TABLE 4 | Antihypertensive drugs at 6- and 12-month of follow-up.

	6-month of follow-up			12-month of follow-up		
	UC ***n* = 42**	**TBC** ***n* = 39**	***p*-value**	**UC** ***n* = 41**	**TBC** ***n* = 35**	***p*-value**
Number of antihypertensive drugs, mean (SD)	2.1 (0.9)	2.1 (1.0)	0.93	2.1 (0.9)	2.3 (0.9)	0.43
Number of antihypertensive drugs, *n* (%)			0.33			0.62
0	0 (0%)	1 (3%)		0 (0%)	0 (0%)	
1	12 (29%)	13 (33%)		10 (24%)	7 (20%)	
2	19 (45%)	11 (28%)		20 (49%)	15 (43%)	
≥ 3	11 (26%)	14 (36%)		11 (27%)	13 (37%)	
Class of antihypertensive drugs used, *n* (%)			0.68			0.57
Diuretics	21 (52%)	16 (41%)		22 (54%)	19 (54%)	
ACE inhibitors	12 (29%)	13 (33%)		11 (27%)	14 (40%)	
Ang II receptor blockers	27 (64%)	22 (56%)		27 (66%)	22 (63%)	
Calcium antagonists	13 (31%)	17 (44%)		14 (34%)	12 (34%)	
Beta-blockers	9 (21%)	12 (31%)		8 (20%)	12 (34%)	
Other	1 (3%)	0 (0%)		2 (5%)	0 (0%)	
Antihypertensive-drug modifications						
Drug changes (change to another class of drug), *n* (%)	2 (5%)	6 (15%)	0.11	4 (10%)	9 (26%)	0.07
Drug intensifications (increase of dosage or number of drugs), *n* (%)	14 (33%)	19 (49%)	0.16	17 (41%)	21 (60%)	0.11
Drug reductions (decrease of dosage or number of drugs), *n* (%)	4 (10%)	7 (18%)	0.27	6 (15%)	4 (11%)	0.68
Any drug modification, *n* (%)	17 (40%)	21 (54%)	0.23	24 (59%)	24 (69%)	0.37
Mean number of drug modifications/patient (min–max)	0.6 (0–3)	1.1 (0–4)	0.04	0.9 (0–3)	1.3 (0–4)	0.06

UC, usual care; TBC, team-based care; SD, standard deviation; ACE, angiotensin converting enzyme; Ang, angiotensin.

to evaluate the effect of a pharmacist intervention to improve adherence among hypertensive patients in primary care (9).

There are however several limitations to our study. One major limitation was the small sample size of the study. Consequently, we have a slightly underpowered study which limits the possibility to get a more confirmative result. This could be one of the reasons why we did not find a statistically significant between-groups difference in mean daytime systolic BP at 6 months of follow-up, despite a favorable trend in the TBC group. Nevertheless, despite the relatively small sample size, the beneficial effect on systolic BP was significantly superior that usual care at 12 months. As with many randomized controlled trials, recruitment of sufficient number of patients was challenging and we did not reach the planned target sample size despite an extension of study time (36). Lack of a structured practitioner database and constrained human and financial resources were barriers to rapidly assess the potential eligibility of patients and ease recruitment. Furthermore, we could not pay healthcare providers to recruit patients.

Another limitation is that we conducted this study in selected outpatient clinics that were interested in implementing a TBC interprofessional model in their practice. This may limit the generalizability of our results. Further studies are needed to evaluate the transferability of our findings to other regions and populations. The absence of effect on diastolic BP is also a weakness. Patients were also not blinded to the intervention. Another limitation is the assessment and monitoring of lifestyles based on subjective assessments of healthcare providers. Digital monitoring technology, e.g., using smartphone (37) would have been better

for a continuous assessment and a stronger involvement of patients (38). More broadly, the use of digital tools could have improved the completeness and effectiveness of the intervention.

Finally, this type of study does not allow the identification of the effects of each component of the TBC: is it the nurse or the pharmacist's intervention that makes a difference? Do changes in patients' diet and lifestyle impact BP control or are only medication changes important? Patients in the TBC group had actually more frequent changes in drug treatment during the follow-up. This suggests that one effect of the intervention was to decrease prescribing physician inertia, and that is consistent with other studies having shown that the intervention of another healthcare professional in the relationship between a patient and the physician improves BP control primarily through a reduction in inertia rather than through other mechanisms (12, 39). The difference in the components of interprofessional interventions also explains the heterogeneity of the effect size in studies having assessed such interventions on BP control and highlight the importance to evaluating locally these types of complex interventions (8). Our study also underlines the complexities of conducting such team-based care approach in real care setting.

CONCLUSION AND FURTHER PERSPECTIVE

While there was not significant effect on BP at 6-months of follow-up, our study shows that a TBC intervention could improve long-term systolic BP control among hypertensive patients in real-life conditions and hence supports interprofessional collaboration between nurses, community pharmacists and physicians to improve BP management in clinical practice, in line with recent North American (19) and European guidelines (ESC/ESH) (20).

Moreover, a team-based care practice or integrated care with, e.g., the support of digital solutions (telemonitoring, home blood pressure monitoring, or electronic health record) may also help manage hypertension by facilitating the exchange of information among the different healthcare professionals and by strengthening patient empowerment (40).

In conclusion, further studies are however still needed to evaluate, at large scale, how to implement efficiently this TBC model, for example by economic analyses, integrating cost and time estimations to provide the TBC intervention (41). These studies may offer policymakers additional compelling arguments and open good perspectives for an extensive implementation of the TBC model.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This multicentric study was approved by the lead Ethics Committee (CER-VD: Cantonal Ethics Committee of Vaud on Research involving humans, ref. number 449/13), and by the local Ethics Committee (CCER: Cantonal Research Ethics Committee of Geneva, ref. number 15/281). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VS, GW, AC, and MB designed and planned the study and accounting for substantial suggestions of LC, PS, and GP and contributed to the development of the training workshop. BP and AC conducted data analyses. VS, GW, and AC directed all aspects of study design and implementation. GW, PS, and MB fostered the clinic participation. VS, AC, and BP drafted the manuscript for publication and all co-authors made substantial contributions. All authors reviewed and approved the final manuscript.

FUNDING

This study was supported by the Health Services Research funding program of the Gottfried and Julia Bangerter-Rhyner-Stiftung, the Swiss Academy of Medical Sciences (SAMS: www.samw.ch/en). This study received funding from the Swiss Society of Hypertension AstraZeneca (unrestricted grant-in-aid). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

ACKNOWLEDGMENTS

The authors thank all nurses, community pharmacists and physicians in Lausanne and Geneva for their support and contribution in recruitment and follow-up participants in the study. We certify that the original work presented in this paper have not been published previously and is not under consideration for publication elsewhere. Partial preliminary results were submitted as an abstract and presented at the 16th World Congress on Public Health in 2020, Rome, Italy on 12–17 October 2020.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.760662/full#supplementary-material

REFERENCES

1. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L et al. Global burden of hypertension and systolic blood pressure of at least 111 to 115 mmHg, 1990-2015. *JAMA*. (2017) 317:165–82. doi: 10.1001/jama.2016.19043
2. Eurostat. *Cardiovascular Disease Statistics*. Available online at: https://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics (Accessed August 9, 2021).
3. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. (2009) 338:b1665. doi: 10.1136/bmj.b1665
4. Merai R, Siegel C, Rakotz M, Basch P, Wright J, Wong B, et al. Grand rounds: a public health approach to detect and control hypertension. *MMWR*. (2016) 65:1261–4. doi: 10.15585/mmwr.mm6545a3
5. Joffres M, Falaschetti E, Gillespie C, Robitaille C, Loustalot F, Poulter N et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. *BMJ Open*. (2013) 3:e003423. doi: 10.1136/bmjopen-2013-003423
6. Mills KT, Obst KM, Shen E, Molina S, Zhang HJ, He H et al. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. *Ann Intern Med*. (2018) 168:110–20. doi: 10.7326/M17-1805
7. Proia KK, Thota AB, Njie GJ, Finnie RK, Hopkins DP, Mukhtar Q et al. Team-based care and improved blood pressure control: a community guide systematic review. *Am J Prev Med*. (2014) 47:86–99. doi: 10.1016/j.amepre.2014.03.004
8. Santschi V, Chiolero A, Colosimo AL, Platt RW, Taffé P, Burnier M et al. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. *J Am Heart Assoc*. (2014) 3:e000718. doi: 10.1161/JAHA.113.000718
9. Santschi V, Rodondi N, Bugnon O, Burnier M. Impact of electronic monitoring of drug adherence on blood pressure control in primary care: a cluster 12-month randomised controlled study. *Eur J Intern Med*. (2008) 19:427–34. doi: 10.1016/j.ejim.2007.12.007
10. Tsuyuki RT, Houle SK, Charrois TL, Kolber MR, Rosenthal MM, Lewanczuk R et al. Randomized trial of the effect of pharmacist prescribing on improving blood pressure in the community: the Alberta clinical trial in optimizing hypertension (RxACTION). *Circulation*. (2015) 132:93–100. doi: 10.1161/CIRCULATIONAHA.115.015464
11. Carter BL, Coffey CS, Ardery G, Uribe L, Ecklund D, James P et al. Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. *Circ Cardiovasc Qual Outcomes*. (2015) 8:235–43. doi: 10.1161/CIRCOUTCOMES.114.001283
12. Margolis KL, Asche SE, Bergdall AR, Dehmer SP, Groen SE, Kadrmas HM et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. *JAMA*. (2013) 310:46–56. doi: 10.1001/jama.2013.6549
13. Bosworth HB, Powers BJ, Olsen MK, McCant F, Grubber J, Smith V et al. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. *Arch Intern Med*. (2011) 171:1173–80. doi: 10.1001/archinternmed.2011.276
14. Carter BL, Rogers M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension: a meta-analysis. *Arch Intern Med*. (2009) 169:1748–55. doi: 10.1001/archinternmed.2009.316
15. Santschi V, Chiolero A, Paradis G, Colosimo AL, Burnand B. Pharmacist interventions to improve cardiovascular disease risk factors in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care*. (2012) 35:2706–17. doi: 10.2337/dc12-0369
16. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. *Arch Intern Med*. (2011) 171:1441–53. doi: 10.1001/archinternmed.2011.399
17. Clark CE, Smith LF, Taylor RS, Campbell JL. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. *BMJ*. (2010) 341:c3995. doi: 10.1136/bmj.c3995
18. Community Preventive Services Task Force. Team-based care to improve blood pressure control: recommendation of the Community Preventive Services Task Force. *Am J Prev Med*. (2014) 47:100–2. doi: 10.1016/j.amepre.2014.03.003
19. 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: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation*. (2018) 138:e426–83. doi: 10.1161/CIR.0000000000000596
20. 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: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. (2018) 36:1953–2041. doi: 10.1097/HJH.0000000000001940
21. Anker D, Tsuyuki RT, Paradis G, Chiolero A, Santschi V. Pharmacist to improve hypertension management—guidelines concordance from North America to Europe. *Can Pharm J*. (2019) 152:180–5. doi: 10.1177/1715163519839675
22. Santschi V, Wuerzner G, Chiolero A, Burnand B, Schaller P, Cloutier L et al. Team-based care for improving hypertension management among outpatients (TBC-HTA): study protocol for a pragmatic randomized controlled trial. *BMC Cardiovasc Disord*. (2017) 17:39. doi: 10.1186/s12872-017-0472-y
23. Parati G, Stergiou G, O'Brien O, Asmar R, Beilin L, Bilo G et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens*. (2014) 32:1359–66. doi: 10.1097/HJH.0000000000000221
24. Stergiou G,Kyriakoulis KG, Kollias A. Office blood pressure measurement types: different methodology-different clinical conclusions. *J Clin Hypertens*. (2018) 20:1683–5. doi: 10.1111/jch.13420
25. Stergiou GS, Giovas PP, Gkinos CP, Patouras JD. Validation of the Microlife WatchBP Home device for self home blood pressure measurement according to the International Protocol. *Blood Press Monit*. (2007) 12:185–8. doi: 10.1097/MBP.0b013e3280b083ce
26. Inkster M, Montgomery A, Donnan P, MacDonald T, Sullivan F, Fahey T. Organisational factors in relation to control of blood pressure: an observational study. *Br J Gen Pract*. (2005) 55:931–7.
27. Salkind NJ. *Last Observation Carried Forward. Encyclopedia of Research Design 2010*. Available at: https://methods.sagepub.com/reference/encyc-of-research-design/n211.xml (accessed September 22, 2021).
28. Murray EJ, Swanson S, Young J, Hernan MA. Guidelines for estimating effects in pragmatic randomized trials. arXiv:1911.06030
29. Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *BMJ*. (2001) 323:1123–4. doi: 10.1136/bmj.323.7321.1123
30. Wentzlaff DM, Carter BL, Ardery G, Franciscus CL, Doucette WR, Chrischilles EA et al. Sustained blood pressure control following discontinuation of a pharmacist intervention. *J Clin Hypertens*. (2011) 13:431–7. doi: 10.1111/j.1751-7176.2011.00435.x
31. Green BB, Anderson ML, Ralston JD, Catz SL, Cook AJ. Blood pressure 1 year after completion of web-based pharmacist care. *JAMA Intern Med*. (2013) 173:1250–2. doi: 10.1001/jamainternmed.2013.1037
32. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA*. (2002) 288:1775–9. doi: 10.1001/jama.288.14.1775
33. Pappaccogli M, Di Monaco S, Perlo E, Burrello J, D'Ascenzo F, Veglio F et al. Comparison of automated office blood pressure with office and out-off-office measurement techniques. *Hypertension*. (2019) 73:481–90. doi: 10.1161/HYPERTENSIONAHA.118.12079
34. Kennelty KA, Polgreen LA, Carter BL. Team-based care with pharmacists to improve blood pressure: a review of recent literature. *Curr Hypertens Rep*. (2018) 20:1. doi: 10.1007/s11906-018-0803-0

35. The Catalogue of Bias. *The Hawthorne Effect*. Available online at: https://catalogofbias.org/biases/hawthorne-effect/ (accessed August 09, 2021).
36. Dumville JC, Worthy G, Bland JM, Cullum N, Dowson C, Iglesias C, et al. VenUS II team Larval therapy for leg ulcers (VenUS II): randomised controlled trial. *BMJ*. (2009) 338:b773. doi: 10.1136/bmj.b773
37. Tison GH. Marcus GM. Will the smartphone become a useful tool to promote physical activity?*Lancet Digit Health*. (2019) 1:e322–3. doi: 10.1016/S2589-7500(19)30154-2
38. Pais B, Buluschek P, DuPasquier G, Nef T, Schütz N, Saner H, et al. Evaluation of 1-year in-home monitoring technology by home-dwelling older adults, family caregivers, and nurses. *Front Public Health*. (2020) 8:518957. doi: 10.3389/fpubh.2020.518957
39. He J, Irazola V, Mills KT, Poggio R, Beratarrechea A, Dolan J, et al. HCPIA investigators. 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
40. Visco V, Finelli R, Pascale AV, Mazzeo P, Ragosa N, Trimarco V, et al. Difficult-to-control hypertension: identification of clinical predictors and use of ICT-based integrated care to facilitate blood pressure control. *J Hum Hypertens*. (2018) 32:467–76.
41. 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

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.

frontiers in Cardiovascular Medicine

REVIEW
published: 17 March 2022
doi: 10.3389/fcvm.2022.859793

Insulin Resistance and Vitamin D Deficiency: A Link Beyond the Appearances

Valentina Trimarco[1], Maria Virginia Manzi[1], Costantino Mancusi[1], Teresa Strisciuglio[1], Ilaria Fucile[1], Antonella Fiordelisi[1], Emanuele Pilato[2], Raffaele Izzo[1], Emanuele Barbato[1], Maria Lembo[1] and Carmine Morisco[1]*

[1] Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy, [2] Department of Cardiac Surgery, School of Medicine, University of Naples Federico II, Naples, Italy

Vitamin D is a steroid hormone that plays a key role in the regulation of body homeostasis, including cardiovascular function. Although the chronic deficiency of vitamin D is associated with cardiovascular risk factors, as well as with an adverse prognosis, randomized controlled trials have failed in demonstrating that dietary vitamin D supplementation could ameliorate the prognosis of patients with cardiovascular diseases, and suggested that vitamin D deficiency is the expression of the effects of other determinants of cardiovascular risk. Thus, the supplementation of vitamin D is not sufficient to improve the cardiovascular risk profile and prognosis. Insulin resistance is a complex phenomenon that plays a key role in the pathogenesis of conventional cardiovascular risk factors. Interestingly, defects of vitamin D and insulin resistance have a superimposable epidemiological distribution. According to the common view, Insulin resistance is considered the direct or indirect consequence of vitamin D deficiency. However, it is also reasonable to speculate that the deficit or the impaired action of vitamin D, in some circumstances, could be the result of the same pathogenic mechanisms responsible of insulin resistance development. In this case, vitamin D deficiency could be considered an epiphenomenon of insulin resistance. Insulin resistance is a reversible condition, being possibly ameliorated by physical activity and hypocaloric diets. Notably, both physical exercise and energy-restricted dietary regimens are associated with an increase of vitamin D levels. These findings indicate that improving insulin resistance condition is a necessary step to ameliorate vitamin D supplementation-based strategies in cardiovascular prevention.

Keywords: type 2 diabetes, metabolic syndrome, arterial hypertension, physical exercise, cardiovascular risk, cardiovascular prevention

OPEN ACCESS

Edited by:
Maria Lorenza Muiesan, University of Brescia, Italy

Reviewed by:
Tlili Barhoumi, King Abdullah International Medical Research Center (KAIMRC), Saudi Arabia
Giuliano Tocci, Sapienza University of Rome, Italy

***Correspondence:**
Maria Lembo
maria.lembo@unina.it

Specialty section:
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

Received: *21 January 2022*
Accepted: *17 February 2022*
Published: *17 March 2022*

Citation:
Trimarco V, Manzi MV, Mancusi C, Strisciuglio T, Fucile I, Fiordelisi A, Pilato E, Izzo R, Barbato E, Lembo M and Morisco C (2022) Insulin Resistance and Vitamin D Deficiency: A Link Beyond the Appearances. Front. Cardiovasc. Med. 9:859793. doi: 10.3389/fcvm.2022.859793

INTRODUCTION

One of the most controversial aspects of modern medical literature is represented by the role that vitamin D has in cardiovascular (CV) prevention. In fact, several epidemiological studies have reported that the deficiency of vitamin D is associated with conventional CV risk factors, as well as with a high rate of major CV events, and with adverse CV prognosis (1, 2). On the other hand, observational studies, randomized controlled trials (RCT), and meta-analyses of RCT have failed

to demonstrate that dietary vitamin D supplementation is able to ameliorate the prognosis of CV diseases (3–5). Several study limitations can account for these conflicting results. In particular, in the majority of trials the value of vitamin D was detected in basal conditions, whereas was not measured at the end of treatment. Furthermore, in diverse studies, different doses and preparations of vitamin D supplements were used and supplement duration was heterogeneous. Finally, the differences in the designs, in the sample size, in the clinical characteristics of the patients enrolled in trials further contributed to generate inconsistent results. However, it is also reasonable to speculate that vitamin D deficiency, rather than being an independent risk factor, could be the expression of the effects of other determinants of CV risk, compromising the availability and/or the biological activity of the vitamin. In general, it is possible to assert that deficiency of vitamin D is a hallmark of poor healthy condition (6). If this is the case, the supplementation of vitamin D is necessary, but not sufficient to ameliorate CV risk profile and prognosis. Thus, the identification and the correction of concomitant pathogenic mechanisms that impair vitamin D action is required to improve vitamin D-based strategies in CV prevention.

Experimental and clinical studies have clearly documented a close relationship between vitamin D deficiency and insulin resistance (IR). IR is a complex phenomenon that plays a key role in the pathogenesis of conventional CV risk factors such as obesity, metabolic syndrome (MS), arterial hypertension, type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD) (7–10). Moreover, IR is involved in the development of asymptomatic organ damage such as left ventricular hypertrophy (LVH), atherosclerosis, and chronic kidney diseases (CKD) (11–13) and in the determinism of CV outcome (14–16). IR is due to an insulin receptor or post-receptor defect, that compromises the hormonal signal transduction mechanisms (17). Notably, insulin receptor is ubiquitously expressed, and insulin exerts not only metabolic effects, but regulates also different biological functions such as cell cycle, neuro-hormonal homeostasis, vascular reactivity, platelet aggregation, ion exchanges and transport (17–19). In addition, IR phenomenon can be organ and/or tissue specific. Therefore, IR, rather than being viewed as a merely metabolic disorder, should be considered as a cluster of abnormalities that impairs several physiological functions.

Vitamin D is a steroid hormone that exerts its effects through vitamin D receptors (VDRs), belonging to the steroid/thyroid receptor family. Like insulin receptors, VDRs are ubiquitously expressed. The binding of the vitamin to its receptor, promotes the translocation of the complex from cytosol into the cellular nucleus, where it interacts with the retinoid x receptors (RXRs). In the nucleus, the heterodimers VDR/RXR bind to the vitamin D response element (VDRE), that, in turn, modulates transcriptional activities of the target genes (20, 21). More than 200 genes (almost 3% of human genome) are up- or down-regulated by vitamin D (22). Actually, vitamin D modulates not only bone metabolism and mineral homeostasis, but also cell cycle, cell proliferation and cell adhesion, immune and inflammatory responses, neuro-hormonal activity, matrix homeostasis, redox status, etc. In addition, VDRs are also expressed on cells membrane. When the ligand binds to VDR on the cell surface, it promotes the activation of several intracellular second messengers, controlling the activity of different kinases such as PKA, PKB, MAPK, etc. These molecular pathways mediate the *non-genomic* effects of vitamin D (23). Definitely, vitamin D, similarly to insulin, can be considered a pleiotropic hormone.

Observational studies have documented that both IR and the deficit of vitamin D are features of similar metabolic and CV disorders (24, 25). In the past years, IR has been considered a direct or indirect consequence of vitamin D deficiency. However, it is also reasonable to speculate that the deficit or the impaired action of vitamin D, in some circumstances, could be the result of the same pathogenic mechanisms responsible for IR development. If it is the case, vitamin D deficiency could be considered an epiphenomenon of IR. Thus, dietary vitamin supplementation alone could result ineffective in CV prevention, if not associated with interventions aimed at restoring insulin sensitivity, or, at least, at ameliorating IR condition.

The aim of this review is A) to outline the principal actions of vitamin D on CV system; B) to summarize the most significant clinical findings regarding the link between the deficit of vitamin D and CV risk; C) to report the principal pathophysiological mechanisms that can account for vitamin D deficiency as consequence of IR; and D) to consider the implication of this association in order to improve vitamin D-based strategies in CV prevention.

VITAMIN D AND CV HOMEOSTASIS

Experimental data indicate that vitamin D plays a key role in the regulation of CV homeostasis (26). In particular, vitamin D exerts cardio- and vasculo-protective effects, as well as, anti-atherogenic and anti-inflammatory actions. The principal effects of vitamin D in the regulation of CV homeostasis are summarized in **Figure 1**.

Dysregulation of the renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the pathogenesis of hypertension, hypertension-induced target organ damage (TOD), CV events, and heat failure (HF) (27, 28). Experimental studies have clearly demonstrated that vitamin D negatively regulates RAAS activity. In particular, in VDR knockout transgenic mice, the different components of RAAS resulted to be upregulated in comparison with wild type control mice. In addition, the cardiac phenotype of these mice was characterized by arterial hypertension and cardiac hypertrophy. These abnormalities were rescued by the administration of vitamin D (29).

The capability of vitamin D to counteract RAAS activity, development of hypertension, and cardiac damage has been confirmed in different experimental studies (30–32). The expression of VDR on cardiac myocytes and fibroblasts suggests that vitamin D plays a relevant role in the regulation of cardiac growth, in physiological as well as in pathological conditions; interestingly, this action results to be independent from hemodynamic forces and neuro-hormonal stimulation. In particular, vitamin D has a protective effect against the development of maladaptive cardiac hypertrophy. Transgenic

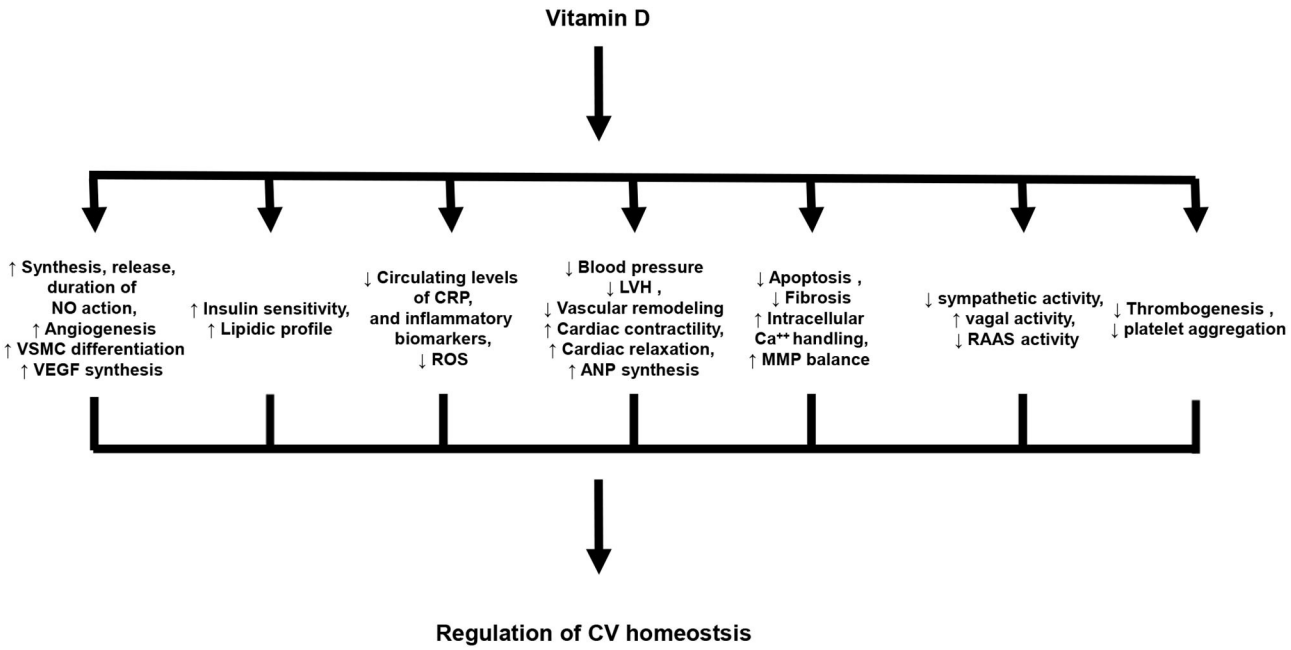


FIGURE 1 | Principal biological effects of vitamin D on cardiovascular system. NO, Nitric oxide; VSMC, vascular smooth muscle cells; VEGF, Vascular endothelial growth factor; CRP, C-reactive protein; ROS, Reactive oxygen species; LVH, Left ventricular hypertrophy; ANP, atrial natriuretic peptide; MMP, Matrix metalloproteinases; RAAS, Renin-angiotensin-aldosterone system.

mice with targeted cardiomyocytes knockout of VDR show, at baseline and after a 7-day infusion of isoproterenol, a greater myocyte size and left ventricular weight/body weight ratio compared with wild type control mice (33). Similarly, the knockout of the gene encoding for 1α-hydroxylase, the enzyme that catalyzes synthesis of the active form of vitamin D, generates a phenotype characterized by enhanced activity of RAAS (21). The cardioprotective effects of vitamin D have been demonstrated also in more complex experimental settings. For instance, in a murine model of left ventricular pressure overload induced by transverse aortic constriction, treatment with *paricalcitol*, a selective agonist of VDR, was documented to prevent the development of left ventricular hypertrophy. This response was associated with the reduction of cardiac fibrosis and the preservation of indexes of left ventricular contraction and relaxation (34). Furthermore, in similar experimental settings, *paricalcitol* was demonstrated to be able to prevent HF worsening and to ameliorate adverse electrophysiological and Ca^{++} handling remodeling, resulting in a reduction of HF-induced arrythmias (35). Noteworthy, vitamin D also exerts a favorable action on both cardiac contractility and relaxation, independently from its anti-hypertrophic action (36–38).

Heart and vasculature represent, at the same time, the sources and target organs of vitamin D. In fact, 1-α-hydroxylase is expressed in cardiac myocytes and in endothelial and smooth muscle cells (SMC) (39, 40). In this context, the autocrine/paracrine activity of vitamin D is extremely relevant. For instance, in mice the selective knock-out of the gene encoding for VDR in the endothelium impairs acetylcholine-induced aortic relaxation, as well as enhances the vasopressor response to angiotensin II, suggesting a mechanistic role of vitamin D in blood pressure (BP) homeostasis and endothelial cell function (41). At a vascular level, the principal effect of vitamin D is an antioxidant action, by superoxide dismutase stimulation (22), counteracting the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, that promotes the synthesis of reactive oxygen species (ROS). As a consequence of its antioxidant action (42, 43), vitamin D exerts beneficial effects on endothelial function (22, 44), platelet aggregation (45, 46), vascular inflammation (47, 48), thrombogenesis (49, 50), and vascular resistances and remodeling (51–53). Of note, vitamin D plays also a role in the regulation of angiogenesis and vascular repair by the synthesis of vascular endothelial growth factor (VEGF) and cell-derived factor 1 (SDF-1), respectively (54, 55). In addition, vitamin D by the inhibition of macrophages transformation in foam cells antagonizes the development of atherosclerosis (56).

Altogether these experimental data clearly demonstrate the key role of vitamin D in the regulation of CV homeostasis. Therefore, the long-term deficit of vitamin D could be relevant for the pathogenesis of the continuum of CV disease.

DEFICIT OF VITAMIN D AND CV RISK

Vitamin D deficiency is a worldwide recognized condition. It has been estimated that, in western countries, from one-third to one-half of adult population is affected by mild to moderate vitamin D deficiency (57). It is noteworthy that this defect shares with

IR an identical epidemiological distribution. In addition, large cross-sectional and prospective studies have reported an inverse relationship between vitamin D levels and prevalence of CV risk factors and events.

DEFICIT OF VITAMIN D AND CV RISK FACTORS

Diabetes, Metabolic Syndrome, and Obesity

A close relationship was identified between the deficit of vitamin D and T2D. In particular, vitamin D deficiency and severe deficiency are detectable in the 91 and 32% of patients with T2D, respectively (58). In addition, several prospective studies demonstrated that a lower vitamin D status was associated with a higher risk of incidence of T2D. The analysis of two cohorts, the Finnish Mobile Clinic Health Examination Survey and the Mini-Finland Health Survey, including individuals free from diabetes with a follow-up ranging from 17 to 22 years carried out in 1973–1976 and in 1978–1980, respectively, demonstrated that individuals in the highest quartile of serum vitamin D had an 82% lower risk to develop T2D compared with those in the lowest quartile after adjusting for BMI, physical activity, smoking status and education, and thus suggesting that vitamin D may exert a protective effect against incident T2D (59). Similar results were obtained by the analysis of the Nurses' Health Study (60), and the Framingham Offspring Study (61). The role of vitamin D status in the development and progression of T2D has been analyzed by a meta-analysis that evaluated 21 prospective studies, involving 76,220 participants. This analysis demonstrated an inverse and significant association between serum levels of vitamin D and risk of T2D occurrence. In particular, it was documented that each 10 nmol/L increase of vitamin D levels was associated with a 4% lower risk of T2D (62). MS is a cluster of CV risk factors and can be considered a typical feature of IR. Consistently with what affirmed for T2D, low vitamin D status is associated with a higher risk to develop MS. A meta-analysis, aimed at analyzing the risk of developing cardiometabolic disorders by the evaluation of vitamin D serum levels, documented a 51% reduction in risk of MS development for individuals with higher serum concentrations of vitamin (63). Deficiency of vitamin D was also found to be associated with obesity. However, this association was documented by meta-analyses that mainly included cross-sectional and not prospective studies (64).

Essential Hypertension

Several cross-sectional and longitudinal studies support the notion that vitamin D deficiency is associated with essential hypertension (65). The third national Health and Nutrition Examination Survey (NHANES III), a large cross-sectional study, performed from 1988 to 1994 that analyzed 12,664 individuals representative of the US population, demonstrated an inverse relationship between vitamin D levels and BP values. In particular, SBP was 3 mmHg lower in the group in the highest vitamin D quartile in comparison with the subjects in the lowest quartile (66). A *post-hoc* analysis of the NHANES III showed that high levels of vitamin D (> 32 ng/ml) decreased by 20% the age-induced increase in systolic BP (67). The association between deficiency of vitamin D and incident hypertension was demonstrated in a longitudinal study by the Health Professional Follow-up and the Nurses' Health Study (68) and by the Finnish study (69).

A meta-analysis revising the results of 14 cross-sectional and four longitudinal studies published between 2005 and 2010, including 78,028 individuals, reported an inverse relationship between vitamin D levels and BP. In particular, a decrease of 16 ng/ml in vitamin levels was demonstrated to be associated with an enhanced risk of hypertension by 16% (70). A further meta-analysis performed only on prospective studies, demonstrated that subjects within the top third of baseline vitamin D levels had a 30% lower probability to develop hypertension compared to the bottom third. In particular, the risk to develop hypertension per increment of 10 mg/ml in basal vitamin D levels was 0.88 (71). These results were consistent with the data of a meta-analysis published by Pittas et al. that documented a risk of 80% to develop hypertension in individuals with low serum levels of vitamin D (72). In general, an inverse relationship between vitamin D status and incidence of hypertension has been described.

Dyslipidemias and Hyperuricemia

There are less and conflicting results about the link between vitamin D status and dyslipidemias. However, vitamin D deficiency was documented to be associated with a worse lipid profile. In a meta-analysis that evaluated 22 cross-sectional studies and 10 RCT, a positive relationship was found between high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and serum levels of vitamin D. However, the ratio between LDL-C or total cholesterol and HDL-C resulted to be beneficial. In addition, an inverse relationship was found between vitamin D and triglycerides (73). Hyperuricemia has been identified as an independent CV risk factor and often represents a feature of MS. Interestingly, an inverse association between vitamin D status and uric acid levels has been reported. The analysis of the National Health and Nutrition Examination Survey (NHANES) 2007–2014, that included 18.596 individuals, documented that the lowest quartile of vitamin D levels had significative higher risk of hyperuricemia in comparison with the highest quartile (74). These data were consistent with studies on different cohorts and meta-analyses (75–77).

DEFICIT OF VITAMIN D AND TARGET ORGAN DAMAGE

Atherosclerosis, LVH, CKD are the principal clinical manifestations of TODs detectable in T2D, hypertension, MS, obesity, etc (78–80). The presence of TOD independently accounts for increased CV risk (81, 82). Experimental and epidemiological data have been depicted a direct association between vitamin D deficiency and occurrence of TODs.

Atherosclerosis

Atherosclerosis can be considered the paradigm of TODs and is the result of the cross-talk between genetic and environmental factors. Experimental data indicate an association between deficiency of vitamin D and atherosclerosis, and its clinical consequences. Indeed, miniature swine fed with vitamin D–deficient diet for 1 year showed a rapid progression of coronary artery disease by a NFkB-dependent mechanism (83).

Endothelial dysfunction represents the first step of atherosclerotic process. Arterial stiffness is a surrogate marker of endothelial dysfunction (84). There is clear evidence that vitamin D status is inversely associated with impaired arterial stiffness. In fact, in a cross-sectional study that recruited 554 healthy individuals an inverse association between the vitamin D levels and the arterial stiffness was found (85). These data were confirmed in different studies that analyzed different cohorts of subjects. In particular, in a cross-sectional study that recruited 150 postmenopausal women with deficit of vitamin D (<30 ng/ml) an inverse relationship between vitamin D levels and aortic wave velocity was detected, the latter representing an index of aortic stiffness (86). Similarly, in 305 diabetic patients (131 male, and 174 female), enrolled in a cross-sectional study, the association between low levels of vitamin D and increased arterial stiffness was confirmed (87). Consistently, in 52 subjects with uncomplicated end-stage of renal disease (ESRD) a negative correlation was detected between vitamin D status and aortic wave velocity (88). Altogether, these results clearly indicate that vitamin D deficiency is already detectable in the initial phases of the atherosclerotic process.

In addition, epidemiological studies have demonstrated an association between low levels of vitamin D and atherosclerosis in the general population. At this regard, the National Health and Nutrition Examination Survey 2001–2004 evaluated the association between serum levels of vitamin D and prevalence of peripheral artery disease (PAD) in the general US community. PAD was defined by the ankle-brachial index (ABI) <0.9 and the study cohort was categorized according to vitamin D quartiles. The analysis, including 4,839 individuals, documented that low levels of vitamin D were associated with PAD (89). These results were confirmed by the ARIC study. This was a prospective study aimed at identifying the causes of atherosclerosis. The study cohort consisted of 11,789 individuals that were followed-up for 17.1 years. The study population was categorized in three groups according to vitamin D levels: deficient (<20 ng/ml), insufficient (20 to 30 ng/ml) or sufficient (≥30 ng/ml). A Cox regression analysis showed that individuals with deficient values of vitamin D had a higher risk to develop PAD (90). In addition, the association between vitamin D status and atherosclerosis has been reported even in patients with T2D. A cross-sectional study that analyzed 1,018 patients with T2DM documented that PAD gradually increased from patients with the highest to the lowest levels of serum vitamin D. Interestingly, this association remained statistically significant even after adjusting for diabetes-induced risk factors for PAD (91). Similar results were reported for patients with CKD. In fact, in non-dialysis patients with CKD vitamin D deficiency was associated with abnormal ABI. Even in this case the association between PAD and vitamin D status resulted to be independent from CKD-related CV risk factors (92).

Definitely, the strong association between vitamin D deficiency and PAD was documented also by different meta-analyses that revised both prospective and cross-sectional studies (93, 94).

Left Ventricular Hypertrophy

LVH is an independent risk factor for CV events (95). For many years, the development of LVH has been viewed as an adaptive response of the left ventricle to pressure or volume overload and was considered a typical manifestation of TOD in hypertension and aortic valve stenosis, or renal failure. Nowadays, experimental evidence indicates that LVH development is a complex and multifaceted process that involves not only mechanical forces but also genetic background, neuro-hormonal stimulation, metabolic and anthropomorphic abnormalities, inflammatory response, oxidative stress (96–98). Clinical data are consistent with this notion. In particular, IR-related metabolic and anthropomorphic alterations seem to play a key role in the development of LVH. For instance, it has been documented that low levels of HDL-C are independent determinants of LVH in untreated patients with hypertension (99). Moreover, it has been reported that insulin and insulin-like growth factor 1 (IGF-1) are independent predictors of LVH in patients with hypertension (11). Several reports documented the association of low levels of vitamin D in patients with LVH in different pathological conditions such as hypertension (100–102), aortic stenosis (103) and CKD (104, 105). The contribution of vitamin D deficiency in pathogenesis of LVH is also corroborated by the evidence that the morphology of the left ventricle was preserved in healthy individuals of the Baltimore Longitudinal Study of Aging having normal levels of vitamin D, while the risk of concentric left ventricular remodeling was higher in those with lower vitamin D concentration (106). To note, hyperuricemia, being associated with poor vitamin D status, was found to be a determinant of LVH in subjects with arterial hypertension (107), supporting the notion that vitamin D status plays a leading role in the pathogenesis of CV risk.

Chronic Kidney Disease

CKD and microalbuminuria are very common features of TODs in hypertension, T2D and MS, and at the same time, are independent determinants of poor outcome in patients with CV diseases (108, 109). Since the kidney is the principal source of the active form of vitamin D, CKD is associated with a severe reduction of the biological activity of the vitamin, without any possibility to regulate its synthesis. In patients with ESRD it has been documented that supplementation of the active form of vitamin D improves survival (110). This result has been confirmed also in patients with CKD not yet treated with hemodialysis (111). Moreover, a strong association between early stages of renal damage and deficiency of vitamin D has been reported. In particular, microalbuminuria and deficit of vitamin D was found in newly diagnosed hypertensive patients (112) and in patients with T2D (113, 114). Interestingly, in patients with T2D, VDR was found to be downregulated and

this phenomenon was independently associated with the severity of albuminuria (114). This phenomenon suggests that further pathogenic mechanisms contribute to impair vitamin D action in presence of CKD.

DEFICIT OF VITAMIN D AND CV EVENTS

There are several large prospective cohort studies that support the notion that the deficit of vitamin D is associated with increased incidence of CV events. The Framingham Offspring Study showed that severe deficiency of vitamin D, during a follow-up period of 7 years (mean 5, 4), was associated with an increase by 62% of incident major CV events, especially in subjects with essential hypertension. This high risk remained unchanged even after adjusting for several confounding factors (115). Similar data were found in the Health Professionals Follow-up Study, reporting a 2 fold increased risk of myocardial infarction in subjects free of CV diseases and with concomitant severe deficit of vitamin D (116), and in the cohort of the Intermountain Healthcare System (1). These data were confirmed in different ethnicities, independently on the distance from the equator and sunlight exposure (117, 118). The association between vitamin D deficiency and the enhanced risk of coronary artery disease and myocardial infarction has been also assessed in a meta-analysis that evaluated 18 prospective studies including a total of 82,982 individuals. This analysis showed that the risk of ischemic heart disease was increased by 39% in the lowest vs. the highest quartile of serum vitamin D levels (119). The deficiency of vitamin D has been also associated with enhanced risk of cerebrovascular events and stroke. The analysis of the Mini-Finland Health Survey Cohort, including 6,219 individuals free from CV diseases at baseline, showed that the lowest quintile of serum levels of vitamin D was predictive of cerebrovascular events (120). This observation was confirmed by several meta-analyses (4, 121).

DEFICIT OF VITAMIN D AND HEART FAILURE AND MORTALITY

There are incontrovertible data showing that vitamin D deficiency is also associated with poor CV prognosis. In particular, cross-sectional and prospective studies have documented that vitamin deficiency is associated with HF and CV death. The community-based prospective cohort of the Atherosclerosis Risk in Community (ARIC) study showed that the low serum levels of vitamin D (<20 ng/ml) were independently associated with a higher risk to develop HF in 12,215 subjects with a median follow-up of 18 years. In particular, after adjusting for conventional risk factors, the white but not the black individuals within the lowest quintile of vitamin D serum levels had a 27% increased risk of incident HF (122). These data are consistent with those obtained in other study cohorts (123). In this regard, the deficiency of vitamin D ($\leq$ 30 ng/ml) was found in the 89% of patients with HF and concomitant ischemic heart disease (124).

Several studies have also documented that the deficiency of vitamin D is associated with enhanced mortality. The analysis of the Health Maintenance Organization in Israel showed that the deficiency of vitamin D is a significant predictor of reduced survival in patients with HF (125). These results were consistent with data recorded in different study cohorts. In particular, the NHANES III study demonstrated in a cohort of 13,331 individuals followed-up for a median of 8.7 years that the mortality increased by 26% in the lowest quartile of vitamin D (<17.8 ng/ml) in comparison with the highest quartile (89). In addition, vitamin D deficiency was found to be associated with an increased risk of sudden death. A *post-hoc* analysis of the cohort of the Cardiovascular Health Study, including 2,312 participants who were free of clinical CV disease at baseline and were followed-up for a median of 14 years, documented that low levels of vitamin D were associated with a 2-fold increased risk of sudden cardiac death (126). These data were also documented in patients with coronary artery disease and with end-stage of CKD (127, 128).

Definitely, cross-sectional and prospective studies clearly indicate that vitamin D deficiency (below 20 ng/ml) is associated with all clinical manifestations of the continuum of CV disease, from the incidence of CV risk factors to the occurrence of major CV events. The evidence that dietary vitamin D supplementation have failed to improve the CV risk profile and CV prognosis seems to support the concept that additional factors are possibly involved in this process.

TABLE 1 | Principal causes of vitamin D deficiency.

Reduced UVB exposure (sunscreen use, winter season, cover-up clothing, air pollution)
Aging*
Low food intake of the vitamin
Gastrointestinal malabsorption
Obesity*
Dark skin pigmentation
Smoking
Sedentary behavior*
Renal diseases*
Liver diseases*
Altitude
Distance from the Equator

**Conditions associated with insulin resistance.*

IR A DETERMINANT OF DEFICIT OF VITAMIN D

In the past decades the deficit of vitamin D has been viewed merely as a nutritional defect, and dietary supplementation of the vitamin was used for the prevention and treatment of rickets in children, and osteoporosis and osteomalacia in adults. Nowadays, it is clear that the deficit of vitamin D is a complex and multifaceted phenomenon with different clinical manifestations.

Epidemiological data indicate that chronic deficit of vitamin D parallels with the clinical manifestations of IR. In fact, in

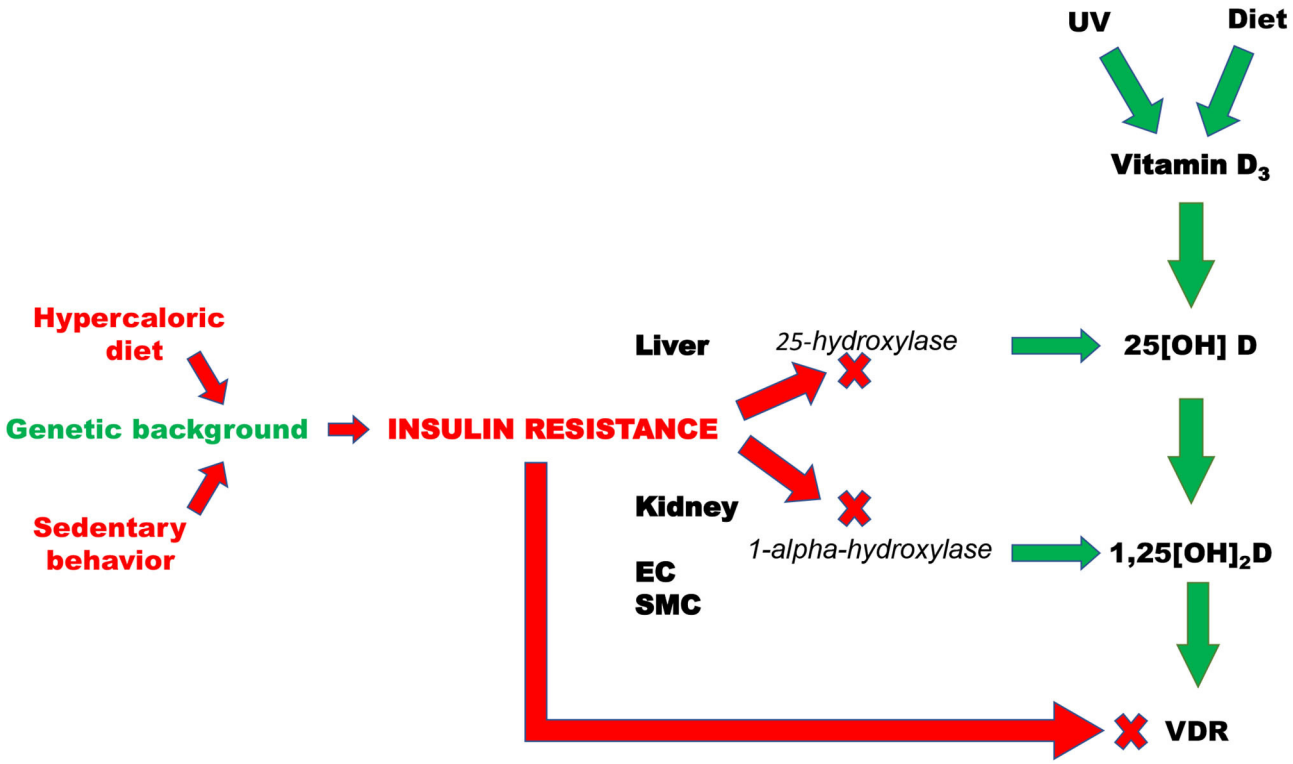


FIGURE 2 | Pathogenic mechanisms that are responsible of insulin resistance-induced deficit of vitamin D. EC, Endothelial cells; SMC, smooth muscle cells; VDR, vitamin D receptor; UV, Ultraviolet radiations.

Western Countries, vitamin D deficiency is highly associated with aging, obesity, sedentary lifestyle, T2D, hypertension, liver and renal diseases, that are also clinical features of IR (24, 25). The principal causes of the deficit of vitamin D are reported in **Table 1**. Of note, in many cases these conditions are associated with IR. These data support the notion that the pathogenic mechanisms responsible for IR development can also, at the same time, account for the deficit or impaired action of vitamin D. Interestingly, the available literature has been focused so far on testing the hypothesis that IR is the consequence of vitamin D deficiency (129–132); on the contrary, whether IR affects vitamin D homeostasis has been poorly investigated.

The majority of vitamin D is obtained from the skin as consequence to ultraviolet B radiations (UVB) exposure, while only 30% is derived from the diet (fatty fish, fish oil, tuna, sardines, egg yolks) (133). The first-rate limiting step in the synthesis of the active form of the vitamin is liver hydroxylation of vitamin D2 (ergocalciferol) or D3 (cholecalciferol) by mitochondrial and microsomal 25-hydroxylase in 25-hydroxy vitamin D (25[OH]D), which, in turn, is converted in the proximal convoluted tubule of the kidney by the 1-alpha-hydroxylase in the active form of the vitamin: 1,25-dihydroxy vitamin D (1,25$[OH]_2$D) (134, 135). Minor fonts of 1,25$[OH]_2$D are cardiac myocytes, vascular smooth muscle and endothelial cells (39, 40). The compromission of vitamin D action can be due to the impaired activity of cellular hydroxylases or to abnormalities in VDR.

IR can be defined as an impaired biological response to insulin, and it is the results of the combination of genetic abnormalities with environmental factors. The hypercaloric diet plays a key role into IR genesis, accounting for the pathogenesis of several diseases, such as obesity, MS, NAFLD, etc. In Wistar rats it has been reported that 6 months of hypercaloric diet induced IR and severe liver steatosis. This effect was associated with a decrease in serum levels of 25[OH]D by 24%, despite an adequate dose of vitamin D was included into the chow. The supplement of vitamin D only in part restored the levels of 25[OH]D (136). These results allow the speculation that the condition of liver steatosis and IR interfere with the synthesis of vitamin D. There are several clinical evidence that documented reduced levels of vitamin D in subjects with liver steatosis or with NAFLD or with non-alcoholic steatohepatitis (NASH) (137–139). To note, in the past years the deficit of vitamin D was interpreted exclusively as a pathogenic mechanism of NALFD or NASH. However, it is also reasonable to evaluate the deficit of vitamin D as a consequence of different forms of liver diseases. This notion is corroborated by experimental and clinical evidence. In particular, it has been demonstrated that high fat diet-induced obesity decreased the hepatic gene expression of 25-hydroxylases in mice (140, 141). Similar data were found in obese subjects, in whom the overweight determined a decreased expression of cytochrome P450 (CYP) 2R1, the main vitamin D 25-hydroxylase, while the weight loss, induced by gastric bypass, increased the expression of CYP 2R1 (142).

TABLE 2 | Vitamin D status classification.

Serum vitamin D concentration (*ng/ml*)	Vitamin D status
≤10	Severe deficiency
10–20	Deficiency
20–30	Insufficiency
≥30	Adequate
40–50	Optimal
50–150	Undetermined data
>150	Toxicity

The final step of the synthesis of vitamin D is mediated by renal 1-alpha-hydroxylase, expressed in tubular epithelial cells. Experimental and clinical data indicate that chronic kidney disease decreases the levels of the active form of vitamin D by reducing the activity of 1-alpha-hydroxylase (143, 144). There are also clear experimental data demonstrating that IR is able to reduce renal 1-alpha-hydroxylase activity. In fact, it has been reported in Wistar rats that IR, induced by 18 weeks of high fat diet, reduced the activity of 1-alpha-hydroxylase (143). Similar results were obtained in experimental settings characterized by different model of IR, such as aging and obesity (145, 146). Minor sources of vitamin D are the vessels and the heart. IR is also associated with low grade of vascular inflammation, that is responsible of endothelial dysfunction (147). Vitamin D deficiency was reported to be associated with endothelial function impairment as well as with elevated expression of inflammation mediators such as nuclear factor κB (NFkB) and interleukin-6 (IL-6) (85, 148). Although, the pathogenic mechanisms that account for this association were not deeply investigated yet, it is reasonable to speculate that inflammation-induced reduction of vascular 1-α hydroxylase activity may be the molecular mechanism that, in part, account for the link between vitamin D insufficiency and impairment of vascular function.

IR can also interfere with VDR gene expression. Indeed, in subjects with MS and T2D a downregulation of VDR gene expression was described (114, 149). The role of IR in the regulation of gene expression has been corroborated by the evidence that in obese, as well as in lean subjects, the independent predictors of gene expression of VDR in sub-cutaneous fat resulted to be body mass index (BMI) and homeostasis model of assessment for insulin resistance (HOMA-IR) (150).

Altogether these results allow to argue that IR rather than being the consequence, can also play a role as pathogenic determinant of vitamin D deficiency (**Figure 2**). If this is the case, dietary vitamin D supplementation without any additional intervention aimed at improving insulin sensitivity would be completely ineffective in CV prevention.

IMPROVEMENT OF THE VITAMIN D-BASED STRATEGIES IN CV PREVENTION

In clinical practice vitamin D status is defined by the serum levels of the 25[OH]D, but not by the active metabolite $1,25[OH]_2D$ (**Table 2**). Noteworthy, the current classification of vitamin D status is based exclusively on the consequences detected on bone metabolism. Thus, nowadays, the ranges of vitamin D required to achieve an adequate CV prevention are still undefined (151). Interestingly, subjects with CV risk factors and with CV diseases are not considered individuals at risk for vitamin D deficiency. Thus, the routine assessment of vitamin D status is not indicated in these subjects (152).

So far, vitamin D supplementation has been viewed as the only treatment option in individuals with vitamin deficiency, and a range of 30–35 ng/ml was proposed to obtain a satisfactory CV prevention (153). However, with the exception of the beneficial effects of supplement of the active form of vitamin D in patients with ESRD, all RCT have failed to demonstrate favorable effects of vitamin supplement on CV outcome (154, 155). On the contrary, there are clear evidence that correction of IR status by both pharmacological and non-pharmacological interventions favorably affects CV risk and prognosis (156–158). Thus, the burning question is whether the improvement of insulin sensitivity contributes to ameliorate the effects of vitamin D supplementation in CV prevention and outcome.

IR and deficiency of vitamin D, with few exceptions, are reversible conditions. In Western countries, physical inactivity and hypercaloric food intake are endemic behaviors. There is clear evidence that exercise training ameliorates insulin sensitivity (159, 160). Notably, physical exercise is associated with an increase of vitamin D levels, independently from sun exposure. In particular, the Third National Health and Nutrition Examination Survey (1988–1994) showed that in old individuals, the frequency of leisure-time physical activity was associated with levels of vitamin D detected in young subjects (161). These data were confirmed by further surveys (2007–2012) (162). Further studies demonstrated the positive effect of physical activity of vitamin D status in different cohorts. The ARIC study demonstrated that in whites but not in black individuals a linear relationship between physical activity and vitamin D levels was described (163).

Although a possible mechanism of exercise-evoked improvement of vitamin D status can be identified in the release of the vitamin from the adipose tissue deposits (164), it is also reasonable to speculate that the improvement of insulin sensitivity can account for this effect. In fact, in an experimental model of T2D, exercise training (swimming) was demonstrated to ameliorate HOMA-IR and metabolic profile, paralleling an improvement of vitamin D status and VDRs expression in skeletal muscle, pancreas and adipose tissue (165).

Similar effects on IR have been also described for dietary habits. The energy-restricted dietary regimens such as the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, the plant-based diets were reported to ameliorate insulin sensitivity and reduce the incidence of T2D (166). In particular, in a *post-hoc* analysis of the Insulin Resistance Atherosclerosis Study cohort, an inverse association between the adherence to the DASH diet and the risk of T2D has been reported (167). Similar results were documented for MS; in this case, the adherence to the DASH diet was associated with a 64% lower risk to develop MS in healthy children and adolescents (168). For the plant-based diets indirect and weaker

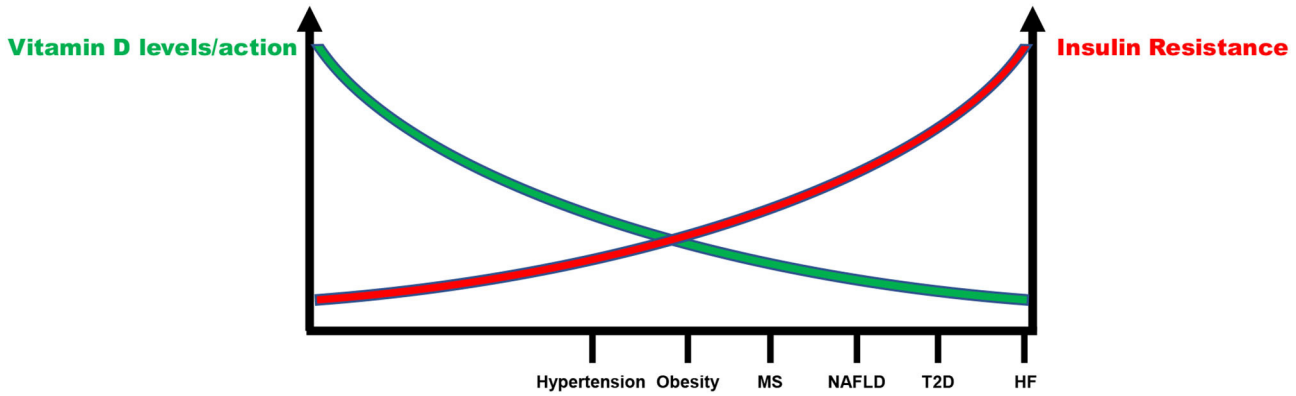


FIGURE 3 | Inverse relationship between insulin resistance and vitamin D status in the continuum of cardiovascular disease. MS, Metabolic syndrome; NAFLD, Non-alcoholic fatty liver disease; T2D, Type 2 diabetes; HF, Heart failure.

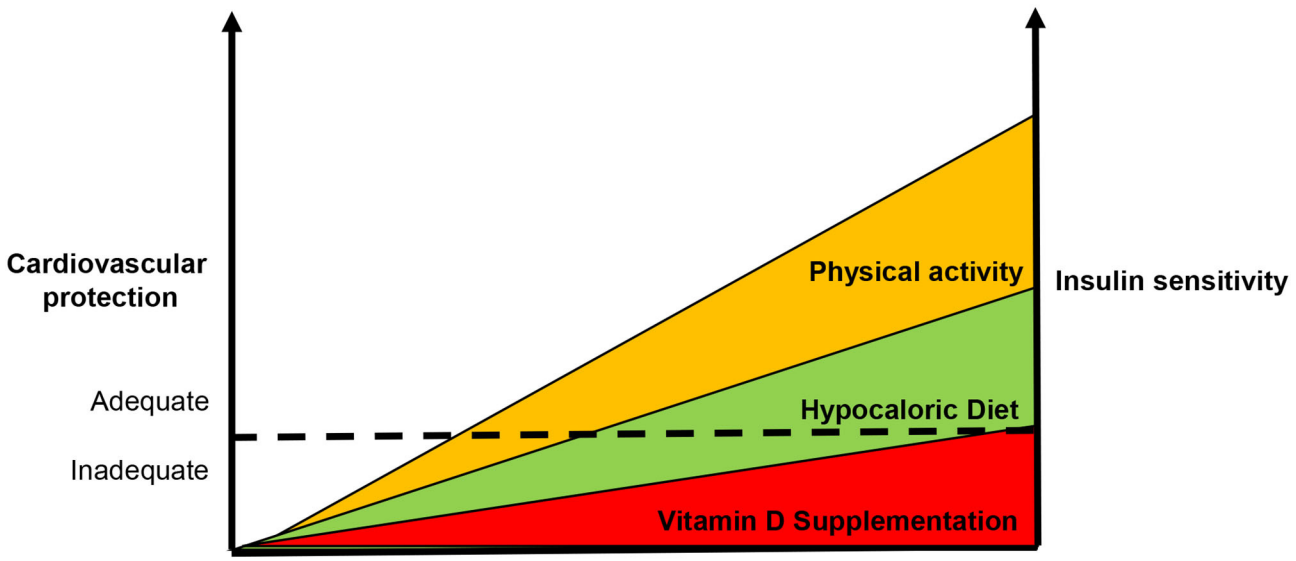


FIGURE 4 | Usefulness of enhanced insulin sensitivity to improve the vitamin d-based strategies in cardiovascular prevention. According our point of view, the supplementation of vitamin D alone is not capable to reduce cardiovascular risk. Since insulin resistance also accounts for the development of vitamin D deficiency, it is necessary to enhance insulin sensitivity in order to improve vitamin D-based strategies in cardiovascular protection. The dot line represents the ideal threshold for the achievement of benefits in terms of cardiovascular prevention.

evidence was reported about the beneficial effects on IR (169). More interestingly, it has been described that the Mediterranean diet can reduce indexes of IR, such as HOMA index (170). In addition, in a cross-sectional study the high adherence to the Mediterranean diet was associated with high serum levels of vitamin D; this association was independent on BMI, waist circumference, physical activity, season and skin pigmentation (171). Similar results were reported in different cohorts of individuals (172, 173), suggesting that the enhancement of insulin sensitivity parallels with the improvement of vitamin D status.

Definitely, there is an inverse relationship between IR and vitamin D status that account for increased CV risk (**Figure 3**). Although few data are available, they support the notion that IR correction is necessary in order to optimize the beneficial effects of vitamin D supplementation in CV prevention (**Figure 4**). CRTs are needed in the next future to clarify this specific issue.

AUTHOR CONTRIBUTIONS

VT, ML, and CMo had the idea for this article. RI, MM, CMa, and TS performed the literature search. AF, MM, IF, TS, CMo, and ML drafted the manuscript. EP and EB critically revised the work. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors are grateful to Federica De Luise for her assistance with manuscript preparation.

REFERENCES

1. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol.* (2010) 106:963–8. doi: 10.1016/j.amjcard.2010.05.027
2. Rai V, Agrawal DK. Role of vitamin D in cardiovascular diseases. *Endocrinol Metab Clin North Am.* (2017) 46:1039–59. doi: 10.1016/j.ecl.2017.07.009
3. Tomson J, Emberson J, Hill M, Gordon A, Armitage J, Shipley M, et al. Vitamin D and risk of death from vascular and non-vascular causes in the Whitehall study and meta-analyses of 12,000 deaths. *Eur Heart J.* (2013) 34:1365–74. doi: 10.1093/eurheartj/ehs426
4. Wang L, Song Y, Manson JE, Pilz S, Marz W, Michaelsson K, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes.* (2012) 5:819–29. doi: 10.1161/CIRCOUTCOMES.112.967604
5. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med.* (2010) 51:228–33. doi: 10.1016/j.ypmed.2010.06.013
6. Pilz S, Verheyen N, Grubler MR, Tomaschitz A, Marz W. Vitamin D and cardiovascular disease prevention. *Nat Rev Cardiol.* (2016) 13:404–17. doi: 10.1038/nrcardio.2016.73
7. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am.* (2004) 33:283–303. doi: 10.1016/j.ecl.2004.03.002
8. Sowers JR, Standley PR, Ram JL, Jacober S, Simpson L, Rose K. Hyperinsulinemia, insulin resistance, and hyperglycemia: contributing factors in the pathogenesis of hypertension and atherosclerosis. *Am J Hypertens.* (1993) 6:260S—70S. doi: 10.1093/ajh/6.7.260S
9. Olefsky J, Farquhar JW, Reaven G. Relationship between fasting plasma insulin level and resistance to insulin-mediated glucose uptake in normal and diabetic subjects. *Diabetes.* (1973) 22:507–13. doi: 10.2337/diab.22.7.507
10. Mancusi C, Izzo R, di Gioia G, Losi MA, Barbato E, Morisco C. Insulin resistance the hinge between hypertension and type 2 diabetes. *High Blood Press Cardiovasc Prev.* (2020) 27:515–26. doi: 10.1007/s40292-020-00408-8
11. Verdecchia P, Reboldi G, Schillaci G, Borgioni C, Ciucci A, Telera MP, et al. Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. *Circulation.* (1999) 100:1802–7. doi: 10.1161/01.CIR.100.17.1802
12. Strisciuglio T, Izzo R, Barbato E, Di Gioia G, Colaiori I, Fiordelisi A, et al. Insulin resistance predicts severity of coronary atherosclerotic disease in non-diabetic patients. *J Clin Med.* (2020) 9:2144. doi: 10.3390/jcm9072144
13. Xu H, Carrero JJ. Insulin resistance in chronic kidney disease. *Nephrology.* (2017) 22:31–4. doi: 10.1111/nep.13147
14. Uetani T, Amano T, Harada K, Kitagawa K, Kunimura A, Shimbo Y, et al. Impact of insulin resistance on post-procedural myocardial injury and clinical outcomes in patients who underwent elective coronary interventions with drug-eluting stents. *JACC Cardiovasc Interv.* (2012) 5:1159–67. doi: 10.1016/j.jcin.2012.07.008
15. Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J. Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation.* (1999) 100:123–8. doi: 10.1161/01.CIR.100.2.123
16. Jing J, Pan Y, Zhao X, Zheng H, Jia Q, Mi D. et al. Insulin Resistance and Prognosis of Nondiabetic Patients With Ischemic Stroke: The ACROSS-China Study (Abnormal Glucose Regulation in Patients With Acute Stroke Across China). *Stroke.* (2017) 48:887–93. doi: 10.1161/STROKEAHA.116.015613
17. Morisco C, Lembo G, Trimarco B. Insulin resistance and cardiovascular risk: new insights from molecular and cellular biology. *Trends Cardiovasc Med.* (2006) 16:183–8. doi: 10.1016/j.tcm.2006.03.008
18. Fu J, Yu MG, Li Q, Park K, King GL. Insulin's actions on vascular tissues: Physiological effects and pathophysiological contributions to vascular complications of diabetes. *Mol Metab.* (2021) 52:101236. doi: 10.1016/j.molmet.2021.101236
19. Singh S, Sharma R, Kumari M, Tiwari S. Insulin receptors in the kidneys in health and disease. *World J Nephrol.* (2019) 8:11–22. doi: 10.5527/wjn.v8.i1.11
20. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiol Rev.* (2016) 96:365–408. doi: 10.1152/physrev.00014.2015
21. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev.* (2008) 29:726–76. doi: 10.1210/er.2008-0004
22. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. *Nutrients.* (2020) 12:575. doi: 10.3390/nu12020575
23. Jamali N, Sorenson CM, Sheibani N. Vitamin D and regulation of vascular cell function. *Am J Physiol Heart Circ Physiol.* (2018) 314:H753–H65. doi: 10.1152/ajpheart.00319.2017
24. Rendina D, De Filippo G, Muscariello R, De Palma D, Fiengo A, De Pascale F, et al. Vitamin D and cardiometabolic disorders. *High Blood Press Cardiovasc Prev.* (2014) 21:251–6. doi: 10.1007/s40292-014-0060-5
25. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease: a narrative review. *Ann Intern Med.* (2011) 155:820–6. doi: 10.7326/0003-4819-155-12-201112200-00004
26. Norman PE, Powell JT. Vitamin D and cardiovascular disease. *Circ Res.* (2014) 114:379–93. doi: 10.1161/CIRCRESAHA.113.301241
27. De Luca MR, Sorriento D, Massa D, Valente V, De Luise F, Barbato E, et al. Effects of inhibition of the renin-angiotensin system on hypertension-induced target organ damage: clinical and experimental evidence. *Monaldi Arch Chest Dis.* (2021) 91. doi: 10.4081/monaldi.2021.1570
28. Probstfield JL, O'Brien KD. Progression of cardiovascular damage: the role of renin-angiotensin system blockade. *Am J Cardiol.* (2010) 105:10A—20A. doi: 10.1016/j.amjcard.2009.10.006
29. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest.* (2002) 110:229–38. doi: 10.1172/JCI0215219
30. Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology.* (2008) 149:558–64. doi: 10.1210/en.2007-0805
31. Simpson RU, Hershey SH, Nibbelink KA. Characterization of heart size and blood pressure in the vitamin D receptor knockout mouse. *J Steroid Biochem Mol Biol.* (2007) 103:521–4. doi: 10.1016/j.jsbmb.2006.12.098
32. Zhou C, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. *Kidney Int.* (2008) 74:170–9. doi: 10.1038/ki.2008.101
33. Chen S, Law CS, Grigsby CL, Olsen K, Hong TT, Zhang Y, et al. Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. *Circulation.* (2011) 124:1838–47. doi: 10.1161/CIRCULATIONAHA.111.032680
34. Meems LM, Cannon MV, Mahmud H, Voors AA, van Gilst WH, Sillje HH, et al. The vitamin D receptor activator paricalcitol prevents fibrosis and diastolic dysfunction in a murine model of pressure overload. *J Steroid Biochem Mol Biol.* (2012) 132:282–9. doi: 10.1016/j.jsbmb.2012.06.004
35. Tamayo M, Martin-Nunes L, Val-Blasco A, MJ GMP, Navarro-Garcia JA, Lage E, et al. Beneficial effects of paricalcitol on cardiac dysfunction and remodelling in a model of established heart failure. *Br J Pharmacol.* (2020) 177:3273–90. doi: 10.1111/bph.15048
36. Walters MR, Ilenchuk TT, Claycomb WC. 1,25-Dihydroxyvitamin D3 stimulates 45Ca2+ uptake by cultured adult rat ventricular cardiac muscle cells. *J Biol Chem.* (1987) 262:2536–41. doi: 10.1016/S0021-9258(18)61537-6
37. Green JJ, Robinson DA, Wilson GE, Simpson RU, Westfall MV. Calcitriol modulation of cardiac contractile performance *via* protein kinase C. *J Mol Cell Cardiol.* (2006) 41:350–9. doi: 10.1016/j.yjmcc.2006.05.019
38. Weishaar RE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. II Direct and indirect effects. *Am J Physiol Cell Physiol.* (1987) 253:E675–83. doi: 10.1152/ajpendo.1987.253.6.E675
39. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, et al. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation.* (2005) 111:1666–71. doi: 10.1161/01.CIR.0000160353.27927.70
40. Zehnder D, Bland R, Chana RS, Wheeler DC, Howie AJ, Williams MC, et al. Synthesis of 1,25-dihydroxyvitamin D(3) by human endothelial

cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. *J Am Soc Nephrol.* (2002) 13:621–9. doi: 10.1681/ASN.V133621
41. Ni W, Watts SW, Ng M, Chen S, Glenn DJ, Gardner DG. Elimination of vitamin D receptor in vascular endothelial cells alters vascular function. *Hypertension.* (2014) 64:1290–8. doi: 10.1161/HYPERTENSIONAHA.114.03971
42. Wee CL, Mokhtar SS, Singh KKB, Yahaya S, Leung SWS, Rasool AHG. Calcitriol supplementation ameliorates microvascular endothelial dysfunction in vitamin D-deficient diabetic rats by upregulating the vascular eNOS protein expression and reducing oxidative stress. *Oxid Med Cell Longev.* (2021) 2021:3109294. doi: 10.1155/2021/3109294
43. Said MA. Vitamin D attenuates endothelial dysfunction in streptozotocin induced diabetic rats by reducing oxidative stress. *Arch Physiol Biochem.* (2020) 1:1–5. doi: 10.1080/13813455.2020.1741645
44. Andrukhova O, Slavic S, Zeitz U, Riesen SC, Heppelmann MS, Ambrisko TD, et al. Vitamin D is a regulator of endothelial nitric oxide synthase and arterial stiffness in mice. *Mol Endocrinol.* (2014) 28:53–64. doi: 10.1210/me.2013-1252
45. Kobzar G. Inhibition of platelet activation using vitamins. *Platelets.* (2020) 31:157–66. doi: 10.1080/09537104.2019.1652262
46. Sultan M, Twito O, Tohami T, Ramati E, Neumark E, Rashid G. Vitamin D diminishes the high platelet aggregation of type 2 diabetes mellitus patients. *Platelets.* (2019) 30:120–5. doi: 10.1080/09537104.2017.1386298
47. Lu C, Yin Y, Cui Y, Wang L, Bai Y, Li J, et al. 1,25(OH)2D3 improves blood lipid metabolism, liver function, and atherosclerosis by constraining the TGF-beta/Smad signaling pathway in rats with hyperlipidemia. *Cell cycle.* (2019) 18:3111–24. doi: 10.1080/15384101.2019.1669389
48. Cimmino G, Morello A, Conte S, Pellegrino G, Marra L, Golino P, et al. Vitamin D inhibits Tissue Factor and CAMs expression in oxidized low-density lipoproteins-treated human endothelial cells by modulating NF-kappaB pathway. *Eur J Pharmacol.* (2020) 885:173422. doi: 10.1016/j.ejphar.2020.173422
49. Mohammad S, Mishra A, Ashraf MZ. Emerging role of vitamin D and its associated molecules in pathways related to pathogenesis of thrombosis. *Biomolecules.* (2019) 9:649. doi: 10.3390/biom9110649
50. Martinez-Moreno JM, Herencia C, Montes de Oca A, Munoz-Castaneda JR, Rodriguez-Ortiz ME, Diaz-Tocados JM, et al. Vitamin D modulates tissue factor and protease-activated receptor 2 expression in vascular smooth muscle cells. *FASEB J.* (2016) 30:1367–76. doi: 10.1096/fj.15-272872
51. Thierry-Palmer M, Carlyle KS, Williams MD, Tewolde T, Caines-McKenzie S, Bayorh MA, et al. Plasma 25-hydroxyvitamin D concentrations are inversely associated with blood pressure of Dahl salt-sensitive rats. *J Steroid Biochem Mol Biol.* (1998) 66:255–61. doi: 10.1016/S0960-0760(98)00037-5
52. Pal E, Hadjadj L, Fontanyi Z, Monori-Kiss A, Mezei Z, Lippai N, et al. Vitamin D deficiency causes inward hypertrophic remodeling and alters vascular reactivity of rat cerebral arterioles. *PLoS ONE.* (2018) 13:e0192480. doi: 10.1371/journal.pone.0192480
53. Enkhjargal B, Malaguit J, Ho WM, Jiang W, Wan W, Wang G, et al. Vitamin D attenuates cerebral artery remodeling through VDR/AMPK/eNOS dimer phosphorylation pathway after subarachnoid hemorrhage in rats. *J Cereb Blood Flow Metab.* (2019) 39:272–84. doi: 10.1177/0271678X17726287
54. Cardus A, Panizo S, Encinas M, Dolcet X, Gallego C, Aldea M, et al. 1,25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF promoter. *Atherosclerosis.* (2009) 204:85–9. doi: 10.1016/j.atherosclerosis.2008.08.020
55. Wong MS, Leisegang MS, Kruse C, Vogel J, Schurmann C, Dehne N, et al. Vitamin D promotes vascular regeneration. *Circulation.* (2014) 130:976–86. doi: 10.1161/CIRCULATIONAHA.114.010650
56. Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, et al. 1,25(OH)2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation.* (2009) 120:687–98. doi: 10.1161/CIRCULATIONAHA.109.856070
57. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol.* (2008) 52:1949–56. doi: 10.1016/j.jacc.2008.08.050
58. Alam U, Najam O, Al-Himdani S, Benoliel S, Jinadev P, Berry JL, et al. Marked vitamin D deficiency in patients with diabetes in the UK: ethnic and seasonal differences and an association with dyslipidaemia. *Diabet Med.* (2012) 29:1343–5. doi: 10.1111/j.1464-5491.2012.03692.x
59. Knekt P, Laaksonen M, Mattila C, Harkanen T, Marniemi J, Heliovaara M, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiology.* (2008) 19:666–71. doi: 10.1097/EDE.0b013e318176b8ad
60. Pittas AG, Sun Q, Manson JE, Dawson-Hughes B, Hu FB. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. *Diabetes Care.* (2010) 33:2021–3. doi: 10.2337/dc10-0790
61. Liu E, Meigs JB, Pittas AG, Economos CD, McKeown NM, Booth SL, et al. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. *Am J Clin Nutr.* (2010) 91:1627–33. doi: 10.3945/ajcn.2009.28441
62. Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care.* (2013) 36:1422–8. doi: 10.2337/dc12-0962
63. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas.* (2010) 65:225–36. doi: 10.1016/j.maturitas.2009.12.013
64. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obes Rev.* (2015) 16:341–9. doi: 10.1111/obr.12239
65. Pilz S, Tomaschitz A, Ritz E, Pieber TR. Vitamin D status and arterial hypertension: a systematic review. *Nature reviews Cardiology.* (2009) 6:621–30. doi: 10.1038/nrcardio.2009.135
66. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens.* (2007) 20:713–9. doi: 10.1016/j.amjhyper.2007.01.017
67. Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr.* (2008) 87:136–41. doi: 10.1093/ajcn/87.1.136
68. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension.* (2007) 49:1063–9. doi: 10.1161/HYPERTENSIONAHA.107.087288
69. Ke L, Graubard BI, Albanes D, Fraser DR, Weinstein SJ, Virtamo J, et al. Hypertension, pulse, and other cardiovascular risk factors and vitamin D status in Finnish men. *Am J Hypertens.* (2013) 26:951–6. doi: 10.1093/ajh/hpt051
70. Burgaz A, Orsini N, Larsson SC, Wolk A. Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. *J Hypertens.* (2011) 29:636–45. doi: 10.1097/HJH.0b013e32834320f9
71. Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. *Eur J Epidemiol.* (2013) 28:205–21. doi: 10.1007/s10654-013-9790-2
72. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, et al. Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med.* (2010) 152:307–14. doi: 10.7326/0003-4819-152-5-201003020-00009
73. Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. *Prog Lipid Res.* (2011) 50:303–12. doi: 10.1016/j.plipres.2011.05.001
74. Han Y, Han K, Zhang Y, Zeng X. Serum 25-hydroxyvitamin D might be negatively associated with hyperuricemia in U.S. adults: an analysis of the National Health and Nutrition Examination Survey 2007–2014. *J Endocrinol Invest.* (2021). doi: 10.1007/s40618-021-01637-x. [Epub ahead of print].
75. Isnuwardana R, Bijukchhe S, Thadanipon K, Ingsathit A, Thakkinstian A. Association between vitamin D and uric acid in adults: a systematic review and meta-analysis. *Horm Metab Res.* (2020) 52:732–41. doi: 10.1055/a-1240-5850
76. Chen Y, Cheng J, Chen Y, Wang N, Xia F, Chen C, et al. Association between serum vitamin D and uric acid in the eastern Chinese population: a population-based cross-sectional study. *BMC Endocr Disord.* (2020) 20:79. doi: 10.1186/s12902-020-00560-1
77. Charoenngam N, Ponvilawan B, Ungprasert P. Vitamin D insufficiency and deficiency are associated with a higher level of serum uric acid: a

systematic review and meta-analysis. *Modern Rheumatology*. (2020) 30:385–90. doi: 10.1080/14397595.2019.1575000
78. Cameli M, Lembo M, Sciaccaluga C, Bandera F, Ciccone MM, D'Andrea A, et al. Identification of cardiac organ damage in arterial hypertension: insights by echocardiography for a comprehensive assessment. *J Hypertens.* (2020) 38:588–98. doi: 10.1097/HJH.0000000000002323
79. Lembo M, Esposito R, Santoro C, Lo Iudice F, Schiano-Lomoriello V, Fazio V, et al. Three-dimensional echocardiographic ventricular mass/end-diastolic volume ratio in native hypertensive patients: relation between stroke volume and geometry. *J Hypertens.* (2018) 36:1697–704. doi: 10.1097/HJH.0000000000001717
80. Lembo M, Manzi MV, Mancusi C, Morisco C, Rao MAE, Cuocolo A, et al. Advanced imaging tools for evaluating cardiac morphological and functional impairment in hypertensive disease. *J Hypertens*. (2021) 40:4–14. doi: 10.1097/HJH.0000000000002967
81. Mancusi C, Trimarco V, Losi MA, Canciello G, Morisco C, Manzi MV, et al. Impact of visit-to-visit blood pressure variability on hypertensive-mediated target organ damage and future cardiovascular events: the Campania salute network. *J Hypertens.* (2021) 39:1852–8. doi: 10.1097/HJH.0000000000002847
82. Manzi MV, Mancusi C, Trimarco V, Izzo R, Franco D, Barbato E, et al. The intergated approach to the management of arterial hypertension: the Campania Salute Network. *Panminerva Med.* (2021) 63:451–7. doi: 10.23736/S0031-0808.21.04384-6
83. Chen S, Swier VJ, Boosani CS, Radwan MM, Agrawal DK. Vitamin D deficiency accelerates coronary artery disease progression in swine. *Arterioscler Thromb Vasc Biol.* (2016) 36:1651–9. doi: 10.1161/ATVBAHA.116.307586
84. Shirwany NA, Zou MH. Arterial stiffness: a brief review. *Acta Pharmacol Sin.* (2010) 31:1267–76. doi: 10.1038/aps.2010.123
85. Al Mheid I, Patel R, Murrow J, Morris A, Rahman A, Fike L, et al. Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. *J Am Coll Cardiol.* (2011) 58:186–92. doi: 10.1016/j.jacc.2011.02.051
86. Pirro M, Manfredelli MR, Helou RS, Scarponi AM, Schillaci G, Bagaglia F, et al. Association of parathyroid hormone and 25-OH-vitamin D levels with arterial stiffness in postmenopausal women with vitamin D insufficiency. *J Atheroscler Thromb.* (2012) 19:924–31. doi: 10.5551/jat.13128
87. Lee JI, Oh SJ, Ha WC, Kwon HS, Sohn TS, Son HS, et al. Serum 25-hydroxyvitamin D concentration and arterial stiffness among type 2 diabetes. *Diabetes Res Clin Pract.* (2012) 95:42–7. doi: 10.1016/j.diabres.2011.09.006
88. London GM, Guerin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, et al. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol.* (2007) 18:613–20. doi: 10.1681/ASN.2006060573
89. Melamed ML, Muntner P, Michos ED, Uribarri J, Weber C, Sharma J, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. *Arterioscler Thromb Vasc Biol.* (2008) 28:1179–85. doi: 10.1161/ATVBAHA.108.165886
90. Rapson IR, Michos ED, Alonso A, Hirsch AT, Matsushita K, Reis JP, et al. Serum 25-hydroxyvitamin D is associated with incident peripheral artery disease among white and black adults in the ARIC study cohort. *Atherosclerosis.* (2017) 257:123–9. doi: 10.1016/j.atherosclerosis.2017.01.016
91. Yuan J, Jia P, Hua L, Xin Z, Yang JK. Vitamin D deficiency is associated with risk of developing peripheral arterial disease in type 2 diabetic patients. *BMC Cardiovasc Disord.* (2019) 19:145. doi: 10.1186/s12872-019-1125-0
92. Capusa C, Stefan G, Stancu S, Ilyes A, Dorobantu N, Mircescu G. Subclinical cardiovascular disease markers and vitamin D deficiency in non-dialysis chronic kidney disease patients. *Arch Med Sci.* (2016) 12:1015–22. doi: 10.5114/aoms.2016.61911
93. Iannuzzo G, Forte F, Lupoli R, Di Minno MND. Association of vitamin D deficiency with peripheral arterial disease: a meta-analysis of literature studies. *J Clin Endocrinol Metab*. (2018). doi: 10.1210/jc.2018-00136. [Epub ahead of print].
94. Nsengiyumva V, Fernando ME, Moxon JV, Krishna SM, Pinchbeck J, Omer SM, et al. The association of circulating 25-hydroxyvitamin D concentration with peripheral arterial disease: a meta-analysis of observational studies. *Atherosclerosis.* (2015) 243:645–51. doi: 10.1016/j.atherosclerosis.2015.10.011
95. Carpinella G, Pagano G, Buono F, Petitto M, Guarino G, Orefice G, et al. Prognostic value of combined target-organ damage in patients with essential hypertension. *Am J Hypertens.* (2015) 28:127–34. doi: 10.1093/ajh/hpu098
96. Cave A, Grieve D, Johar S, Zhang M, Shah AM. NADPH oxidase-derived reactive oxygen species in cardiac pathophysiology. *Philos Trans R Soc Lond B Biol Sci.* (2005) 360:2327–34. doi: 10.1098/rstb.2005.1772
97. Kannan A, Janardhanan R. Hypertension as a risk factor for heart failure. *Curr Hypertens Rep*. (2014) 16:447. doi: 10.1007/s11906-014-0447-7
98. Mohan M, Dihoum A, Mordi IR, Choy AM, Rena G, Lang CC. Left ventricular hypertrophy in diabetic cardiomyopathy: a target for intervention. *Front Cardiovasc Med.* (2021) 8:746382. doi: 10.3389/fcvm.2021.746382
99. Schillaci G, Vaudo G, Reboldi G, Verdecchia P, Lupattelli G, Pasqualini L, et al. High-density lipoprotein cholesterol and left ventricular hypertrophy in essential hypertension. *J Hypertens.* (2001) 19:2265–70. doi: 10.1097/00004872-200112000-00021
100. Fallo F, Catena C, Camozzi V, Luisetto G, Cosma C, Plebani M, et al. Low serum 25-hydroxyvitamin D levels are associated with left ventricular hypertrophy in essential hypertension. *Nutr Metab Cardiovasc Dis.* (2012) 22:871–6. doi: 10.1016/j.numecd.2011.06.001
101. Pludowski P, Jaworski M, Niemirska A, Litwin M, Szalecki M, Karczmarewicz E, et al. Vitamin D status, body composition and hypertensive target organ damage in primary hypertension. *J Steroid Biochem Mo*. (2014) 144:180–4. doi: 10.1016/j.jsbmb.2013.10.026
102. Seker T, Gur M, Ucar H, Turkoglu C, Baykan AO, Ozaltun B, et al. Lower serum 25-hydroxyvitamin D level is associated with impaired myocardial performance and left ventricle hypertrophy in newly diagnosed hypertensive patients. *Anatol J Cardiol.* (2015) 15:744–50. doi: 10.5152/akd.2014.5637
103. Verdoia M, Solli M, Ubertini E, Erbetta R, Gioscia R, Afifeh AMS, et al. Low vitamin D levels affect left ventricular wall thickness in severe aortic stenosis. *J Cardiovasc Med.* (2020) 21:905–11. doi: 10.2459/JCM.0000000000001084
104. Gluba-Brzozka A, Franczyk B, Cialkowska-Rysz A, Olszewski R, Rysz J. Impact of Vitamin D on the cardiovascular system in advanced chronic kidney disease (CKD) and dialysis patients. *Nutrients*. (2018) 10:709. doi: 10.3390/nu10060709
105. Lai S, Coppola B, Dimko M, Galani A, Innico G, Frassetti N, et al. Vitamin D deficiency, insulin resistance, and ventricular hypertrophy in the early stages of chronic kidney disease. *Ren Fail.* (2014) 36:58–64. doi: 10.3109/0886022X.2013.832308
106. Ameri P, Canepa M, Milaneschi Y, Spallarossa P, Leoncini G, Giallauria F, et al. Relationship between vitamin D status and left ventricular geometry in a healthy population: results from the Baltimore Longitudinal Study of Aging. *J Intern Med.* (2013) 273:253–62. doi: 10.1111/joim.12007
107. Visco V, Pascale AV, Virtuoso N, Mongiello F, Cinque F, Gioia R, et al. Serum Uric Acid and Left Ventricular Mass in Essential Hypertension. *Front Cardiovasc Med.* (2020) 7:570000. doi: 10.3389/fcvm.2020.570000
108. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation.* (2007) 116:85–97. doi: 10.1161/CIRCULATIONAHA.106.678342
109. Meccariello A, Buono F, Verrengia E, Orefice G, Grieco F, Romeo F, et al. Microalbuminuria predicts the recurrence of cardiovascular events in patients with essential hypertension. *J Hypertens.* (2016) 34:646–53. doi: 10.1097/HJH.0000000000000846
110. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo CA Jr, et al. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *JASN.* (2005) 16:1115–25. doi: 10.1681/ASN.2004070573
111. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K. Association of activated vitamin D treatment and mortality in chronic kidney disease. *Arch Intern Med.* (2008) 168:397–403. doi: 10.1001/archinternmed.2007.110
112. Yilmaz F, Sozel H. Relationship between 25-hydroxyvitamin D and microalbuminuria in patients with newly diagnosed essential hypertension. *Clin Exp Hypertens.* (2021) 43:217–22. doi: 10.1080/10641963.2020.1847129
113. Ali MI, Fawaz LA, Sedik EE, Nour ZA, Elsayed RM. Vitamin D status in diabetic patients (type 2) and its relation to glycemic control & diabetic nephropathy. *Diabetes Metab Syndr*. (2019) 13:1971–3. doi: 10.1016/j.dsx.2019.04.040

114. Ucak S, Sevim E, Ersoy D, Sivritepe R, Basat O, Atay S. Evaluation of the relationship between microalbuminuria and 25-(OH) vitamin D levels in patients with type 2 diabetes mellitus. *Aging Male.* (2019) 22:116–20. doi: 10.1080/13685538.2018.1479385
115. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation.* (2008) 117:503–11. doi: 10.1161/CIRCULATIONAHA.107.706127
116. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med.* (2008) 168:1174–80. doi: 10.1001/archinte.168.11.1174
117. Kojima G, Bell C, Abbott RD, Launer L, Chen R, Motonaga H, et al. Low dietary vitamin D predicts 34-year incident stroke: the Honolulu Heart Program. *Stroke.* (2012) 43:2163–7. doi: 10.1161/STROKEAHA.112.651752
118. Chaudhuri JR, Mridula KR, Alladi S, Anamika A, Umamahesh M, Balaraju B, et al. Serum 25-hydroxyvitamin D deficiency in ischemic stroke and subtypes in Indian patients. *J Stroke.* (2014) 16:44–50. doi: 10.5853/jos.2014.16.1.44
119. Brondum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. *Arterioscler Thromb Vasc Biol.* (2012) 32:2794–802. doi: 10.1161/ATVBAHA.112.248039
120. Kilkkinen A, Knekt P, Aro A, Rissanen H, Marniemi J, Heliovaara M, et al. Vitamin D status and the risk of cardiovascular disease death. *Am J Epidemiol.* (2009) 170:1032–9. doi: 10.1093/aje/kwp227
121. Brondum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M. 25-hydroxyvitamin D and symptomatic ischemic stroke: an original study and meta-analysis. *Ann Neurol.* (2013) 73:38–47. doi: 10.1002/ana.23738
122. Lutsey PL, Michos ED, Misialek JR, Pankow JS, Loehr L, Selvin E, et al. Race and Vitamin D binding protein gene polymorphisms modify the association of 25-hydroxyvitamin D and incident heart failure: the ARIC (Atherosclerosis Risk in Communities) study. *JACC Heart Fail.* (2015) 3:347–56. doi: 10.1016/j.jchf.2014.11.013
123. D'Amore C, Marsico F, Parente A, Paolillo S, De Martino F, Gargiulo P, et al. Vitamin D deficiency and clinical outcome in patients with chronic heart failure: a review. *Nutr Metab Cardiovasc Dis.* (2017) 27:837–49. doi: 10.1016/j.numecd.2017.07.009
124. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Card.* (2008) 102:1540–4. doi: 10.1016/j.amjcard.2008.06.067
125. Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, et al. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. *Eur J Heart Fail.* (2012) 14:357–66. doi: 10.1093/eurjhf/hfr175
126. Deo R, Katz R, Shlipak MG, Sotoodehnia N, Psaty BM, Sarnak MJ, et al. Vitamin D, parathyroid hormone, and sudden cardiac death: results from the cardiovascular health study. *Hypertension.* (2011) 58:1021–8. doi: 10.1161/HYPERTENSIONAHA.111.179135
127. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab.* (2008) 93:3927–35. doi: 10.1210/jc.2008-0784
128. Drechsler C, Pilz S, Obermayer-Pietsch B, Verduijn M, Tomaschitz A, Krane V, et al. Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. *Eur Heart J.* (2010) 31:2253–61. doi: 10.1093/eurheartj/ehq246
129. Sung CC, Liao MT, Lu KC, Wu CC. Role of vitamin D in insulin resistance. *J Biomed Biotechnol.* (2012) 2012:634195. doi: 10.1155/2012/634195
130. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Endocrinology and metabolism clinics of North America. (2010) 39:419–46. doi: 10.1016/j.ecl.2010.02.013
131. Martini LA, Wood RJ. Vitamin D status and the metabolic syndrome. *Nutr Rev.* (2006) 64:479–86. doi: 10.1111/j.1753-4887.2006.tb00180.x
132. Wallace IR, Wallace HJ, McKinley MC, Bell PM, Hunter SJ. Vitamin D and insulin resistance. *Clin Endocrinol.* (2016) 84:159–71. doi: 10.1111/cen.12760
133. Holick MF. Vitamin D and bone health. *J Nutr.* (1996) 126:1159S—64S. doi: 10.1093/jn/126.suppl_4.1159S
134. Holick MF. Vitamin D deficiency. *N Engl J Med.* (2007) 357:266–81. doi: 10.1056/NEJMra070553
135. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. *Am J Med Sci.* (2009) 338:40–4. doi: 10.1097/MAJ.0b013e3181aaee91
136. Mazzone G, Morisco C, Lembo V, D'Argenio G, D'Armiento M, Rossi A, et al. Dietary supplementation of vitamin D prevents the development of western diet-induced metabolic, hepatic and cardiovascular abnormalities in rats. *United European Gastroenterol J.* (2018) 6:1056–64. doi: 10.1177/2050640618774140
137. Chen LW, Chien CH, Kuo SF, Yu CY, Lin CL, Chien RN. Low vitamin D level was associated with metabolic syndrome and high leptin level in subjects with nonalcoholic fatty liver disease: a community-based study. *BMC Gastroenterol.* (2019) 19:126. doi: 10.1186/s12876-019-1040-y
138. Wang D, Lin H, Xia M, Aleteng Q, Li X, Ma H, et al. Vitamin D levels are inversely associated with liver fat content and risk of non-alcoholic fatty liver disease in a Chinese middle-aged and elderly population: the Shanghai Changfeng study. *PLoS ONE.* (2016) 11:e0157515. doi: 10.1371/journal.pone.0157515
139. Zhai HL, Wang NJ, Han B, Li Q, Chen Y, Zhu CF, et al. Low vitamin D levels and non-alcoholic fatty liver disease, evidence for their independent association in men in East China: a cross-sectional study (Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China)). *Br J Nutr.* (2016) 115:1352–9. doi: 10.1017/S0007114516000386
140. Park JM, Park CY, Han SN. High fat diet-Induced obesity alters vitamin D metabolizing enzyme expression in mice. *BioFactors.* (2015) 41:175–82. doi: 10.1002/biof.1211
141. Roizen JD, Long C, Casella A, O'Lear L, Caplan I, Lai M, et al. Obesity decreases hepatic 25-hydroxylase activity causing low serum 25-hydroxyvitamin D. *J Bone Miner Res.* (2019) 34:1068–73. doi: 10.1002/jbmr.3686
142. Elkhwanky MS, Kummu O, Piltonen TT, Laru J, Morin-Papunen L, Mutikainen M, et al. Obesity represses CYP2R1, the vitamin D 25-hydroxylase, in the liver and extrahepatic tissues. *JBMR Plus.* (2020) 4:e10397. doi: 10.1002/jbm4.10397
143. Huang CQ, Ma GZ, Tao MD, Ma XL, Liu QX, Feng J. The relationship among renal injury, changed activity of renal 1-alpha hydroxylase and bone loss in elderly rats with insulin resistance or Type 2 diabetes mellitus. *J Endocrinol Invest.* (2009) 32:196–201. doi: 10.1007/BF03346452
144. Docs J, Banyai D, Flasko T, Szanto A, Kovacs G. Impaired vitamin D signaling is associated with frequent development of renal cell tumor in end-stage kidney disease. *Anticancer Res.* (2020) 40:6525–30. doi: 10.21873/anticanres.14676
145. Chang-Quan H, Bi-Rong D, Qian X, Ping H, Qun-Fang D, Zhen-Chan L, et al. Renal injury, abnormal vitamin D metabolism and bone homeostasis in aged rats with insulin resistance or type 2 diabetes mellitus. *J Investig Med.* (2008) 56:872–7. doi: 10.2310/JIM.0b013e31817c4270
146. Chang-Quan H, Bi-Rong D, Ping H, Zhen-Chan L, Xiao-Dong P. Insulin resistance, renal injury, renal 1-alpha hydroxylase, and bone homeostasis in aged obese rats. *Arch Med Res.* (2008) 39:380–7. doi: 10.1016/j.arcmed.2007.12.008
147. Fiordelisi A, Iaccarino G, Morisco C, Coscioni E, Sorriento D. NFkappaB is a key player in the crosstalk between inflammation and cardiovascular diseases. *Int J Mol Sci.* (2019) 20:1599. doi: 10.3390/ijms20071599
148. Jablonski KL, Chonchol M, Pierce GL, Walker AE, Seals DR. 25-hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. *Hypertension.* (2011) 57:63–9. doi: 10.1161/HYPERTENSIONAHA.110.160929
149. de Albuquerque Borborema ME, Oliveira DC, de Azevedo Silva J. Down regulation of VDR gene expression in metabolic syndrome and atherosclerosis' patients: cause or consequence? *Gene.* (2021) 771:145341. doi: 10.1016/j.gene.2020.145341
150. Yuzbashian E, Asghari G, Hedayati M, Zarkesh M, Mirmiran P, Khalaj A. Determinants of vitamin D receptor gene expression in visceral and subcutaneous adipose tissue in non-obese, obese, and morbidly obese subjects. *J Steroid Biochem Mol Biol.* (2019) 187:82–7. doi: 10.1016/j.jsbmb.2018.11.004

151. Bouillon R, Van Schoor NM, Gielen E, Boonen S, Mathieu C, Vanderschueren D, et al. Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. *J Clin Endocrinol Metab.* (2013) 98:E1283–304. doi: 10.1210/jc.2013-1195
152. Al Mheid I, Quyyumi AA. Vitamin D and cardiovascular disease: controversy unresolved. *J Am Coll Cardiol.* (2017) 70:89–100. doi: 10.1016/j.jacc.2017.05.031
153. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr.* (2012) 95:91–100. doi: 10.3945/ajcn.111.014779
154. Jenkins DJA, Spence JD, Giovannucci EL, Kim YI, Josse RG, Vieth R, et al. Supplemental vitamins and minerals for cardiovascular disease prevention and treatment: JACC focus seminar. *J Am Coll Cardiol.* (2021) 77:423–36. doi: 10.1016/j.jacc.2020.09.619
155. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA cardiology.* (2019) 4:765–76. doi: 10.1001/jamacardio.2019.1870
156. Pigeyre M, Sjaarda J, Chong M, Hess S, Bosch J, Yusuf S, et al. ACE and type 2 diabetes risk: a mendelian randomization study. *Diabetes Care.* (2020) 43:835–42. doi: 10.2337/dc19-1973
157. Posadzki P, Pieper D, Bajpai R, Makaruk H, Konsgen N, Neuhaus AL, et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. *BMC Public Health.* (2020) 20:1724. doi: 10.1186/s12889-020-09855-3
158. Ashton RE, Tew GA, Aning JJ, Gilbert SE, Lewis L, Saxton JM. Effects of short-term, medium-term and long-term resistance exercise training on cardiometabolic health outcomes in adults: systematic review with meta-analysis. *Br J Sports Med.* (2020) 54:341–8. doi: 10.1136/bjsports-2017-098970
159. Iaccarino G, Franco D, Sorriento D, Strisciuglio T, Barbato E, Morisco C. Modulation of insulin sensitivity by exercise training: implications for cardiovascular prevention. *J Cardiovasc Transl Res.* (2021) 14:256–70. doi: 10.1007/s12265-020-10057-w
160. Giallauria F, Strisciuglio T, Cuomo G, Di Lorenzo A, D'Angelo A, Volpicelli M, et al. Exercise training: the holistic approach in cardiovascular prevention. *High Blood Press Cardiovasc Prev.* (2021) 28:561–77. doi: 10.1007/s40292-021-00482-6
161. Scragg R, Camargo CA Jr. Frequency of leisure-time physical activity and serum 25-hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* (2008) 168:577–86. doi: 10.1093/aje/kwn163
162. Orces CH. Association between leisure-time aerobic physical activity and vitamin D concentrations among US older adults: the NHANES 2007-2012. *Aging Clin Exp Res.* (2019) 31:685–93. doi: 10.1007/s40520-018-1031-9
163. Chin K, Zhao D, Tibuakuu M, Martin SS, Ndumele CE, Florido R, et al. Physical activity, vitamin D, and incident atherosclerotic cardiovascular disease in whites and blacks: the ARIC study. *J Clin Endocrinol Metab.* (2017) 102:1227–36. doi: 10.1210/jc.2016-3743
164. Sun X, Cao ZB, Taniguchi H, Tanisawa K, Higuchi M. Effect of an acute bout of endurance exercise on serum 25(OH)D concentrations in young adults. *J Clin Endocrinol Metab.* (2017) 102:3937–44. doi: 10.1210/jc.2017-00146
165. Aly YE, Abdou AS, Rashad MM, Nassef MM. Effect of exercise on serum vitamin D and tissue vitamin D receptors in experimentally induced type 2 diabetes mellitus. *J Adv Res.* (2016) 7:671–9. doi: 10.1016/j.jare.2016.07.001
166. Castro-Barquero S, Ruiz-Leon AM, Sierra-Perez M, Estruch R, Casas R. Dietary strategies for metabolic syndrome: a comprehensive review. *Nutrients.* (2020) 12:2983. doi: 10.3390/nu12102983
167. Yashpal S, Liese AD, Boucher BA, Wagenknecht LE, Haffner SM, Johnston LW, et al. Metabolomic profiling of the dietary approaches to stop hypertension diet provides novel insights for the nutritional epidemiology of type 2 diabetes mellitus. *Br J Nutr.* (2021) 13:1–11. doi: 10.1017/S0007114521003561
168. Asghari G, Yuzbashian E, Mirmiran P, Hooshmand F, Najafi R, Azizi F. Dietary approaches to stop hypertension (DASH) dietary pattern is associated with reduced incidence of metabolic syndrome in children and adolescents. *J Pediatr.* (2016) 174:178–84.e1. doi: 10.1016/j.jpeds.2016.03.077
169. Kahleova H, Levin S, Barnard N. Cardio-metabolic benefits of plant-based diets. *Nutrients.* (2017) 9:848. doi: 10.3390/nu9080848
170. Santulli G, Pascale V, Finelli R, Visco V, Giannotti R, Massari A, et al. We are what we eat: impact of food from short supply chain on metabolic syndrome. *J Clin Med.* (2019) 8:2061. doi: 10.3390/jcm8122061
171. Dalamaga M, Muscogiuri G, Paganitsa G, Parvouleskou G, Syriou V, Karagkoynis P, et al. Adherence to the Mediterranean diet is an independent predictor of circulating vitamin D levels in normal weight and non-smoker adults: an observational cross-sectional study. *Int J Food Sci Nutr.* (2021) 72:848–60. doi: 10.1080/09637486.2021.1878488
172. Barrea L, Muscogiuri G, Laudisio D, Pugliese G, de Alteriis G, Colao A, et al. Influence of the Mediterranean diet on 25- hydroxyvitamin D levels in adults. *Nutrients.* (2020) 12:1439. doi: 10.3390/nu12051439
173. Zupo R, Lampignano L, Lattanzio A, Mariano F, Osella AR, Bonfiglio C, et al. Association between adherence to the Mediterranean Diet and circulating Vitamin D levels. *Int J Food Sci Nutr.* (2020) 71:884–90. doi: 10.1080/09637486.2020.1744533

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.

frontiers | Frontiers in Cardiovascular Medicine

REVIEW
published: 03 June 2022
doi: 10.3389/fcvm.2022.905504

Hypertension in Women

Tatjana Tasić[1], *Marijana Tadić*[2]* *and Maja Lozić*[3]

[1] School of Dental Medicine, University of Belgrade, Belgrade, Serbia, [2] Clinic for Internal Medicine II, Cardiology Department, University Clinic of Ulm, Ulm, Germany, [3] Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom

Hypertension is one of the main causes of morbidity and mortality in the human population. Nevertheless, the intricate network of pathophysiological mechanisms that lead to the development of hypertension in women still awaits to be fully understood. From young age to maturity and senescence, the female body transits through different stages, each of them characterized with specific physiological features and disposition to particular pathological conditions, and that is exactly what makes the understanding of the genesis and adequate treatment of hypertension in women so challenging. Clinical and experimental findings emphasize the role of sex hormones, autonomic nervous system, renin-angiotensin-aldosterone system and arterial stiffness in the development of chronically elevated blood pressure in females. The purpose of this review is to briefly summarize the knowledge of the mechanisms and treatment of hypertension in women.

Keywords: postmenopausal hypertension, pregnancy induced hypertension, antihypertensive treatment, sex hormones, sex differences

OPEN ACCESS

Edited by:
Daniela Sorriento,
University of Naples Federico II, Italy

Reviewed by:
Dulaney Wilson,
Medical University of South Carolina, United States
Christine Lalonde,
Nipissing University, Canada

***Correspondence:**
Marijana Tadić
marijana_tadic@hotmail.com

Specialty section:
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

Received: *27 March 2022*
Accepted: *17 May 2022*
Published: *03 June 2022*

Citation:
Tasić T, Tadić M and Lozić M (2022) Hypertension in Women. Front. Cardiovasc. Med. 9:905504. doi: 10.3389/fcvm.2022.905504

INTRODUCTION

Hypertension is a major risk factor for cardiovascular events and one of the leading causes of morbidity and mortality worldwide. It is known that adult women in the reproductive period have slightly lower blood pressure than men of the same age. Many clinical studies pointed out that men have a higher prevalence of hypertension than premenopausal women, but postmenopausal women with hypertension are more susceptible to development of isolated systolic hypertension, with less efficient therapeutic response compared to the age-matched men (1). According to the National Health and Nutrition Examination Survey (NHANES) conducted on 9,623 participants of the U.S. adult population, the prevalence of hypertension among women older than 75 years was 78% (2). Also, it has been noticed that elderly women are under high cardiovascular event risk, probably due to impaired dipping pattern (3). Impaired dipping pattern is a predictor of cardiovascular events with prognostically unfavorable outcomes (4–7) and may be defined either as a decrease in blood pressure during sleep that exceeds 20% of blood pressure values measured during wake time, or increase in blood pressure during sleep. Hypertension that occurs in women seems to be more sensitive to salt loading and it is more frequently associated with the metabolic syndrome than it is in men. These specific features of hypertension in women that were somewhat overlooked in the past might lead to the diminished responsiveness to the existing antihypertensive therapy (8, 9). Also, it is worth mentioning that women, more likely than men, will develop side effects on antihypertensive drugs (9). All of this suggests that more comprehensive, sex-oriented approach to the treatment of hypertension should be considered in future (9, 10). This review will try to elucidate the mechanisms, outcome and treatment of hypertension in women.

PREMENOPAUSAL HYPERTENSION

Before reaching menopause at the age of 45 to 55 years, women have slightly lower blood pressure levels and also lower chance to develop hypertension than the age-matched men. A large body of evidence indicates that sex hormones are responsible for the sex differences in the regulation of blood pressure (11). It has been shown that sex hormones affect systems that are considered to play an important part in the development of hypertension, such as renin angiotensin aldosterone system, endothelin, nitric oxide (NO) system and immune system. Estrogen is believed to have beneficial effects on cardiovascular system and it possibly exerts its protective role in women in reproductive age through enhancement of NO-mediated vasodilatation and modulation of action of powerful vasoconstrictor endothelin-1 action (11). Expression of endothelin-1 receptor ET_{1A} is significantly higher in hypertensive male rats than it is in the hypertensive females of the same age, and this difference in receptor density is assigned to the opposing effects of androgens and estrogen on endothelin receptor expression (11). In addition, the differences in endothelin-1 levels were registered in human population, with men having higher levels of endothelin-1 than women (11). Also, brain estrogen has modulatory role in control of the cardiovascular system and this matter will be elaborated later in the text.

In general, causes, outcome and treatment of the primary (essential) hypertension do not differ significantly between young adult women and men of the same age. Although, some particular clinical features distinguish hypertension in premenopausal period, for instance increased cardiac index and left ventricular ejection time, higher values of resting heart rate, but decreased plasma renin levels, blood volume and total peripheral vascular resistance (12). In contrast to elderly women, who are predominantly diagnosed with essential hypertension, hypertension in premenopausal women is usually caused by another condition or a disease. Major causes of the secondary hypertension in younger women are obesity, polycystic ovarian syndrome, obstructive sleep apnea, coarcatation of aorta, Turner syndrome, autoimmune diseases, endocrine disorders (hyperaldosteronism, hypothyroidism, hyperthyroidism, hyperparathyroidism, pheochromocytoma, diabetes mellitus), kidney diseases and drug usage (e.g., corticosteroids, hormonal contraceptives, etc.) (13–15). Use of oral contraceptives has been linked to the higher incidence of hypertension in the population of women in the reproductive age (16, 17), and the existing evidence shows that estrogen component in particular leads to the activation of renin angiotensin aldosteron system, potentiates sodium retention and plasma volume expansion (18). Therefore, contraceptive pills containing only progestin or combined oral contraceptives comprising of drospirenone (progestin with antimineralcorticoid activity) and low dose of the estradiol are recommended for women with the risk of developing hypertension (18, 19).

POSTMENOPAUSAL HYPERTENSION

Changes in heart morphology, function and compliance of arterial blood vessels have all been recognized and described in postmenopausal hypertension. Postmenopausal women have higher incidence of left ventricular hypertrophy and they are at greater risk to developed diastolic dysfunction compared to young adult women (20). Groban et al. (21) showed that female Lewis rats that underwent bilateral ovariectomy developed progressive diastolic dysfunction. Mori et al. (22) reported that ovariectomized hypertensive rats had cardiac hypertrophy, myocardial fibroses and diastolic dysfunction, but 17β-estradiol replacement treatment prevented these changes. The isolated systolic hypertension in postmenopausal women is related to aortic stiffness, probably caused by smooth muscle cells proliferation, collagen accumulation and increased levels of vasoconstrictor molecules in the blood vessel wall due to the lack of estrogen protective effect (20). Maiello et al. (23) showed that global pulse wave velocity, a reliable indicator of aortic stiffness, is highly increased in postmenopausal women with hypertension.

Role of Estrogen in Postmenopausal Hypertension

The complex regulatory pattern and multiple factors are associated with postmenopausal hypertension. Estrogen deprivation might be one of the leading causes of hypertension in postmenopausal women. Previously performed studies had shown that estradiol reduces blood pressure in rat animal models with genetic or induced hypertension (24). It has been reported that aged spontaneously hypertensive female rats, used as an animal model of postmenopausal hypertension, have reduced serum levels of estradiol and increased levels of androgens after cessation of regular cycling (25). Furthermore, mice treated with 4-vinylcyclohexene diepoxide (VCD), which causes ovarian failure, achieved increase in blood pressure compared to control animals and estradiol treatment had protective role on VCD mice (26). Epidemiological and experimental data imply that estrogen could cause vasodilatation due to effects on the renin angiotensin system, NO system, endothelin, and immune system (8, 27, 28). The renin angiotensin aldosteron system is important for hydromineral balance and it has a well-established role in the genesis of hypertension. Estradiol increases angiotensinogen gene expression due to modulation of gene promoter, reduces gene expression of angiotensin AT_1 receptors, suppresses angiotensin converting enzyme and plasma renin activity (3). Further, estradiol stimulates production of endothelial NO synthase that provides NO, important factor for vasodilatation. The lack of estradiol can also affect NO bioavailability due to reduced activity of superoxide dismutase (25, 28). Best et al. (29) reported that treatment with 17β-estradiol reduced plasma nitric oxide and endothelin-1 in postmenopausal women. The elevated level of powerful vasoconstrictor agent endothelin is registered in postmenopausal women and postcycling spontaneously

Abbreviations: ACE, angiotension converting enzyme; AT, angiotensin; ET, endothelin; NO, nitric oxide; VCD, vinylcyclohexene; 20-HETE-20, Hydroxyeicosatetraenoic acid; SNA, sympathetic nerve activity; PVN, paraventricular nucleus; NTS, nucleus tractus solitaries; RVLM, rostral ventrolateral medulla; CVLM, central ventrolateral medulla; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; CYPs, cytochrome P450.

hypertensive rats. It is found that estrogens inhibit endothelin synthesis and decrease endothelin ET_{1A} receptors expression (11, 28). Noteworthy, preclinical studies showed that angiotensin II stimulates endothelin production, and postmenopause is characterized by enhanced activity of renin angiotensin system (28). Furthermore, the role of estrogen as immune system modulator could not be neglected in postmenopausal hypertension. Estrogen might have antiinflammatory role in immune response by affecting humoral immune system and T cellular immune system (11, 30).

One Look at "Overlooked" Hormones: Progesterone and Androgens in Postmenopausal Hypertension

Menopause, as well as ovariectomy, does not result only in the loss of estrogen. Several studies have shown that precipitous decline in progesterone levels might be, at least in part, associated with the occurrence of arterial hypertension in postmenopausal women. Barbagallo et al. (31) demonstrated that progesterone acts as a vasoactive hormone, preventing noradrenaline-induced vasoconstriction by acting directly on vascular smooth muscle cells. These results further confirm previous *in vitro* findings of Jiang et al. (32) that revealed endothelium-independent vasodilatory effect of progesterone on rabbit coronary arteries. In a pilot study conducted in humans, natural progesterone lowered diastolic and mean blood pressure values in both men and postmenopausal women (33), while Seely et al. (34) noticed that intravaginal progesterone in combination with transdermal estrogen lowers night time blood pressure in healthy postmenopausal women. In postmenopausal women with arterial stiffness and grade 1 hypertension, introduction of progesterone to the ongoing estrogen-replacing treatment did not adversely affect positive cardiovascular effects achieved by estrogen (35). According to another study, micronized progesterone in combination with conjugated equine estrogen can induce even larger decrease in systolic blood pressure in hypertensive postmenopausal women than estrogen alone (36). At the first glance, these novel findings seem to contradict the results of studies published in the past (37) that offered evidence of dose-dependent hypertensive effect of progestogens in oral contraceptives. The reason for this discrepancy possibly lies in the fact that, unlike natural progesterone, synthetic progestins in oral contraceptives and hormone replacement therapy possess androgenic activity (38).

Androgens have been implied to participate in the development of cardiovascular disorders in postmenopausal women, although their exact role in the etiopathogenesis of postmenopausal hypertension still remains ambiguous. Given the fact that in the reproductive period men have higher risk of developing cardiovascular disorders in comparison to age-matched women, it has been assumed that androgen steroids have detrimental impact on cardiovascular system (39). This assumption seemed to be further substantiated with the results showing that women with polycystic ovary syndrome, the condition characterized by increased level of plasma androgens, were found to be at greater risk of developing hypertension (14). In a basic study conducted in normotensive rats of both sexes, daily administration of dihydrotestosterone (androgen steroid derived from testosterone) for 2 weeks induced significant increase in systolic blood pressure, possibly through mechanisms that promote the production of cytochrome P450-derived metabolites of arachidonic acid with potent vasoconstrictor properties (e.g., 20-Hydroxyeicosatetraenoic acid) (40). Androgen steroid propensity to increase blood pressure and potentiate adrenergic vasoconstriction of aorta was also noticed after addition of testosterone to the estrogen replacement therapy in ovariectomized spontaneously hypertensive female rats (41). Other mechanisms that might be involved in androgen-induced hypertension are stimulation of renin angiotensin system, vasoconstriction caused by potentiation of endothelin activity and oxidative stress (25, 28).

Nevertheless, there is a considerable amount of published data showing that it is not hyperandrogenemia, but androgen deficiency that is associated with the development of cardiovascular disorders (42–45). In the Rancho-Bernardo study, Laughlin et al. (46) showed that when compared to men with normal levels of testosterone, older men with low levels of total testosterone had 40% higher risk of death over the following 20 years, independently of age, body weight or life style. In postmenopausal women, low levels of dehydroepiandrosterone sulfate, androgen and precursor of steroid hormones, have been associated with higher cardiovascular mortality and with the increase in all-cause mortality (45, 47).

Role of Autonomic Nervous System in Postmenopausal Hypertension

Development of postmenopausal hypertension may be linked to the age-related alterations in autonomic nervous system (48).

Sympathetic nerve activity (SNA), which can be regarded as an output of central sympathetic outflow, progressively increases with age, and in menopausal women, this increase in SNA appears to be significantly steeper than in men of the same age (49, 50). Denervation of renal sympathetic nerve in spontaneously hypertensive female rats reduced blood pressure more efficiently in old dams than in young counterparts (51). Barnes et al. (52) reported that ganglionic blockade caused a larger drop of blood pressure in postmenopausal women compared to young women. The greater vasoconstrictor response following the administration of noradrenaline accompanied with blunted beta receptor-mediated vasodilatory protective effect is also noticed in postmenopausal women when compared to young women (53).

There are two crucial changes in autonomic regulation that arise during menopause that are able to facilitate the development of hypertension–increase in central sympathetic outflow and enhancement of adrenergic sensitivity in peripheral blood vessels (48). Here, we will focus only on the changes in the central autonomic control in postmenopausal women.

The major centers in the brain that adjust sympathetic outflow to the periphery are hypothalamic paraventricular nucleus (PVN), nucleus tractus solitarius (NTS), rostral ventrolateral medulla (RVLM) and central ventrolateral medulla (CVLM)

(54, 55). Sympathetic tone is generated in RVLM which integrates inputs from other parts of the brain (PVN, NTS, CVLM), and from RVLM nerve impulses are transmitted to sympathetic preganglionic neurons in intermediolateral column (ILC) of the thoracolumbar part of the spinal cord. From ILC sympathetic nerves further transmit nerve impulses to effector organs (heart, kidney, adrenal gland and blood vessels) (55). Parasympathetic tone is generated in NTS. The afferent nerve fibers transmit nerve signals from baroreceptors in the carotid sinus and aortic arch to the NTS in brainstem. From NTS, these signals are further conveyed to the nucleus ambiguous and dorsal motor nucleus of vagus and via parasympathetic nerve fibers they reach the heart (55).

Estrogen receptors (ERα and ER_β) are found in all of the aforementioned brain centers involved in the central control of cardiovascular system (56, 57) and according to the number of studies, their activation consequently leads to the sympathoinhibition.

In one of these studies (58), sympathoinhibitory effect of estrogen was demonstrated in the group of postmenopausal women, who experienced the decrease in muscle sympathetic activity after transdermal application of estrogen. Experiments in laboratory animals also suggest that estrogen wields regulatory influence on the autonomic nervous system during and after menopause. Intracerebroventricular administration of estrogen attenuated hypertension in female rats that were subjected to ovariectomy (56), while injections of estrogen into the NTS, RVLM, nucleus ambiguous and several other hindbrain nuclei, decreased mean blood pressure and renal sympathetic nerve activity and enhanced cardiac baroreflex in ovariectomized female rats (59). Similar effect on blood pressure was noticed after estrogen application into one of the major integrative autonomic centers - PVN. The activation of ER_β receptors in the PVN leads to decline in production of reactive oxygen species and activates the neural nitric oxide synthetase, promoting the production of nitric oxide (48, 56). Exciting results from the recent study (57) reveal that the administration of ER_β receptor agonist in the PVN of perimenopausal female mice prevents the increase in blood pressure in the angiotensin II-induced neurogenic hypertension. The importance of ER_β receptor signaling in the modulation of central autonomic control is further confirmed by the findings that demonstrate that estradiol inhibits pressor effects originating from RVLM *via* activation of ER_β/PI3K/Akt signaling pathway (60).

Role of Immune System in Hypertension-Sex Differences

Recent studies have shown possible role of immune system in the development of hypertension (61–63). It has been hypothesized that dysregulation of the T cells immune response may contribute to hypertension (64). Results obtained from both hypertensive animals and humans registered decline of blood pressure after administration of immunosuppressant mycphenolate mofetil, indicating the possible link between inflammation and the development of hypertension (61, 62).

Studies on recombinant activating gene-1 defficient ($Rag^{-/-}$) mice that lack both T and B cells, showed that T cells in females have lower proinflammatory and prohypertensive potential in respect to T cells of males (62, 65). Furthermore, spontaneously hypertensive males have increased number of pro-inflammatory and pro-hypertensive T helper 17 (Th17) cells in kidneys, while increased count of T regulatory cells has been found in kidneys of female hypertensive rats (61). Abovementioned difference in T-cell subpopulations found in kidneys of female and male rats may be a consequence of different cytokine profile found between sexes. Tipton and Sullivan (61) reported elevated levels of transforming growth factor-β, tumor necrosis factor-α, interleukin-10 in female spontaneously hypertensive rats, in contrast to higher levels of interleukin-6 and interleukin-17 found in renal cells. Furthermore, different expression and activation of Toll-like receptors present on immune cells could be responsible for more pronounced proinflammatory response and the development of hypertension in males (63).

PREGNANCY INDUCED HYPERTENSION

There are different types of pregnancy induced hypertension: preeclampsia, chronic hypertension with superimposed preeclampsia, gestational hypertension and chronic hypertension (66). Preeclampsia consists of hypertension that arises 20 weeks after gestation combined with proteinuria (66). Chronic hypertension with superimposed preeclampsia sublimes preexisting hypertension with other hallmarks of preeclampsia (66). Gestational hypertension develops 20 weeks after gestation and it is maintained only up to 12 weeks after parturition (66). Chronic hypertension may be defined as elevated blood pressure that appears before week 20 of gestation or as hypertension diagnosed for the first time 20 weeks after gestation and that continues to persists 12 weeks after the labor (66). Previous epidemiological studies showed that pregnancy-induced hypertension could cause consequences on either maternal or fetal health. During normal pregnancy mother's organism goes through numerous physiological changes necessary to adapt to the fetus. The cardiac output increases due to the increment in heart rate and stroke volume. The arterial blood pressure rises during pregnancy, but it decreases near the time of the term, ultimately reaching pregestational values. Due to diminished response of peripheral blood vessels to angiotensin II, peripheral vascular resistance decreases during the normal pregnancy. With the approaching labor, circulatory volume increases by 40% in order to provide proper fetal supply of oxygen and nutrients, and to prepare mother for blood loss during labor. Many of the hemodynamic adaptations during pregnancy may be assigned to relaxin. This polypeptide is synthetized by corpus luteum and it is mainly responsible for vascular remodeling and vasodilatation, which is predominantly achieved by the stimulation of NO system and alteration in the expression of endothelin ET_{1B} receptors (67). Beside aforementioned hemodynamic changes,

pregnancy is also characterized by the increase in renal blood flow, glomerular filtration rate, activity of the renin angiotensin aldosterone system and enhanced activity of the sympathetic nervous system.

Preeclampsia is the major risk factor that can lead to the vast number of life threatening complications like preterm delivery, placental abruption, ischemic stroke, disseminated intravascular coagulation, renal failure, Elevated Liver Enzymes and Low Platelets syndrome (HELLP), fetal growth restriction and fetal intrauterine death (66). Although the exact mechanisms underlying the development of preeclampsia still need to be elucidated, it is assumed that the factors produced by placenta, altered immune system and genetic factors have a role in the of genesis preeclampsia. Healthy pregnancy is accompanied by fetal cytotrophoblast invasion of mother's spiral arteries in order to supply fetus with oxygen and other nutrients. Studies showed that placentas of women with preeclampsia have damaged uteroplacental blood flow based on no adequate modification of spiral arteries and their increased resistance (68). It is hypothesized that endothelial dysfunction caused by disbalance among molecules responsible for angiogenesis contribute to the occurrence of preeclampsia. Placental failure to adequately respond in preeclampsia is linked with its production of solubile fms-like tyrosine kinase 1 and soluble Endoglin (69). These factors are receptors of vascular endothelial growth factor, placental growth factor and transforming growth factor β, which are the main molecules in the regulation and adaptation of maternal-fetal blood flow. The role of immune system in pathogenesis of preeclampsia cannot be neglected. Changes in placenta implementation is probably responsible for the impaired immune response and development of preeclampsia. Women with preeclampsia have decreased regulatory T cells and overexpressed different types of Toll-like receptors in respect to normotensive pregnant women (61, 63).

ANTIHYPERTENSION THERAPY IN WOMEN

Except during pregnancy, available guidelines for the management of hypertension do not offer different therapeutic approach to women and men. Firstly, lifestyle modification is highly recommended for blood pressure control in women (8, 12). Hypertension in postmenopausal women tends to be salt sensitive, so reduction of sodium intake could have benefit on blood pressure decrease. Further, weight lost, increased physical activity, decreased alcohol consumption, diet based on vegetables and fruits with elimination of fat dairy products have their role in hypertension management (70). Some studies pointed out that diet based on phytoestrogens might have protective effects on cardiovascular system (20). Many studies showed the prevalence and effects of the antihypertensive drugs (beta blockers, renin angiotensin aldosterone system inhibitors, calcium channel blockers, diuretics) usage in women and men (10). Briefly, men were more frequently treated with calcium channel blockers, angiotensin converting enzyme inhibitors, but were less frequently treated with diuretics, beta blockers and angiotensin II receptor blockers in respect to women. The sex difference response to pharmacotherapy is probably related to different metabolism of drugs and diseases linked to hypertension that are more common in women than men. Thus, hypertension in postmenopausal women is often associated with metabolic syndrome and autoimmune diseases which lead to less therapy efficacy and higher risk of cardiovascular complications (9). The absorption, distribution, metabolism and excretion of antihypertensive drugs are different between women and men probably due to influence of sex hormones on the absorption transporters (P-glycoprotein), distribution volume, activity of cytochrome P450 (CYPs) and renal clearance (10, 13). For example, women drug metabolism is altered in respect to men due to increased activity of CYP3A4, CYP2A6, CYP2B6 and decreased activity of CYP1A2, CYP2E1 and P-glycoprotein (10, 13). It is reported that side effects of some antihypertensive treatment are more common in women than men (12). Hence, women treated with angiotensin converting enzyme inhibitors have induced cough more frequently than men, also treatment with diuretics is associated with hyponatremia and hypokalemia in women (3, 19). Opposite to that, postmenopausal women have decreased risk of bone fracture if diuretics are recommended treatment (3). Furthermore, women are more prone to peripheral edema development during calcium channel blocker usage and minoxidil induced hirsutism, in respect to men (3, 19). During pregnancy some of antihypertensive drugs are not recommended in order to escape fetal toxicity and malformation (15, 18). Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and direct renin inhibitors could cause fetal growth restriction and death (15). American College of Cardiology/American Heart Hypertension Guideline recommended methyldopa, nifedipine and labetalol for hypertension treatment during pregnancy (13).

CONCLUSION

There are still many controversies and unsolved questions in the attempts to comprehend the mechanisms that lie behind pathophysiology of hypertension in women, which surpass our need to merely satisfy scientific curiosity. With hypertension as one of the major risk factors for cardiovascular events in elderly women, and preeclampsia still being the leading cause of maternal death in the countries of developed world, better understanding of hypertension in women is needed for reevaluation of our approach to the treatment of this condition.

AUTHOR CONTRIBUTIONS

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

REFERENCES

1. Ong KL, Tso AWK, Lam KSL, Cheung BMY. Gender difference in blood pressure control and cardiovascular risk factors in Americans with diagnosed hypertension. *Hypertension.* (2008) 51:1142–8. doi: 10.1161/HYPERTENSIONAHA.107.105205
2. Whelton PK, Carey RM, Aronow WS, Casey DEJr, 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: a report of the american college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* (2018) 71:e127–248. doi: 10.1016/j.jacc.2017.11.006
3. Giosia P, Giorgini P, Stamerra CA, Petrarca M, Ferri C, Sahebkar A. Gender differences in epidemiology, pathophysiology, and treatment of hypertension. *Curr Atheroscler Rep.* (2018) 20:13. doi: 10.1007/s11883-018-0716-z
4. Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? *Eur Heart J.* (2020) 22:E1–6. doi: 10.1093/eurheartj/suaa061
5. Tadic M, Cuspidi C, Sljivic A, Pencic B, Mancia G, Bombelli M, et al. Do reverse dippers have the highest risk of ventricular remodeling? *Hypertens Res.* (2020) 43:213–9. doi: 10.1038/s41440-019-0351-2
6. Palatini P, Reboldi G, Saladini F, Angeli F, Mos L, Rattazzi M, et al. Dipping pattern and short- term blood pressure variability are stronger predictors of cardiovascular events than average 24-hour blood pressure in young hypertensive subjects. *Eur J Prev Cardiol.* (2020) 1:zwac020. doi: 10.1097/01.hjh.0000745140.69504.b6
7. Palatini P, Reboldi G, Saladini F, Angeli F, Mos L, Rattazzi M, et al. (2022). Dipping pattern and short-term blood pressure variability are stronger predictors of cardiovascular events than average 24-hour blood pressure in young hypertensive subjects. *Eur J Prev Cardiol*. 1:zwac020. doi: 10.1093/eurjpc/zwac020
8. Leuzzi C, Modena MG. Hypertension in postmenopausal women: pathophysiology and treatment. *High Blood Press Cardiovasc Prev.* (2011) 18:13–8. doi: 10.2165/11588030-000000000-00000
9. Lodi E, Carollo A, Martinotti V, Modena MG. Hypertension and pharmacological therapy in women. *High Blood Press Cardiovasc Prev.* (2018) 25:147–50. doi: 10.1007/s40292-018-0257-0
10. Tadic M, Cuspidi C, Grassi G, Ivanovic B. Gender-specific therapeutic approach in arterial hypertension - Challenges ahead. *Pharmacol Res.* (2019) 141:181–8. doi: 10.1016/j.phrs.2018.12.021
11. Song JJ, Ma Z, Wang J, Chen LX, Zhong JC. Gender differences in hypertension. *J Cardiovasc Transl Res.* (2020) 13:47–54. doi: 10.1007/s12265-019-09888-z
12. August P, Oparil S. Hypertension in women. *J Clin Endocrinol Metab*. (1999) 84:1862–6. doi: 10.1210/jcem.84.6.5724
13. Wenger NK, Arnold A, Merz CNB, Cooper-DeHoff RM, Ferdinand KC, Fleg JL, et al. Hypertension across a woman's life cycle. *J Am Coll Cardiol.* (2018) 71:1797–813. doi: 10.1016/j.jacc.2018.02.033
14. Amiri M, Ramezani Tehrani F, Behboudi-Gandevani S, Bidhendi-Yarandi R, Carmina E. Risk of hypertension in women with polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Reprod Biol Endocrinol.* (2020) 18:23. doi: 10.1186/s12958-020-00576-1
15. Ghazi L, Bello NA. Hypertension in women across the lifespan. *Curr Atheroscler Rep.* (2021) 23:43. doi: 10.1007/s11883-021-00941-4
16. Ribeiro CCM, Shimo AKK, Lopes MHBM, Lamas JLT. Effects of different hormonal contraceptives in women's blood pressure values. *Rev Bras Enferm.* (2018) 71:1453–9. doi: 10.1590/0034-7167-2017-0317
17. Afshari M, Alizadeh-Navaei R, Moosazadeh M. Oral contraceptives and hypertension in women: results of the enrolment phase of Tabari Cohort Study. *BMC Womens Health.* (2021) 21:224. doi: 10.1186/s12905-021-01376-4
18. Brahmbhatt Y, Gupta M, Hamrahian S. Hypertension in premenopausal and postmenopausal women. *Curr Hypertens Rep.* (2019) 21:74. doi: 10.1007/s11906-019-0979-y
19. Pimenta E. Hypertension in women. *Hypertens Res.* (2012) 35:148–52. doi: 10.1038/hr.2011.190
20. McBride SM, Flynn FW, Ren J. Cardiovascular alteration and treatment of hypertension: do men and women differ? *Endocrine.* (2005) 28:199–207. doi: 10.1385/ENDO:28:2:199
21. Groban L, Yamaleyeva LM, Westwood BM, Houle TT, Lin M, Kitzman DW, et al. Progressive diastolic dysfunction in the female mRen(2). lewis rat: influence of salt and ovarian hormones. *J Gerontol A Biol Sci Med Sci.* (2008) 63:3–11. doi: 10.1093/gerona/63.1.3
22. Mori T, Kai H, Kajimoto H, Koga M, Kudo H, Takayama N, et al. Enhanced cardiac inflammation and fibrosis in ovariectomized hypertensive rats: a possible mechanism of diastolic dysfunction in postmenopausal women. *Hypertens Res.* (2011) 34:496–502. doi: 10.1038/hr.2010.261
23. Maiello M, Zito A, Ciccone MM, Palmiero P. How aortic stiffness in postmenopausal women is related to common cardiovascular risk factors. *Cardiol Res Pract.* (2014) 2014:216080. doi: 10.1155/2014/216080
24. Kotchen MJ, Kotchen TA. Impact of female hormones on blood pressure: review of potential mechanisms and clinical studies. *Curr Hypertens Rep.* (2003) 5:505–12. doi: 10.1007/s11906-003-0059-0
25. Yanes LL, Reckelhoff JF. Postmenopausal hypertension. *Am J Hypertens.* (2011) 24:740–9. doi: 10.1038/ajh.2011.71
26. Brooks HL, Pollow DP, Hoyer PB. The VCD mouse model of menopause and perimenopause for the study of sex differences in cardiovascular disease and the metabolic syndrome. *Physiology.* (2016) 31:250–7. doi: 10.1152/physiol.00057.2014
27. Ramirez LA, Sullivan JC. Sex differences in hypertension: where we have been and where we are going. *Am J Hypertens.* (2018) 31:1247–54. doi: 10.1093/ajh/hpy148
28. Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. *Hypertension.* (2004) 43:918–23. doi: 10.1161/01.HYP.0000124670.03674.15
29. Best PJ, Berger PB, Miller VM, Lerman A. The effect of estrogen replacement therapy on plasma nitric oxide and endothelin-1 levels in postmenopausal women. *Ann Intern Med.* (1998) 128:285–8. doi: 10.7326/0003-4819-128-4-199802150-00006
30. Maric-Bilkan C, Gilbert EL, Ryan MJ. Impact of ovarian function on cardiovascular health in women: focus on hypertension. *Int J Womens Health.* (2014) 6:131–9. doi: 10.2147/IJWH.S38084
31. Barbagallo M, Dominguez LJ, Licata G, Shan J, Bing L, Karpinski E, et al. Vascular effects of progesterone: role of cellular calcium regulation. *Hypertension.* (2001) 37:142–7. doi: 10.1161/01.HYP.37.1.142
32. Jiang CW, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Progesterone induces endothelium-independent relaxation of rabbit coronary artery in vitro. *Eur J Pharmacol.* (1992) 211:163–7. doi: 10.1016/0014-2999(92)90524-8
33. Rylance PB, Brincat M, Lafferty K, De Trafford JC, Brincat S, Parsons V, et al. Natural progesterone and antihypertensive action. *Br Med J.* (1985) 290:13–4. doi: 10.1136/bmj.290.6461.13
34. Seely EW, Walsh BW, Gerhard MD, Williams GH. Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women. *Hypertension.* (1999) 33:1190–4. doi: 10.1161/01.HYP.33.5.1190
35. Yoon BK, Sung J, Song YM, Kim SM, Son KA, Yoo JH, et al. Effects of menopausal hormone therapy on ambulatory blood pressure and arterial stiffness in postmenopausal Korean women with grade 1 hypertension: a randomized, placebo-controlled trial. *Clin Hypertens.* (2021) 27:18. doi: 10.1186/s40885-021-00175-1
36. Lee DY, Kim JY, Kim JH, Choi DS, Kim DK, Koh KK, et al. Effects of hormone therapy on ambulatory blood pressure in postmenopausal Korean women. *Climacteric.* (2011) 14:92–9. doi: 10.3109/13697137.2010.491924
37. Khaw KT, Peart WS. Blood pressure and contraceptive use. *Br Med J.* (1982) 285:403–7. doi: 10.1136/bmj.285.6339.403
38. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovasc Res.* (2002) 53:688–708l. doi: 10.1016/S0008-6363(01)00527-2
39. Liu JD, WU YQ. Anabolic-androgenic steroids and cardiovascular risk. *Chin Med J.* (2019) 132:2229–36. doi: 10.1097/CM9.0000000000000407
40. Singh H, Schwartzman ML. Renal vascular cytochrome P450-derived eicosanoids in androgen-induced hypertension. *Pharmacol Rep.* (2008) 60:29–37.
41. Costa TJ, Ceravolo GS, Echem C, Hashimoto CM, Costa BP, Santos-Eichler RA, et al. Detrimental effects of testosterone addition to estrogen therapy involve cytochrome p-450-induced 20-HETE synthesis

in aorta of ovariectomized spontaneously hypertensive rat (SHR), a model of postmenopausal hypertension. *Front Physiol.* (2018) 9:490. doi: 10.3389/fphys.2018.00490
42. Svartberg J, von Mühlen D, Schirmer H, Barrett-Connor E, Sundfjord J, Jorde R. Association of endogenous testosterone with blood pressure and left ventricular mass in men. the tromsø study. *Eur J Endocrinol.* (2004) 150:65–71. doi: 10.1530/eje.0.1500065
43. Svartberg J, von Mühlen D, Mathiesen E, Joakimsen O, Bønaa KH, Stensland-Bugge E. Low testosterone levels are associated with carotid atherosclerosis in men. *J Intern Med.* (2006) 259:576–82. doi: 10.1111/j.1365-2796.2006.01637.x
44. Vikan T, Johnsen SH, Schirmer H, Njølstad I, Svartberg J. Endogenous testosterone and the prospective association with carotid atherosclerosis in men: the Tromsø study. *Eur J Epidemiol.* (2009) 24:289–95. doi: 10.1007/s10654-009-9322-2
45. Moretti C, Lanzolla G, Moretti M, Gnessi L, Carmina E. Androgens and hypertension in men and women: a unifying view. *Curr Hypertens Rep.* (2017) 19:44. doi: 10.1007/s11906-017-0740-3
46. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab.* (2008) 93:68–75. doi: 10.1210/jc.2007-1792
47. Shufelt C, Bretsky P, Almeida CM, Johnson BD, Shaw LJ, Azziz R, et al. DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the national institutes of health–national heart, lung, and blood institute (NHLBI)-sponsored women's ischemia syndrome evaluation (WISE). *J Clin Endocrinol Metab.* (2010) 95:4985–92. doi: 10.1210/jc.2010-0143
48. Vongpatanasin W. Autonomic regulation of blood pressure in menopause. *Semin Reprod Med.* (2009) 27:338–45. doi: 10.1055/s-0029-1225262
49. Matsukawa T, Sugiyama Y, Watanabe T, Kobayashi F, Mano T. Gender difference in age-related changes in muscle sympathetic nerve activity in healthy subjects. *Am J Physiol.* (1998) 275:R1600–4. doi: 10.1152/ajpregu.1998.275.5.R1600
50. Narkiewicz K, Phillips BG, Kato M, Hering D, Bieniaszewski L, Somers VK. Gender-selective interaction between aging, blood pressure, and sympathetic nerve activity. *Hypertension.* (2005) 45:522–5. doi: 10.1161/01.HYP.0000160318.46725.46
51. Maranon RO, Lima R, Mathbout M, Carmo JM, Hall JE, Roman RJ, et al. Postmenopausal hypertension: role of the sympathetic nervous system in an animal model. *Am J Physiol Regul Integr Comp Physiol.* (2014) 306:R248–56. doi: 10.1152/ajpregu.00490.2013
52. Barnes JN, Hart EC, Curry TB, Nicholson WT, Eisenach JH, Wallin BG, et al. Aging enhances autonomic support of blood pressure in women. *Hypertension.* (2014) 63:303–8. doi: 10.1161/HYPERTENSIONAHA.113.02393
53. Baker SE, Limberg JK, Ranadive SM, Joyner MJ. Neurovascular control of blood pressure is influenced by aging, sex, and sex hormones. *Am J Physiol Regul Integr Comp Physiol.* (2016) 311:R1271–5. doi: 10.1152/ajpregu.00288.2016
54. Dampney RAL. Central neural control of the cardiovascular system: current perspectives. *Adv Physiol Educ.* (2016) 40:283–96. doi: 10.1152/advan.00027.2016
55. Silvani A, Calandra- Buonaura G, Damney RAL, Cortelli P. Brain- heart interaction: physiology and clinical implications. *Philos Trans A Math Phys Eng Sci.* (2016) 374:20150181. doi: 10.1098/rsta.2015.0181
56. Hay M, Xue B, Johnson AK. Yes! Sex matters: sex, the brain and blood pressure. *Curr Hypertens Rep.* (2014) 16:458. doi: 10.1007/s11906-014-0458-4
57. Milner TA, Contoreggi NH, Yu F, Johnson MA, Wang G, Woods C, et al. Estrogen receptor β contributes to both hypertension and hypothalamic plasticity in a mouse model of peri-menopause. *J Neurosci.* (2021) 41:5190-205. doi: 10.1523/JNEUROSCI.0164-21.2021
58. Weitz G, Elam M, Born J, Fehm HL, Dodt C. Postmenopausal estrogen administration suppresses muscle sympathetic nerve activity. *J Clin Endocrinol Metab.* (2001) 86:344–8. doi: 10.1210/jc.86.1.344
59. Saleh MC, Connell BJ, Saleh TM. Autonomic and cardiovascular reflex responses to central estrogen injection in ovariectomized female rats. *Brain Res.* (2000) 879:105–14. doi: 10.1016/S0006-8993(00)02757-8
60. Wang G, Drake CT, Rozenblit M, Zhou P, Alves SE, Herrick SP, et al. Evidence that estrogen directly and indirectly modulates C1 adrenergic bulbospinal neurons in the rostral ventrolateral medulla. *Brain Res.* (2006) 1094:163–78. doi: 10.1016/j.brainres.2006.03.089
61. Tipton AJ, Sullivan JC. Sex differences in T cells in hypertension. *Clin Ther.* (2014) 36:1882–900. doi: 10.1016/j.clinthera.2014.07.011
62. Sandberg K, Ji H, Einstein G, Au A, Hay M. Is immune system-related hypertension associated with ovarian hormone deficiency? *Exp Physiol.* (2016) 101:368–74. doi: 10.1113/EP085149
63. Justina VD, Giachini FR, Sullivan JC, Webb C. Toll-like receptors contribute to sex differences in blood pressure regulation. *J Cardiovasc Pharmacol.* (2020) 76:255–66. doi: 10.1097/FJC.0000000000000869
64. Crislip GR, Sullivan JC. T-cell involvement in sex differences in blood pressure control. *Clin Sci.* (2016) 130:773–83. doi: 10.1042/CS20150620
65. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *Exp Med.* (2007) 204:2449–60. doi: 10.1084/jem.20070657
66. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol.* (2011) 25:391–403. doi: 10.1016/j.bpobgyn.2011.01.006
67. Jelinic M, Marshall SA, Leo CH, Parry LJ, Tare M. From pregnancy to cardiovascular disease: Lessons from relaxin-deficient animals to understand relaxin actions in the vascular system. *Microcirculation.* (2019) 26:e12464. doi: 10.1111/micc.12464
68. Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiolgy. *Cardiovasc J Afr.* (2016) 27:71–8. doi: 10.5830/CVJA-2016-009
69. Hod T, Cerdeira AS, Karumanchi SA. Molecular mechanisms of preeclampsia cold. *Spring Harb Perspect Med.* (2015) 5:a023473. doi: 10.1101/cshperspect.a023473
70. Engberding N, Wenger NK. Management of hypertension in women. *Hypertens Res.* (2012) 35:251–60. doi: 10.1038/hr.2011.210

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.

frontiers | Frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 16 June 2022
doi: 10.3389/fcvm.2022.874764

Characterizing Diagnostic Inertia in Arterial Hypertension With a Gender Perspective in Primary Care

*Vicente Pallares-Carratala[1,2], Concepcion Carratala-Munuera[3], Adriana Lopez-Pineda[3], Jose Antonio Quesada[3], Vicente Gil-Guillen[3], Domingo Orozco-Beltran[3], Jose L. Alfonso-Sanchez[4,5], Jorge Navarro-Perez[6] and Jose M. Martin-Moreno[4,6]**

[1] Health Surveillance Unit, Castellon Mutual Insurance Union, Castellón, Spain, [2] Department of Medicine, Jaume I University, Castellón, Spain, [3] Clinical Medicine Department, Miguel Hernandez University, Elche, Spain, [4] Department of Preventive Medicine and Public Health, School of Medicine, University of Valencia, Valencia, Spain, [5] Preventive Medicine Department, General Hospital of Valencia, Valencia, Spain, [6] Biomedical Research Institute INCLIVA, Clinic University Hospital of Valencia, University of Valencia, Valencia, Spain

Background and Objectives: Substantial evidence shows that diagnostic inertia leads to failure to achieve screening and diagnosis objectives for arterial hypertension (AHT). In addition, different studies suggest that the results may differ between men and women. This study aimed to evaluate the differences in diagnostic inertia in women and men attending public primary care centers, to identify potential gender biases in the clinical management of AHT.

Study Design/Materials and methods: Cross-sectional descriptive and analytical estimates were obtained nested on an epidemiological ambispective cohort study of patients aged ≥30 years who attended public primary care centers in a Spanish region in the period 2008–2012, belonging to the ESCARVAL-RISK cohort. We applied a consistent operational definition of diagnostic inertia to a registry- reflected population group of 44,221 patients with diagnosed hypertension or meeting the criteria for diagnosis (51.2% women), with a mean age of 63.4 years (62.4 years in men and 64.4 years in women).

Results: Of the total population, 95.5% had a diagnosis of hypertension registered in their electronic health record. Another 1,968 patients met the inclusion criteria for diagnostic inertia of hypertension, representing 4.5% of the total population (5% of men and 3.9% of women). The factors significantly associated with inertia were younger age, normal body mass index, elevated total cholesterol, coexistence of diabetes and dyslipidemia, and treatment with oral antidiabetic drugs. Lower inertia was associated with age over 50 years, higher body mass index, normal total cholesterol, no diabetes or dyslipidemia, and treatment with lipid-lowering, antiplatelet, and anticoagulant drugs. The only gender difference in the association of factors with diagnostic inertia was found in waist circumference.

Conclusion: In the ESCARVAL-RISK study population presenting registered AHT or meeting the functional diagnostic criteria for AHT, diagnostic inertia appears to be greater in men than in women.

Keywords: diagnostic inertia, arterial hypertension, gender, equity, primary care

OPEN ACCESS

Edited by:
Guido Iaccarino, University of Naples Federico II, Italy

Reviewed by:
Enoch Odame Anto, Kwame Nkrumah University of Science and Technology, Ghana
Luciana Nobre, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Brazil

***Correspondence:**
Jose M. Martin-Moreno
jose.martin-moreno@uv.es

Specialty section:
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

Received: *17 February 2022*
Accepted: *24 May 2022*
Published: *16 June 2022*

Citation:
Pallares-Carratala V, Carratala-Munuera C, Lopez-Pineda A, Quesada JA, Gil-Guillen V, Orozco-Beltran D, Alfonso-Sanchez JL, Navarro-Perez J and Martin-Moreno JM (2022) Characterizing Diagnostic Inertia in Arterial Hypertension With a Gender Perspective in Primary Care. Front. Cardiovasc. Med. 9:874764. doi: 10.3389/fcvm.2022.874764

INTRODUCTION

Arterial hypertension (AHT) is a major modifiable risk factor for cardiovascular disease and death; its adequate control is a strategy with a high degree of evidence and population benefit (1). Given its prevalence, patients with AHT in primary health care (PHC) clinics are diverse, which means that no single therapeutic approach exists (2). The most recent AHT guidelines (3, 4) recommend lower blood pressure (BP) control targets to reduce cardiovascular events, particularly in high-risk patients.

A critical analysis of the guidelines, adapted to the context of PHC, proposes that all patients with hypertension should have a target BP of <140/90 (5). At present, only 58.5% of patients achieve these targets (6), but the more ambitious target of BP < 130/80, if well-tolerated, is potentially achievable for most hypertensive patients, especially those at high or very high cardiovascular risk (5, 6).

The European guidelines (3) specifically emphasize the need to avoid therapeutic inertia. When treatment is ineffective, a proper follow-up plan is best, with the PHC team of medical and nursing professionals detecting and correcting the possible causes of poor control (5).

Therefore, greater knowledge of clinical practice guidelines by clinicians and individualized prescription of treatment are key to avoiding inertia, which will benefit hypertensive patients and contribute to improving the health of the population. Analyzing whether this has implications according to the sex (biological factors) and gender (sociocultural factors) of patients is presently essential.

Classically, differences between sexes have been estimated in the cardiovascular (CV) area. Men are more likely to develop coronary heart disease as the first event, whereas women are more likely to have cerebrovascular disease or heart failure as the first manifestation, although these appear more frequently at advanced ages (7). Another issue is the potential inequity in clinical care that has been observed by gender, due to biases conditioned by social attributes or differences in opportunity for men and women (8). In May 2021, The Lancet Women and Cardiovascular Disease Commission published its "call to action" report including recommendations to reduce the global burden of CV disease in women by 2030. This reflects the necessity to include gender objectives in achieving CV health objectives to achieve equity in clinical care practice (9).

Despite recent progress in basic and clinical research on the differences in the management and outcomes of AHT in men and women, the main guidelines of the leading AHT societies continue not to identify gender differences due to the lack of conclusive results in clinical trials (3, 4, 10). One of the most recent and high-impact trials, the SPRINT study, failed to recruit 50% women as planned (including only 36%) and was therefore underpowered for gender analysis (11).

Subgroup analyses comparing results between women and men have been subsequently published, but they only contributed to highlight that their results were inconclusive for women and that implementation of their results concerning sex should be considered with caution (12–14). In subsequent studies, the inclusion of women has been increased, such as ACCOMPLISH (39.5%) (15), VALUE (42%) (16), and HOPE 3 (46%) (17). However, a paucity remains of sex-specific data to guide the treatment of hypertension in non-pregnant women, despite the fact that nearly 800 million women worldwide are hypertensive (18). Clearly, much work remains since the antihypertensive treatment proposed by HTA guidelines based on a gender approach may overlook sex- linked pathophysiologic and therapeutic considerations (19–22). Therefore, we consider that a gender-specific approach to hypertension prevention, diagnosis, and treatment programs should be implemented to address the more than likely gender differences to achieve more effective health promotion outcomes.

This study aimed to analyze, within the ESCARVAL-RISK study cohort, the difference in the diagnostic management and results of AHT between women and men attending public primary care centers, including those meeting the criteria for AHT diagnosis and, according to clinical practice guidelines, not properly diagnosed or treated in the PHC setting. In addition, it aimed to describe the profile of patients affected by diagnostic inertia (DI).

METHODS

This was a cross-sectional epidemiological study nested on an epidemiological ambispective cohort study carried out in the Valencian Community (an autonomous community of Spain with an estimated population of over 5 million people) in 2020 (23). This study was approved by an ethical committee and was conducted following the guidelines of the Declaration of Helsinki. The details of the protocol for this study have been previously described (24).

Patients were selected from the ESCARVAL-RISK cohort (19). This included women and men with cardiovascular risk factors (CVRF) and free of events (hospital admission for ischemic heart disease or stroke) who were seen in PHC consultations for routine clinical practice between 2008 and 2012. Baseline data were obtained from the electronic health record (EHR) of patients who met the inclusion criteria. Eligible patients were women and men aged 30 years or older and with AHT.

A patient was considered to have AHT if, during a baseline window period of 6 months from inclusion: (a) they had AHT coded in the EHR (Code I10–5 according to the International Classification of Diseases, ICD-10) and were being treated for this (pharmacological or non-pharmacological intervention) or (b) despite no diagnosis of AHT, they had been prescribed antihypertensive drugs or had two altered systolic (SBP) or diastolic (DBP) blood pressure readings (SBP $\geq$ 140 or DBP $\geq$ 90), in accordance with the criteria established by the clinical practice guidelines for the period analyzed (25, 26). Patients with inconsistent or incomplete data in their EHR were excluded.

Study Variables

The primary variable was DI in AHT, considered operationally when a patient had two altered blood pressure readings (SBP $\geq$ 140 or DBP $\geq$ 90), as established by clinical guidelines (25, 26), during a 6-months baseline window period from inclusion, and

neither the diagnosis of hypertension was coded in the EHR, nor the patient was treated with antihypertensive drugs.

Other variables studied were sociodemographic variables (age and sex/gender), clinical variables (body mass index [BMI], waist circumference, SBP, and DBP), variables related to lifestyle (smoking status), and analytical indicators (glycosylated hemoglobin [HbA1c], high-density lipoprotein cholesterol [HDL-c], triglycerides, and total cholesterol). A value was considered missing when no data existed for the variable in the EHR ($\geq$ 50%). In addition, variables corresponding to pathologies recorded in the EHR according to the ICD-9 code were collected: diabetes mellitus (250.0), dyslipidemia (272.0), proteinuria (791.0), retinopathy (362.0), metabolic syndrome (277.7), ischemic heart disease (410.0–14.0), heart failure (428.0), peripheral artery disease (440.20), atrial fibrillation (427.31), and chronic kidney disease (585.9). Finally, variables related to medication were collected: antihypertensive treatment, lipid-lowering drugs (statins and others), oral antidiabetic drugs, insulin, and antiplatelet or anticoagulant agents.

The source of information for all the variables was the ABUCASIS EHR, which is centralized and unique for the entire Valencian Community.

Statistical Analysis

To estimate the prevalence of DI, the number and frequency of inertia cases were calculated for the total and by sex. To evaluate the patient profile according to their DI in each category of qualitative variables, double-entry tables were made by applying the Chi-Square statistical test.

Prevalence ratios (PRs) and 95% confidence intervals (95% CIs) of inertia at each level of the explanatory variables were estimated using multivariate Poisson regression models with robust variance (27), differentiating by sex. A stepwise variable selection procedure was performed, based on the Akaike information criterion (AIC). The multicollinearity of the variables in the construction of the models was studied. The goodness-of-fit likelihood ratio test (LRT), AIC value, and receiver operating characteristic (ROC) area of each model were performed. To avoid the multiplicity problem due to the analysis by subgroups due to sex/gender, the type I error was adjusted by the Bonferroni method to 0.025. The analyses were performed using IBM SPSS Statistics for Windows, *v.* 26.0 (IBM Corporation, Armonk, NY, United States) and R software, *v.* 4.0.2 (R Core Team, Vienna, Austria).

RESULTS

A total of 44,221 patients with diagnosed AHT, or meeting the diagnostic criteria for AHT and undiagnosed or on antihypertensive treatment and coded in the EHR, were included (51.2% women). The mean age of the patients was 63.4 years (range 30–97 years), being 62.4 years in men (range 30–95 years) and 64.4 years in women (range 30–97 years).

A total of 1,968 patients were identified who met the DI inclusion criteria and had no coded diagnosis of AHT, representing 4.5% of the total population studied. By sex, 5% were men and 3.9% were women ($p < 0.001$; **Table 1**).

TABLE 1 | Diagnostic inertia in hypertension for all hypertensive patients and by gender.

		Diagnostic AHT		DI		
		n	%	*n*	%	*p*-value
Gender	Men	20,512	95.0%	1.082	5.0%	<0.001
	Women	21,741	96.1%	886	3.9%	
	Total	42,253	95.5%	1.968	4.5%	

AHT, arterial hypertension; DI, diagnostic inertia.

Tables 2, **3** show the analysis of DI with respect to the population diagnosed with hypertension in the sociodemographic and clinical variables and sexes. Statistically significant differences of more DI were found in men with normal BMI ($p < 0.001$) and waist circumference ($p < 0.001$), who were smokers ($p < 0.02$), with normal HDL ($p < 0.001$), and with cholesterol >200 mg/dL ($p < 0.001$). In women, the highest DI was associated with the youngest age group ($p < 0.013$), normal BMI ($p < 0.001$), and total cholesterol >200 mg/dL ($p < 0.001$).

Tables 4, **5** show the analysis of DI according to comorbidities and treatments in men and women, respectively. Statistically significant differences and higher DI were found in men without heart failure ($p < 0.028$) or peripheral artery disease ($p < 0.001$), with diabetes ($p < 0.001$) and dyslipidemia ($p < 0.016$), on oral antidiabetic treatment ($p < 0.001$), and not taking lipid-lowering, antiplatelet, or anticoagulant treatment ($p < 0.001$). In women, the highest DI was observed in those with diabetes and dyslipidemia ($p < 0.001$), without heart failure ($p < 0.018$), treated with oral antidiabetic drugs ($p < 0.001$), and not on antiplatelet or anticoagulant therapy ($p < 0.001$).

Table 6 shows the PRs of DI in AHT, estimated by multivariate Poisson regression models. One model was fitted for men and another for women. The statistically significant factors associated with DI were age, BMI, waist circumference, total cholesterol, diabetes, dyslipidemia, lipid-lowering treatment, oral antidiabetic drugs, and antiplatelet and anticoagulant treatments. The observed pattern of DI between men and women was similar, except for waist circumference, where a waist circumference $\geq$102 cm in men was associated with lower DI, whereas a waist circumference $\geq$88 cm in women was associated with higher DI (**Figure 1**). Additionally, treatment for dyslipidemia was associated with lower DI in men and not associated in women. The model sample size was 21,594 with 1,082 cases of DI in men, and 22,627 with 886 cases of DI in women. Both models fit the data well (LRT $p < 0.001$) and presented adequate classification indicators (ROC area 0.72 and 0.69, respectively).

DISCUSSION

This study aimed to shed light on the magnitude of DI in the study population, that is, individuals who were undiagnosed and untreated for arterial hypertension despite meeting the criteria that should have led to being diagnosed and adequately treated for this condition. The highest DI occurred in the population

TABLE 2 | Prevalence of diagnostic inertia in hypertensive patients in sociodemographic and clinical variables (men).

	Total		Diagnostic AHT		DI		*p*-value
	n	%	*n*	%	*n*	%	
Age groups (yrs)							
30–49	3,106	14.4%	2,935	94.5%	171	5.5%	0.409
50–59	4,932	22.8%	4,699	95.3%	233	4.7%	
60–69	7,246	33.6%	6,892	95.1%	354	4.9%	
≥70	6,310	29.2%	5,986	94.9%	324	5.1%	
BMI[a]							
Normal	1,970	9.1%	1,814	92,1%	156	7.9%	<0.001
Overweight	8,617	39.9%	8,122	94.3%	495	5.7%	
Obesity	8,387	38.8%	8,012	95.5%	375	4.5%	
Missing	2,620	12.1%	2,564	97.9%	56	2.1%	
Abdominal perimeter							
Normal	4,182	19.4%	3,867	92.5%	315	7.5%	<0.001
≥88/102 cm	6,737	31.2%	6,396	94.9%	341	5.1%	
Missing	10,675	49.4%	10,249	96.0%	426	4.0%	
Smoking status							
No	7,867	36.4%	7,488	95.2%	379	4.8%	0.020
Si	6,028	27.9%	5,686	94.3%	342	5.7%	
Quit smoking	7,699	35.7%	7,338	95.3%	361	4.7%	
PP							
<40 mmHg	2,396	11.1%	2,281	952%	115	4.8%	0.910
40–60 mmHg	7,183	33.3%	6,814	94.9%	369	5.1%	
>60 mmHg	1,791	8.3%	1,700	94.9%	91	5.1%	
Missing	10,224	47.3%	9,717	95.0%	507	5.0%	
DBP							
Normal	7,774	36.0%	7,390	95.1%	384	4.9%	0.662
≥90 mmHg	3,596	16.7%	3,405	94.7%	191	5.3%	
Missing	10,224	47.3%	9,717	95.0%	507	5.0%	
SBP							
Normal	6,622	30.7%	6,290	95.0%	332	5.0%	0.917
≥140 mmHg	4,748	22.0%	4,505	94.9%	243	5.1%	
Missing	10,224	47.3%	9,717	95.0%	507	5.0%	
HDL-Cholesterol							
Normal	5,677	26.3%	5,348	94.2%	329	5.8%	<0.001
≤45 mg/dL	5,328	24.7%	5,044	94.7%	284	5.3%	
Missing	10,589	49.0%	10,120	95.6%	469	4.4%	
Total cholesterol							
Normal	5,727	26.5%	5,465	95.4%	262	4.6%	<0.001
≥200 mg/dL	5,973	27.7%	5,579	93.4%	394	6.6%	
Missing	9,894	45.8%	9,468	95.7%	426	4.3%	

AHT, arterial hypertension; DI, diagnostic inertia; BMI, body mass index; PP, pulse pressure; DBP, diastolic blood pressure; SBP, diastolic blood pressure; HDL, high density lipoprotein.

[a]Normal < 25 kg/m^2; overweight 25.0–29.9 kg/m^2; obese ≥30.0 kg/m^2.

TABLE 3 | Prevalence of diagnostic inertia in hypertensive patients in sociodemographic and clinical variables (women).

	Total		Diagnostic AHT		DI		*p*-value
	n	%	*n*	%	*n*	%	
Age groups (yrs)							
30–49	2,449	10.8%	2,324	94.9%	125	5.1%	0.013
50–59	4,719	20.9%	4,547	96.4%	172	3.6%	
60–69	7,297	32.2%	7,013	96.1%	284	3.9%	
≥70	8,162	36.1%	7,857	96.3%	305	3.7%	
BMI[a]							
Normal	2,700	11.9%	2,550	94.4%	150	5.6%	<0.001
Overweight	7,274	32.1%	6,947	95.5%	327	4.5%	
Obesity	9,948	44.0%	9,607	96.6%	341	3.4%	
Missing	2,705	12.0%	2,637	97.5%	68	2.5%	
Abdominal perimeter							
Normal	1,431	6.3%	1,377	96.2%	54	3.8%	0.051
≥88/102	10,109	44.7%	9,678	95.7%	431	4.3%	
Missing	11,087	49.0%	10,686	96.4%	401	3.6%	
Smoking status							
No	18,192	80.4%	17,467	96.0%	725	4.0%	0.398
Si	2,950	13.0%	2,838	96.2%	112	3.8%	
Quit smoking	1,485	6.6%	1,436	96.7%	49	3.3%	
PP							
<40	2,532	11.2%	2,428	95.9%	104	4.1%	0.957
40–60	7,512	33.2%	7,220	96.1%	292	3.9%	
>60	1,913	8.5%	1,840	96.2%	73	3.8%	
Missing	10,670	47.2%	10,253	96.1%	417	3.9%	
DBP							
Normal	8,158	36.1%	7,834	96.0%	324	4.0%	0.919
≥90	3,799	16.8%	3,654	96.2%	145	3.8%	
Missing	10,670	47.2%	10,253	96.1%	417	3.9%	
SBP							
Normal	6,860	30.3%	6,584	96.0%	276	4.0%	0.803
≥140	5,097	22.5%	4,904	96.2%	193	3.8%	
Missing	10,670	47.2%	10,253	96.1%	417	3.9%	
HDL-Cholesterol							
Normal	9,164	40.5%	8,774	95.7%	390	4.3%	0.080
≤45	2,395	10.6%	2,302	96.1%	93	3.9%	
Missing	11,068	48.9%	10,665	96.4%	403	3.6%	
Total cholesterol							
Normal	4,755	21.0%	4,607	96.9%	148	3.1%	<0.001
>200	7,485	33.1%	7,123	95.2%	362	4.8%	
Missing	10,387	45.9%	10,011	96.4%	376	3.6%	

AHT, arterial hypertension; DI, diagnostic inertia; BMI, body mass index; PP, pulse pressure; DBP, diastolic blood pressure; SBP, diastolic blood pressure; HDL, high density lipoprotein.

[a]Normal < 25 kg/m^2; overweight 25.0–29.9 kg/m^2; obese ≥ 30.0 kg/m^2.

aged 30–49 years, with normal BMI, elevated cholesterol (≥ 200 mg/dl), coexistence of diabetes and dyslipidemia, and taking oral antidiabetic treatment. Gender differences in DI were detected in women with a waist circumference ≥ 88 cm. In the population of the ESCARVAL-RISK cohort with AHT criteria, the percentage was 4.5%, being higher in men than in women (5 vs. 3.9%; $p < 0.001$). Although this may seem low, the great difference from other studies is that the denominator in our study is not the entire population but only those with hypertension or meeting diagnostic criteria. Therefore, these figures are particularly relevant from the clinical viewpoint.

TABLE 4 | Prevalence of diagnostic inertia in hypertensive patients with comorbidity and treatments (men).

	Total		Diagnostic AHT		DI		*p*-value
	n	%	*n*	%	*n*	%	
Heart failure							
No	21,286	98.6%	20,213	95.0%	1,073	5.0%	0.028
Yes	306	1.4%	299	97.7%	7	2.3%	
Proteinuria							
No	21,449	99.3%	20,372	95.0%	1,077	5.0%	0.387
Yes	145	0.7%	140	96.6%	5	3.4%	
PAD							
No	21,084	97.7%	20,015	94.9%	1,069	5.1%	0.001
Yes	506	2.3%	497	98.2%	9	1.8%	
Atrial fibrillation							
No	21,413	99.2%	20,338	95.0%	1,075	5.0%	0.173
Yes	179	0.8%	174	97.2%	5	2.8%	
Diabetes mellitus							
No	14,537	67.3%	14,100	97.0%	437	3.0%	<0.001
Yes	7,057	32.7%	6,412	90.9%	645	9.1%	
Dyslipidemia							
No	10,470	48.5%	9,984	95.4%	486	4.6%	0.016
Yes	11,124	51.5%	10,528	94.6%	596	5.4%	
CKD							
No	21,375	99.0%	20,300	95.0%	1,075	5.0%	0.067
Yes	217	1.0%	212	97.7%	5	2.3%	
Retinopathy							
No	21,484	99.5%	20,408	95.0%	1,076	5.0%	0.831
Yes	110	0.5%	104	94.5%	6	5.5%	
Insulin							
No	21,117	97.8%	20,060	95.0%	1,057	5.0%	0.816
Yes	477	2.2%	452	94.8%	25	5.2%	
Oral antidiabetics							
No	18,519	85.8%	17,686	95.5%	833	4.5%	<0.001
Yes	3,075	14.2%	2,826	91.9%	249	8.1%	
Lipid-lowering							
No	16,326	75.6%	15,445	94.6%	881	5.4%	<0.001
Yes	5,268	24.4%	5,067	96.2%	201	3.8%	
Antiplatelet agents							
No	17,952	83.1%	16,950	94.4%	1,002	5.6%	<0.001
Yes	3,642	16.9%	3,562	97.8%	80	2.2%	
Anticoagulants							
No	18,648	86.4%	17,646	94.6%	1,002	5.4%	<0.001
Yes	2,946	13.6%	2,866	97.3%	80	2.7%	

AHT, arterial hypertension; DI, diagnostic inertia; PAD, peripheral artery disease; CKD, chronic kidney disease.

TABLE 5 | Prevalence of diagnostic inertia in hypertensive patients with comorbidity and treatments (women).

	Total		Diagnostic AHT		DI		*p*-value
	n	%	*n*	%	*n*	%	
Heart failure							
No	22,211	98.2%	21,333	96.0%	878	4.0%	0.018
Yes	415	1.8%	408	98.3%	7	1.7%	
Proteinuria							
No	22,520	99.5%	21,639	96.1%	881	3.9%	0.578
Yes	105	0.5%	102	97.1%	3	2.9%	
PAD							
No	22,478	99.3%	21,596	96.1%	882	3.9%	0.235
Yes	148	0.7%	145	98.0%	3	2.0%	
Atrial fibrillation							
No	22,496	99.4%	21,612	96.1%	884	3.9%	0.064
Yes	130	0.6%	129	99.2%	1	0.8%	
Diabetes mellitus							
No	16,511	73.0%	16,012	97.0%	499	3.0%	<0.001
Yes	6,116	27.0%	5,729	93.7%	387	6.3%	
Dyslipidemia							
No	10,313	45.6%	9,995	96.9%	318	3.1%	<0.001
Yes	12,314	54.4%	11,746	95.4%	568	4.6%	
CKD							
No	22,486	99.4%	21,603	96.1%	883	3.9%	0.052
Yes	139	0.6%	138	99.3%	1	0.7%	
Retinopathy							
No	22,522	99.5%	21,638	96.1%	884	3.9%	0.287
Yes	105	0.5%	103	98.1%	2	1.9%	
Insulin							
No	22,042	97.4%	21,178	96.1%	864	3.9%	0.845
Yes	585	2.6%	563	96.2%	22	3.8%	
Oral antidiabetics							
No	19,995	88.4%	19,267	96.4%	728	3.6%	<0.001
Yes	2,632	11.6%	2,474	94.0%	158	6.0%	
Lipid-lowering							
No	17,154	75.8%	16,459	95.9%	695	4.1%	0.062
Yes	5,473	24.2%	5,282	96.5%	191	3.5%	
Antiplatelet agents							
No	17,053	75.4%	16,261	95.4%	792	4.6%	<0.001
Yes	5,574	24.6%	5,480	98.3%	94	1.7%	
Anticoagulants							
No	20,633	91.2%	19,791	95.9%	842	4.1%	<0.001
Yes	1,994	8.8%	1,950	97.8%	44	2.2%	

AHT, arterial hypertension; DI, diagnostic inertia; PAD, peripheral artery disease; CKD, chronic kidney disease.

The increase in the prevalence of chronic diseases, including AHT, is a worldwide problem with multifactorial and complex causes (3–5). Despite the increasing knowledge in the field of AHT, its high prevalence, the low degree of control, the associated morbidity and mortality, the associated costs, and the rates of non-compliance with both lifestyle measures and pharmacological treatment continue to be alarming (2–6, 18). In a PHC setting and a hypertensive population, 4.5% of the adults who met the diagnostic criteria for AHT had no recorded diagnosis or treatment prescribed. The patients who presented more DI were younger, had a normal weight, and took oral antidiabetic drugs (diabetes confers a higher CV risk), a pattern that differed slightly between men and women. In addition, many clinical variables not recorded in the EHR were detected. In a previous study of the same cohort but a dyslipidemic population, 18% of adults met the diagnostic criteria for dyslipidemia and

TABLE 6 | Multivariable Poisson regression, prevalence ratios (PRs) for diagnostic inertia, by sex.

		Men			Women		
		PR	**(95% CI)**	***p* value**	**PR**	**(95% CI)**	***p* value**
Age groups (yrs)	30–49	1			1		
	50–59	0.72	(0.59–0.87)	0.001	0.64	(0.51–0.80)	<0.001
	60–69	0.73	(0.61–0.87)	<0.001	0.66	(0.53–0.81)	<0.001
	≥70	0.79	(0.66–0.95)	0.013	0.64	(0.52–0.79)	<0.001
Body mass index[a]	Normal	1			1		
	Overweight	0.71	(0.60–0.84)	<0.001	0.72	(0.59–0.88)	0.001
	Obese	0.54	(0.45–0.66)	<0.001	0.52	(0.42–0.63)	<0.001
	Missing	0.35	(0.26–0.48)	<0.001	0.45	(0.34–0.60)	<0.001
Waist	<88/102	1			1		
circumference	≥88/102	0.83	(0.7–0.98)	0.025	1.43	(1.06–1.92)	0.018
	Missing	0.72	(0.62–0.83)	<0.001	1.31	(0.98–1.76)	0.066
Total cholesterol[b]	Normal	1			1		
	Elevated	1.54	(1.32–1.79)	<0.001	1.63	(1.36–1.97)	<0.001
	Missing	1.09	(0.94–1.26)	0.252	1.35	(1.12–1.62)	0.001
Comorbidities	Diabetes	3.17	(2.77–3.62)	<0.001	2.24	(1.91–2.61)	<0.001
	Dislipemia	1.20	(1.06–1.36)	0.003	1.47	(1.29–1.68)	<0.001
Treatments	Antiplatelets	0.45	(0.36–0.56)	<0.001	0.38	(0.30–0.47)	<0.001
	Oral antidiabetics	1.24	(1.06–1.46)	0.008	1.25	(1.02–1.52)	0.028
	Antithrombotics	0.51	(0.40–0.64)	<0.001	0.53	(0.39–0.72)	<0.001
	TTO DLP	0.74	(0.62–0.88)	0.001			
N		21,594			22,627		
N with diagnostic inertia		1,082			886		
LRT (*p* value)	656	(<0.001)		384	(<0,001)		
AIC		8,020			7,161		
Area under the ROC (95% CI)	0.727	(0.712–0.742)		0.688	(0.672–0.705)		

AIC, akaike information criterion; CI, confidence interval; LRT, likelihood ratio test.
[a]*Normal <05 kg/m^2; overweight 25.0–29.9 kg/m^2; obese ≥ 30.0 kg/m^2.*
[b]*Normal ≤ 200 mg/dL, elevated > 200 mg/dL.*

had no recorded diagnosis or treatment prescribed (DI), with DI greater in women, young age, normal weight, no smoking habit, and those with alterations in SBP, HDL cholesterol, total cholesterol, LDL cholesterol, or triglycerides, or missing values in their EHR (28). A similar pattern exists between both sexes, and in DI in both hypertension and dyslipidemia, there is a lack of assessment of subclinical disease (comorbidities). This may promote clinical and therapeutic inertia and determine a different course in the continuum of cardiovascular disease.

A diagnosis of AHT and older age (>70 years) had a greater association with DI in men than in women, in contrast to the results observed by Meador et al. (29) in the USA, where younger, white, healthy-weight women were less likely to be diagnosed. In a previous study analyzing only patients with BP recordings ≥140/90 mmHg on EHR and no decision made (i.e., DI), the association of inertia was higher in men and older age (30).

Gil-Guillén et al. (31) observed a higher level of inertia in women with hypertension, and an association between inertia and not smoking, which in our study was only observed in men ($p < 0.02$). Ji et al. (32) analyzed sex differences in hypertension and observed that, although the prevalence was higher in men than women in the younger and middle ages of life, this reversed after the seventh decade, when the rates in women exceeded those in men. These higher BP levels in older women were associated with a higher risk of stroke than in men of the same age group.

Notably, the increased risk of stroke with higher BP levels seemed to be almost twice as high in women as in men (9). The DI detected could be a reason for an increased risk of stroke in our population. All these findings indicate the need to continue exploring possible biases or other factors, not specifically clinical, in the "non-diagnosis" of AHT (33).

Precedent exists for different strategies to improve intervention at the health care system level to reduce inertia (34). The EHR quality improvement initiative of Kaiser Permanente of Northern California, reaching more than 650,000 patients within its hypertension registry program (35), was focused on creating a registry of reporting AHT control rates (every 1–3 months) by each affiliated medical center and generating clinical practice guideline recommendations on a case-by-case basis. The effort led to improving the BP control rate in their hypertensive population to 80%, compared with a national average of 64% (36). If this were applied to our system, we are convinced of the potential improvement of inertia, not only therapeutic but also diagnostic, given the high accessibility of healthcare in our system that makes it possible to screen the population (37).

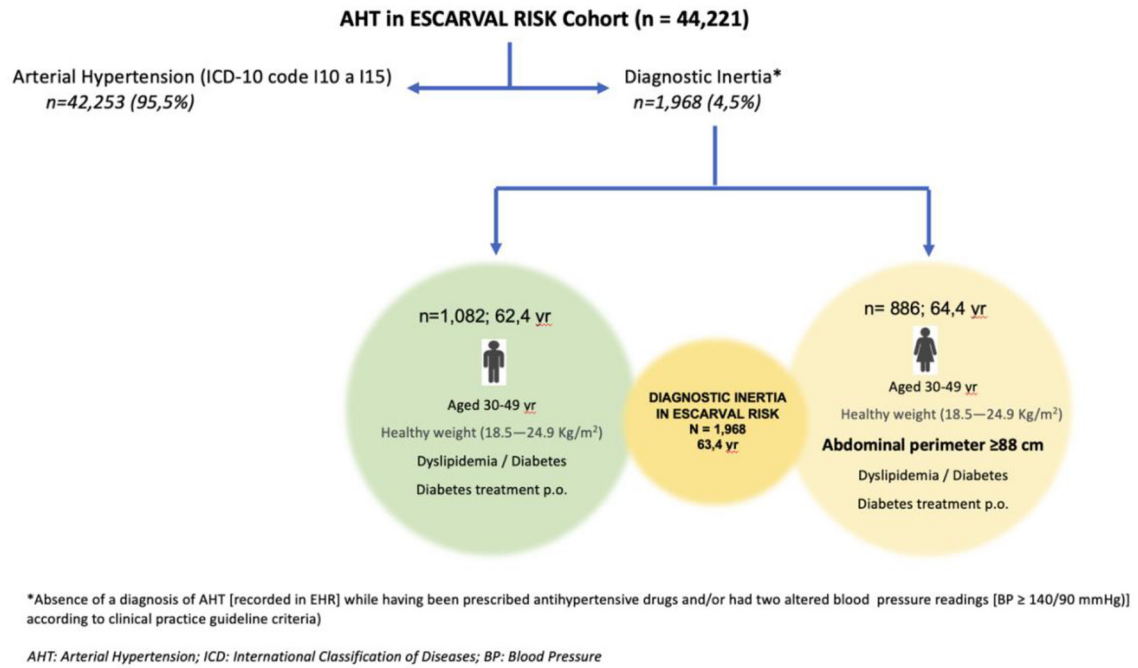


FIGURE 1 | Associated factors with diagnostic inertia in hypertensive patients according to gender in the ESCARVAL RISK Cohort. * Absence of a diagnosis of AHT (recorded in EHR) while having been prescribed antihypertensive drugs and/or had two altered blood pressure readings (BP ≥ 140/90 mmHg) according to clinical practice guideline criteria. AHT, arterial hypertension; ICD, International Classification of Disease; BP, blood pressure.

In this study, we have analyzed a hypertensive population according to sex/gender, observing many possibilities for improvement in diagnostic confirmation. We have a great capacity for improvement in DI, as long as the possible solutions contemplate three domains: health professionals, patients, and governmental agencies; promoting active health policies; and improving the tools with which the family physician currently works.

Strengths and Limitations

The great strength of this study is its information source, which corresponds to a single electronic health registry that integrates all the information on the population attending primary care centers. In addition, it exhaustively addresses the important problem of DI in AHT and its gender differences, with a large sample size, which minimizes random error when drawing conclusions from the results obtained. The fact that the information was obtained from all the PHC centers, and that it quantifies the problem of DI in all the professionals working in these centers, offers greater validity to our results and means that they can be generalized to other geographical areas with similar healthcare systems. Therefore, it would be interesting to carry out similar studies in other countries with different health policies through projects that could integrate many patients and health professionals.

The main theoretical limitation of this study is that, although it works on the basis of an epidemiological cohort study, its strict design is cross-sectional. Establishing a temporal sequence between the factors and the dependent variable (inertia) is not realizable, although the status of undiagnosed hypertensive patients can be assessed and their needs determined, which are key elements in the fight against the lack of awareness of this problem and provide a basis for prioritizing better health planning. We are aware that the main potential bias that could have threatened the validity of this study is in selection, but we have tried to minimize this. Furthermore, the virtue of the study is that it translates routine clinical practice and is based on the fact that these are all patients attending PHC centers. We must also ask ourselves about the precise quality of the data obtained from the EHR and entered by the health professionals. To minimize this potential error, all physicians have previously been given the opportunity to participate in courses on cardiovascular risk (online, voluntary, and free), providing training on cardiovascular diseases, their risk factors, and their control objectives (38). Additionally, the service provider (*Consellería de Sanitat de la Generalitat Valenciana, Valencian Community, Spain*) has made efforts to ensure that all primary care offices had validated and calibrated BP measurement devices.

Clinical Implications

Physicians attending PHC consultations should be attentive to BP values ≥140/90 mmHg, verify them, confirm them, and record them in the EHR, in addition to properly coding patients who are already on antihypertensive treatment to reduce the DI in AHT. Although it should be all patients,

special attention should be paid to young women who are not properly identified, thus avoiding possible health inequalities derived from DI. In our study, the overall DI was higher in men than in women; this difference may be due to the type of population more likely to seek consultation in PHC, corresponding to women and older patients. The information provided by this study could be valuable for improving clinical practice in the PHC setting and could favor future research to explore the reasons for the conservative attitude of PHC physicians regarding this type of patient. Future studies should address the causes of the gender difference in the prevalence of DI in AHT and whether it affects other entities that increase CV morbidity and mortality. Therefore, the strategy should be comprehensive and close any knowledge gap, optimizing the diagnosis and control of AHT at a global level.

CONCLUSIONS

When comparing the population diagnosed with AHT with the population not diagnosed but presenting diagnostic criteria, the highest DI (in both men and women) was in the population aged 30–49 years, with normal BMI, high cholesterol, and coexistence of diabetes and dyslipidemia, and taking oral antidiabetic treatment. The lowest DI was in the population over 50 years of age, with overweight or obesity by BMI, normal cholesterol, no diabetes or dyslipidemia, and taking antiplatelet, anticoagulant, or lipid- lowering therapy. The only gender difference in this study was found in waist circumference. In women, a greater DI was found from 88 cm, and in men, the higher the BMI, the lower the DI.

Although AHT is simple to diagnose and relatively easy to treat with currently low-cost drugs (plus healthy lifestyle recommendations), important gaps exist in the diagnosis that can have a negative impact on prognosis and evolution, which should be identified and addressed.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: data on all patients registered in Primary Care of the Health System of the Valencian Community in Spain. The data were anonymised after a rigorous validation process, and are subject to personal data protection regulations. Requests to access these datasets should be directed to Conselleria de Sanitat Universal i Salut Pública, psalud_val@gva.es.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Valencia Hospital Clinic, Valencia, Spain. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, writing—review and editing, and funding acquisition: VP-C, CC-M, AL-P, JQ, VG-G, DO-B, JA-S, JN-P, and JM-M. Writing—original draft preparation and supervision: VP-C, CC-M, VG-G, and JM-M. Project administration: JM-M. All authors have read and agreed to the published version of the manuscript.

FUNDING

The authors acknowledge support from the Health Research Projects—Strategic Action in Health (Reference: PI18/01937) of the Spanish *Fondo de Investigación Sanitaria—Instituto de Salud Carlos III*, co-funded by the European Regional Development Fund/European Social Fund: A way to make Europe/Investing in Your Future. This funding source had no role in the design of the study, its execution and analyses, the interpretation of the data, or the decision to submit results.

REFERENCES

1. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA.* (2017) 317:165–82. doi: 10.1001/jama.2016.19043
2. Cinza-Sanjurjo S, Micó-Pérez RM, Velilla-Zancada S, Prieto-Díaz MA, Rodríguez-Roca GC, Barquilla García A, et al. En representación de los investigadores del estudio IBERICAN. Factores asociados al riesgo cardiovascular y enfermedad cardiovascular y renal en el estudio IBERICAN (Identificación de la poBlación Española de RIesgo CArdiovascular y reNal): Resultados Definitivos. *Semergen.* (2020) 46:368–78. doi: 10.1016/j.semerg.2020.06.027
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. Authors/Task Force Members. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European society of hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European society of hypertension. *J Hypertens.* (2018) 36:1953–2041. doi: 10.1093/eurheartj/ehy339
4. 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: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* (2018) 71:e127–248. doi: 10.1016/j.jacc.2017.11.006
5. Pallarés Carratalá V, Divisón Garrote JA, Prieto Díaz MA, García Matarín L, Seoane Vicente MC, Molina Escribano F, et al. Posicionamiento para el manejo de la hipertensión arterial en atención primaria a partir del análisis crítico de las guías Americana (2017) y Europea (2018). sociedad Española de médicos de atención primaria (semergen). *Semergen.* (2019) 45:251–72. doi: 10.1016/j.semerg.2019.02.003
6. Cinza Sanjurjo S, Prieto Díaz MÁ, Llisterri Caro JL, Pallarés Carratalá V, Barquilla García A, Rodríguez Padial L, et al. En representación de los investigadores del estudio IBERICAN. Características basales y manejo clínico de los primeros 3000 pacientes incluidos en el estudio IBERICAN [Identificación de la población española de riesgo cardiovascular y renal]. *Semergen.* (2017) 43:493–500. doi: 10.1016/j.semerg.2016.07.006

7. Leening MJ, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. *BMJ.* (2014) 349:g5992. doi: 10.1136/bmj.g5992
8. Connelly PJ, Azizi Z, Alipour P, Delles C, Pilote L, Raparelli V. The importance of gender to understand sex differences in cardiovascular disease. *Can J Cardiol.* (2021) 37:699–710. doi: 10.1016/j.cjca.2021.02.005
9. Vogel B, Acevedo M, Appelman Y, Merz CNB, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet.* (2021) 397:2385–438. doi: 10.1016/S0140-6736(21)00684-X
10. Madsen TE, Howard G, Kleindorfer DO, Furie KL, Oparil S, Manson JE, et al. Sex differences in hypertension and stroke risk in the REGARDS study: a longitudinal cohort study. *Hypertension.* (2019) 74:749–55. doi: 10.1161/HYPERTENSIONAHA.119.12729
11. SPRINT Research Group, Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* (2015) 373:2103–16. doi: 10.1056/NEJMoa1511939
12. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 75:2602–18. doi: 10.1016/j.jacc.2020.03.060
13. Foy CG, Lovato LC, Vitolins MZ, Bates JT, Campbell R, Cushman WC, et al. Gender, blood pressure, and cardiovascular and renal outcomes in adults with hypertension from the systolic blood pressure intervention trial. *J Hypertens.* (2018) 36:904–15. doi: 10.1097/HJH.0000000000001619
14. Ochoa-Jimenez R, Viquez-Beita K, Daluwatte C, Zusterzeel R. Sex differences of patients with systemic hypertension (from the analysis of the systolic blood pressure intervention trial [SPRINT]). *Am J Cardiol.* (2018) 122:985–93. doi: 10.1016/j.amjcard.2018.05.046
15. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med.* (2008) 359:2417–28. doi: 10.1056/NEJMoa 0806182
16. Zanchetti A, Julius S, Kjeldsen S, McInnes GT, Hua T, Weber M, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. *J Hypertens.* (2006) 24:2163–68. doi: 10.1097/01.hjh.0000249692.96488.46
17. Yusuf S, Lonn E, Pais P, Bosch J, López-Jaramillo P, Zhu J, et al. HOPE-3 investigators. blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med.* (2016) 374:2032–43. doi: 10.1056/NEJMoa1600177
18. 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
19. Pallarés-Carratalá V, Bonig-Trigueros I, Palazón-Bru A, Esteban-Giner MJ, Gil-Guillén VF, Giner-Galvañ V. Clinical inertia in hypertension: a new holistic and practical concept within the cardiovascular *continuum* and clinical care process. *Blood Press.* (2019) 28:217–28. doi: 10.1080/08037051.2019.1608134
20. Tadic M, Cuspidi C, Grassi G, Ivanovic B. Gender-specific therapeutic approach in arterial hypertension—challenges ahead. *Pharmacol Res.* (2019) 141:181–88. doi: 10.1016/j.phrs.2018.12.021
21. Gerdts E, Regitz-Zagrosek V. Sex differences in cardiometabolic disorders. *Nat Med.* (2019) 25:1657–66. doi: 10.1038/s41591-019-0643-8
22. Kalibala J, Pechère-Bertschi A, Desmeules J. Gender differences in cardiovascular pharmacotherapy- the example of hypertension: a mini review. *Front Pharmacol.* (2020) 11:564. doi: 10.3389/fphar.2020.00564
23. Instituto Nacional de Estadística (INE). *Spanish Statistical Office*. (2022). Available online at: https://www.ine.es/jaxiT3/Datos.htm?t=2915 (accessed February 5, 2022).
24. Carratala-Munuera C, Lopez-Pineda A, Orozco-Beltran D, Quesada JA, Alfonso-Sanchez JL, Pallarés-Carratalá V, et al. Gender inequalities in diagnostic inertia around the three most prevalent cardiovascular risk studies: protocol for a population-based cohort study. *Int J Environ Res Public Health.* (2021) 18:4054. doi: 10.3390/ijerph18084054
25. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al.; ESH-ESC task force on the management of arterial hypertension. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC task force on the management of arterial hypertension. *J Hypertens.* (2007) 25:1751–62. doi: 10.1097/HJH.0b013e3282f0580f
26. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. European society of hypertension reappraisal of European guidelines on hypertension management: a European society of hypertension task force document. *J Hypertens.* (2009) 27:2121–58. doi: 10.1097/HJH.0b013e328333146d
27. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* (2004) 159:702–6. doi: 10.1093/aje/kwh090
28. Soriano-Maldonado C, Lopez-Pineda A, Orozco-Beltran D, Quesada JA, Alfonso-Sanchez JL, Pallarés-Carratalá V, et al. Gender differences in the diagnosis of dyslipidemia: ESCARVAL-GENERO. *Int J Environ Res Public Health.* (2021) 18:12419. doi: 10.3390/ijerph182312419
29. Meador M, Lewis JH, Bay RC, Wall HK, Jackson C. Who are the undiagnosed? Disparities in hypertension diagnoses in vulnerable populations. *Fam Community Health.* (2020) 43:35–45. doi: 10.1097/FCH.0000000000000242
30. Pallares-Carratalá V, Bonig-Trigueros I, Palazón-Bru A, Lorenzo-Piqueres A, Valls-Roca F, Orozco-Beltrán D, et al. Steering committee ESCARVAL study. Analysing the concept of diagnostic inertia in hypertension: a cross-sectional study. *Int J Clin Pract.* (2016) 70:619–24. doi: 10.1111/ijcp.12825
31. Gil-Guillén V, Orozco-Beltrán D, Pérez RP, Alfonso JL, Redón J, Pertusa-Martínez S, et al. Clinical inertia in diagnosis and treatment of hypertension in primary care: quantification and associated factors. *Blood Press.* (2010) 19:3–10. doi: 10.3109/08037050903350762
32. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex differences in blood pressure trajectories over the life course. *JAMA Cardiol.* (2020) 5:19–26. doi: 10.1001/jamacardio.2019.5306
33. Pallarés-Carratalá V, Pascual Pérez R. Non-compliance and therapeutic inertia: two unanswered questions in clinical practice. *Curr Med Res Opin.* (2014) 30:839–40. doi: 10.1185/03007995.2013.879442
34. Josiah Willock R, Miller JB, Mohyi M, Abuzaanona A, Muminovic M, Levy PD. Therapeutic inertia and treatment intensification. *Curr Hypertens Rep.* (2018) 20:4. doi: 10.1007/s11906-018-0802-1
35. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. *JAMA.* (2013) 310:699–705. doi: 10.1001/jama.2013.108769
36. Sim JJ, Handler J, Jacobsen SJ, Kanter MH. Systemic implementation strategies to improve hypertension: the Kaiser Permanente Southern California experience. *Can J Cardiol.* (2014) 30:544–52. doi: 10.1016/j.cjca.2014.01.003
37. Ministerio de Sanidad, Servicios Sociales e Igualdad. *Sistema Nacional de Salud. España 2012.* Madrid (2012). Available online at: http://www.msssi.gob.es (accessed February 5, 2022).
38. Gil-Guillén V, Hermida E, Pita-Fernandez S, Palazon-Bru A, Durazo-Arvizu R, Pallares-Carratala V, et al. A cardiovascular educational intervention for primary care professionals in Spain: positive impact in a quasi-experimental study. *Br J Gen Pract.* (2015) 65:e32–40. doi: 10.3399/bjgp15X683137

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.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 26 September 2022
DOI 10.3389/fcvm.2022.928948

OPEN ACCESS

EDITED BY
Guido Iaccarino,
University of Naples Federico II, Italy

REVIEWED BY
Gaetano Santulli,
Albert Einstein College of Medicine,
United States
Hao Tian,
Southern Methodist University,
United States

*CORRESPONDENCE
Yushan Wang
wangyus8877@163.com
Yi Zhou
zhouyi@mail.sysu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 26 April 2022
ACCEPTED 29 August 2022
PUBLISHED 26 September 2022

CITATION
Ji W, Zhang Y, Cheng Y, Wang Y and Zhou Y (2022) Development and validation of prediction models for hypertension risks: A cross-sectional study based on 4,287,407 participants. *Front. Cardiovasc. Med.* 9:928948. doi: 10.3389/fcvm.2022.928948

Development and validation of prediction models for hypertension risks: A cross-sectional study based on 4,287,407 participants

Weidong Ji[1†], Yushan Zhang[2†], Yinlin Cheng[1], Yushan Wang[3*] and Yi Zhou[1*]

[1]Department of Medical Information, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China, [2]Department of Maternal and Child Health, School of Public Health, Sun Yat-sen University, Guangzhou, China, [3]Center of Health Management, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, China

Objective: To develop an optimal screening model to identify the individuals with a high risk of hypertension in China by comparing tree-based machine learning models, such as classification and regression tree, random forest, adaboost with a decision tree, extreme gradient boosting decision tree, and other machine learning models like an artificial neural network, naive Bayes, and traditional logistic regression models.

Methods: A total of 4,287,407 adults participating in the national physical examination were included in the study. Features were selected using the least absolute shrinkage and selection operator regression. The Borderline synthetic minority over-sampling technique was used for data balance. Non-laboratory and semi-laboratory analyses were carried out in combination with the selected features. The tree-based machine learning models, other machine learning models, and traditional logistic regression models were constructed to identify individuals with hypertension, respectively. Top features selected using the best algorithm and the corresponding variable importance score were visualized.

Results: A total of 24 variables were finally included for analyses after the least absolute shrinkage and selection operator regression model. The sample size of hypertensive patients in the training set was expanded from 689,025 to 2,312,160 using the borderline synthetic minority over-sampling technique algorithm. The extreme gradient boosting decision tree algorithm showed the best results (area under the receiver operating characteristic curve of non-laboratory: 0.893 and area under the receiver operating characteristic curve of semi-laboratory: 0.894). This study found that age, systolic blood pressure, waist circumference, diastolic blood pressure, albumin, drinking frequency, electrocardiogram, ethnicity (uyghur, hui, and other), body mass index, sex (female), exercise frequency, diabetes mellitus, and total bilirubin are important factors reflecting hypertension. Besides, some algorithms included in the semi-laboratory analyses showed less improvement in the predictive performance compared to the non-laboratory analyses.

Conclusion: Using multiple methods, a more significant prediction model can be built, which discovers risk factors and provides new insights into the prediction and prevention of hypertension.

KEYWORDS

hypertension, machine learning, prediction model, classifier, LASSO

Introduction

Nowadays, hypertension has affected 1.13 billion people worldwide (1). It exacerbates the burden of stroke, ischemic heart disease, other vascular diseases, and kidney disease (2). The number of people with hypertension worldwide exceeded 1 billion in 2019, which was doubled since 1990 (3). In China, the proportion of adults with hypertension has increased substantially over the past 40 years, and people's awareness regarding hypertension, the diagnosis, treatment, and control rates of hypertension are low, especially in the western region (4, 5). Therefore, it is of vital importance to strengthen the pre-screening of hypertension and carry out preventive intervention and treatment for high-risk and potential groups (6).

The prediction model has been proven to be an effective and economical tool to identify individuals with a high risk of hypertension (7). However, many studies have confirmed that the risk prediction models developed for one population cannot be effectively applied to other populations (8–11). Although some hypertension risk prediction models have been established in China in the past 10 years (12–16), there were some disadvantages, such as small sample size and lack of important features (ethnicity and poor prediction effect), which limits the generalizability of models. Therefore, it is urgent to establish a hypertension prediction model with a good prediction effect and strong generalizability in China.

Machine learning (ML) is a collection of techniques that automatically learn features from data and do not require the data structure, and mainly includes classification and regression tree (CART), random forest (RF), extreme gradient boosting decision tree (XGBoost), naive Bayes (NB), and artificial neural network (ANN). ML shows an excellent performance in disease prediction in recent years (17, 18). The application of ML algorithms to predict hypertension can provide some new ideas for understanding the pathophysiological mechanisms underlying hypertension and for exploring therapeutic targets. However, some studies showed that the incremental predictive performance beyond standard methods might be limited (19–21), while others showed that there were no advantages of ML over classical statistical models, such as logistic regression (LR) (22, 23). In the aspect of hypertension prediction, most studies only test the predictive performance of ML models or LR models alone, without conducting comparative studies (13, 16, 24–26). Therefore, it is unclear whether the ML method is better than traditional classical statistical models in the prediction of potential hypertension populations.

Currently, no studies investigated the predictive ability of the semi-laboratory analyses and the non-laboratory analyses. Therefore, in this study, we constructed and compared the tree-based ML models, such as CART, RF, adaboost with decision tree (ADABoost), XGBoost, other ML models, such as NB and ANN, and traditional LR models based on non-laboratory and semi-laboratory analyses, respectively, aiming to develop optimal hypertension screening model for large populations. As we know, the hypertension screening model presented in this study is the first to be established by comparing various algorithms systematically and comprehensively with multi-ethnic and large samples.

Methods

Study population

The national physical examination (NPE) is a free physical examination provided by the Chinese government for all Xinjiang people. Epidemiologists and medical staff at Xinjiang Uygur Autonomous Region Center for Disease Control and Prevention have designed a standard physical examination form, which mainly consisted of a questionnaire survey, routine examinations, and laboratory tests in three parts. All examinations were conducted by a professional medical team with medical qualifications and fieldwork experience. All participants were required to take their unique identity document (ID) card, which was used as the only proof of identity.

All data were aggregated to the Health Management Hospital of Xinjiang Medical University. For routine examination, the items included standing height, weight, waist circumference (WC), heart rate (HR), blood pressure, and abdominal ultrasound. In addition, three 10 ml samples of non-fasting blood samples were collected into vacuum tubes, and then the samples were kept in a portable insulated cold box with ice packs and taken to a local research laboratory for immediate processing. Blood test indicators contained blood sugar and blood biochemistry.

The data in this study were collected from the NPE project, and a total of 4,336,239 people who had signed informed consent forms were included. The excluded criteria were (i) age < 18 years and (ii) the data missing rate > 20%. A total of 4,287,407 participants from 14 regions in Xinjiang Province were finally included in this study for further analysis after strict screening procedures. Detailed population distributions were as follows: Hotan (662,643), Ili (614,468), Aksu (590,630), Changji (339,019), Tacheng (266,494), Bayingolin Mongolia (206,897), Altay (184,948), Turpan (154,105), Bortala Mongolia (86,864), Hami (83,560), Kizilsu Kirgiz (82,078), Karamay (271), Kashgar (622,610), and Urumqi (392,820).

Furthermore, nearly 200 variables irrelevant to this study were deleted, such as names, home addresses, and contact numbers, and then the missing and extreme values of the remaining variables were processed. Continuous variables were imputed by means, while categorical variables were imputed by mode. Figure 1 shows the detailed analysis process. This study was conducted in accordance with the principles outlined in the "Helsinki Declaration" and was approved by the Ethics Committee and Institutional Review Committee of the Xinjiang Uygur Autonomous Region Center for Disease Control and Prevention.

Definition of hypertension

Hypertension patients met the following criteria: systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg in the absence of antihypertensive drugs, or someone with a hypertension history, though the blood pressure did not reach the above level when undertaking antihypertensive drugs.

Predictors considered

With the characteristics of large data size, multiple variables, and the existence of many outliers and gaps, pre-processing of the data is important. In total 30 variables from the three components were used to construct the predictive model and evaluate the potential risk factors of hypertension. Variables are listed in Table 1.

Statistical analysis

Continuous variables were expressed as median (IQR: inter-quartile range), and categorical variables were expressed as counts (percentage). Variables were compared between hypertension and non-hypertension groups. The *t*-test or Mann–Whitney test was used for continuous variables, while for categorical variables, the chi-square test or Fisher's exact test was used. Statistical significance was inferred at a two-tailed *P*-value<0.05.

Grouping and feature selection

The population was randomly divided into the training set (3,001,185), the validation set (857,482), and the test set (428,740), with a ratio of 7: 2: 1. Then, the least absolute shrinkage and selection operator (LASSO) regression were used to select the variables in the training set (27). LASSO regression was characterized by variable selection and regularization while fitting a generalized linear model, which was suitable for continuous, binary, and multivariate discrete variables.

Data imbalance processing

In this study, the number of non-hypertension participants was larger than the hypertension participants, which indicates that the sample size was imbalanced, while minority classes were harder to predict using ML methods (28, 29). An over-sampling technique, that is, borderline synthetic minority over-sampling technique (Borderline-SMOTE), was used to deal with the negative influence due to the imbalanced classification problem.

The synthetic minority over-sampling technique (SMOTE) was introduced by Chawla et al. (30), as a way to deal with the minority classes in a dataset. The fundamental idea of this algorithm is to analyze and simulate, and add the new sample simulated artificially into the original dataset to balance the classes in the original data. But there were two obvious shortcomings of SMOTE: (1) prone to sample overlap and (2) the attribute characteristics and the distribution characteristics of adjacent samples are not considered. Therefore, many adaptive sampling methods are developed to solve the above limitations, among which the Borderline-SMOTE algorithm is the most representative one (31).

Borderline-SMOTE is an advanced over-sampling algorithm based on SMOTE, which uses minority class samples on the boundary to synthesize new samples, and therefore improves the class distribution of the samples. In Borderline-SMOTE sampling, the minority class samples are divided into three categories: safe, danger, and noise. Safe means more than half of the surrounding samples are minority class samples. Danger means that more than half of the surrounding samples are majority class samples, which are regarded as boundary samples. Besides, noise refers to the majority class of samples around the sample, which is regarded as noise. Finally, only the minority class samples that behave as danger are over-sampled.

Variable coding

The preprocessing.LabelEncoder algorithm of sklearn.preprocessing library in python software was used to digitize the labels, and preprocessing.OrdinalEncoder

FIGURE 1
Flow chart. LASSO, least absolute shrinkage and selection operator; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic curve.

algorithm was used to digitize the orderly categorical variables of characteristics. The preprocessing.OneHotEncoder algorithm was used to convert the nominal variables to the dummy variables.

Prediction models

This study established three kinds of hypertension predictive models, including tree-based ML models (CART, RF, ADABoost, and XGBoost), other ML models (ANN and NB), and traditional LR models. On the basis of the above models, we analyzed non-laboratory and semi-laboratory features separately depending on whether blood test data were included or not.

The CART algorithm is based on tree arrangement and describes the classification process depending on input features. There were some advantages of CART, such as fast computing, high accuracy, no requirement of domain knowledge or parametric assumptions, and suitable for high-dimensional data, but it has some shortcomings, such as high variance and over-fitting phenomenon, which limits its practicality as an independent predictive model. RF is an algorithm that combines bagged ensemble learning theory with random subspace methods (32), aiming at constructing many independent evaluators and then selecting the results supported by most evaluators or choosing the mean values. ADABoost and XGBoost algorithms (33) aim at combining the power of the weak evaluator to predict the hard-to-evaluate samples repeatedly, in order to construct a strong evaluator.

The ANN is a computing system based on human brain neurons (34). ANN can deal with the interactions between complex and non-linear variables. ANN consists of a multi-hidden layer neural network and a single hidden layer neural network. Each layer contains some neurons connected by directed arcs with variable weights. In this study, the neural network contains three layers: the input layer accepts all risk factors, the hidden layer processes the information, and the

TABLE 1 Information description of included variables.

Data sources	Variable	Variable type
Questionnaire	Age	Continuous variable
	Sex	Categorical variable ("male" or "female")
	Ethnicity	Categorical variable ("han," "uyghur," "kazakh," "hui," "other ethnic groups")
	EF	Categorical variable ("not exercising," "occasionally," "more than once a week," "daily")
	SS	Categorical variable ("never smoked," "smoking," "quit smoking")
	DF	Categorical variable ("never," "occasionall," "often," "every day")
	DM	Categorical variable (yes or no)
	PH	Categorical variable (yes or no)
Routine examination	Hight	Continuous variable
	Weight	Continuous variable
	BMI	Continuous variable
	SBP	Continuous variable
	DBP	Continuous variable
	WC	Continuous variable
	ECG	Categorical variable (normal or abnormal)
	HR	Categorical variable (normal or abnormal)
Laboratory test	HGB	Continuous variable
	WBC	Continuous variable
	PLT	Continuous variable
	FBG	Continuous variable
	SGPT	Continuous variable
	SGOT	Continuous variable
	ALB	Continuous variable
	TBIL	Continuous variable
	SCR	Continuous variable
	BUN	Continuous variable
	TC	Continuous variable
	TG	Continuous variable
	LDLC	Continuous variable
	HDLC	Continuous variable

Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. The height-weight scale had been calibrated before using. Light clothes and no shoes were required for the participants. BMI was calculated as weight (Kg)/height2 (m2). EF, exercise frequency; SS, smoking status; DF, drinking frequency; DM, diabetes mellitus; PH, parental hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; ECG, electrocardiogram; HR, heart rate; HGB, hemoglobin; WBC, white blood cell; PLT, platelet; FBG, fasting blood glucose; SGPT, serum glutamic-pyruvic transaminase; SGOT, serum glutamic-oxaloacetic transaminase; ALB, albumin; TBIL, total bilirubin; SCR, serum creatinine; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol.

output layer calculates the response. NB is a classical ML algorithm, which calculates the probabilities of each attribute by applying Bayes' rule and predicts the class based on the highest prior probability (35).

The LR is a generalized linear regression analysis model, and aims to find out the best fitting model to describe the relationship between the dependent variables and independent predictors (36). This model was most extensively applied because of the good effect of disease predictions.

Model evaluation

To optimize the model effect, we adjust the parameters of each model based on the learning curve and grid search, so as to find the optimal combination of parameters. Besides, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, Youden index, and area under the receiver operating characteristic (AUC) curve of each model based on the confusion matrix to evaluate the pros and cons.

Feature importance ranking

According to the results of the LR model, the absolute values of the regression model Z statistic (23, 37) were calculated and adjusted the sum to 1 (the higher the value, the greater the effect on hypertension). Then, the feature importance ranking plot of the LR model was drawn.

Machine Learning algorithms can also measure the importance of different features. Different from the odds ratio (OR) of the regression model, the machine algorithm cannot evaluate a simple explanatory value because the relationship fitted by the machine algorithm is complex. Therefore, the relationship is usually not directly generalized to any one parameter, and there is no causal relationship, not even a statistical explanation (18). This measure is usually viewed as the sorting of how important each variable is to the model fit, which is a method to generate hypotheses in order to identify the factors requiring further study and also provides insight into the factors having the greatest impact on predictions. Therefore, a feature importance ranking plot was drawn for the ML algorithm which showed the best prediction.

All analyses were carried out with the python 3.8.3 version. Null and outlier determination and interpolation were performed by the "Pandas" library, "NumPy" library, and "Matplotlib" library. Data imbalance was solved by the "Imlearn" library, and build and validate ML models by the "Sklearn" library. LASSO penalized LR was performed by the "Glmnet" package of the R software 4.1.0 version.

Results

Gender and age differences in hypertension

After pre-processing of data, 4,287,407 people were left, consisting of 2,009,970 men (46.9%) and 2,277,437 women (53.1%). From Table 2, we can observe that the prevalence of hypertension was 22.1% in men and 23.7% in women, and the prevalence of hypertension was higher in women than in men ($P < 0.001$). This study further analyzed the differences in the prevalence of hypertension in two genders with different age groups, and we found that in the 18–29 age group and 30–45 age group, men had a higher prevalence ($P < 0.001$), while in the 46–65 age group and over 65 age group, women had a higher prevalence ($P < 0.001$). The prevalence of hypertension increases sharply with age in both genders.

Basic characteristics

The general characteristics of participants in this study are shown in Table 3. A total of 985,431 patients with hypertension were recruited. Compared with non-hypertension people, the median values of age, SBP, DBP, body mass index (BMI), WC, hemoglobin (HGB), white blood cell (WBC), fasting blood glucose (FBG), serum glutamic-pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), serum creatinine (SCR), blood urea nitrogen (BUN), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDLC) were higher in people with hypertension, and the latter are more likely to have parental hypertension (PH) and diabetes mellitus (DM). On the contrary, higher platelet (PLT) and higher albumin (ALB) levels were more common in participants without hypertension.

Features extraction

In this study, the LASSO regression model was used to select the features of the training set data. The results show that there were 24 variables with non-zero coefficients in the LASSO regression model (Figure 2), including sex, age, ethnicity, SBP, DBP, BMI, WC, exercise frequency (EF), drinking frequency (DF), PH, DM, HGB, WBC, PLT, FBG, electrocardiogram (ECG), SGOT, ALB, total bilirubin (TBIL), BUN, TC, TG, LDLC, and high-density lipoprotein cholesterol (HDLC). These 24 variables were used in three types of hypertension prediction models.

Class balance

The sample size of hypertensive patients in the training set was expanded to 2,312,160 by the Borderline-SMOTE algorithm, and finally, 4,624,320 non-hypertensive and hypertensive samples were obtained (Table 4).

TABLE 2 Differences in the prevalence of hypertension between men and women in this study ($N = 4,287,407$).

Variables	Total	Non–Hypertensive	Hypertension	Prevalence of hypertension	P-value
Sex, *n*(%)					<0.001
Female	2,277,437 (53.1)	1,736,267 (52.6)	541,170 (54.9)	23.7	
Male	2,009,970 (46.9)	1,565,709 (47.4)	444,261 (45.1)	22.1	
Age group, *n*(%)					
18–29					<0.001
Female	273,841 (52.6)	273,391 (52.7)	450 (29.4)	0.2	
Male	246,490 (47.4)	245,411 (47.3)	1,079 (70.6)	0.4	
30–45					<0.001
Female	560,689 (53.9)	538,282 (54.3)	22,407 (46.3)	4.0	
Male	479,894 (46.1)	453,897 (45.7)	25,997 (53.7)	5.4	
46–65					<0.001
Female	1,054,532 (53.6)	755,022 (52.5)	299,510 (56.4)	28.4	
Male	913,697 (46.4)	682,213 (47.5)	231,484 (43.6)	25.3	
65 over					<0.001
Female	388,375 (51.2)	169,572 (47.9)	218,803 (54.1)	56.3	
Male	369,889 (48.8)	184,188 (52.1)	185,701 (45.9)	50.2	

TABLE 3 Characteristics of participants in this study.

Characteristics	Total ($n = 4,287,407$)	Non–Hypertensive ($n = 3,301,976$)	Hypertension ($n = 985,431$)	*P*–value
Age (median [IQR])	50.00 [38.00, 61.00]	47.00 [34.00, 55.00]	62.00 [54.00, 70.00]	<0.001
Sex (%)				<0.001
Female	2,277,437 (53.1)	1,736,267 (52.6)	541,170 (54.9)	
Male	2,009,970 (46.9)	1,565,709 (47.4)	444,261 (45.1)	
Ethnicity (%)				<0.001
Han	1,255,170 (29.3)	983,889 (29.8)	271,281 (27.5)	
Hui	198,028 (4.6)	151,551 (4.6)	46,477 (4.7)	
Kazakh	408,666 (9.5)	307,380 (9.3)	101,286 (10.3)	
Other nationalities	138,776 (3.2)	109,309 (3.3)	29,467 (3.0)	
Uyghur	2,286,767 (53.3)	1,749,847 (53.0)	536,920 (54.5)	
EF (%)				<0.001
Daily	301,849 (7.0)	197,356 (6.0)	104,493 (10.6)	
More than once a week	91,594 (2.1)	61,264 (1.9)	30,330 (3.1)	
Not exercising	3,751,779 (87.5)	2,945,712 (89.2)	806,067 (81.8)	
Occasionally	142,185 (3.3)	97,644 (3.0)	44,541 (4.5)	
SS (%)				<0.001
Never smoked	3,820,572 (89.1)	2,922,174 (88.5)	898,398 (91.2)	
Quit smoking	29,746 (0.7)	19,743 (0.6)	10,003 (1.0)	
Smoking	437,089 (10.2)	360,059 (10.9)	77,030 (7.8)	
DF (%)				<0.001
Every day	5,235 (0.1)	3,626 (0.1)	1,609 (0.2)	
Never	3,964,939 (92.5)	3,036,309 (92.0)	928,630 (94.2)	
Occasionall	293,659 (6.8)	242,935 (7.4)	50,724 (5.1)	
Often	23,574 (0.5)	19,106 (0.6)	4,468 (0.5)	
PH (%)				<0.001
No	4,085,273 (95.3)	3,169,978 (96.0)	915,295 (92.9)	
Yes	202,134 (4.7)	131,998 (4.0)	70,136 (7.1)	
DM (%)				<0.001
No	4,003,394 (93.4)	3,195,815 (96.8)	807,579 (82.0)	
Yes	284,013 (6.6)	106,161 (3.2)	177,852 (18.0)	
SBP (median [IQR])	120.00 [110.00, 130.00]	120.00 [110.00, 126.00]	126.00 [119.58, 140.00]	<0.001
DBP (median [IQR])	72.00 [67.00, 80.00]	70.00 [65.00, 80.00]	80.00 [70.00, 90.00]	<0.001
BMI (median [IQR])	24.80 [22.32, 27.44]	24.29 [22.03, 26.93]	26.06 [23.83, 29.00]	<0.001
Wc (median [IQR])	86.00 [79.00, 95.00]	85.00 [78.00, 92.00]	91.00 [83.00, 100.00]	<0.001
HR (%)				<0.001
Abnormal	39345 (0.9)	28326 (0.9)	11019 (1.1)	
Normal	4248062 (99.1)	3273650 (99.1)	974412 (98.9)	
ECG (%)				<0.001
Abnormal	895654 (20.9)	607733 (18.4)	287921 (29.2)	
Normal	3391753 (79.1)	2694243 (81.6)	697510 (70.8)	
HGB (median [IQR])	141.00 [129.00, 153.00]	140.70 [128.00, 153.00]	143.00 [132.00, 153.00]	<0.001
WBC (median [IQR])	6.20 [5.25, 7.27]	6.15 [5.20, 7.20]	6.37 [5.36, 7.45]	<0.001
PLT (median [IQR])	236.00 [198.00, 276.00]	236.00 [199.00, 276.00]	235.00 [196.00, 276.00]	<0.001
FBG (median [IQR])	5.23 [4.74, 5.74]	5.20 [4.69, 5.63]	5.43 [4.94, 6.10]	<0.001
SGPT (median [IQR])	20.90 [15.00, 28.70]	20.90 [15.00, 28.90]	21.00 [15.00, 28.30]	<0.001
SGOT (median [IQR])	21.60 [17.40, 26.70]	21.50 [17.30, 26.60]	21.80 [17.60, 27.00]	<0.001

(Continued)

TABLE 3 (Continued)

Characteristics	Total ($n = 4,287,407$)	Non–Hypertensive ($n = 3,301,976$)	Hypertension ($n = 985,431$)	*P*–value
ALB (median [IQR])	14.15 [14.15, 14.15]	14.15 [14.15, 14.15]	14.15 [14.15, 14.15]	<0.001
TBIL (median [IQR])	12.71 [9.56, 15.17]	12.71 [9.52, 15.20]	12.71 [9.60, 15.02]	0.008
SCR (median [IQR])	65.50 [54.95, 78.00]	65.20 [54.60, 77.60]	66.40 [55.56, 78.70]	<0.001
BUN (median [IQR])	4.95 [3.98, 5.99]	4.89 [3.92, 5.90]	5.11 [4.16, 6.21]	<0.001
TC (median [IQR])	4.40 [3.76, 5.10]	4.32 [3.70, 5.01]	4.60 [3.99, 5.30]	<0.001
TG (median [IQR])	1.22 [0.89, 1.68]	1.20 [0.85, 1.61]	1.34 [1.00, 1.89]	<0.001
LDLC (median [IQR])	2.46 [1.95, 3.04]	2.41 [1.92, 3.00]	2.57 [2.03, 3.20]	<0.001
HDLC (median [IQR])	1.33 [1.10, 1.64]	1.33 [1.10, 1.64]	1.32 [1.10, 1.63]	<0.001

For continuous variables, the data were expressed as median [IQR: inter–quartile range], and for categorical variables, the data were expressed as counts (percentage). EF, exercise frequency; SS, smoking status; DF, drinking frequency; DM, diabetes mellitus; PH, parental hypertension; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; ECG, electrocardiogram; HR, heart rate; HGB, hemoglobin; WBC, white blood cell; PLT, platelet; FBG, fasting blood glucose; SGPT, serum glutamic–pyruvic transaminase; SGOT, serum glutamic–oxaloacetic transaminase; ALB, albumin; TBIL, total bilirubin; SCR, serum creatinine; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; LDLC, low–density lipoprotein cholesterol; HDLC, high–density lipoprotein cholesterol.

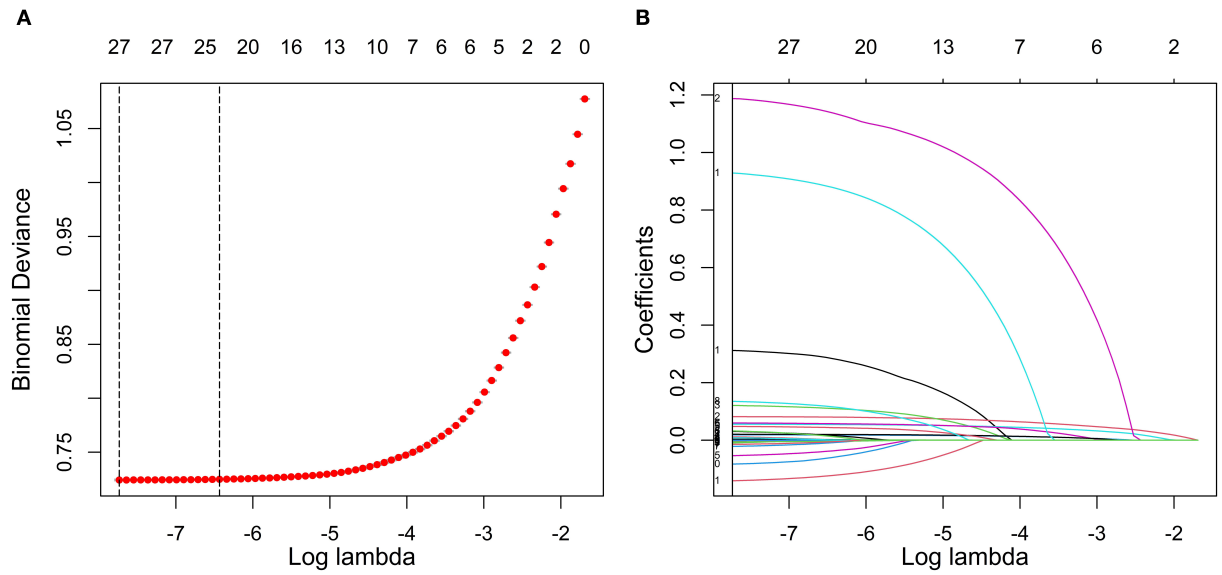


FIGURE 2
Feature selection using LASSO regression in the training set. **(A)** Cross-validation was performed 10 times to select the optimal parameters (lambda) of the LASSO model. **(B)** LASSO coefficient profile of 24 characteristics. In the LASSO algorithm, with the change of lambda, the trajectory of each hypertension-related characteristic coefficient is observed in the LASSO coefficient profile. LASSO, least absolute shrinkage and selection operator.

Tuning of parameters

In the non-laboratory and semi-laboratory analyses, we optimally adjusted the training set parameters of the four "tree" models, and listed the score (accuracy) of each parameter under the different models in the validation set. The results showed that, on the basis of the optimization of the other parameters, the "tree" depths of CART, RF, ADABoost, and XGBoost in the non-laboratory analyses were 24, 40, 5, and 6, respectively (Figure 3) while in the semi-laboratory analyses were 22, 44, 7, and 5, respectively (Figure 4). Thus, a relatively economical and accurate classification tree model is obtained, respectively.

Comparison of model performance

We constructed three classification models of tree-based ML models (CART, RF, ADABoost, and XGBoost), other ML models (ANN and NB), and traditional classical models (LR) in this study. Supplementary Tables S1, S2 presented the algorithm

TABLE 4 Borderline–SMOTE over–sampling balanced dataset description.

Dataset	Non–Hypertensive/Hypertensive	Ratio	Description
Training set data	2,312,160/689,025	3.36:1	Original data with full instances
Borderline–SMOTE data	2,312,160/2,312,160	1:1	Dataset is balanced utilizing Borderline–SMOTE oversampling

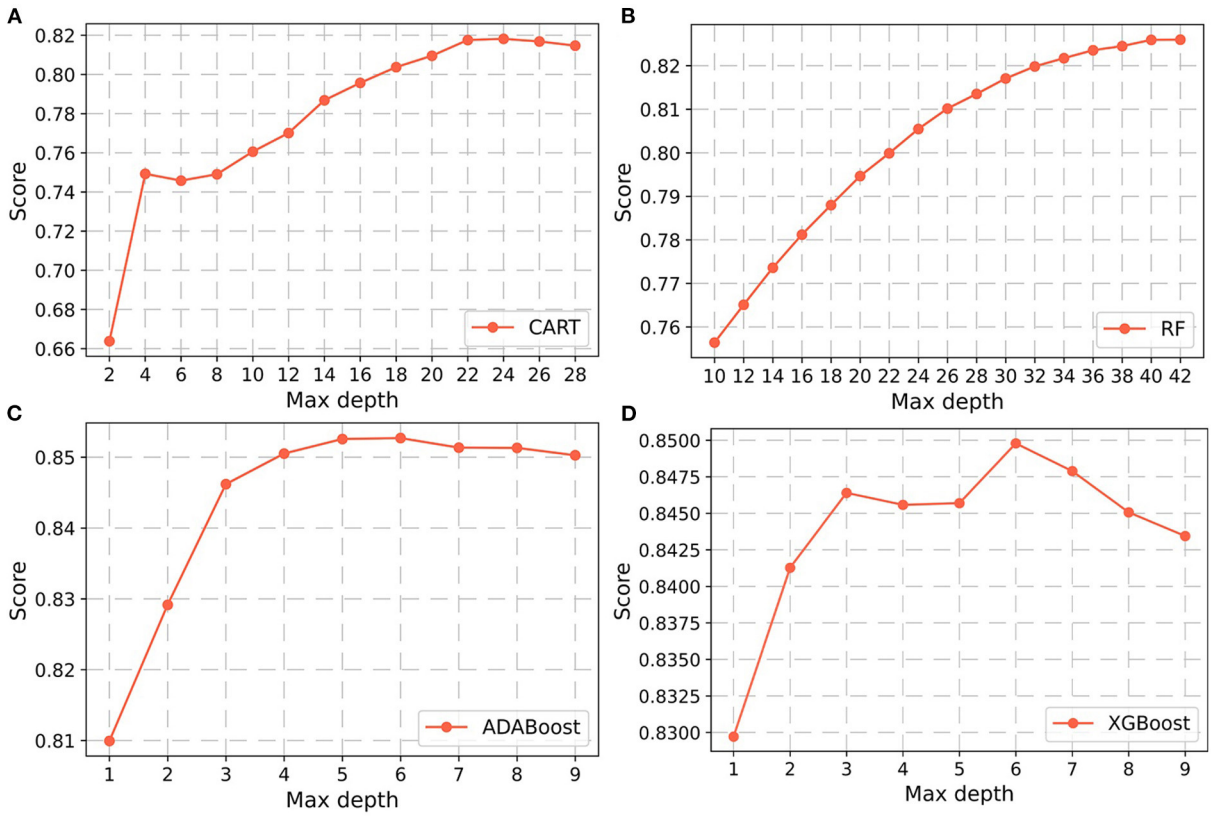


FIGURE 3
Parameter selection for four non-laboratory prediction models. Using the learning curves for **(A)** CART. **(B)** RF. **(C)** ADABoost, and **(D)** XGBoost respectively, the scores (accuracy) of each algorithm at different tree depths are shown in Figure. Abbreviations: CART, classification and regression tree; RF, random forest; ADABoost, adaboost with decision tree; XGBoost, extreme gradient boosting decision tree.

performances of non-laboratory and semi-laboratory analyses in the validation set, respectively. Tables 5, 6 presented the algorithm performances of non-laboratory and semi-laboratory analyses in the test set, respectively. The heat map showed the confusion matrix, where the larger the value, the darker the color of the area, i.e., the color of the TN and TP areas were closer to red or blue. On the contrary, the lighter the color of the FN and FP regions, the higher the accuracy of the classification model. XGBoost algorithm had a great performance in predicting the risk of hypertension in a large population of China, whose AUC of non-laboratory and semi-laboratory was 0.893 and 0.894, respectively. The NB algorithm was less effective in predicting hypertension. Some of the algorithms (RF, ADABoost, and XGBoost) in the semi-laboratory analysis incorporating blood test data showed little improvement in predictive performance compared to the non-laboratory analysis. Supplementary Figures S1, S2, and Figure 5 show the receiver operating characteristic (ROC) curve of all classifiers.

Importance of features

In this study, the importance of each feature was ranked by the LR model (Figure 6), and it was found that age, DBP, ECG, SBP, BMI, DF, sex (female), WC, ethnicity (uyghur, hui, and other), and FBG were the factors that had a greater impact on hypertension. Afterward, feature importance ranking was

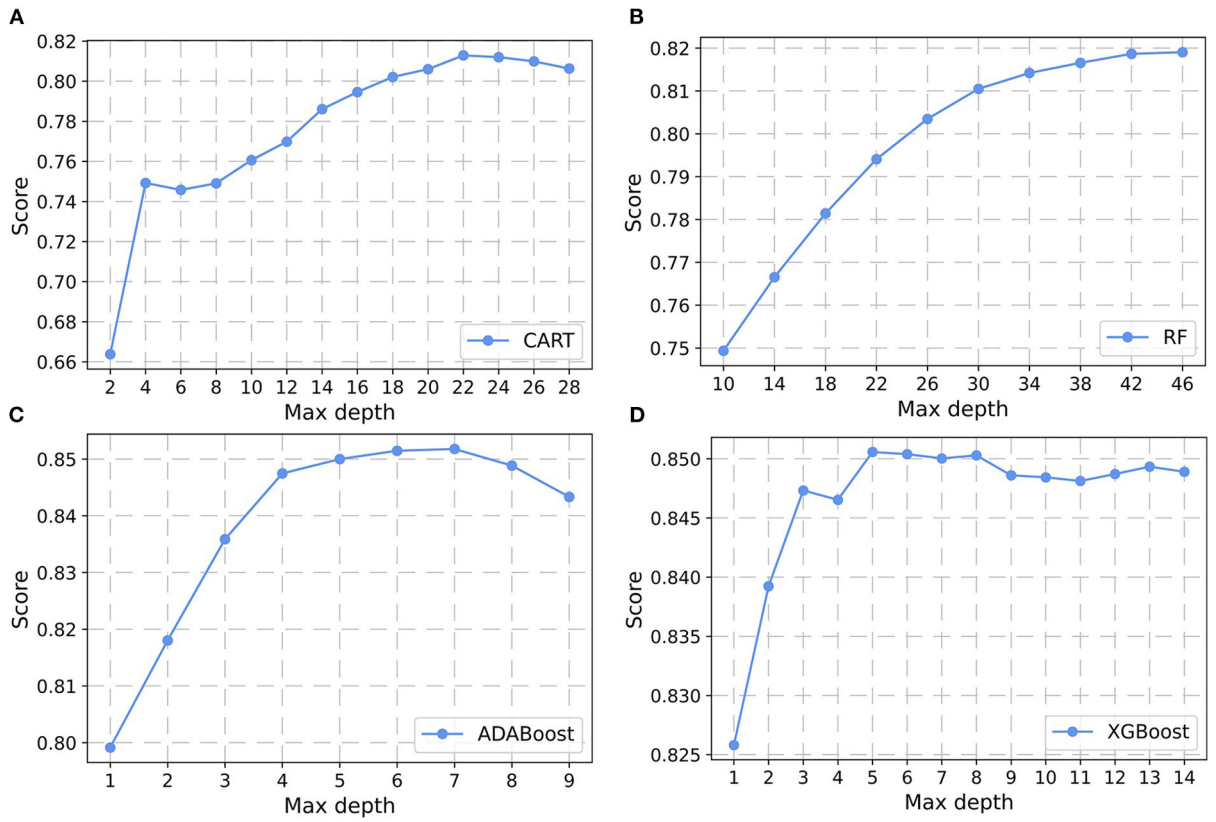


FIGURE 4
Parameter selection for four semi-laboratory prediction models. Using the learning curves for **(A)** CART. **(B)** RF. **(C)** ADABoost, and **(D)** XGBoost, respectively, the scores (accuracy) of each algorithm at different tree depths are shown in Figure. CART, classification and regression tree; RF, random forest; ADABoost, adaboost with decision tree; XGBoost, extreme gradient boosting decision tree.

conducted for the ML algorithms which performed best in the non-laboratory analyses and semi-laboratory analyses.

In conclusion, considering the results of LR and XGBoost, age, SBP, WC, DBP, ALB, DF, ECG, ethnicity (uyghur, hui, and other), BMI, sex (female), EF, DM, TBIL, and FBG were identified as important factors of hypertension.

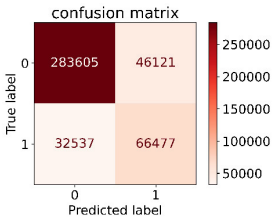
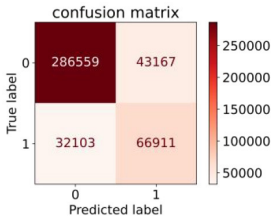
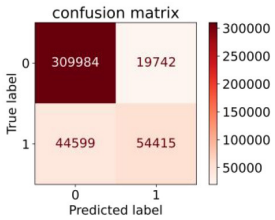
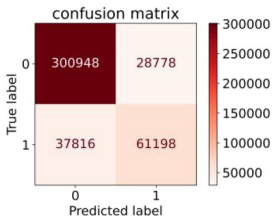
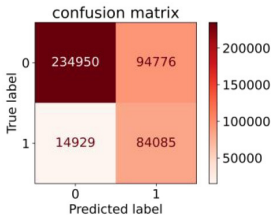
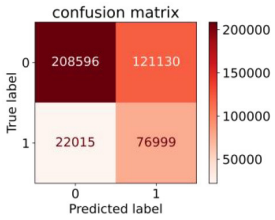
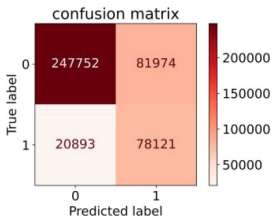
Finally, the algorithm architecture proposed in the paper is shown in Figure 8. We have constructed the optimal XGBoost algorithm based on non-laboratory and semi-laboratory influencing factors to achieve the prediction of hypertension prevalence in a large-scale population in Xinjiang.

XGBoost provides three ways to calculate the importance of each feature, and "gain" was chosen as the calculation method of feature contribution, because it could easily find the most direct features. It was found that age, SBP, WC, ECG, DBP, ethnicity (uyghur and other nationalities), DF, DM, and sex (female) were identified as the top 10 most important factors in the non-laboratory analyses with XGBoost algorithms, while age, SBP, WC, DBP, ALB, DF, ECG, ethnicity (uyghur, hui, and other nationalities), BMI, sex (female), EF, DM, and TBIL were identified as the top 15 most important features in the semi-laboratory analyses with the XGBoost algorithms (Figure 7).

Discussion

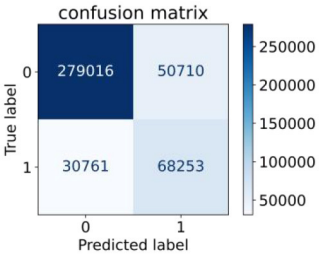
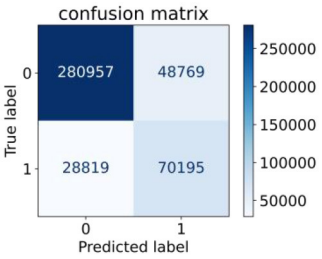
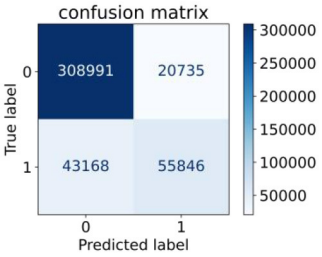
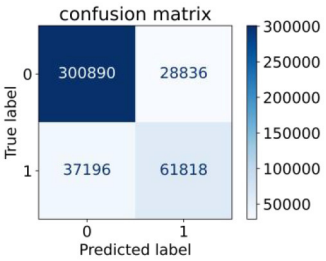
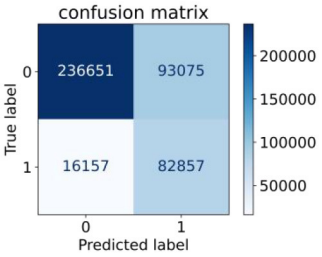
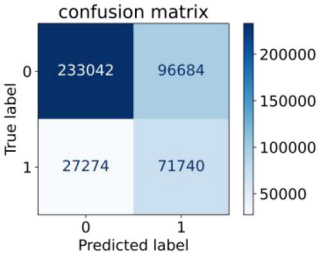
Between 2012 and 2015, the prevalence of hypertension in China was increasing to a high level (46.4%) according to the 2017 American College of Cardiology/American Heart Association guidelines (38). However, the control and treatment of hypertension are not perfect enough, and people's awareness regarding hypertension was lacking (39). Identifying these potential hypertension patients and initiating appropriate treatment are of priority. In this study, we incorporated 4,287,407 adults who had national physical examinations for non-laboratory and semi-laboratory analyses, respectively, and figured out an optimal prediction of hypertension risk in a large Chinese population by comparing tree-based ML models (CART, RF, ADABoost, and XGBoost), other ML models (NB and ANN), and traditional LR models.

TABLE 5 Performance of each algorithm in the test set for non–laboratory analysis (n = 428,740).

Models	Sub–Algorithms	Confusion matrix	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Tree–based ML models	CART		0.671	0.860	0.590	0.897	0.817	0.852
	RF		0.676	0.869	0.608	0.899	0.824	0.883
	ADABoost		0.550	0.940	0.734	0.874	0.850	0.892
	XGBoost		0.618	0.913	0.680	0.888	0.845	0.893
Other methods–based ML models	ANN		0.849	0.713	0.470	0.940	0.744	0.859
	NB		0.778	0.633	0.389	0.905	0.666	0.765
Classic Model	LR		0.789	0.751	0.488	0.922	0.760	0.848

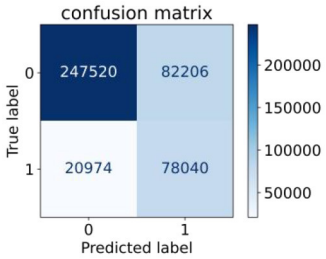
ML, machine learning; CART, classification and regression tree; RF, random forest; ADABoost, adaboost with decision tree; XGBoost, extreme gradient boosting decision tree; ANN, artificial neural network; NB, naive Bayes; LR, logistic regression; AUC, the area under the receiver operating characteristic curve.

TABLE 6 Performance of each algorithm in the test set for semi–laboratory analysis (n = 428,740).

Models	Sub–Algorithms	Confusion matrix	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Tree–based ML models	CART		0.689	0.846	0.574	0.901	0.810	0.850
	RF		0.709	0.852	0.590	0.907	0.819	0.885
	ADABoost		0.564	0.937	0.729	0.877	0.850	0.893
	XGBoost		0.624	0.913	0.682	0.890	0.846	0.894
Other methods–based ML models	ANN		0.837	0.718	0.471	0.936	0.745	0.858
	NB		0.725	0.707	0.426	0.895	0.711	0.763

(Continued)

TABLE 6 (Continued)

Models	Sub–Algorithms	Confusion matrix	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Classic Model	LR		0.788	0.751	0.487	0.922	0.759	0.846

ML, machine learning; CART, classification and regression tree; RF, random forest; ADABoost, adaboost with decision tree; XGBoost, extreme gradient boosting decision tree; ANN, artificial neural network; NB, naive Bayes; LR, logistic regression; AUC, the area under the receiver operating characteristic curve.

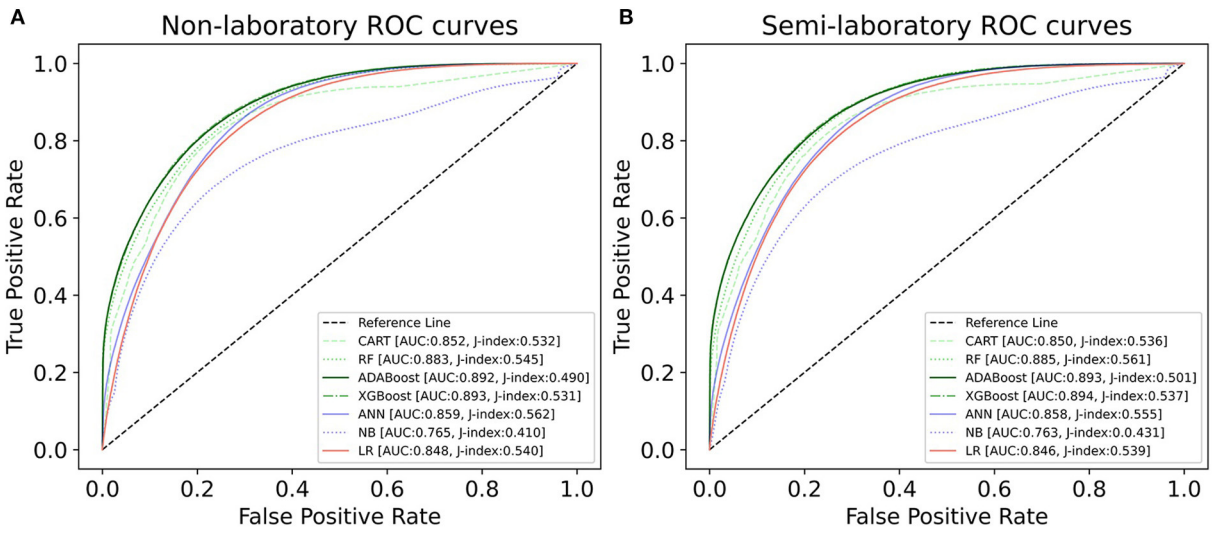


FIGURE 5
ROC curves for each classification algorithm for the non-laboratory and semi-laboratory models. **(A)** Non-laboratory model. **(B)** Semi-laboratory model. Youden's J-index combines sensitivity and specificity into a single measure (sensitivity + specificity−1) and has a value between 0 and 1. In a perfect test, Youden's index equals 1. ROC, receiver operating characteristic; CART, classification and regression tree; RF, random forest; ADABoost, adaboost with decision tree; XGBoost, extreme gradient boosting decision tree; ANN, artificial neural network; NB, naive Bayes; LR, logistic regression; AUC, the area under the ROC curve.

Hypertension is a significant public health issue. The ability to predict the risk of developing hypertension could contribute to disease prevention strategies. At present, many models for hypertension have been established, which show good predicting results. However, these models are limited to a specific population (40–44) or disease (45–47). For example, Xu Y et al. (41) established a prediction model for hypertension in the Xinjiang kazak population by using 14 predictors, including age, smoking, alcohol consumption, baseline BMI, baseline DBP, baseline SBP, daily salt intake, and yak butter intake. Kanegae H et al. (43) developed a high-precision prediction model for hypertension based on artificial intelligence by incorporating age, BMI, WC, SDP, DBP, Cardio-Ankle vascular index, uric acid, and other factors. Qi H et al. (45) established a micro-RNA screening and prediction model for salt-sensitive hypertension at the miRNA molecular level. Factors unique to these studies may be the main reason why the model achieves good predictive results in different populations. The classic hypertension prediction model Framingham Risk Score (FRS) (7) believes that age, sex, SDP, DBP, BMI, PH, and smoking are important influencing factors of hypertension. FRS has been verified in European population studies and has shown good differentiation and calibration (9). Carson AP et al. (40) also applied it to the prediction and assessment of hypertension risk in young people and achieved good results. However, a study about the FRS model indicated that it is not suitable

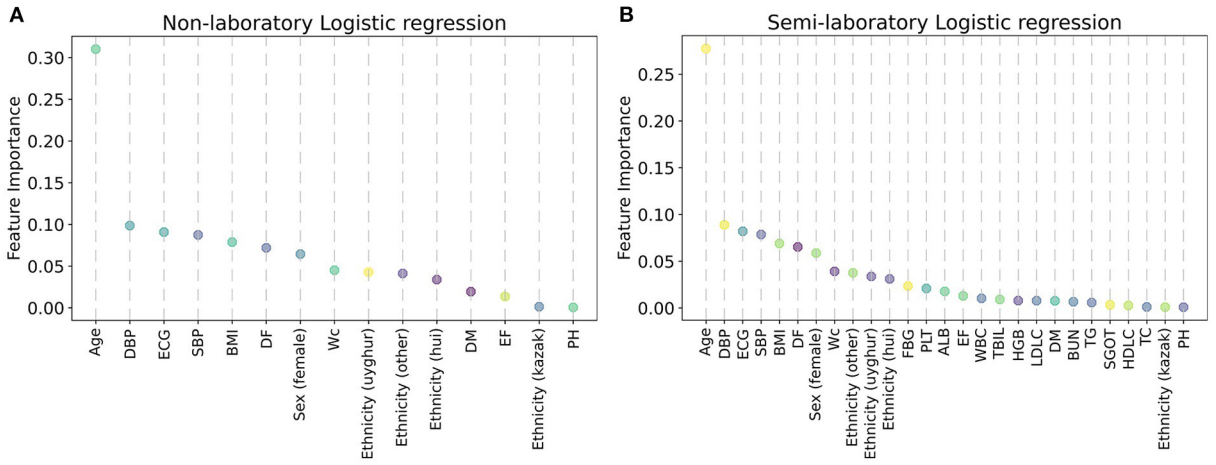


FIGURE 6
Variable importance of the predictors for the predictive models for hypertension, using logistic regression. **(A)** Non-laboratory model. **(B)** Semi-laboratory model. The variable importance was calculated using the absolute z-statistic of each predictor. SBP, systolic blood pressure; WC, waist circumference; DBP, diastolic blood pressure; ALB, albumin; DF, drinking frequency; ECG, electrocardiogram; BMI, body mass index; EF, exercise frequency; DM, diabetes mellitus; TBIL, total bilirubin; SGOT, serum glutamic-oxaloacetic transaminase; TG, triglyceride; HGB, hemoglobin; PH, parental hypertension; WBC, white blood cell; FBG, fasting blood glucose; HDLC, high density lipoprotein cholesterol; TC, total cholesterol; LDLC, low density lipoprotein cholesterol; BUN, blood urea nitrogen; PLT, platelet; Sex (female) and Sex (male) are dummy variables of sex; ethnicity (uyghur), ethnicity (hui), ethnicity (other), and ethnicity (kazak) are dummy variables of ethnicity.

for the Chinese population (11). Therefore, this study included ethnicity, WC, EF, ECG, DM, and other characteristics based on FRS, which gained good predicting results.

It has been widely confirmed that the prevalence of hypertension in different genders was diverse (48–51). This study showed that differences existed between the two genders. In the age groups of 18–29 and 30–45, the prevalence of hypertension in men was significantly higher than in women, while in the 46–65 and over 65 age groups, an opposite trend was observed. This difference might be due to hormonal differences or lifestyle differences (50, 52). Studies have shown that the blood pressure of premenopausal women was often lower than that of men of the same age. After menopause, the prevalence of hypertension in women gradually increased, and after the age of 65, the prevalence of hypertension in women was significantly higher than in men (51, 53). The above findings indicated that there were gender differences in the underlying pathological mechanisms of hypertension.

Previous studies have demonstrated differences in the prevalence of hypertension between different ethnicities (54–57) and confirmed that ethnicity could be a predictor of hypertension (58). Therefore, ethnicity was incorporated into the prediction model, and the results also indicated that it could be an important predictor of hypertension in the Chinese population, especially in uygur, hui, and other nationalities.

According to the World Health Organization (WHO), the global increase in the prevalence of hypertension has been attributed to persistent stress, excess weight, physical inactivity, harmful alcohol consumption, and an unhealthy diet (59). Also, our model also proved that WC, BMI, EF, and DF are important influencing factors of hypertension. Our findings also suggest that ECG was an important predictor of hypertension, which was consistent with other studies (60–62). The pathogenesis of DM and hypertension mutually promote and influence each other (63–65), which makes the prediction models have a general limitation and may not be applicable to the DM population (7, 13, 66). In order to avoid this deficiency, this important factor was considered in the inclusion of risk factors and was included as a predictor of hypertension, and the results also showed its important role in predicting hypertension. The semi-laboratory analyses of this study showed that ALB levels were important influencing features of hypertension. Hypertension is associated with endothelial dysfunction, insulin resistance, inflammation, and oxidative stress (67, 68), while ALB has anti-inflammatory and antioxidant effects (69). The study by Oda E et al. (70) also showed the same findings about ALB as our study. A report published by Nilsson PM in 2019 showed that after multiple adjustments for age, sex, body mass index, smoking, drinking habits, dyslipidemia, chronic kidney disease, and blood uric acid, fasting blood glucose at a high baseline level was an independent risk marker for new-onset hypertension. Afterward, TatSumi et al. (71) showed that fasting blood glucose was a good predictor of hypertension through a 5-year cohort study, which was consistent with our findings.

This study implied that the semi-laboratory analyses incorporating blood test indicators did not show a significant

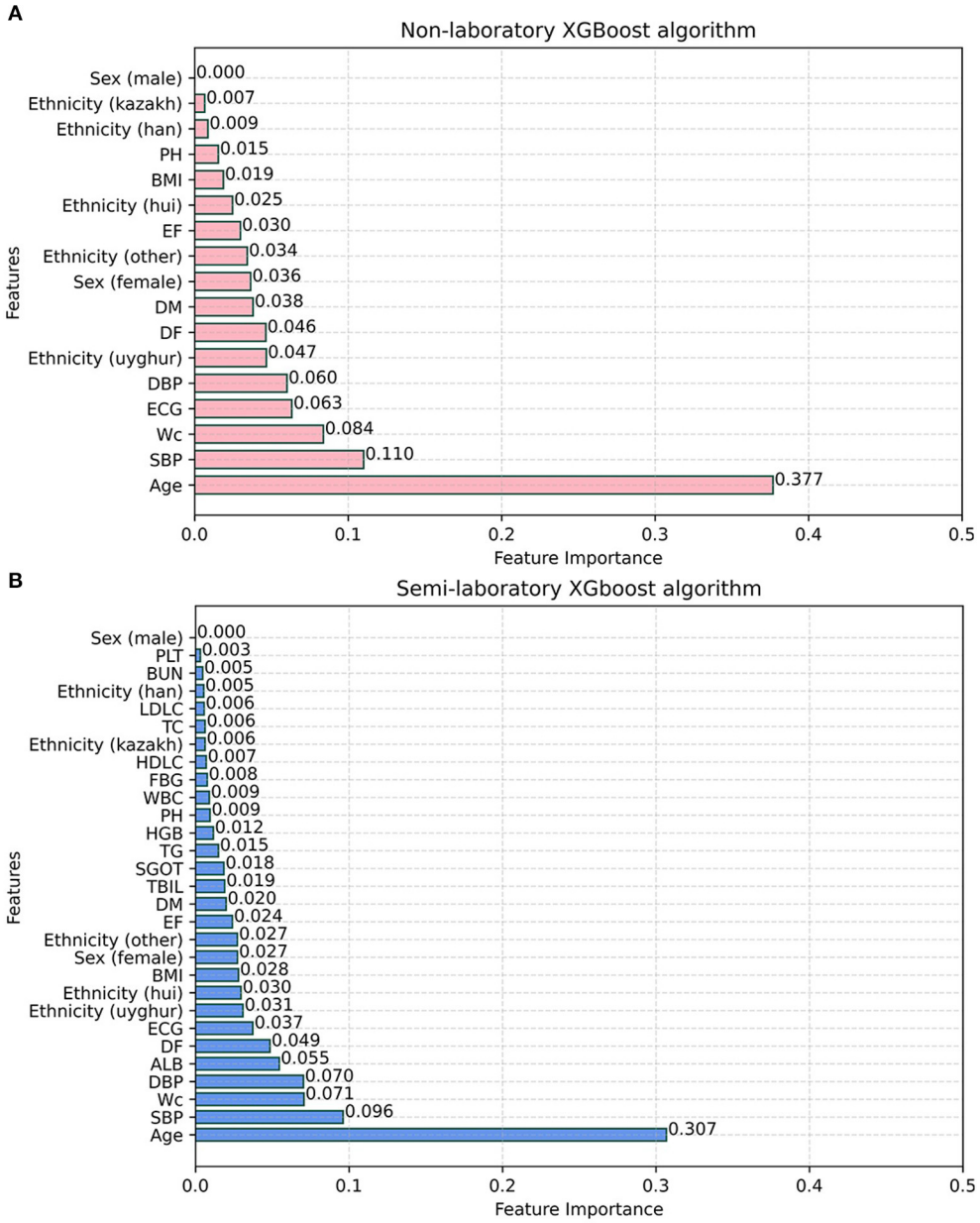


FIGURE 7
Feature importance of XGBoost algorithm. **(A)** Non-laboratory model. **(B)** Semi-laboratory model. SBP, systolic blood pressure; WC, waist circumference; DBP, diastolic blood pressure; ALB, albumin; DF, drinking frequency; ECG, electrocardiogram; BMI, body mass index; EF, exercise frequency; DM, diabetes mellitus; TBIL, total bilirubin; SGOT, serum glutamic-oxaloacetic transaminase; TG, triglyceride; HGB, hemoglobin; PH, parental hypertension; WBC, white blood cell; FBG, fasting blood glucose; HDLC, high density lipoprotein cholesterol; TC, total cholesterol; LDLC, low density lipoprotein cholesterol; BUN, blood urea nitrogen; PLT, platelet; Sex (female) and Sex (male) are dummy variables of sex; ethnicity (uyghur), ethnicity (hui), ethnicity (other), and ethnicity (kazak) are dummy variables of ethnicity.

improvement in predictive performance compared to the non-laboratory analyses. The feature importance ranking plot of the XGBoost algorithm also showed that the blood test factors were not very important for the identification of hypertension.

There are several advantages to this study. First, this study was based on a large amount of population data in China, which was highly generalizable and representative. In addition, our dataset included multiple major ethnic groups in China, which better assessed the characteristics of the Chinese population. Besides, we carried out both non-laboratory analyses and semi-laboratory analyses, respectively, and found two optimal models that were suitable for people in different regions. Especially, in

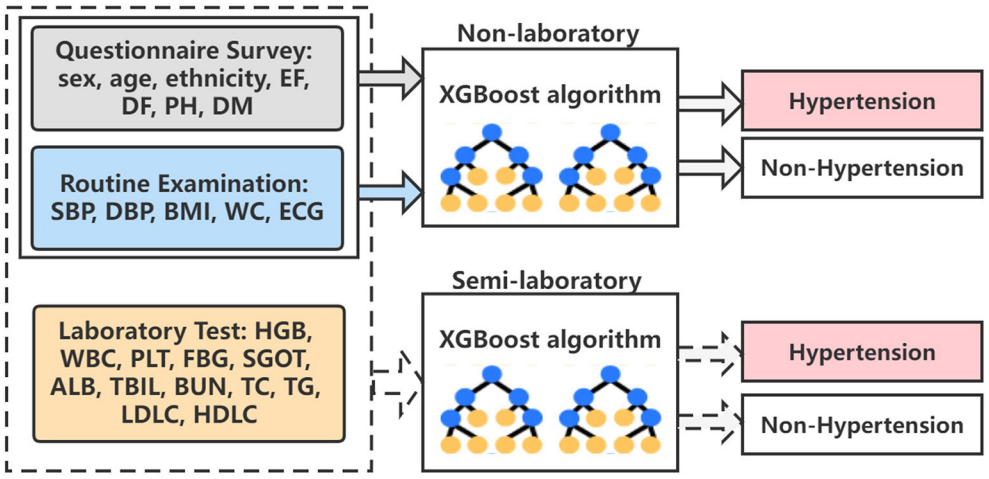


FIGURE 8
The overall algorithm architecture diagram. EF, exercise frequency; DF, drinking frequency; PH, parental hypertension; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; ECG, electrocardiogram; HGB, hemoglobin; WBC, white blood cell; PLT, platelet; FBG, fasting blood glucose; SGOT, serum glutamic-oxaloacetic transaminase; ALB, albumin; TBIL, total bilirubin; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; LDLC, low density lipoprotein cholesterol; HDLC, high density lipoprotein cholesterol.

non-laboratory analyses, simple and easily available variables were used to build a predictive model with high performance, which saves blood testing and extra manpower, as well as greatly promotes the diagnosis and screening of hypertension in economically underdeveloped remote areas (15). We obtained a satisfied predictive effect of our models, for example, the AUC values of XGBoost were 0.893 and 0.894, respectively. As far as we know, the effects of our model were better than most of the known models, which might be due to the fact that the model was built on many features and included a big sample.

There are several limitations to this study. First, the causal relationship cannot be analyzed from the cross-sectional data of the health screening component, which needs to be further verified in future studies. Second, the data of this study were based on the physical examination data of residents in the Xinjiang region of China, which may limit the extrapolation of results. Third, EF, DF, and DM are all based on a questionnaire survey, and participants reported themselves through recall, which can lead to memory errors. Considering privacy and other reasons, participants failed to truthfully fill in their DM status, so the prevalence of diabetes was underestimated. Finally, in the current study, only self-reported parental history of hypertension was available. A previous study indicated that children's self-reported parental history of hypertension had a high positive predictive value but a low negative predictive value, suggesting that more participants may classify their parents as normotensive while their parents were actually hypertensive (72).

Conclusion

In summary, on the basis of a cross-sectional study involving 4,287,407 participants, we carried out the non-laboratory and semi-laboratory analyses, by constructing the tree-based ML models, other ML models, and traditional LR model and obtaining the optimal algorithm for predicting the risk of hypertension in a large-scale Chinese population. This study showed that tree-based ML models (XGBoost algorithm) performed excellently in identifying hypertensive patients, while blood test factors had little effect on improving the hypertension prediction model. As we know, this study is the first one to establish non-laboratory and semi-laboratory hypertension prediction models on the basis of multi-ethnic and large samples by systematically and comprehensively comparing various algorithms, which provided a new approach to the prediction and prevention of hypertension.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by this study was conducted in accordance with the principles outlined in the Helsinki Declaration and was

approved by the Ethics Committee and Institutional Review Committee of the Xinjiang Uygur Autonomous Region Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YiZ and YW conceived the study. WJ and YuZ collected the data. WJ and YC performed the statistical analyses. WJ and YuZ drafted the manuscript. YiZ critically reviewed and edited the manuscript. All authors contributed to data analysis, drafting, and revising of the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Key Research and Development Program of China [No. 2018YFC0116900], the National Natural Science Foundation of China (NSFC) [No. 61876194], the Key Research and Development Program of Guangdong Province, China [No. 2018B010109006], the Science and Technology Innovation Special Project of Guangdong Province, China [No. 202011020004], and the Natural Science Foundation of Guangdong Province, China [No. 2021A1515011897].

Acknowledgments

Thanks to the health commission of Xinjiang Uygur Autonomous Region and the Health Management Institute of Xinjiang Medical University for data support. Thanks to all the participants for their help.

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.2022.928948/full#supplementary-material

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet.* (2017) 389:37–55. doi: 10.1016/S0140-6736(16)31919-5

2. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet.* (2016) 388:2665–712. doi: 10.1016/S0140-6736(16)31134-5

3. 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

4. Li W, Gu H, Teo KK, Bo J, Wang Y, Yang J, et al. Hypertension prevalence, awareness, treatment, and control in 115 rural and urban communities involving 47 000 people from China. *J Hypertens.* (2016) 34:39–46. doi: 10.1097/HJH.0000000000000745

5. Lewington S, Lacey B, Clarke R, Guo Y, Kong XL, Yang L, et al. The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China. *JAMA Intern Med.* (2016) 176:524–32. doi: 10.1001/jamainternmed.2016.0190

6. Li D, Lv J, Liu F, Liu P, Yang X, Feng Y, et al. Hypertension burden and control in mainland China: analysis of nationwide data 2003-2012. *Int J Cardiol.* (2015) 184:637–44. doi: 10.1016/j.ijcard.2015.03.045

7. Parikh NI, Pencina MJ, Wang TJ, Benjamin EJ, Lanier KJ, Levy D, et al. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. *Ann Intern Med.* (2008) 148:102–10. doi: 10.7326/0003-4819-148-2-200801150-00005

8. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol.* (2015) 3:339–55. doi: 10.1016/S2213-8587(15)00081-9

9. Kivimäki M, Batty GD, Singh-Manoux A, Ferrie JE, Tabak AG, Jokela M, et al. Validating the Framingham hypertension risk score: results from the Whitehall II study. *Hypertension.* (2009) 54:496–501. doi: 10.1161/HYPERTENSIONAHA.109.132373

10. Muntner P, Woodward M, Mann DM, Shimbo D, Michos ED, Blumenthal RS, et al. Comparison of the framingham heart study hypertension model with blood pressure alone in the prediction of risk of hypertension: the multi-ethnic study of atherosclerosis. *Hypertension.* (2010) 55:1339–45. doi: 10.1161/HYPERTENSIONAHA.109.149609

11. Zheng L, Sun Z, Zhang X, Li J, Hu D, Chen J, et al. Predictive value for the rural Chinese population of the Framingham hypertension risk model: results from Liaoning Province. *Am J Hypertens.* (2014) 27:409–14. doi: 10.1093/ajh/hpt229

12. Niu M, Wang Y, Zhang L, Tu R, Liu X, Hou J, et al. Identifying the predictive effectiveness of a genetic risk score for incident hypertension using machine learning methods among populations in rural China. *Hypertens Res.* (2021) 44:1483–91. doi: 10.1038/s41440-021-00738-7

13. Chen Y, Wang C, Liu Y, Yuan Z, Zhang W, Li X, et al. Incident hypertension and its prediction model in a prospective northern urban Han

Chinese Cohort Study. *J Hum Hypertens.* (2016) 30:794–800. doi: 10.1038/jhh.2016.23

14. Du M, Yin S, Wang P, Wang X, Wu J, Xue M, et al. Self-reported hypertension in Northern China: a cross-sectional study of a risk prediction model and age trends. *BMC Health Serv Res.* (2018) 18:475. doi: 10.1186/s12913-018-3279-3

15. Xu F, Zhu J, Sun N, Wang L, Xie C, Tang Q, et al. Development and validation of prediction models for hypertension risks in rural Chinese populations. *J Glob Health.* (2019) 9:020601. doi: 10.7189/jogh.09.020601

16. Ren Z, Rao B, Xie S, Li A, Wang L, Cui G, et al. A novel predicted model for hypertension based on a large cross-sectional study. *Sci Rep.* (2020) 10:10615. doi: 10.1038/s41598-020-64980-8

17. Churpek MM, Yuen TC, Winslow C, Meltzer DO, Kattan MW, Edelson DP. Multicenter comparison of machine learning methods and conventional regression for predicting clinical deterioration on the wards. *Crit Care Med.* (2016) 44:368–74. doi: 10.1097/CCM.0000000000001571

18. Goldstein BA, Navar AM, Carter RE. Moving beyond regression techniques in cardiovascular risk prediction: applying machine learning to address analytic challenges. *Eur Heart J.* (2017) 38:1805–14. doi: 10.1093/eurheartj/ehw302

19. Selker HP, Griffith JL, Patil S, Long WJ, D'Agostino RB. A comparison of performance of mathematical predictive methods for medical diagnosis: identifying acute cardiac ischemia among emergency department patients. *J Investig Med.* (1995) 43:468–76.

20. Wade NJ. Chapter 32: sensory and perceptual disorders. *Handb Clin Neurol.* (2010) 95:489–500. doi: 10.1016/S0072-9752(08)02132-5

21. Choi SB, Kim WJ, Yoo TK, Park JS, Chung JW, Lee YH, et al. Screening for prediabetes using machine learning models. *Comput Math Methods Med.* (2014) 2014:618976. doi: 10.1155/2014/618976

22. Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B, et al. systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol.* (2019) 110:12–22. doi: 10.1016/j.jclinepi.2019.02.004

23. Nusinovici S, Tham YC, Chak Yan MY, Wei Ting DS Li J, Sabanayagam C, et al. Logistic regression was as good as machine learning for predicting major chronic diseases. *J Clin Epidemiol.* (2020) 122:56–69. doi: 10.1016/j.jclinepi.2020.03.002

24. Sakr S, Elshawi R, Ahmed A, Qureshi WT, Brawner C, Keteyian S, et al. Using machine learning on cardiorespiratory fitness data for predicting hypertension: The Henry Ford ExercIse Testing (FIT) Project. *PLoS ONE.* (2018) 13:e0195344. doi: 10.1371/journal.pone.0195344

25. Lafreniere D, Zulkernine F, Barber D, Martin K. *Using machine learning to predict hypertension from a clinical dataset.*2016 IEEE Symposium Series on Computational Intelligence (SSCI) IEEE. (2016).

26. Kublanov VS, Dolganov AY, Belo D, Gamboa H. Comparison of machine learning methods for the arterial hypertension diagnostics. *Appl Bionics Biomech.* (2017) 2017:5985479. doi: 10.1155/2017/5985479

27. Liu J, Sun D, Chen L, Fang Z, Song W, Guo D, et al. Radiomics analysis of dynamic contrast-enhanced magnetic resonance imaging for the prediction of sentinel lymph node metastasis in breast cancer. *Front Oncol.* (2019) 9:980. doi: 10.3389/fonc.2019.00980

28. Lee BJ, Ku B, Nam J, Pham DD, Kim JY. Prediction of fasting plasma glucose status using anthropometric measures for diagnosing type 2 diabetes. *IEEE J Biomed Health Inform.* (2014) 18:555–61. doi: 10.1109/JBHI.2013.2264509

29. Yu H, Yang X, Zheng S, Sun C. Active learning from imbalanced data: a solution of online weighted extreme learning machine. *IEEE Trans Neural Netw Learn Syst.* (2019) 30:1088–103. doi: 10.1109/TNNLS.2018.2855446

30. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE Synthetic Minority Over-Sampling Technique. *J Artificial Intelligence Res.* (2002) 16:321–57. doi: 10.1613/jair.953

31. Wang KJ, Adrian AM, Chen KH, Wang KM. A hybrid classifier combining Borderline-SMOTE with AIRS algorithm for estimating brain metastasis from lung cancer: a case study in Taiwan. *Comput Methods Programs Biomed.* (2015) 119:63–76. doi: 10.1016/j.cmpb.2015.03.003

32. Breiman L. Random forests, machine learning 45. *J Clin Microbiol.* (2001) 2:199–228. doi: 10.1023/A:1010933404324

33. Freund Y, Schapire R E, A. Decision-Theoretic generalization of on-line learning and an application to boosting. *J Computer Sys Sci.* (1997). 55, 1:119–39. doi: 10.1006/jcss.1997.1504

34. Eladia María P. Ale Hampl, J Havel. Artificial neural networks in medical diagnosis. *J Applied Biomed.* (2013) 11:47–58. doi: 10.2478/v10136-012-0031-x

35. Dugan TM, Mukhopadhyay S, Carroll A, Downs S. Machine learning techniques for prediction of early childhood obesity. *Appl Clin Inform.* (2015) 6:506–20. doi: 10.4338/ACI-2015-03-RA-0036

36. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol.* (2001) 54:979–85. doi: 10.1016/s0895-4356(01)00372-9

37. Mahmoudian M, Venäläinen MS, Klén R, Elo LL. Stable iterative variable selection. *Bioinformatics.* (2021) 37:4810–7. doi: 10.1093/bioinformatics/btab501

38. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, et al. Status of hypertension in China: results from the China Hypertension survey, 2012-2015. *Circulation.* (2018) 137:2344–56. doi: 10.1161/CIRCULATIONAHA.117.032380

39. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet.* (2017) 390:2549–58. doi: 10.1016/S0140-6736(17)32478-9

40. Carson AP, Lewis CE, Jacobs DR Jr, Peralta CA, Steffen LM, Bower JK, et al. Evaluating the Framingham hypertension risk prediction model in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Hypertension.* (2013) 62:1015–20. doi: 10.1161/HYPERTENSIONAHA.113.01539

41. Xu Y, Liu J, Wang J, Fan Q, Luo Y, Zhan H, et al. Establishment and verification of a nomogram prediction model of hypertension risk in Xinjiang Kazakhs. *Medicine (Baltimore).* (2021) 100:e27600. doi: 10.1097/MD.0000000000027600

42. Cogswell R, Kobashigawa E, McGlothlin D, Shaw R, De Marco T. Validation of the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) pulmonary hypertension prediction model in a unique population and utility in the prediction of long-term survival. *J Heart Lung Transplant.* (2012) 31:1165–70. doi: 10.1016/j.healun.2012.08.009

43. Kanegae H, Suzuki K, Fukatani K, Ito T, Harada N, Kario K. Highly precise risk prediction model for new-onset hypertension using artificial intelligence techniques. *J Clin Hypertens (Greenwich).* (2020) 22:445–50. doi: 10.1111/jch.13759

44. Kanegae H, Oikawa T, Suzuki K, Okawara Y, Kario K. Developing and validating a new precise risk-prediction model for new-onset hypertension: the Jichi Genki hypertension prediction model (JG model). *J Clin Hypertens (Greenwich).* (2018) 20:880–90. doi: 10.1111/jch.13270

45. Qi H, Liu Z, Liu B, Cao H, Sun W, Yan Y, et al. microRNA screening and prediction model construction for diagnosis of salt-sensitive essential hypertension. *Medicine (Baltimore).* (2017) 96:e6417. doi: 10.1097/MD.0000000000006417

46. Cogswell R, Pritzker M, De Marco T. Performance of the REVEAL pulmonary arterial hypertension prediction model using non-invasive and routinely measured parameters. *J Heart Lung Transplant.* (2014) 33:382–7. doi: 10.1016/j.healun.2013.12.015

47. Qin L, Zhang Y, Yang X, Wang H. Development of the prediction model for hypertension in patients with idiopathic inflammatory myopathies. *J Clin Hypertens (Greenwich).* (2021) 23:1556–66. doi: 10.1111/jch.14267

48. Gillis EE, Sullivan JC. Sex differences in hypertension: recent advances. *Hypertension.* (2016) 68:1322–7. doi: 10.1161/HYPERTENSIONAHA.116.06602

49. Di Pilla M, Bruno RM, Taddei S, Virdis A. Gender differences in the relationships between psychosocial factors and hypertension. *Maturitas.* (2016) 93:58–64. doi: 10.1016/j.maturitas.2016.06.003

50. Bruno RM, Pucci G, Rosticci M, Guarino L, Guglielmo C, Agabiti Rosei C, et al. Association between lifestyle and systemic arterial hypertension in young adults: a national, survey-based, cross-sectional study. *High Blood Press Cardiovasc Prev.* (2016) 23:31–40. doi: 10.1007/s40292-016-0135-6

51. Yanes LL, Reckelhoff JF. Postmenopausal hypertension. *Am J Hypertens.* (2011) 24:740–9. doi: 10.1038/ajh.2011.71

52. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation.* (2012) 125:e2–e220. doi: 10.1161/CIR.0b013e31823ac046

53. Gu Q, Burt VL, Paulose-Ram R, Dillon CF. Gender differences in hypertension treatment, drug utilization patterns, and blood pressure control among US adults with hypertension: data from the National Health and Nutrition Examination Survey 1999-2004. *Am J Hypertens.* (2008) 21:789–98. doi: 10.1038/ajh.2008.185

54. Joint Committee for Guideline Revision. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol.* (2019) 16:182–241. doi: 10.11909/j.issn.1671-5411.2019.03.014

55. Sun Z, Zheng L, Zhang X, Li J, Hu D, Sun Y. Ethnic differences in the incidence of hypertension among rural Chinese adults: results from Liaoning Province. *PLoS ONE.* (2014) 9:e86867. doi: 10.1371/journal.pone.0086867

56. Heizhati M, Wang L, Yao X, Li M, Hong J, Luo Q, et al. Prevalence, awareness, treatment and control of hypertension in various ethnic groups (Hui, Kazakh, Kyrgyz, Mongolian, Tajik) in Xinjiang, Northwest China. *Blood Press.* (2020) 29:276–84. doi: 10.1080/08037051.2020.1745055

57. Paynter NP, Cook NR, Everett BM, Sesso HD, Buring JE, Ridker PM. Prediction of incident hypertension risk in women with currently normal blood pressure. *Am J Med.* (2009) 122:464–71. doi: 10.1016/j.amjmed.2008.10.034

58. Organization W H. *A Global Brief on Hypertension: Silent Killer, Global Public Health Crisis: World Health Day 2013*. World Health Organization. (2013).

59. Kautzky-Willer A, Dorner T, Jensby A, Rieder A. Women show a closer association between educational level and hypertension or diabetes mellitus than males: a secondary analysis from the Austrian HIS. *BMC Public Health.* (2012) 12:392. doi: 10.1186/1471-2458-12-392

60. Tedesco MA, Di Salvo G, Caputo S, Natale F, Ratti G, Iarussi D, et al. Educational level and hypertension: how socioeconomic differences condition health care. *J Hum Hypertens.* (2001) 15:727–31. doi: 10.1038/sj.jhh.1001249

61. Duarte CD, Wannier SR, Cohen AK, Glymour MM, Ream RK, Yen IH, et al. Lifecourse educational trajectories and hypertension in midlife: an application of sequence analysis. *J Gerontol A Biol Sci Med Sci.* (2022) 77:383–91. doi: 10.1093/gerona/glab249

62. Santisteban MM, Iadecola C. Hypertension, dietary salt and cognitive impairment. *J Cereb Blood Flow Metab.* (2018) 38:2112–28. doi: 10.1177/0271678X18803374

63. Grossman A, Grossman E. Blood pressure control in type 2 diabetic patients. *Cardiovasc Diabetol.* (2017) 16:3. doi: 10.1186/s12933-016-0485-3

64. Yano Y, Kario K. Nocturnal blood pressure, morning blood pressure surge, and cerebrovascular events. *Curr Hypertens Rep.* (2012) 14:219–27. doi: 10.1007/s11906-012-0261-z

65. Deng X, Hou H, Wang X, Li Q, Li X, Yang Z, et al. Development and validation of a nomogram to better predict hypertension based on a 10-year retrospective cohort study in China. *Elife.* (2021) 10:e66419. doi: 10.7554/eLife.66419

66. Katagiri H, Yamada T, Oka Y. Adiposity and cardiovascular disorders: disturbance of the regulatory system consisting of humoral and neuronal signals. *Circ Res.* (2007) 101:27–39. doi: 10.1161/CIRCRESAHA.107.151621

67. Oda E. Metabolic syndrome: its history, mechanisms, and limitations. *Acta Diabetol.* (2012) 49:89–95. doi: 10.1007/s00592-011-0309-6

68. Halliwell B. Albumin–an important extracellular antioxidant? *Biochem Pharmacol.* (1988) 37:569–71. doi: 10.1016/0006-2952(88)90126-8

69. Oda E. Decreased serum albumin predicts hypertension in a Japanese health screening population. *Intern Med.* (2014) 53:655–60. doi: 10.2169/internalmedicine.53.1894

70. Nilsson PM. Blood glucose and hypertension development: the hen and egg controversy. *J Hypertens.* (2019) 37:11–2. doi: 10.1097/HJH.0000000000001946

71. Tatsumi Y, Morimoto A, Asayama K, Sonoda N, Miyamatsu N, Ohno Y, et al. Fasting blood glucose predicts incidence of hypertension independent of HbA1c levels and insulin resistance in middle-aged Japanese: the Saku study. *Am J Hypertens.* (2019) 32:1178–85. doi: 10.1093/ajh/hpz123

72. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med.* (2004) 140:434–40. doi: 10.7326/0003-4819-140-6-200403160-00010

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 11 October 2022
DOI 10.3389/fcvm.2022.946433

OPEN ACCESS

EDITED BY
Mary C. Wallingford,
Tufts Medical Center, United States

REVIEWED BY
Ramu Adela,
National Institute of Pharmaceutical Education and Research, India
Polona Žigon,
University Medical Centre Ljubljana, Slovenia

*CORRESPONDENCE
Zheng Cao
zhengcao2011@ccmu.edu.cn
Zhen Zhao
zhz9010@med.cornell.edu
Xiaowei Liu
liuxiaowei@mail.ccmu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 17 May 2022
ACCEPTED 27 September 2022
PUBLISHED 11 October 2022

CITATION
Zhao S, Yin C, Zhai Y, Jia Z, Su S, Lu Y, Meng L, Li C, Liu X, Cong Y, Li Y, Liu Y, Chen L, Wang J, Xu Z, Zheng Y, Sun Z, Luo RY, Yu X, Yang HS, Liu X, Zhao Z and Cao Z (2022) Serum peptidomic screening identified circulating peptide biomarkers predictive for preeclampsia. *Front. Cardiovasc. Med.* 9:946433. doi: 10.3389/fcvm.2022.946433

Serum peptidomic screening identified circulating peptide biomarkers predictive for preeclampsia

Shenglong Zhao[1†], Chenghong Yin[2†], Yanhong Zhai[3,4†], Zhaoxia Jia[5], Shaofei Su[2], Yifan Lu[3], Lanlan Meng[3], Chunbo Li[6], Xiang Liu[6], Yuting Cong[6], Youran Li[3,4], Ying Liu[3,4], Lu Chen[3], Jing Wang[3], Zhengwen Xu[3], Yuanyuan Zheng[1], Zhi Sun[7,8], Ruben Y. Luo[9], Xiaobo Yu[10], He S. Yang[11], Xiaowei Liu[1*], Zhen Zhao[11*] and Zheng Cao[3,4*]

[1]Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital, Beijing Maternal and Child Health Care Hospital, Capital Medical University, Beijing, China, [2]Central Laboratory, Beijing Obstetrics and Gynecology Hospital, Beijing Maternal and Child Health Care Hospital, Capital Medical University, Beijing, China, [3]Department of Laboratory Medicine, Beijing Obstetrics and Gynecology Hospital, Beijing Maternal and Child Health Care Hospital, Capital Medical University, Beijing, China, [4]Center of Clinical Mass Spectrometry, Beijing Obstetrics and Gynecology Hospital, Beijing Maternal and Child Health Care Hospital, Capital Medical University, Beijing, China, [5]Department of Information and Statistics, Beijing Obstetrics and Gynecology Hospital, Beijing Maternal and Child Health Care Hospital, Capital Medical University, Beijing, China, [6]SCIEX, Shanghai, China, [7]Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [8]Henan Engineering Research Center of Clinical Mass Spectrometry for Precision Medicine, Zhengzhou, China, [9]Department of Pathology, School of Medicine, Stanford University, Stanford, CA, United States, [10]State Key Laboratory of Proteomics, Beijing Proteome Research Center, National Center for Protein Sciences-Beijing (PHOENIX Center), Beijing Institute of Lifeomics, Beijing, China, [11]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, United States

Background: Reliable biomarkers are needed to improve preeclampsia (PE) prediction accuracy. With the investigational tool of peptidomics, we aimed to identify and validate potential serum peptide biomarkers in cohorts suspected for PE development in middle or late pregnancy.

Methods: Totally 195 serum samples were prospectively collected from pregnant women with PE-related syndromes who were followed up for PE development until delivery. Serum peptidomic analysis was performed in the discovery cohort of 115 samples using matrix-assisted laser desorption ionization-time of flight coupled with Linear Trap Quadropole Orbitrap mass spectrometry. The candidate biomarkers were further validated using an in-house developed liquid chromatography tandem mass spectrometry (LC-MS/MS) method in an independent validation cohort of 80 serum samples.

Results: We identified 8 peptides that were differentially expressed and originated from fibrinogen alpha chain (FGA), inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) and complement component 3. In the subsequent LC-MS/MS quantitation analysis, the levels of the three peptides (FGA-1033.4, ITIH4-2026.9, ITIH4-2051.1) exhibited a significant difference between the PE-positive and PE-negative groups. Further, the three-peptide panel yielded an area under the ROC curve (AUC) of 0.985

[95% confidence interval (CI) 0.965–1.000] and 0.923 (95% CI 0.845–1.000) in the discovery and validation cohorts respectively, with negative predictive values of 98.1–98.8% and positive predictive values of 73.1–85.3% that were much improved when compared with that of soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio.

Conclusions: We have discovered and validated a novel three-peptide biomarker panel predictive for the occurrence PE in pregnant women.

KEYWORDS

preeclampsia, prediction, peptidomics, peptides, mass spectrometry

Introduction

Preeclampsia (PE) is a pregnancy associated complication characterized by high blood pressure and proteinuria after 20 weeks of gestation and accompanied by multiple organ damage, such as heart, brain, and kidney (1, 2). PE related complications include but not limited to high risks of iatrogenic preterm delivery, intrauterine growth restriction, placental abruption, and perinatal mortality, along with maternal morbidity and mortality (3, 4). Currently, there is no reliable early warning indicators for PE due to a lack of effective diagnostic testing method, which poses a serious threat to the health of pregnant women and infants.

Extensive efforts have been invested in the search of PE predictive biomarkers. Some of the previous studies have focused on the risk assessment in the first trimester of pregnancy (5). However, the PE predictive models in early pregnancy, which often combines maternal background risk factors, imaging tests and serum biomarkers to increase sensitivity, displayed poor positive predictive values (PPV, 8–33%) in general population in which the prevalence of PE is low (6). False-positive patients who did not develop PE may have undergone unnecessary tests and prophylactic interventions with little benefit. Other investigations of PE predictive biomarkers have focused on suspected patients at a later stage of pregnancy (>20 gestational weeks) presenting with PE associated symptoms and/or unusual laboratory results (7, 8). For instance, the soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) has been proven to be effective in excluding PE with a negative predictive value (NPV) of 99.3%, although the PPV was still lower than 40% (7). Similar observation was made with renal function tests such as uric acid and cystatin C (9).

Peptidomics, a comprehensive analysis of native peptides using high performance liquid chromatography (HPLC) coupled with mass spectrometry (MS), is a powerful technology for unbiased screening of biomarkers of human diseases (10). Unlike proteomics, peptidomics focuses on the analysis of naturally occurring and endogenous low molecular weight (LMW) peptides and proteolytic fragments (MW < 10 kDa) which are considered as pathophysiological surrogates in signaling, proteolytic, and anti-proteolytic pathways in systemic diseases such as PE (11). For instance, using peptidomics, Wen et al. (11) identified the degradation patterns of serum specific protein throughout the progression of PE and discovered a 19-peptide panel that could be potentially used in PE prediction and differential diagnosis. Furthermore, despite a small cohort ($n = 6$, 3 PE and 3 controls), Dai et al. (12) found that the differentially expressed peptides were engaged in enzyme regulator activity, biological regulation, and coagulation cascades during pathological changes of PE. However, these previous peptidomic studies of PE prediction were hampered by their retrospective study design in nature and a lack of peptide quantitative validation in independent cohorts.

In this work, we have carried out a prospective peptidomic analysis in the suspected patients during PE development and progression. An analytical workflow of matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) combined with high-resolution mass spectrometry was applied to identify differentially expressed peptides. The selected peptide candidate biomarkers were further verified and validated using an in-house developed liquid chromatography-tandem mass spectrometry (LC-MS/MS) quantitative method in two independent cohorts.

Materials and methods

Subjects and sample collection

The enrollment criteria for women with suspected PE are described as follows (9). The recruited singleton pregnant women were at least 18 years old and between 20 and 36 gestational weeks (GWs). In addition, one of the following recruiting criteria had to be met for patient recruitment: new onset of elevated blood pressure (BP) (systolic BP

>120 and <160 mmHg and/or diastolic BP >80 and <110 mmHg) or proteinuria (≥2+ by dipstick); aggravation of preexisting hypertension or proteinuria; or persistent symptoms of upper abdominal pain, edema, headache, visual impairment, abnormal weight gain (>1 kg/week), decreased platelets (<150*109/L), elevated liver transaminase (alanine transferase >55 U/L or aspartate transaminase >34 U/L), fetal growth restriction (estimated fetal weight or abdominal circumference <10th percentile according to the charts routinely used by Obstetric Department at our institute), increased pulsatility index (PI) of the uterine artery (PI > 0.878), abnormal uterine ultrasound perfusion during mid-pregnancy, or uterine artery flow notching. The exclusion criteria included: confirmed diagnosis of PE or Hemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome at enrollment. The recruited pregnant subjects had their sera collected at their first visits with onset of the suspected symptoms, and followed up for the presence ("PE-positive" group) or absence ("PE-negative" group) of preeclampsia until delivery.

The preeclampsia diagnosis was determined with the diagnostic criteria proposed by the 2019 ACOG Practice Bulletin (6), in which preeclampsia was defined as gestational hypertension (systolic/diastolic blood pressure ≥140/90 mmHg) in previously normotensive women accompanied by proteinuria (urine protein ≥300 mg/24 h) or end-organ damage after 20 weeks of gestation. The methods for serum levels of sFlt-1 and PlGF were listed in the Supplementary Methods.

Biomarker study design

The study design of biomarker development followed the principles of the PRoBE (prospective-specimen collection, retrospective-blinded-evaluation) (13), in which all the serum samples were prospectively collected from the enrolled patients before PE development. As depicted in Figure 1, with 1,023 singleton pregnant women screened by the clinician team, totally 215 subjects meeting recruiting criteria were initially enrolled. Twenty of them were excluded due to incomplete follow-up ($n = 4$), low serum sample volume ($n = 1$) or receiving anti-hypertensive treatment during pregnancy ($n = 15$). For peptidomic analysis, peptide biomarker discovery and verification, 115 pregnant women (30 PE-positive and 85 PE-negative) enrolled from January 2018 to August 2018 were included. For the peptide candidates validation, an independent cohort of 80 subjects (20 PE-positive and 60 PE-negative, recruited from Oct 2018 to Jan 2019) was used. The schematic diagram of the study designed for the two phases of serum peptide biomarker development for PE prediction was shown in Figure 1.

Mass spectrometry-based serum peptidomics and peptide candidates quantitation

The method details for serum pretreatment, peptidomic profiling, data processing (14, 15), peptide candidates identification (16) and quantitation by liquid chromatography tandem mass spectrometry (LC-MS/MS) (17) were summarized in the Supplementary Methods. In the peptide quantitation, the details for calibration curve setup, internal standard spiking concentration and mass spectrometry parameter setting were included in Supplementary Table 1.

Statistical analysis

Data analysis was performed using statistical software SPSS 23.0. The Kolmogorov–Smirnov test was used to evaluate the normality of the data distribution. Numerical values were expressed as the mean and standard deviation (SD) for variables with normal distribution and as the median and percentiles for non-normally distributed data. Comparisons between the two groups were performed using the *t*-test (for normal distribution) or Mann-Whitney-*U* test (for non-normal distribution). Categorical variables were expressed as frequencies and proportion; comparisons between the two groups were tested by Chi-square test. The receiver operating characteristics (ROC) curve was used to analyze the predictive values of the markers for preeclampsia. Multivariate logistic regression analysis was applied to obtain the combined ROC curve. Sensitivity, specificity and cut-off values determined by the Youden's index were reported. The correlation analysis adopted in present study was Kendall's correlation method.

Results

Discovery and identification of differently expressed peptides between PE-positive and PE negative groups

Following the PRoBE design and the enrollment criteria, totally 195 suspected subjects with PE-relevant clinical symptoms or abnormal laboratory results had their serum sample collected right upon recognition by our clinical team. The demographic information for the recruited patients, including age, pre-pregnancy BMI, gravidity, parity, and sampling gestation week, were summarized in Table 1. Supplementary Tables 2, 3 listed detailed information of each participant in the discovery cohort ($n = 115$) and the validation cohort ($n = 80$) respectively. As shown in Table 1, for any of

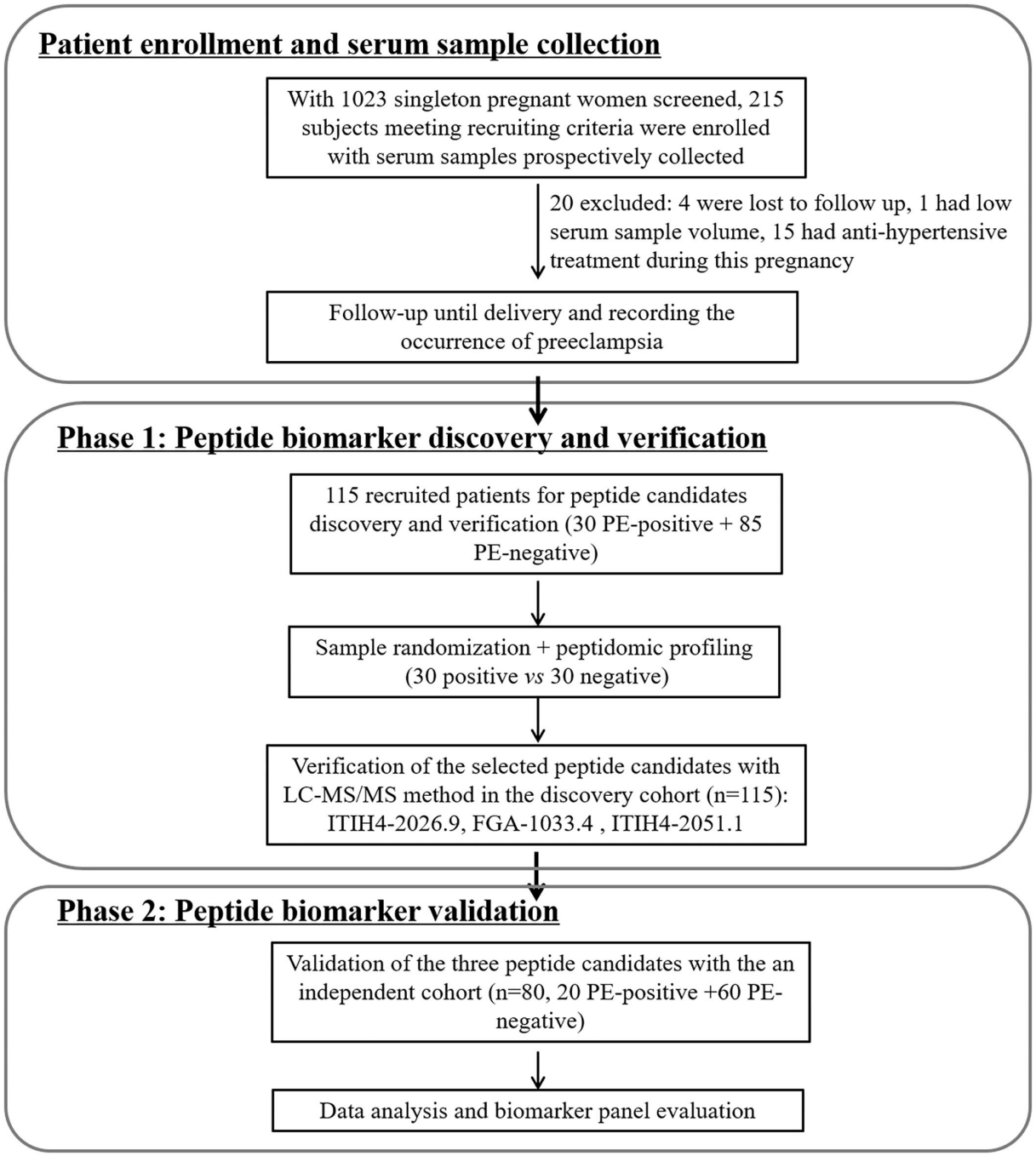


FIGURE 1
Schematic diagram for patient enrollment and peptide biomarker candidates discovery and validation for preeclampsia prediction.

the listed subjects' demographic factors, there was no significant difference between the PE-posiive and PE-negative groups.

As depicted in Figure 1, the peptide biomarker development consisted of 2 phases: discovery and validation. In the discovery group, serum samples from all PE-positive subjects (n = 30) and 30 PE-negative patients with matching demographic information were used for the peptide discovery study. A total of 117 informative peaks were detected using the MALDI-TOF

TABLE 1 Demographic information for the discovery cohort and the validation cohort.

	Age	Pre-pregnancy BMI	Gravidity (*n*, %)			Parity (*n*, %)			Sampling week
			1	2	≥3	0	1	2	
Discovery cohort (*n* = 115)									
PE-positive (*n* = 30)	33.4 ± 4.0	25.4 ± 4.4	10 (33.3%)	10 (33.3%)	10 (33.3%)	20 (66.7%)	9 (30.0%)	1 (3.3%)	28.4 ± 4.4
PE-negative subgroup (*n* = 30)	31.0 ± 4.2	24.0 ± 3.8	12 (42.9%)	9 (32.1%)	7 (25.0%)	20 (71.4%)	8 (28.6%)	0 (0.0%)	27.6 ± 5.0
PE-negative total (*n* = 85)	32.9 ± 4.4	24.2 ± 4.3	34 (43.0%)	24 (30.4%)	21 (26.6%)	54 (68.4%)	23 (29.1%)	2 (2.5%)	28.9 ± 5.3
p^a	0.120	0.222		0.706			0.609		0.528
p^b	0.640	0.217		0.632			0.968		0.561
Validation cohort (*n* = 80)									
PE-positive (*n* = 20)	32.6 ± 5.6	24.5 ± 4.2	8 (40.0%)	5 (25.0%)	7 (35.0%)	13 (65.0%)	7 (35.0%)	0 (0.0%)	29.6 ± 3.1
PE-negative (*n* = 60)	33.8 ± 4.4	25.1 ± 4.6	19 (35.8%)	19 (35.8%)	15 (28.3%)	33 (62.3%)	19 (35.8%)	1 (1.9%)	28.3 ± 4.6
p^c	0.310	0.619		0.669			0.820		0.149

[a]Comparison between PE-positive (*n* = 30) and PE-negative subgroup (*n* = 30) of the discovery cohort; [b]comparison between PE-positive (*n* = 30) and PE-negative (*n* = 85) of the discovery cohort; [c]comparison between PE-positive (*n* = 20) and PE-negative (*n* = 60) of the validation cohort.

peptidomic analytical platform described above. Thirty-two out of the 117 features were significantly different between the PE-positive and PE-negative groups ($p < 0.05$), with a fold-change of ≥2.00 or ≤0.40 and an average peak intensity of ≥100 in at least one group (Table 2, Supplementary Table 4).

Using LTQ-Orbitrap-MS analysis, 8 of 32 differentially expressed peptides were identified by matching the Sequest™ database (Table 2). With predicted peptide sequences listed in Table 2, the peptides 1,033.40 *m/z*, 3,260.46 *m/z*, 3,276.45 *m/z*, 5,900.70 *m/z* were identified to be fibrinogen alpha chain (FGA); the peptides 2,026.94 *m/z*, 2,051.08 *m/z* were identified to be Inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4); the peptides 1,876.85 *m/z*, 2,192.10 *m/z* were identified to be complement component 3 (C3). Considering the redundancy of the identified peptide sequences and convenience of peptide synthesis, the following four peptides were carried forward for the next absolute quantitation step by LC-MS/MS: FGA-1033.4, ITIH4-2026.9, ITIH4-2051.1, C3-1876.9.

Peptide biomarker quantitation by LC-MS/MS and sFlt-1/PlGF measurements

The selection of precursor and product ion of each peptide candidate was performed by direct infusion of the synthesized standard peptides. The resulting ion transition pairs chosen, calibrator and MS parameter setting were listed (Supplementary Table 1). As seen in Supplementary Figure 1, the identical peaks were observed in both calibrators and pooled patient samples for all the target peptides analyzed except C3-1876.9. As shown in Supplementary Figure 1, no corresponding peak for C3-1876.9 was observed in the pooled patient serum, suggesting that C3-1876.9 identified by high-resolution MS was a pseudo-target which was not further investigated in the following experiments. All of the calibration curves were linear within the concentration ranges set for each of the peptides ($r > 0.995$) (Supplementary Figure 2). The original peptide quantitation data using the in-house established LC-MS/MS method and the measurements of serum levels of sFlt-1/PlGF in both discovery and validation cohorts were recorded in Supplementary Tables 2, 3.

Performance of the peptide biomarker candidates and sFlt-1/PlGF ratio in PE prediction

With the similar changing pattern seen in the peptidomic study by MALDI-TOF, all three peptides, including FGA-1033.4, ITIH4-2026.9, ITIH4-2051.1, were found significantly elevated ($p < 0.001$) in the PE-positive group in the discovery cohort ($n = 115$) (Supplementary Table 5, Figure 2). Interestingly, a three-dimensional (3-D) scattered plot also showed almost complete separation of the PE-positive and PE-negative patients, suggesting their potential discriminating power when used in a combinational panel (Supplementary Figure 3). Moreover, in the ROC analysis with the discovery cohort, the area under curves (AUCs) of the three candidate peptides and sFlt-1/PlGF ratio were listed in the order of decreasing values: 0.985 (95% CI, 0.965–1.000) (three peptides combined), 0.946 (95% CI, 0.905–0.988) (ITIH4-2026.9), 0.939 (95% CI, 0.898–0.980) (FGA-1033.4), 0.820 (95% CI, 0.744–0.896) (ITIH4-2051.1), 0.637 (95% CI, 0.525–0.750) (sFlt-1/PlGF). The predictive panel containing 3 peptides showed higher accuracy in PE prediction than any of the peptide biomarker along ($p < 0.05$) (Figure 3), and achieved a sensitivity of 96.7%, a specificity of 94.1%, PPV

TABLE 2 Significantly differentially expressed mass peaks with peptide identification by LTQ-Orbitrap-MS.

Mass, m/z[a]	FDR-adjusted p-value	PE-positive ($n = 30$)		PE-negative ($n = 30$)		FC[c]	Peptide ID and sequence
		Mean	SD[b]	Mean	SD		
2026.94	1.02E-09	284.3	171.3	19.3	8.5	14.76	ITIH4: QLGLPGPPDVPDHAAYHPF
1876.85	1.33E-09	105.7	65.1	16.9	10.3	6.24	Complement C3: YSIITPNILRLESEET
3276.45	1.30E-09	152.9	59.9	34.6	22.6	4.42	FGA: SSSYSKQFTSSTSYNRGDSTFESKSYKM (+15.99)A[d]
3260.46	1.23E-09	1117.7	419.9	270.3	164.9	4.14	FGA: SSSYSKQFTSSTSYNRGDSTFESKSYKMA
2192.10	1.56E-03	113.2	103.1	45.6	32.8	2.48	Complement C3: SPMYSIITPNILRLESEET
1033.40	1.62E-03	110.2	63.9	46.2	31.1	2.38	FGA: SSSYSKQFT
2051.08	5.75E-04	436.8	330.0	218.4	260.1	2.00	ITIH4: YYLQGAKIPKPEASFSPR
5900.70	1.56E-04	430.0	282.0	1065.5	718.6	0.40	FGA: SSSYSKQFTSTSYNRGDSTFESKSYKMADEAGS-EADHEGTHSTKRGHAKSRPV

[a]Mass determined by LTQ-Orbitrap-MS; [b]standard deviation; [c]fold change; [d](+15.99) indicating oxidation on the methylsulfinyl group of methionine residue. ITIH4, Inter-alpha-trypsin inhibitor heavy chain H4; FGA, Fibrinogen alpha chain.

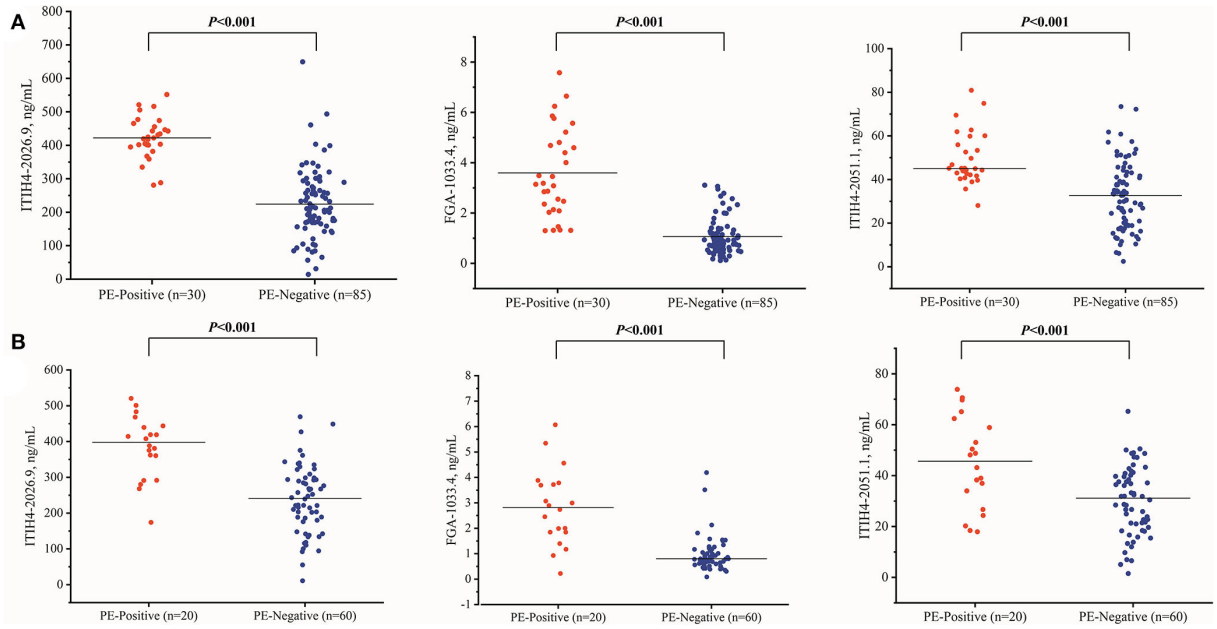


FIGURE 2
The three peptide candidates quantitation of the PE-positive and PE-negative groups in the discovery **(A)** (PE-positive $n = 30$, PE negative $n = 85$) and validation **(B)** (PE-positive $n = 20$, PE negative $n = 60$) cohorts.

of 85.3%, and NPV of 98.8% at the cutoff determined by the Youden's index (Table 3).

In the independent validation cohort, the three peptides exhibited significantly higher levels in the PE-positive group in comparison to the PE-negative group (Supplementary Table 5, Figure 2). Similar separation pattern was observed between the PE-positive and PE-negative patients in the 3-D scatter plot (Supplementary Figure 3). In the ROC analysis, the FGA-1033.4 showed the best predictive power with an AUC of 0.896 (95% CI, 0.795–0.997), followed by ITIH4-2026.9 (AUC = 0.866, with 95% CI of 0.771–0.961), ITIH4-2051.1 (AUC = 0.734, with 95% CI of 0.598–0.871) and sFlt-1/PlGF (AUC = 0.733, with 95%

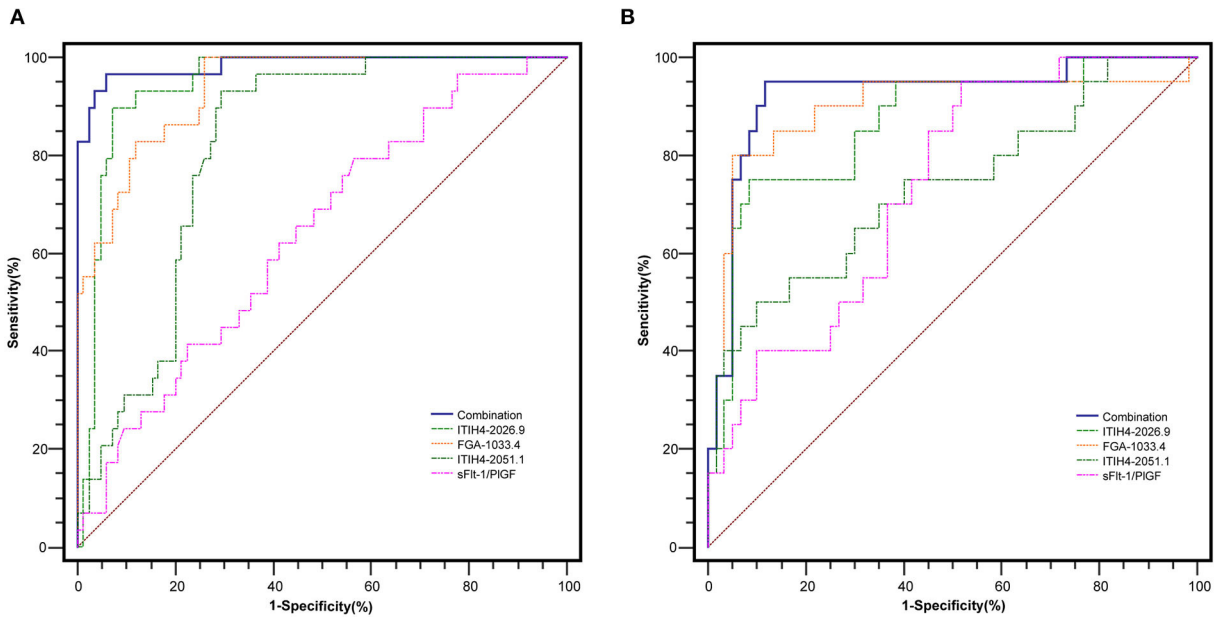


FIGURE 3
The ROC analysis of the peptide candidates for PE prediction in the discovery **(A)** (PE-positive $n = 30$, PE negative $n = 85$) and validation **(B)** (PE-positive $n = 20$, PE negative $n = 60$) cohorts.

TABLE 3 ROC analysis of the sFlt-1/PlGF and peptide biomarker candidates in preeclampsia prediction.

	sFlt-1/PlGF	ITIH4-2026.9	FGA-1033.4	ITIH4-2051.1	Combined[a]
Discovery cohort ($n = 115$)					
AUC (95% CI)	0.637 (0.525–0.750)	0.946 (0.905–0.988)	0.939 (0.898–0.980)	0.820 (0.744–0.896)	0.985 (0.965–1.000)
Sensitivity, %	79.3	90.0	100.0	93.3	96.7
Specificity, %	43.5	92.9	74.1	70.6	94.1
Positive predictive value, %	32.4	81.8	57.7	52.8	85.3
Negative predictive value, %	86.0	96.3	100.0	96.8	98.8
p-value of AUCs comparison	<0.001	0.036[b]	0.026[c]	<0.001[d]	–
Validation cohort ($n = 80$)					
AUC (95% CI)	0.733 (0.617–0.850)	0.866 (0.771–0.961)	0.896 (0.795–0.997)	0.734 (0.598–0.871)	0.923 (0.845–1.000)
Sensitivity, %	95.0	75.0	80.0	50.0	95.0
Specificity, %	48.3	91.7	95.0	90.0	88.3
Positive predictive value, %	38.0	75.0	84.2	62.5	73.1
Negative predictive value, %	96.7	91.7	93.4	84.4	98.1
p-value of AUCs comparison	0.004	0.040[b]	0.185[c]	0.002[d]	–

[a]The three-peptide combined panel in ROC analysis; [b]AUCs comparison between ITIH4-2026.9 and three-peptide panel; [c]AUCs comparison between FGA-1033.4 and three-peptide panel; [d]AUCs comparison between ITIH4-2051.1 and three-peptide panel. ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval.

CI of 0.617–0.850). The three-peptide panel yielded a better AUC (0.923, with 95% CI of 0.845–1.000) than that of sFlt-1/PlGF, ITIH4-2051.1 or ITIH4-2026.9, but not FGA-1033.4. With the cut-off determined with Youden's Index, the three-peptide panel showed a sensitivity of 95.0%, a specificity of 88.3%, PPV of 73.1%, and NPV of 98.1% (Table 3). As shown in Table 4, interestingly, all of the three peptides showed slightly negative correlation with serum PlGF and marginally positively correlation with sFlt-1/PlGF ratio. No significant correlation was observed between any of the three peptide candidates and the rest of parameters included, such as sFlt-1, age, pre-pregnancy BMI, gravidity and parity.

TABLE 4 Peptide candidates' correlation analysis with clinical markers.

	sFlt-1	PlGF	sFlt-1/PlGF	Age	Pre-pregnancy BMI	Gravidity	Parity
ITIH4-2026.9, r^d	0.101	−0.105	0.136	0.068	0.035	0.102	0.124
FGA-1033.4, r^d	0.011	−0.120	0.084	0.000	−0.005	0.094	0.040
ITIH4-2051.1, r^d	0.055	−0.116	0.109	0.027	−0.003	0.108	0.143
p^a	0.054	0.045	0.010	0.211	0.502	0.082	0.051
p^b	0.828	0.023	0.112	0.995	0.928	0.111	0.530
P^c	0.297	0.027	0.037	0.613	0.955	0.066	0.024

[a]Comparison between ITIH4-2026.9 and other clinical markers; [b]comparison between FGA-1033.4 and other clinical markers; [c]comparison between ITIH4-2051.1 and other clinical markers; [d]r stands for the calculated correlation coefficient with the Kendall's method.

Discussion

Using the state-of-the-art MALDI-TOF coupled with Linear Trap Quadropole Orbitrap mass spectrometry, our study discovered a novel three-peptide panel which has exhibited promising performance in the prediction of PE occurrence in pregnant women. The finding was further validated in an independent cohort with comparable accuracy, sensitivity and specificity. Furthermore, this three-peptide model yielded a significantly improved PPV of 73.1–85.3% compared with that of sFlt-1/PlGF ratio as predictive markers (32.4–38.0%), which was close to what was observed in our previous study (9). Therefore, our panel is more accurate in PE prediction with suspected patients and offers a feasible and efficient strategy for "rule-in" and "rule-out" high risk patients who may need extra clinical care.

MALDI-TOF-MS is a cutting-edge technology that offers sensitive and accurate identification of proteomic biomarkers of disease condition (18). The bead-based fractionation method, which selectively separates peptides according to different chemical chromatographic surfaces on the outer layer of magnetic beads, has been developed for direct use in MALDI-TOF-MS analysis (19). In combination with the bioinformatics BE Software™ (Bioyong Tech., Beijing, China), weak cation exchange magnetic beads (WCX-MB) pretreatment and MALDI-TOF-MS analysis provides a powerful tool for analyzing and identifying novel biologically informative molecules and has been successfully applied to biomarker research (20). In this work, the MALDI-TOF peptidomic analysis in combination with a high-resolution mass spectrometry identified 8 differentially expressed peptide candidates belonging to three proteins: FGA, ITIH4 and C3 (Table 2). However, the peptideC3-1876.9 was not found in the pooled serum of pregnant women by the LC-MS/MS method. This apparent discrepancy may be explained by the different serum pretreatment steps applied in the MALDI/QE-based peptidomic analysis vs. the LC-MS/MS peptide quantitation.

Intriguingly, according to an earlier retrospective peptidomic study, 13 peptides from FGA and 1 peptide from ITIH4 (different peptide sequences compared with our peptide candidates) were found remarkably upregulated in PE, suggesting the pathological relevance of the two proteins in PE disease progression (11). Similar observation was made in our peptidomic study in which 4 peptides from FGA and 2 peptides from ITIH4 were differentially expressed and identified, suggesting there is a disease-specific proteolytic degradation pattern of the parent proteins. The fact that multiple peptides from the same proteins were identified further confirmed the accuracy and reliability of our discovery.

FGA and ITIH4 are derived from proteins known to be involved in the pathophysiology of PE in acute inflammatory and defense response. FGA is encoded by the human FGA gene, which is a component of fibrinogen that consists of pairs of three different polypeptide chains, including the α, β and γ chains joined by disulfide bonds to form a symmetric dimeric structure (21). Fibrinogen is involved in blood clotting, but has also been implicated as an inflammatory mediator in several diseases, including rheumatoid arthritis (RA), multiple sclerosis, and Alzheimer's disease (22). The up-regulation of FGA is believed to contribute to the pathogenesis of preeclampsia by participating in the trophoblast recast of uterine spiral artery, activation of systemic inflammatory response and injury of endothelial cells (23). Furthermore, FGA was found to be an independent risk factor associated with increased cardiovascular morbidity and mortality in PE patients (24).

Inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) refer to the heavy chains of protein members belonging to the ITI family, which is involved in stabilization of the extracellular matrix (25). ITIH4 is a 120-kDa serum glycoprotein secreted primarily by liver and is associated with inflammation and carcinogenesis. As an acute phase response protein, ITIH4 is increased in response to infection and inflammation, and may provide important diagnostic information during surgical trauma (26). In previous studies, it has been indicated that ITIH4 was significantly up-regulated in serum samples of patients with ovarian, breast or bladder cancers (27). Interestingly, in pigs, endometrial gene expression of a 30-kDa fragment of ITI-H4 was detected during the estrous cycle and early

pregnancy. Geisert and his colleagues suggested that the ITIH4 may be expressed to protect the maternal uterus as an acute phase protein during primary pregnancy (28). Further, ITIH4 is believed to contribute the pathogenesis of preeclampsia through excessive activation of inflammatory immunity, leading to disturbance of maternal-fetal immune balance and resulting in "shallow implantation of the placenta". Another previous study showed that overexpression of the 36-kDa fragmented form ITIH4 may induce a strong inflammatory response in pregnant women, and consequently the pregnancy may fail (29). However, the exact biological function of ITIH4 in PE is still not fully understood.

While a large number of studies have focused on preeclampsia prediction during pregnancy, very few serum predictive markers were successfully implemented in clinical practice mainly due to low accuracy. With the low prevalence of preeclampsia in the general pregnant population, it would be economically inefficient to universally apply laboratory biomarker test(s) during pregnancy. In the publication of evaluating sFlt-1/PlGF ratio in PE prediction by Zeisler et al. (7), the authors narrowed down the targeting patients who presented with PE-related clinical and/or laboratory abnormalities. A similar patient recruiting strategy was adopted in our study. With a straight focus on the subgroup of suspected patients with relevant symptoms, it allows medical resources to be better targeted on the patients that are more likely to develop preeclampsia.

In our study, the three peptides FGA-1033.4, ITIH4-2026.9, ITIH4-2051.1 were found to be able to accurately predict the occurrence of PE in middle or late pregnancy. However, the exact biological roles of FGA and ITIH4 in PE development are still largely unknown and need to be further investigated. In addition, with the help of the peptide quantitation method developed and validated in present study, the cut-off values of the three peptides should be determined in a large and multi-center study for future clinical application.

This work is a well-designed prospective study, with rigorous technical design of discovery and validation studies using state-of-the-art MS in independent patient cohorts. However, a few limitations still exist. First, all the participants included in our study were Chinese; the performance of this peptide panel in diverse ethnic backgrounds especially in Western countries needs to be further tested. Second, the overall size of the cohorts was relatively small and all the patients were from a single site.

Conclusions

Our study is the first to develop and validate a predictive panel consisting of three circulating peptides that can effectively rule-out or rule-in PE development in the suspected patients. The changes in these peptides predated the onset of the disease and were present in both of the discovery and validation cohorts. With the implement of a straightforward LC-MS/MS quantitation method, these circulating peptides may provide information on PE development and act as potential biomarkers for PE prediction in clinical practice. However, the pathological mechanism in which the identified peptide markers may participate requires further investigation.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.iprox.cn/page/project.html?id=IPX0004482000.

Ethics statement

This study was approved on 07 June 2021, by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (approval number: 2021-KY-059-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SZ: conceptualization, data curation, and writing—original draft. CY: project administration and supervision. YZha: conceptualization, data curation, and funding acquisition. ZJ and SS: investigation and methodology. YLu and LM: investigation. CL, XianL, and YC: methodology. YLi, YLiu, LC, JW, and ZX: data curation. YZhe: data curation and investigation. ZS, RL, XY, and HY: writing—review and editing. XiaoL: conceptualization, data curation, and project administration. ZZ: conceptualization, supervision, and writing—review and editing. ZC: conceptualization, supervision, funding acquisition, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Capital Medical University (No. PYZ20056) and the Beijing Municipal Administration of Hospitals Incubating Program (No. PX2020060). The funding bodies did not take part in the design of the study, the collection, analysis and interpretation of the data, or manuscript writing.

Acknowledgments

The MALDI-TOF spectrum alignment and interpretation was kindly assisted by Yanyan Niu, Beijing LinkStart Med-Tech Co., Ltd.

Conflict of interest

Authors CL, XianL, and YC were employed by company SCIEX.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.946433/full#supplementary-material

References

1. Ling L, Huang H, Zhu L, Mao T, Shen Q, Zhang H. Evaluation of plasma endothelial microparticles in pre-eclampsia. *J Int Med Res.* (2014) 42:42–51. doi: 10.1177/0300060513504362

2. Peng B, Zhang L, Yan J, Qi H, Zhang W, Fan L, et al. Assessment of the diagnostic value of a urinary adipsin rapid strip test for pre-eclampsia: a prospective multicenter study. *J Obstet Gynaecol Res.* (2017) 43:30–3. doi: 10.1111/jog.13156

3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* (2008) 371:75–84. doi: 10.1016/S0140-6736(08)60074-4

4. McClure JH, Cooper GM, Clutton-Brock TH. Centre for maternal and child enquiries. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008: a review. *Br J Anaesth.* (2011) 107:127–32. doi: 10.1093/bja/aer192

5. De Kat AC, Hirst J, Woodward M, Kennedy S, Peters SA. Prediction models for preeclampsia: a systematic review. *Pregnancy Hypertens.* (2019) 16:48–66. doi: 10.1016/j.preghy.2019.03.005

6. ACOG Practice Bulletin No. 202. Summary: gestational hypertension and preeclampsia. *Obstet Gynecol.* (2019) 133:211–4. doi: 10.1097/AOG.0000000000003242

7. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med.* (2016) 374:13–22. doi: 10.1056/NEJMoa1414838

8. Huhn EA, Hoffmann I, Martinez D, Tejada B, Lange S, Sage KM, et al. Maternal serum glycosylated fibronectin as a short-term predictor of preeclampsia: a prospective cohort study. *BMC Pregn Childbirth.* (2020) 20:128. doi: 10.1186/s12884-020-2809-2

9. Wang J, Hu H, Liu X, Zhao S, Zheng Y, Jia Z, et al. Predictive values of various multiple serum biomarkers in women with suspected preeclampsia: a prospective study. *J Clin Lab Anal.* (2021) 35:e23740. doi: 10.1002/jcla.23740

10. Schrader M. Origins, technological development, and applications of peptidomics. *Methods Mol Biol.* (2018) 1719:3–39. doi: 10.1007/978-1-4939-7537-2_1

11. Wen Q, Liu LY, Yang T, Alev C, Wu S, Stevenson DK, et al. Peptidomic identification of serum peptides diagnosing preeclampsia. *PLoS ONE.* (2013) 8:e65571. doi: 10.1371/journal.pone.0065571

12. Dai X, Song X, Rui C, Meng L, Xue X, Ding H, et al. Peptidome analysis of human serum from normal and preeclamptic pregnancies. *J Cell Biochem.* (2017) 118:4341–8. doi: 10.1002/jcb.26087

13. Pepe MS, Feng Z, Janes H, Bossuyt PM, Potter JD. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. *J Natl Cancer Inst.* (2008) 100:1432–8. doi: 10.1093/jnci/djn326

14. Jia K, Li W, Wang F, Qu H, Qiao Y, Zhou L, et al. Novel circulating peptide biomarkers for esophageal squamous cell carcinoma revealed by a magnetic bead-based MALDI-TOFMS assay. *Oncotarget.* (2016) 7:23569–80. doi: 10.18632/oncotarget.8123

15. Liu Y, Wei F, Wang F, Li C, Meng G, Duan H, et al. Serum peptidome profiling analysis for the identification of potential biomarkers in cervical intraepithelial neoplasia patients. *Biochem Biophys Res Commun.* (2015) 465:476–80. doi: 10.1016/j.bbrc.2015.08.042

16. Zheng H, Li R, Zhang J, Zhou S, Ma Q, Zhou Y, et al. Salivary biomarkers indicate obstructive sleep apnea patients with cardiovascular diseases. *Sci Rep.* (2014) 4:7046. doi: 10.1038/srep07046

17. Campbell J, Rezai T, Prakash A, Krastins B, Dayon L, Ward M, et al. Evaluation of absolute peptide quantitation strategies using selected reaction monitoring. *Proteomics.* (2011) 11:1148–52. doi: 10.1002/pmic.201000511

18. Banks RE, Dunn MJ, Hochstrasser DF, Sanchez JC, Blackstock W, Pappin DJ, et al. Proteomics: new perspectives, new biomedical opportunities. *Lancet.* (2000) 356:1749–56. doi: 10.1016/S0140-6736(00)03214-1

19. Zhang X, Leung SM, Morris CR, Shigenaga MK. Evaluation of a novel, integrated approach using functionalized magnetic beads, bench-top MALDI-TOF-MS with prestructured sample supports, and pattern recognition software for profiling potential biomarkers in human plasma. *J Biomol Tech.* (2004) 15:167–75.

20. Wu S, Xu K, Chen G, Zhang J, Liu Z, Xie X. Identification of serum biomarkers for ovarian cancer using MALDI-TOF-MS combined with magnetic beads. *Int J Clin Oncol.* (2012) 17:89–95. doi: 10.1007/s10147-011-0259-6

21. Zhang WC, Wang YG, Zhu ZF, Wu FQ, Peng YD, Chen ZY, et al. Regulatory T cells protect fine particulate matter-induced inflammatory responses in human umbilical vein endothelial cells. *Mediat Inflamm.* (2014) 2014:869148. doi: 10.1155/2014/869148

22. Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. *Semin Immunopathol.* (2012) 34:43–62. doi: 10.1007/s00281-011-0290-8

23. Sargent IL, Germain SJ, Sacks GP, Kumar S, Redman CW. Trophoblast deportation and the maternal inflammatory response in pre-eclampsia. *J Reprod Immunol.* (2003) 59:153–60. doi: 10.1016/S0165-0378(03)00044-5

24. Lowe GD. Fibrinogen and cardiovascular disease: historical introduction. Eur Heart J. (1995) 16(Suppl A):2–5. doi: 10.1093/eurheartj/16.suppl_A.2

25. Bost F, Diarra-Mehrpour M, Martin JP. Inter-alpha-trypsin inhibitor proteoglycan family: a group of proteins binding and stabilizing the extracellular matrix. *Eur J Biochem.* (1998) 252:339–46. doi: 10.1046/j.1432-1327.1998.2520339.x

26. Diamandis EP. Peptidomics for cancer diagnosis: present and future. *J Proteome Res.* (2006) 5:2079–82. doi: 10.1021/pr060225u

27. Wang Z, Yip C, Ying Y, Wang J, Meng XY, Lomas L, et al. Mass spectrometric analysis of protein markers for ovarian cancer. *Clin Chem.* (2004) 50:1939–42. doi: 10.1373/clinchem.2004.036871

28. Geisert RD, Yelich JV, Pratt T, et al. Expression of an inter-alpha-trypsin inhibitor heavy chain-like protein in the pig endometrium during the oestrous cycle and early pregnancy. *J Reprod Fertil.* (1998) 114:35–43. doi: 10.1530/jrf.0.1140035

29. Kim MS, Gu BH, Song S, et al. ITI-H4, as a biomarker in the serum of recurrent pregnancy loss (RPL) patients. *Mol Biosyst.* (2011) 7:1430–40. doi: 10.1039/c0mb00219d

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 10 November 2022
DOI 10.3389/fcvm.2022.1033606

OPEN ACCESS

EDITED BY
Daniela Sorriento,
University of Naples Federico II, Italy

REVIEWED BY
Giuliano Tocci,
Sapienza University of Rome, Italy
(EE) Marius Miglinas,
Vilnius University, Lithuania

*CORRESPONDENCE
Renata Cífková
renata.cifkova@ftn.cz

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 31 August 2022
ACCEPTED 28 October 2022
PUBLISHED 10 November 2022

CITATION
Cífková R, Bruthans J, Strilchuk L, Wohlfahrt P, Krajčoviechová A, Šulc P, Jozífová M, Eremiášová L, Pudil J, Linhart A, Widimský J Jr, Filipovský J, Mayer O Jr, Škodová Z and Lánská V (2022) Longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension in the Czech population. Are there any sex differences?
Front. Cardiovasc. Med. 9:1033606. doi: 10.3389/fcvm.2022.1033606

Longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension in the Czech population. Are there any sex differences?

Renata Cífková[1,2]*, Jan Bruthans[1], Larysa Strilchuk[1,3], Peter Wohlfahrt[1], Alena Krajčoviechová[1], Pavel Šulc[1], Marie Jozífová[1], Lenka Eremiášová[2], Jan Pudil[2], Aleš Linhart[2], Jiří Widimský Jr[4], Jan Filipovský[5], Otto Mayer Jr[5], Zdenka Škodová[6] and Věra Lánská[7]

[1]Center for Cardiovascular Prevention, First Faculty of Medicine and Thomayer University Hospital, Charles University in Prague, Prague, Czechia, [2]Department of Medicine II, First Faculty of Medicine, Charles University in Prague, Prague, Czechia, [3]Department of Therapy No. 1, Medical Diagnostics, Hematology and Transfusiology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine, [4]Department of Medicine III, First Faculty of Medicine, Charles University, Prague, Czechia, [5]Department of Medicine II, Faculty of Medicine, Charles University, Pilsen, Czechia, [6]Department of Preventive Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czechia, [7]Medical Statistics Unit, Institute for Clinical and Experimental Medicine, Prague, Czechia

Background: Hypertension is the most common cardiovascular disease which substantially increases cardiovascular morbidity and mortality. Despite the broad availability of antihypertensive medication, control of hypertension is not satisfactory worldwide.

Objective: The study aim was to assess longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension in a representative population sample of the Czechia from 1985 to 2016/2017, focusing on sex differences.

Methods: A total of 7,606 men and 8,050 women aged 25–64 years were screened for major CV risk factors in seven independent cross-sectional surveys run consistently in the same six country districts of the Czechia between 1985 and 2016/2017. The population samples were randomly selected.

Results: Over a study period of 31/32 years, there was a significant decline in systolic and diastolic blood pressure in both sexes, whereas the prevalence of hypertension decreased only in women. There was an increase in hypertension awareness in both sexes over the entire study period with consistently higher rates in women. The proportion of individuals treated with antihypertensive drugs increased significantly in both sexes throughout the

study, again with consistently higher rates in women. Control of hypertension increased significantly over the study period with consistently higher rates in women. The age-adjusted trends in blood pressure, prevalence, awareness, and treatment of hypertension were significantly different in men and women, always in favor of women. The age-adjusted trends in control of hypertension in treated patients were equally poor in both sexes.

Conclusion: There are significant differences in longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension between men and women, always in favor of women except for the control of hypertension in treated patients, where it is equally poor in both sexes.

KEYWORDS

Czech MONICA, Czech post-MONICA study, epidemiology of hypertension, population random sample, response rate

Introduction

Hypertension is the most prevalent cardiovascular disease affecting 30 – 50% of the adult population worldwide, with significant regional differences (1). Hypertension is also a major risk factor for developing stroke, coronary heart disease, heart and renal failure, peripheral arterial disease, aortic aneurysm, atrial fibrillation, and cognitive dysfunction/dementia (2, 3). Large clinical trials have convincingly shown that treatment of hypertension is followed by a decrease in cardiovascular morbidity and mortality (4, 5).

Hypertension can be easily detected and treated in primary care facilities. However, control of hypertension remains a major challenge throughout the global population. The Global Burden of Disease Study 2019 identified high systolic blood pressure (BP) (defined as a theoretical minimum risk exposure level of $\geq$110 – 115 mm Hg) as the leading Level 2 risk factor for death worldwide (3, 6).

The burden of hypertension can be reduced by simultaneously approaching the reduction of hypertension prevalence through primary prevention, and by increasing treatment and control of hypertension.

This analysis aimed to assess the longitudinal trends in BP, prevalence, awareness, treatment, and control of hypertension in a representative population sample of the Czechia from 1985 to 2016/2017, focusing on sex differences.

Materials and methods

Study population

A total of 7,606 men and 8,050 women aged 25–64 years were screened for major CV risk factors in seven independent cross-sectional surveys run in the same six country districts of the Czechia between 1985 and 2016/2017. The initial three surveys in 1985, 1988, and 1992 were conducted within the WHO MONICA Project (7), further referred to as the Czech MONICA Study.

The study population was always randomly selected as a one percent population sample within each district, stratified by age and sex, within an age range of 25–64 years. The details are published elsewhere (8).

The Czech MONICA and Czech post-MONICA studies (the last four surveys) were approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czechia. All participants provided informed consent.

Screening examination

The methods used were detailed elsewhere (9). In short, the examination consisted of a questionnaire which was completed by a physician. Currently prescribed drugs were recorded and verified (when possible) against drug containers.

Height and body weight measurements were taken in the standing position without shoes and outer garments. BP measurement was performed consistently on the right arm (supported at the heart level), in the sitting position, after a minimum 5-min rest, using standard mercury sphygmomanometers and properly sized cuffs. Blood pressure values were recorded to the nearest 2 mmHg. In 1985, 1988, and 1992, two consecutive BP measurements were performed with their mean values used for the longitudinal trend analysis. In 1997/98, 2000/01, 2007/08, and 2016/17 the study protocol was extended by including three consecutive BP measurements;

TABLE 1 Survey sample sizes, response rates, BMI, and obesity prevalence by sex and year of survey.

	1985	1988	1992	1997/98	2000/01	2007/08	2016/17	*p* for trend
Total	**2,570**	**2,768**	**2,343**	**1,990**	**2,055**	**2,246**	**1,684**	
Age, yrs (mean ± SD)	44.9 ± 11.38	45.1 ± 11.26	44.7 ± 10.87	45.6 ± 10.64	46.2 ± 11.9	47.1 ± 11.46	47.8 ± 10.85	<0.001
Men	**1,253**	**1,357**	**1,134**	**969**	**1,003**	**1,102**	**788**	
Age, years (mean ± SD)	45.0 ± 11.39	45.3 ± 11.29	44.6 ± 10.76	45.8 ± 10.63	46.7 ± 11.07	47.9 ± 11.65	48.0 ± 10.83	<0.001
Response rate (%)	81.5	85.5	73.2	63.2	62.0	62.1	43.1	<0.001
Age group, *n* (%)								
25–34	307 (24.5)	322 (23.7)	246 (21.7)	194 (20.0)	187 (18.6)	208 (18.9)	116 (14.7)	<0.001
35–44	296 (23.6)	323 (23.8)	350 (30.9)	230 (23.7)	230 (22.9)	251 (22.8)	198 (25.1)	ns
45–54	334 (26.7)	361 (26.6)	310 (27.3)	332 (34.3)	295 (29.4)	231 (21.0)	210 (26.7)	ns
55–64	316 (25.2)	351 (25.9)	228 (20.1)	213 (22.0)	291 (29.0)	412 (37.4)	264 (33.50)	ns
BMI, kg/m^2, (mean ± SD)								
Total, 25–64 y	27.0 ± 4.0	27.7 ± 3.8	27.1 ± 3.8	27.5 ± 3.8	28.1 ± 4.4	28.5 ± 4.6	29.2 ± 5.1	0.001
25–34 y	25.5 ± 3.4	26.2 ± 3.3	25.2 ± 3.2	25.9 ± 3.2	26.2 ± 4.3	26.3 ± 4.3	27.5 ± 4.9	0.011
35–44 y	26.8 ± 3.8	27.1 ± 3.7	26.8 ± 3.6	26.7 ± 3.3	27.6 ± 3.9	28.0 ± 4.5	28.2 ± 4.8	<0.001
45–54 y	27.7 ± 3.8	28.1 ± 3.7	27.8 ± 3.6	28.2 ± 3.9	28.5 ± 4.2	28.7 ± 4.4	29.5 ± 5.0	<0.001
55–64 y	28.1 ± 4.3	29.2 ± 3.9	28.6 ± 4.1	28.8 ± 3.8	29.5 ± 4.6	29.8 ± 4.6	30.4 ± 5.3	<0.001
BMI ≥ 30 kg/m^2, *n* (%)	246 (19.7)	343 (25.3)	225 (19.9)	244 (25.2)	295 (29.5)	370 (33.6)	297 (37.7)	<0.001
Women	**1,317**	**1,411**	**1,209**	**1,021**	**1,052**	**1,144**	**896**	
Age, years (mean ± SD)	44.9 ± 11.38	44.9 ± 11.24	44.9 ± 10.97	45.3 ± 10.65	45.8 ± 11.10	46.4 ± 11.23	47.6 ± 10.88	<0.001
Response rate (%)	85.0	88.4	76.7	66.4	63.8	63.1	48.6	<0.001
Age group, *n* (%)								
25–34	322 (24.4)	342 (24.2)	266 (22.0)	212 (20.8)	213 (20.2)	235 (20.5)	147 (16.4)	<0.001
35–44	340 (25.8)	369 (26.2)	356 (29.4)	266 (26.1)	276 (26.2)	284 (24.8)	204 (22.8)	ns
45–54	343 (26.0)	360 (25.5)	311 (25.7)	326 (31.9)	285 (27.1)	299 (26.1)	282 (31.5)	ns
55–64	312 (23.7)	340 (24.1)	276 (22.8)	217 (21.3)	278 (26.4)	326 (28.5)	263 (29.4)	ns
BMI, kg/m^2, (mean ± SD)								
Total, 25–64 y	27.3 ± 5.4	27.7 ± 5.4	26.9 ± 5.3	27.1 ± 5.5	27.3 ± 5.7	27.3 ± 5.7	27.3 ± 6.0	ns
25–34 y	23.9 ± 4.1	24.3 ± 3.9	23.6 ± 4.0	24.2 ± 4.6	23.8 ± 4.1	23.8 ± 4.8	24.7 ± 5.4	ns
35–44 y	26.5 ± 4.7	26.9 ± 4.9	25.8 ± 4.9	25.8 ± 4.9	26.4 ± 5.5	26.6 ± 5.7	26.5 ± 6.0	ns
45–54 y	28.6 ± 4.9	29.0 ± 5.0	28.3 ± 5.5	28.4 ± 5.6	27.7 ± 5.1	27.9 ± 5.7	27.4 ± 5.6	0.007
55–64 y	30.4 ± 5.4	30.7 ± 5.4	29.9 ± 5.1	29.7 ± 5.0	30.4 ± 5.9	30.2 ± 5.9	29.4 ± 6.2	ns
BMI ≥ 30 kg/m^2, *n* (%)	367 (28.0)	423 (30.0)	308 (25.5)	270 (26.5)	292 (27.8)	344 (28.1)	247 (27.6)	ns

BMI, body mass index; SD, standard deviation.

however, for the purpose of longitudinal trend analysis, only the mean of the first two readings was used.

Definition of obesity and hypertension

We defined obesity as body mass index (BMI) ≥30 kg/m^2 for both sexes.

Hypertension was defined as a mean SBP ≥140 mmHg, and/or a mean DBP ≥90 mmHg, or current treatment with antihypertensive drugs. Study participants who reported previously diagnosed hypertension or current use of antihypertensive medication were considered aware of their hypertension. Treatment of hypertension was defined as the current use of prescribed BP lowering medication. Control of hypertension was defined as a proportion of individuals with hypertension achieving both SBP <140 mmHg and DBP < 90 mmHg. We also provide data on the control of hypertension in drug-treated hypertensives, defined as the proportion of drug-treated hypertensive individuals achieving both SBP <140 mmHg and DBP <90 mmHg.

Statistical analysis

Statistical analyses were performed using JMP® 15.2.0 statistical software (2019, SAS Institute Inc.). Trends for means were tested by linear contrast in one-way ANOVA, and trends for percentage by Cochran Armitage trend test of proportions. ANCOVA and logistic regression with an interaction of sex and the year of examination were used to determine a possible influence of sex on trends, and the year(s)

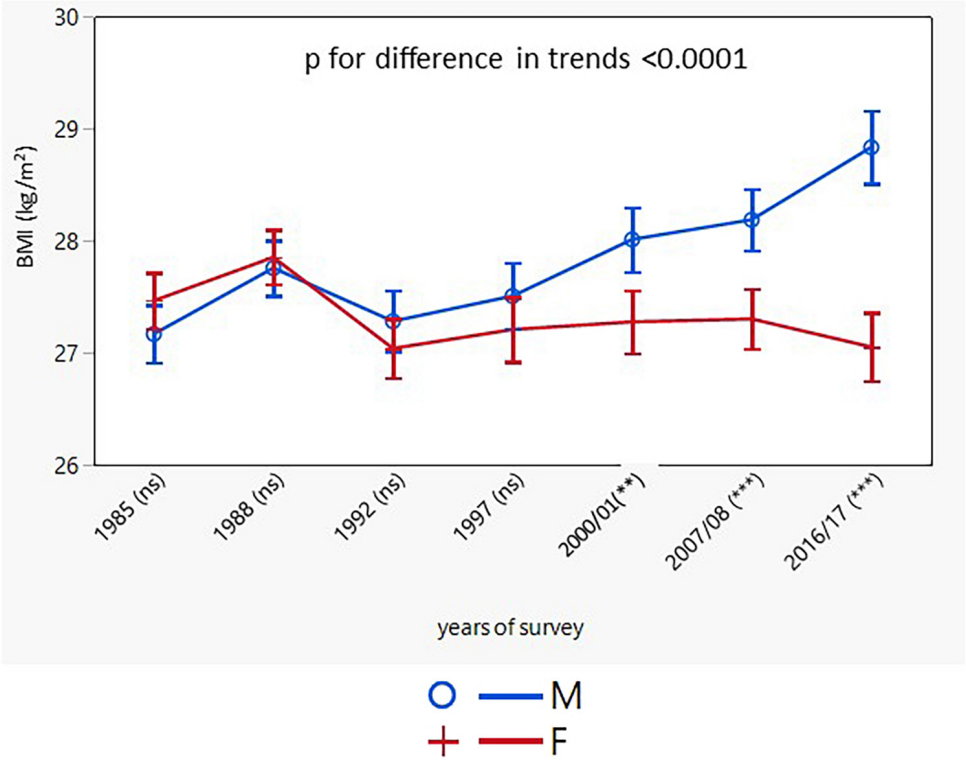


FIGURE 1
Age-adjusted trends in BMI (95% confidence interval). BMI, body mass index; M, males; F, females; *p* for differences in trends between males and females. NS or asterisks in brackets after survey years indicates the sex differences in respective surveys after Bonferroni correction; $^{**}p < 0.01$; $^{***}p < 0.001$.

of examination on tested variables. When necessary, Bonferroni correction for the adjustment of p values was applied. All p values are two-sided and $p < 0.05$ is considered statistically significant.

Results

Population sample characteristics

A total of 15,656 Caucasians participated in seven independent cross-sectional surveys (Table 1). The response rates showed a significant downward linear trend in both sexes, with a sharp decrease in the most recent survey, particularly in the youngest age groups. Women consistently had higher response rates than men throughout all age groups and surveys. Over the entire study period of 31–32 years, BMI significantly increased in men in all age groups, whereas BMI in women did not change and even declined in the age group of 45–54 years. Adjusted for age, the longitudinal trends in BMI in men and women differed ($p < 0.0001$) (Figure 1). Between 1985 and 1997/1998 trends in BMI in both sexes remained similar. In the 2001 survey, a sharp increase in BMI in men occurred and continued, whereas women's BMI remained largely unchanged.

Longitudinal trends in blood pressure and the prevalence, awareness, treatment, and control of hypertension

SBP and DBP declined in both sexes with a greater decline in women (men: from 135.8 ± 19.2/85.9 ± 11.0 to 131.1 ± 14.9/84.7 ± 9.1 mmHg; $p < 0.001$; women: from 131.6 ± 20.9/82.5 ± 11.3 to 124.8 ± 16.9/80.0 ± 9.4 mmHg; $p < 0.001$) (Table 2). SBP and DBP values in the two youngest male age groups did not change, whereas in women no change was observed only for DBP in the youngest age group. The trends in SBP and DBP, adjusted for age, were different in men and women, with BP values remaining constantly higher in men over the entire study period (Figures 2, 3).

The prevalence of hypertension declined only in women (from 42.5% in 1985 to 33.5% in 2016/17; $p < 0.001$; the decrease was significant in all age groups, except for the youngest one). In the male study population, there was no change in the prevalence of hypertension, except for two middle-aged groups

TABLE 2 Blood pressure (mean ± SD) between 1985 and 2016/17 in six districts of the Czechia.

	1985	1988	1992	1997/98	2000/01	2007/08	2016/17	*p* for trend
Men								
SBP, mmHg								
Total, 25–64 y	135.8 ± 19.2	134.9 ± 19.2	134.2 ± 20.0	132.3 ± 16.9	131.9 ± 16.8	132.5 ± 17.3	131.1 ± 14.9	<0.001
25–34 y	125.7 ± 14.6	125.5 ± 13.6	123.9 ± 13.4	124.3 ± 11.4	125.0 ± 15.3	124.8 ± 11.7	124.9 ± 12.6	ns
35–44 y	129.9 ± 15.7	128.1 ± 15.5	128.2 ± 15.4	127.9 ± 13.7	126.4 ± 13.9	127.6 ± 13.9	127.1 ± 13.1	ns
45–54 y	139.9 ± 18.9	137.7 ± 19.1	140.5 ± 20.1	132.4 ± 15.9	132.8 ± 16.0	131.3 ± 16.6	131.6 ± 14.2	<0.001
55–64 y	146.7 ± 19.4	146.7 ± 19.9	146.0 ± 22.8	144.3 ± 19.1	139.7 ± 17.1	139.9 ± 18.7	136.5 ± 15.6	<0.001
DBP, mmHg								
Total, 25–64 y	85.9 ± 11.0	84.4 ± 11.0	86.1 ± 11.4	84.5 ± 10.0	83.7 ± 9.7	84.4 ± 10.1	84.7 ± 9.1	<0.001
25–34 y	81.1 ± 10.0	79.9 ± 10.3	80.8 ± 9.7	80.0 ± 8.7	79.7 ± 9.7	79.9 ± 8.5	81.2 ± 9.6	ns
35–44	84.8 ± 9.8	82.7 ± 10.3	84.9 ± 10.1	83.2 ± 9.5	82.7 ± 9.2	84.1 ± 10.4	84.0 ± 8.5	ns
45–54 y	88.7 ± 11.2	86.5 ± 11.1	86.4 ± 11.4	86.4 ± 9.6	85.2 ± 9.2	85.2 ± 8.9	85.8 ± 9.2	<0.001
55–64 y	88.5 ± 11.2	87.9 ± 10.4	89.3 ± 11.7	87.0 ± 10.8	85.5 ± 9.6	86.5 ± 10.6	85.7 ± 8.9	<0.001
Women								
SBP, mmHg								
Total, 25–64 y	131.6 ± 20.9	130.7 ± 20.9	130.2 ± 22.0	125.2 ± 18.1	125.9 ± 18.8	126.7 ± 19.2	124.8 ± 16.9	<0.001
25–34 y	116.6 ± 13.7	116.0 ± 12.2	115.6 ± 13.3	113.7 ± 9.9	112.9 ± 11.0	114.5 ± 12.2	114.7 ± 12.4	0.004
35–44 y	125.8 ± 15.8	124.3 ± 16.0	121.1 ± 16.0	118.9 ± 14.6	118.7 ± 12.7	120.1 ± 15.5	119.2 ± 13.4	<0.001
45–54 y	136.0 ± 19.1	135.7 ± 18.4	137.1 ± 21.0	129.0 ± 17.9	128.9 ± 17.8	128.6 ± 17.0	125.1 ± 16.3	<0.001
55–64 y	148.6 ± 19.9	147.1 ± 21.7	148.0 ± 21.2	138.2 ± 18.3	140.2 ± 19.1	139.5 ± 20.2	134.4 ± 17.0	<0.001
DBP, mmHg								
Total, 25–64 y	82.5 ± 11.3	81.4 ± 11.2	82.5 ± 12.1	79.3 ± 9.8	79.3 ± 9.8	80.6 ± 9.6	80.0 ± 9.4	<0.001
25–34 y	74.8 ± 9.2	74.4 ± 8.7	75.0 ± 9.1	73.8 ± 7.7	73.5 ± 7.9	75.7 ± 8.5	75.9 ± 9.3	ns
35–44 y	81.4 ± 9.9	79.1 ± 10.1	79.0 ± 10.5	77.1 ± 9.0	76.9 ± 8.8	79.3 ± 8.8	78.2 ± 9.0	<0.001
45–54 y	85.1 ± 10.7	84.5 ± 10.5	86.9 ± 11.9	81.7 ± 10.0	80.9 ± 8.8	82.0 ± 9.3	81.0 ± 9.2	<0.001
55–64 y	88.7 ± 10.3	87.6 ± 10.6	89.1 ± 11.5	83.9 ± 8.8	84.5 ± 10.0	84.2 ± 9.3	82.6 ± 8.8	<0.001

p, statistical significance for linear trend. SBP, systolic blood pressure, DBP, diastolic blood pressure.

(35–44 and 45–54 years) (Table 3). The age-adjusted trends in the prevalence of hypertension were different for men and women with consistently higher rates in men (Figure 4).

There was an increase in hypertension awareness in both sexes over the entire study period with consistently higher rates in women (men: from 41.4% in 1985 to 74.6% in 2016/17; $p < 0.001$; women: from 58.9% in 1985 to 77.7% in 2016/17; $p < 0.001$) (Table 3). However, there was no increase in awareness of hypertension in the youngest age groups of both sexes. The age-adjusted trends in awareness were different in men and women (Figure 5).

The proportion of individuals treated with antihypertensive drugs increased significantly in both sexes throughout the study, again with consistently higher rates in women (men: from 21.1 to 60.9%; $p < 0.001$; women: from 38.9 to 64.8%; $p < 0.001$) (Table 3). There was no change in the younger age groups of both sexes. The age-adjusted trends in the treatment of hypertension differed between men and women (Figure 6).

Control of hypertension increased significantly over the 30-year study period with consistently higher rates in women. The improvement in the control of hypertension was consistent in both sexes across all the age groups, except for the youngest female group (Table 4). The age-adjusted trends for control of hypertension were different for men and women only when control of hypertension was presented as the proportion of individuals with BP <140/90 mmHg in all hypertensive individuals, but not only in drug-treated hypertensive patients (Figures 7, 8).

Discussion

The current analysis is, to the best of our knowledge, the first one assessing the longitudinal trends in BP, prevalence, awareness, treatment, and control of hypertension, paying special attention to sex differences. The main message is that there are significant differences, always in favor of women, in trends in all parameters listed above, except for in the control of hypertension in treated patients, where results were equally poor in both sexes. There are only a few countries with longitudinal data on the epidemiology of hypertension derived from representative population samples (USA, Canada, Korea, Sweden, Lithuania, and Finland) (10–15). Trends in BP and various aspects of the epidemiology of hypertension were

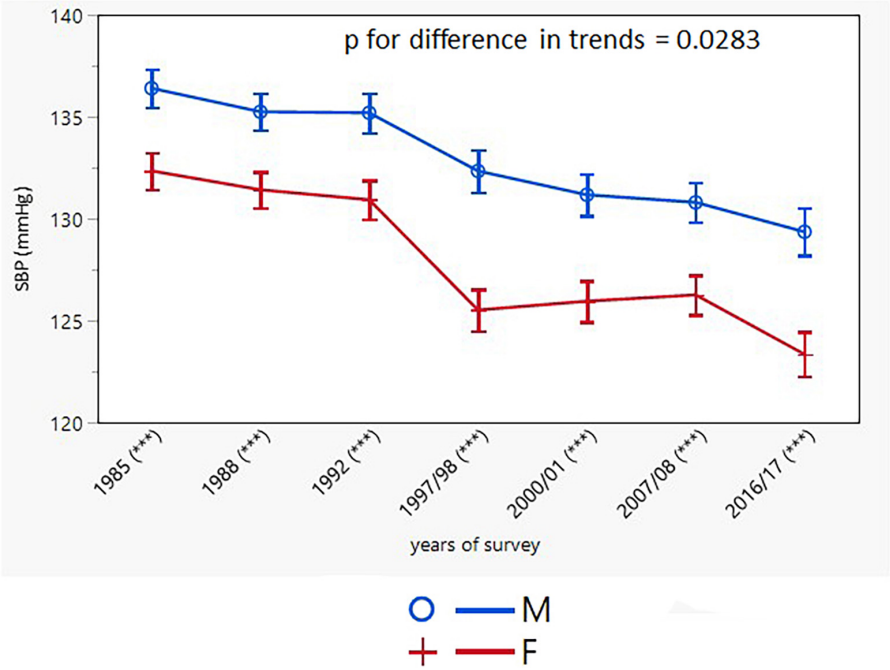


FIGURE 2
Age-adjusted trends in systolic blood pressure (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. Asterisks in brackets after survey years indicates the sex differences in respective surveys after Bonferroni correction; ***$p < 0.001$.

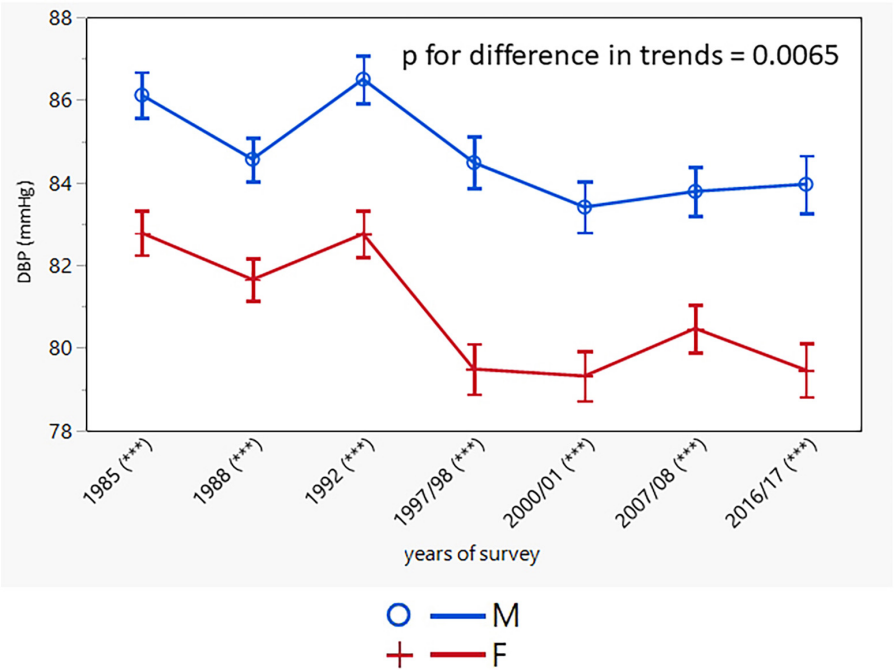


FIGURE 3
Age-adjusted trends in diastolic blood pressure (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. Asterisks indicates in brackets after survey years the sex differences in respective surveys after Bonferroni correction; ***$p < 0.001$.

TABLE 3 Prevalence, awareness, and treatment of hypertension between 1985 and 2016/17 in six districts of the Czechia.

	1985	1988	1992	1997/98	2000/01	2007/08	2016/17	*p* for trend
Men								
Prevalence of HT, %								
Total, 25–64 y, *n* (%)	650 (51.9)	639 (47.1)	508 (44.8)	408 (42.1)	457 (45.6)	553 (50.2)	399 (50.6)	Ns
25–34 y	85 (27.7)	67 (20.8)	46 (18.7)	35 (18.0)	34 (18.2)	43 (20.7)	26 (22.4)	0.0730
35–44 y	123 (41.6)	119 (36.8)	126 (36.0)	61 (26.5)	69 (30.0)	82 (32.7)	66 (33.3)	0.049
45–54 s	208 (62.3)	198 (54.9)	186 (60.0)	161 (48.5)	147 (49.8)	122 (52.8)	107 (51.0)	0.009
55–64 y	234 (74.1)	255 (72.7)	150 (65.8)	151 (70.9)	207 (71.1)	306 (74.3)	200 (75.8)	Ns
Awareness of HT, *n* (%)								
Total, 25–64 y	269 (41.4)	320 (50.1)	232 (45.7)	230 (56.4)	284 (62.1)	378 (68.4)	290 (74.6)	<0.001
25–34 y	23 (27.1)	27 (40.3)	17 (37.0)	12 (34.3)	13 (38.2)	13 (30.2)	15 (62.5)	Ns
35–44 y	38 (30.9)	53 (44.5)	52 (41.3)	29 (47.5)	37 (53.6)	45 (54.9)	45 (68.2)	<0.0001
45–54 y	91 (43.8)	87 (43.9)	82 (44.1)	88 (54.7)	91 (61.9)	82 (67.2)	69 (64.5)	<0.0001
55–64 y	117 (50.0)	153 (60.0)	81 (54.0)	101 (66.9)	143 (69.1)	238 (77.8)	161 (80.9)	<0.0001
Medication for HT, *n* (%)								
Total, 25–64 y	137 (21.1)	197 (30.8)	123 (24.2)	151 (37.0)	191 (41.8)	322 (58.2)	241 (60.9)	<0.001
25–34 y	3 (3.5)	8 (11.9)	1 (2.2)	6 (17.1)	3 (8.9)	4 (9.3)	4 (15.4)	0.0909
35–44 y	16 (13.0)	22 (18.5)	20 (15.9)	11 (18.0)	17 (24.6)	26 (31.7)	31 (47.0)	<0.0001
45–54 y	50 (24.0)	55 (27.8)	54 (29.0)	58 (36.0)	62 (42.2)	72 (59.0)	57 (53.3)	<0.0001
55–64 y	68 (29.1)	112 (43.9)	48 (32.0)	76 (50.3)	109 (52.7)	220 (71.9)	149 (74.5)	<0.0001
Women								
Prevalence of HT, *n* (%)								
Total, 25–64 y	560 (42.5)	552 (39.1)	460 (38.0)	323 (31.6)	347 (33.0)	426 (37.3)	300 (33.5)	<0.001
25–34 y	30 (9.3)	27 (7.9)	22 (8.3)	7 (3.3)	10 (4.7)	16 (6.8)	7 (4.8)	ns
35–44 y	98 (28.8)	88 (23.9)	67 (18.8)	41 (15.4)	37 (13.4)	62 (21.9)	26 (12.8)	<0.001
45–54 y	186 (54.2)	180 (50.0)	166 (53.4)	134 (41.1)	110 (38.6)	124 (41.5)	111 (39.4)	<0.001
55–64 y	246 (78.9)	257 (75.6)	205 (74.3)	141 (65.0)	190 (68.4)	224 (68.7)	156 (59.3)	<0.001
Awareness of HT, *n* (%)								
Total, 25–64 y	330 (58.9)	330 (59.8)	255 (55.4)	221 (68.4)	256 (73.8)	304 (71.4)	233 (77.7)	<0.001
25–34 y	14 (46.7)	15 (55.6)	6 (27.3)	1 (14.3)	4 (40.0)	9 (56.3)	6 (85.7)	ns
35–44 y	40 (40.8)	42 (47.7)	30 (44.8)	27 (65.9)	26 (70.3)	36 (58.0)	19 (73.1)	0.0001
45–54 y	109 (58.6)	105 (58.3)	91 (54.8)	83 (61.9)	72 (65.5)	94 (75.8)	78 (70.3)	0.0003
55–64 y	167 (67.9)	168 (65.4)	128 (62.4)	110 (78.0)	154 (81.1)	165 (73.7)	130 (83.3)	<0.0001
Medication for HT, *n* (%)								
Total, 25–64 y	218 (38.9)	233 (42.2)	159 (34.6)	187 (57.9)	205 (59.1)	251 (58.9)	193 (64.8)	<0.001
25–34 y	5 (16.7)	5 (18.5)	2 (9.1)	0 (0.0)	1 (10.0)	4 (25.0)	1 (14.3)	ns
35–44 y	13 (13.27)	24 (27.3)	8 (11.9)	22 (53.4)	16 (43.2)	26 (41.9)	13 (50.0)	<0.0001
45–54 y	82 (44.1)	73 (40.6)	54 (32.5)	64 (47.8)	59 (53.6)	77 (62.1)	67 (60.4)	<0.0001
55–64 y	118 (48.0)	131 (51.0)	95 (46.3)	101 (71.6)	129 (67.9)	144 (64.3)	112 (71.8)	<0.0001

p, statistical significance for linear trend. SBP, systolic blood pressure, DBP, diastolic blood pressure, HT, hypertension.

described for several European countries but, as far as we know, none of the other studies specifically compared the trends in men and women.

Strengths and limitations

The strength of our study is that it was always conducted in the same six districts of the Czechia using standardized methods, which were introduced by the WHO MONICA Project. The study protocol respected seasonal variations. The gold-standard mercury sphygmomanometer was used to measure BP in all seven cross-sectional surveys. The study period lasted 31/32 years, covering the transition from a totalitarian regime to democracy in the Czechia.

A decline in the response rate is a possible study limitation. This may have resulted in the population sample coming from a higher socio-economic background, which is usually associated with higher health consciousness. Therefore,

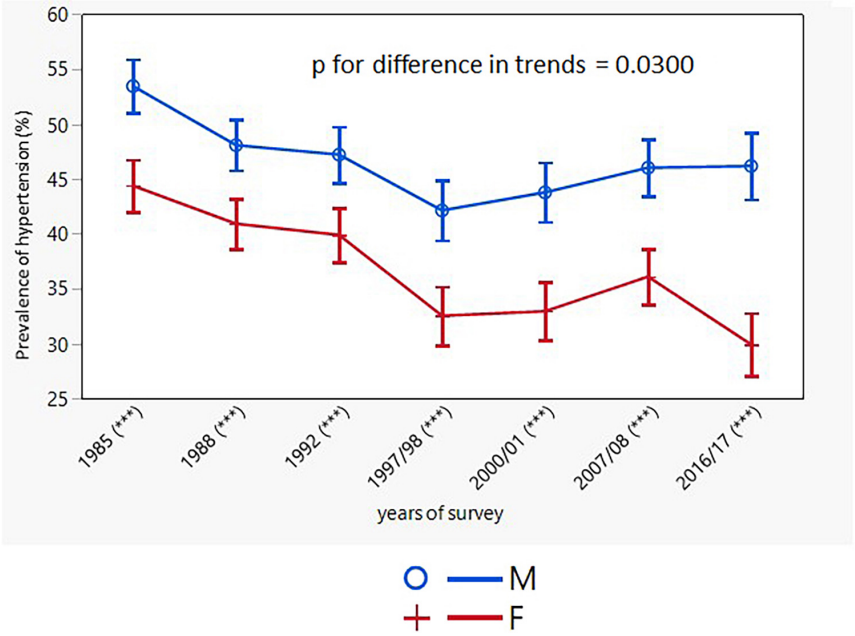


FIGURE 4
Age-adjusted trends in prevalence of hypertension (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. Asterisks indicates in brackets after survey years the sex differences in respective surveys after Bonferroni correction; ***$p < 0.001$.

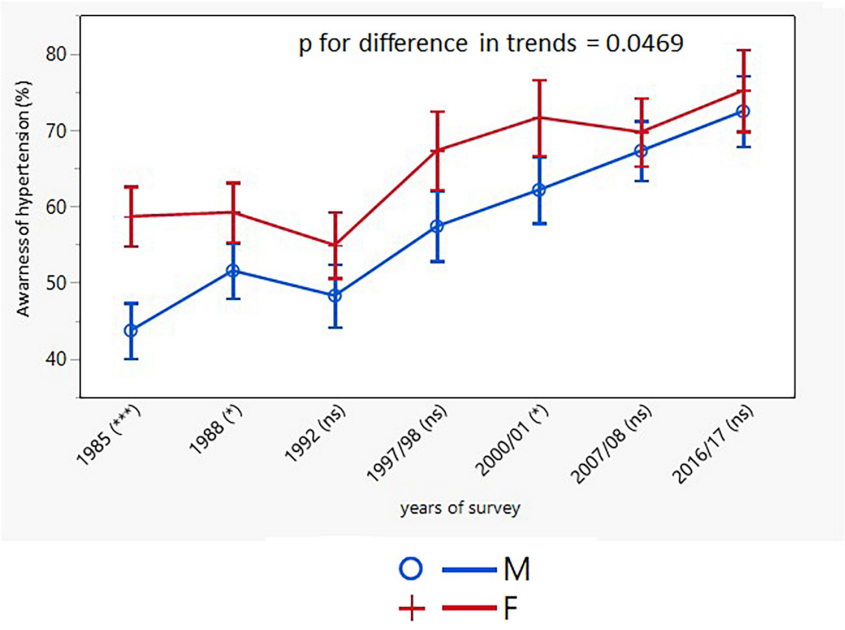


FIGURE 5
Age-adjusted trends in awareness of hypertension (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. NS or asterisks indicates in brackets after survey years the sex differences in respective surveys after Bonferroni correction; *$p < 0.05$; ***$p < 0.001$.

our results might be slightly more favorable than in the actual general population. It should be noted that a decline in response rates has occurred in epidemiological studies worldwide, with recently reported rates below 40% (16–18). The European Health Examination Survey Pilot Project, conducted 2009-2012 in 12 countries involving individuals of

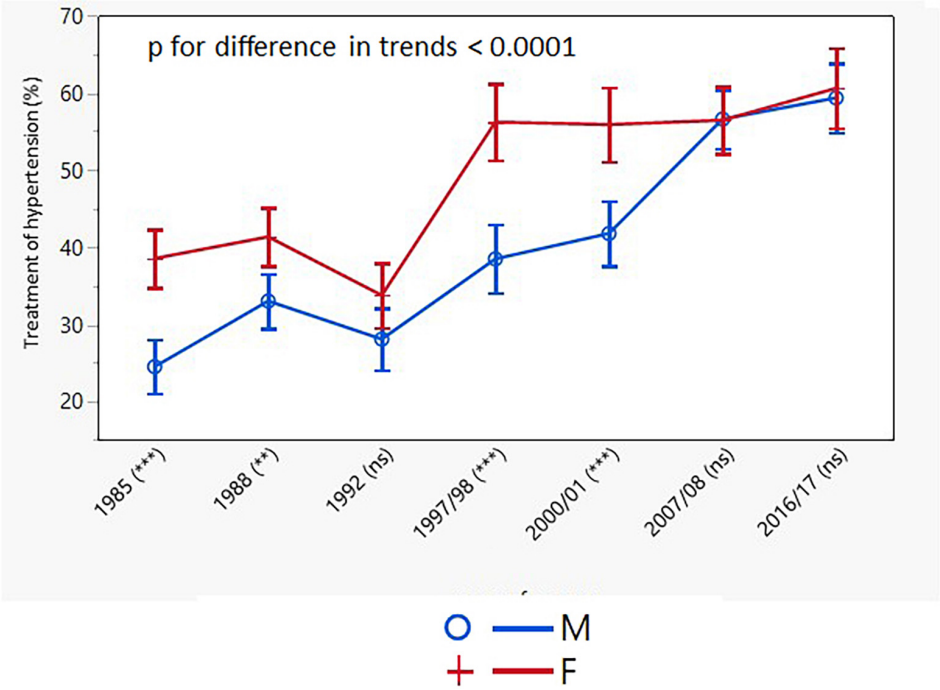


FIGURE 6
Age-adjusted trends in treatment of hypertension (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. NS or asterisks indicates in brackets after survey years the sex differences in respective surveys after Bonferroni correction; $^{**}p < 0.01$; $^{***}p < 0.001$.

the same age as our study population (25–64 years), found the participation rates to be 16-57% in men and 31–74% in women (16). The WHO MONICA Project examined non-respondents who were found more likely to be single, less educated, with poorer lifestyles, and worse health profiles than respondents (19).

Trends in blood pressure and prevalence

A pooled analysis of 1,479 studies including 19.1 million adults found a decline in mean systolic and mean diastolic pressure from 1975 to 2015 in high-income western and high-income Asia Pacific super-regions (20). A later analysis by the same research group also reported a decrease in systolic BP in women in central and eastern Europe, but not in men (21).

An Austrian representative population-based study (n = 178,818), which included self-reported data from five health surveys between 1973 and 2007, showed that during the study period the age-standardized hypertension prevalence increased from 1.0 to 18.8%, with a considerable rise from 1991 onward. There was a positive trend in all subpopulations, especially in obese women (+ 50.2%) and obese individuals aged 75 years and older (+ 54.4%) (22).

Analysis of Lithuanian data from three MONICA health surveys (1983, 1986, and 1992) and one survey according to MONICA protocol (2002) concluded that during this period hypertension prevalence in men was 52.1 to 58.7% (no significant changes), whereas in women it decreased from 61.0 to 51.0% (15). The German National Health Interview and Examination Survey 1998 and 2008 to 2011 reported a decrease in age- and sex-standardized mean systolic and diastolic BP. The mean systolic and diastolic BP decrease was achieved in treated hypertensive patients, but there was also a BP decrease in normotensive individuals. The prevalence of hypertension increased only in men (29.8 to 33.4%; $p < 0.03$) (23).

In our study, there was a decline in the mean SBP and DBP in both sexes, however, the changes were more pronounced in women. The more favorable decline in BP in women can be partly explained by their BMI showing no significant change, whereas men's BMI increased in all age groups over the entire study period.

The NCD Risk Factor Collaboration group reported a stable age-standardized prevalence of hypertension in adults aged 30-79 years a net effect of a decline in high-income countries and for women also in central and eastern Europe, and a rise in some low-income and middle-income countries. The results from our study mirrored these trends, with consistently lower rates and greater changes in women (**Table 3** and **Figure 4**).

TABLE 4 Control of hypertension between 1985 and 2016/17 in six districts of the Czechia.

	1985	1988	1992	1997/98	2000/01	2007/08	2016/17	*p* for trend
Men								
Control of hypertension (% of all hypertensive patients)								
Total, 25–64 y	18 (2.8)	33 (5.2)	14 (2.8)	50 (12.3)	60 (13.1)	135 (24.4)	119 (29.8)	<0.001
25–34 y	0 (0.0)	1 (1.5)	0 (0.0)	2 (5.7)	0 (0.0)	4 (9.3)	1 (3.9)	0.009
35–44 y	2 (1.6)	6 (5.0)	2 (1.6)	5 (8.2)	6 (8.7)	11 (13.4)	17 (25.8)	<0.0001
45–54 y	9 (4.3)	11 (5.6)	8 (4.3)	21 (13.0)	18 (12.2)	37 (30.3)	28 (26.2)	<0.0001
55–64 y	7 (3.0)	15 (5.9)	4 (2.7)	22 (14.6)	36 (17.4)	83 (27.1)	73 (36.5)	<0.0001
Control of hypertension (% of all drug-treated hypertensive patients)								
Total, 25–64 y	18 (13.1)	33 (16.8)	14 (11.4)	50 (33.1)	60 (31.4)	135 (41.9)	119 (49.4)	<0.0001
25–34 y	0 (0.0)	1 (12.5)	0 (0.0)	2 (33.3)	0 (0.0)	4 (100.0)	1 (25.0)	0.040
35–44 y	2 (12.5)	6 (27.3)	2 (10.0)	5 (45.5)	6 (36.3)	11 (42.3)	17 (54.8)	0.0005
45–54 y	9 (18.0)	11 (20.0)	8 (14.8)	21 (36.2)	18 (29.0)	37 (51.4)	28 (49.1)	<0.0001
55–64 y	7 (10.3)	15 (13.4)	4 (8.3)	22 (29.0)	36 (33.0)	83 (37.7)	73 (49.0)	<0.0001
Women								
Control of hypertension (% of all hypertensive patients)								
Total, 25–64 y	29 (5.2)	51 (9.2)	28 (6.1)	70 (21.7)	77 (22.2)	106 (24.9)	111 (37.0)	<0.001
25–34 y	0 (0.0)	2 (7.4)	1 (4.6)	0 (0.0)	1 (10.0)	1 (6.25)	0 (0.0)	ns
35–44 y	4 (4.1)	8 (9.1)	5 (7.5)	10 (24.4)	7 (19.0)	17 (27.4)	9 (34.6)	<0.0001
45–54 y	17 (9.1)	19 (10.6)	9 (5.4)	26 (19.4)	26 (23.6)	33 (26.6)	44 (39.6)	<0.0001
55–64 y	8 (3.3)	22 (8.6)	13 (6.3)	34 (24.1)	43 (22.6)	55 (24.6)	58 (37.2)	<0.0001
Control of hypertension (% of all drug-treated hypertensive patients)								
Total, 25–64 y	29 (13.3)	51 (21.9)	28 (17.6)	70 (37.4)	77 (37.6	106 (42.2)	111 57.5)	<0.0001
25–34 y	0 (0.0)	2 (40.0)	1 (50.0)	NA	1 (100.0)	1 (25.0)	0 (0.0)	ns
35–44 y	4 (30.8)	8 (33.3)	5 (62.5)	10 (45.5)	7 (43.8)	17 (65.4)	9 (69.2)	0.0065
45–54 y	17 (20.7)	19 (26.0)	9 (16.7)	26 (40.6)	26 (44.1)	33 (42.9)	44 (65.7)	<0.0001
55–64 y	8 (6.8)	22 (16.8)	13 (13.7)	34 (33.7)	43 (33.3)	55 (38.2)	58 (51.8)	<0.0001

p, statistical significance for linear trend; NA, not applicable as no individuals reported medication for hypertension.

Awareness, treatment, and control of hypertension

Awareness of hypertension dramatically improved throughout our study in both sexes, with women having started in a better position (58.9%) than men (41.4%). Both sexes achieved around 75% awareness by 2016/2017 (men 74.6%, women 77.7%), which is substantially better than in the NCD Risk Factor Collaboration report (globally, men 51%, women 41%). A similar increase in hypertension awareness was noted in Lithuania from 1983 to 2002 in both men and women (from 45.0 to 64.4% and 47.7 to 72.3%, respectively) and in treated hypertensives (from 55.4 to 68.3% in men and 65.6 to 86.2% in women) (15). Awareness and treatment of hypertension increased in Germany in both sexes (awareness: men from 65-78%, women from 74 to 87%; treatment: men from 48 to 65%, women from 62 to 79%) from 1998 to 2008 to 2011 (23).

Hypertension treatment and control have improved in most countries since 1990, with the greatest improvement in high-income countries and central Europe (21). The trends in treatment and hypertension control in the Czechia are in parallel with these findings. As with awareness of hypertension, women were treated for hypertension more frequently than men until the start of the millennium. Due to a greater increase in treatment of hypertension in men, no differences between the sexes were found in the last two surveys in the Czechia (final survey: men 60.9%, women 64.8%). On the other hand, in 2019 only 38% of men and 47% of women were treated globally (21).

Control of hypertension in the Czechia improved significantly in both men and women. The improvement mostly ran in parallel throughout the study, particularly in treated hypertensive patients. However, the final numbers for control of hypertension are still not sufficient (treated hypertensive patients: men 49.4%, women 57.5%). According to the NCD Risk Factor Collaboration report, the control rates in high-income countries rose to 60% (21). The Swedish primary care register shows that from 2010 to 2017 the proportion of patients with BP < 140/90 mmHg increased from 38.9 to 49.1% (24). Authors of the analysis of German Health Examination Surveys even claim that the control rate among treated hypertensives increased from 23% in 1998 to 51% in 2008 to 2011 (men from 20 to 45%, women from 25% to 58%) (23).

It is an alarming finding of our study that awareness, treatment, and control of hypertension did not improve in the

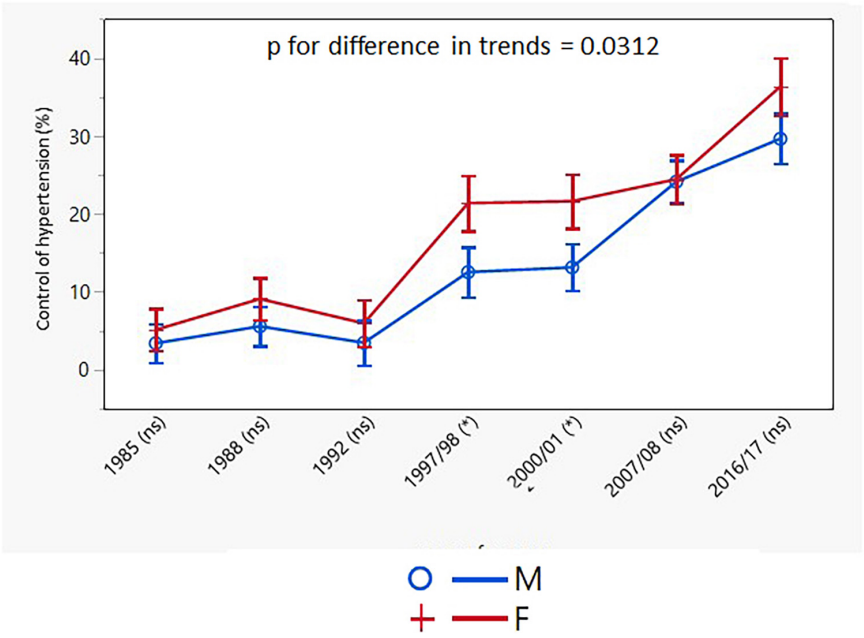


FIGURE 7
Age-adjusted trends in control of hypertension in all hypertensive individuals (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. NS or asterisks indicates in brackets after survey years the sex differences in respective surveys after Bonferroni correction; $*p < 0.05$.

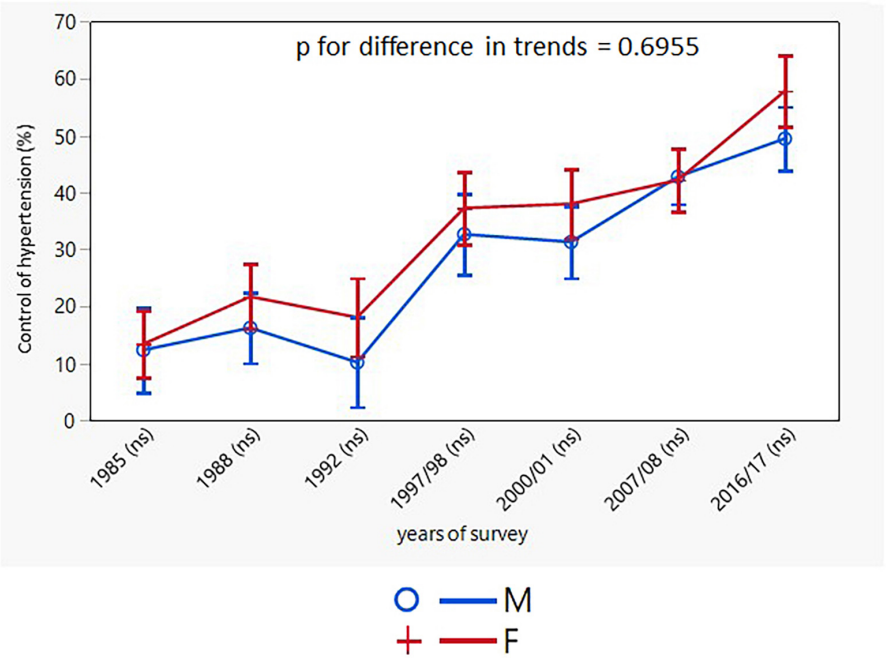


FIGURE 8
Age-adjusted trends in control of hypertension in drug treated hypertensives (95% confidence interval). M, males; F, females; *p* for differences in trends between males and females. NS indicates in brackets after survey years the sex differences in respective surveys after Bonferroni correction.

youngest age group in both sexes. Hypertension was newly detected predominantly in young men with only a small proportion of them being treated for it. In the youngest age group hypertension was poorly controlled in both sexes. This is in concordance with other studies reporting poor levels of treatment and control in young adults compared with older adults (25–27).

It is a surprising fact that women who had lower SBP and DBP as well as a lower prevalence of hypertension were more frequently aware of the disease and were reported to be more frequently treated by antihypertensive drugs but they did not show better control of hypertension. This could be explained by less aggressive treatment in women or by their lower adherence to medication. Unfortunately, we have more precise data on the antihypertensive medication only for the last four surveys. Age-adjusted trends in hypertensive medication did not differ between men and women from 1997/98 to 2016/17, both increasing over time but staying significantly higher in men, meaning men took on average more antihypertensive drugs than women. Clearly, when we analyzed the proportion of monotherapy, a combination of two drugs, and a combination of three and more drugs, there was a significant increase over time favoring the triple and more combination in both sexes. However, this increase was steeper in men (in the last survey, 44.9% of men were treated with a combination of ≥3 drugs, compared to 36.1% of women). The less aggressive treatment of hypertension in women may correspond with the finding that women with coronary heart disease are less likely to be treated following the guidelines than men (28).

Another reason for women having unexpectedly equally poor control of their hypertension could be worse adherence to antihypertensive medication. This issue is controversial, depending on the method used to assess adherence. A meta-analysis of 82 studies which included 15,517,457 men and 18,537,599 women showed no significant differences in adherence between the sexes. However, this analysis was based on self-reported adherence and pharmacy refill records (29). On the other hand, studies on apparent treatment-resistant hypertension employing therapeutic drug monitoring showed that antihypertensive drug adherence was lower in women (30). Heterogeneity in published results must be acknowledged, partly due to various methods being used for assessing adherence.

Conclusion and further perspective

We found significant differences in longitudinal age-adjusted trends in BP, prevalence, awareness, treatment, and control of hypertension between the sexes. The differences were always in favor of women except for control of hypertension in treated patients, which did not show any difference between men and women.

In conclusion, the trends in BP, prevalence, awareness, treatment, and control of hypertension in women showed similar pattern as women in high-income countries, whereas men are lagging in their awareness rates.

Future epidemiological studies in hypertension should also assess adherence to medication using objective methods rather than relying on self-reported data.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://www.ftn.cz/data-monica-1117/.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Institute for Clinical and Experimental Research and Thomayer University Hospital Prague, Czechia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

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

Funding

This study was supported by grant No. 15-27109A provided by the Ministry of Health of the Czechia.

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. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol.* (2021) 18:785–802.

2. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet.* (2014) 383:1899–911. doi: 10.1016/S0140-6736(14)60685-1

3. Sharp SI, Aarsland D, Day S, Sønnesyn H, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *Int J Geriatr Psychiatry.* (2011) 26:661–9.

4. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* (2009) 338:b1665. doi: 10.1136/bmj.b1665

5. 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

6. 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.

7. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet.* (1999) 353:1547–57. doi: 10.1016/s0140-6736(99)04021-0

8. Cífková R, Bruthans J, Wohlfahrt P, Krajčoviechová A, Šulc P, Jozífová M, et al. 30-year trends in major cardiovascular risk factors in the Czech population, Czech MONICA and Czech post-MONICA, 1985 - 2016/17. *PLoS One.* (2020) 15:e0232845. doi: 10.1371/journal.pone.0232845

9. Cífková R, Skodová Z, Bruthans J, Adámková V, Jozífová M, Galovcová M, et al. Longitudinal trends in major cardiovascular risk factors in the Czech population between 1985 and 2007/8. Czech MONICA and Czech post-MONICA. *Atherosclerosis.* (2010) 211:676–81. doi: 10.1016/j.atherosclerosis.2010.04.007

10. Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension.* (1995) 26:60–9. doi: 10.1161/01.hyp.26.1.60

11. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, et al. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA.* (2020) 324:1190–200.

12. McAlister FA, Wilkins K, Joffres M, Leenen FH, Fodor G, Gee M, et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. *CMAJ.* (2011) 183:1007–13.

13. Choi HM, Kim HC, Kang DR. Sex differences in hypertension prevalence and control: analysis of the 2010-2014 Korea national health and nutrition examination survey. *PLoS One.* (2017) 12:e0178334. doi: 10.1371/journal.pone.0178334

14. Törmä E, Carlberg B, Eriksson M, Jansson JH, Eliasson M. Long term trends in control of hypertension in the Northern Sweden MONICA study 1986-2009. *BMC Public Health.* (2015) 15:957. doi: 10.1186/s12889-015-2280-6

15. Reklaitiene R, Tamosiunas A, Virviciute D, Baceviciene M, Luksiene D. Trends in prevalence, awareness, treatment, and control of hypertension, and the risk of mortality among middle-aged Lithuanian urban population in 1983-2009. *BMC Cardiovasc Disord.* (2012) 12:68. doi: 10.1186/1471-2261-12-68

16. Tolonen H, Ahonen S, Jentoft S, Kuulasmaa K, Heldal J. Differences in participation rates and lessons learned about recruitment of participants–the European Health Examination Survey Pilot Project. *Scand J Public Health.* (2015) 43:212–9. doi: 10.1177/1403494814565692

17. Leenen FH, Dumais J, McInnis NH, Turton P, Stratychuk L, Nemeth K, et al. Results of the Ontario survey on the prevalence and control of hypertension. *CMAJ.* (2008) 178:1441–9.

18. Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord.* (2008) 8:6. doi: 10.1186/1471-2261-8-6

19. Tolonen H, Dobson A, Kulathinal S. Effect on trend estimates of the difference between survey respondents and non-respondents: results from 27 populations in the WHO MONICA Project. *Eur J Epidemiol.* (2005) 20:887–98. doi: 10.1007/s10654-005-2672-5

20. NCD Risk Factor Collaboration [NCD-RisC]. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet.* (2017) 389:37–55. doi: 10.1016/S0140-6736(16)31919-5

21. 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

22. Großschädl F, Stolz E, Mayerl H, Rásky É, Freidl W, Stronegger WJ. Prevalent long-term trends of hypertension in austria: the impact of obesity and socio-demography. *PLoS One.* (2015) 10:e0140461. doi: 10.1371/journal.pone.0140461

23. Neuhauser HK, Adler C, Rosario AS, Diederichs C, Ellert U. Hypertension prevalence, awareness, treatment and control in Germany 1998 and 2008-11. *J Hum Hypertens.* (2015) 29:247–53. doi: 10.1038/jhh.2014.82

24. Bager JE, Mourtzinis G, Andersson T, Nåtman J, Rosengren A, Björck S, et al. Trends in blood pressure, blood lipids, and smoking from 259 753 patients with hypertension in a Swedish primary care register: results from QregPV. *Eur J Prev Cardiol.* (2022) 29:158–66. doi: 10.1093/eurjpc/zwab087

25. Kim JS, Kim CG. Gender differences in hypertension treatment and control in young adults. *J Nurs Res.* (2020) 28:e88.

26. Hales CM, Carroll MD, Simon PA, Kuo T, Ogden CL. Hypertension prevalence, awareness, treatment, and control among adults aged =18 years - Los Angeles County, 1999-2006 and 2007-2014. *MMWR Morb Mortal Wkly Rep.* (2017) 66:846–9. doi: 10.15585/mmwr.mm6632a3

27. Zhang Y, Moran AE. Trends in the prevalence, awareness, treatment, and control of hypertension among young adults in the United States, 1999 to 2014. *Hypertension.* (2017) 70:736–42.

28. DeFilippis EM, Collins BL, Singh A, Biery DW, Fatima A, Qamar A, et al. Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the mass general Brigham YOUNG-MI registry. *Eur Heart J.* (2020) 41:4127–37. doi: 10.1093/eurheartj/ehaa662

29. Biffi A, Rea F, Iannaccone T, Filippelli A, Mancia G, Corrao G. Sex differences in the adherence of antihypertensive drugs: a systematic review with meta-analyses. *BMJ Open.* (2020) 10:e036418.

30. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, et al. Risk factors for nonadherence to antihypertensive treatment. *Hypertension.* (2017) 69:1113–20.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 23 November 2022
DOI 10.3389/fcvm.2022.1006104

OPEN ACCESS

EDITED BY
Daniela Sorriento,
University of Naples Federico II, Italy

REVIEWED BY
Vasilii S. Chulkov,
South Ural State Medical University, Russia
Akihiko Ueda,
Kyoto University, Japan

*CORRESPONDENCE
T. Craig Cheetham
tcraigcheetham@icloud.com

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 28 July 2022
ACCEPTED 31 October 2022
PUBLISHED 23 November 2022

CITATION
Cheetham TC, Shortreed SM, Avalos LA, Reynolds K, Holt VL, Easterling TR, Portugal C, Zhou H, Neugebauer RS, Bider Z, Idu A and Dublin S (2022) Identifying hypertensive disorders of pregnancy, a comparison of two epidemiologic definitions.
Front. Cardiovasc. Med. 9:1006104.
doi: 10.3389/fcvm.2022.1006104

Identifying hypertensive disorders of pregnancy, a comparison of two epidemiologic definitions

T. Craig Cheetham[1]*, Susan M. Shortreed[2], Lyndsay A. Avalos[3], Kristi Reynolds[4], Victoria L. Holt[5], Thomas R. Easterling[6], Cecilia Portugal[4], Hui Zhou[4], Romain S. Neugebauer[3], Zoe Bider[4], Abisola Idu[2] and Sascha Dublin[2]

[1]School of Pharmacy, Chapman University, Irvine, CA, United States, [2]Kaiser Permanente Washington Health Research Institute, Seattle, WA, United States, [3]Kaiser Permanente Northern California Division of Research, Oakland, CA, United States, [4]Kaiser Permanente Southern California Department of Research and Evaluation, Pasadena, CA, United States, [5]Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, United States, [6]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, United States

Introduction: Studies of hypertension in pregnancy that use electronic health care data generally identify hypertension using hospital diagnosis codes alone. We sought to compare results from this approach to an approach that included diagnosis codes, antihypertensive medications and blood pressure (BP) values.

Materials and methods: We conducted a retrospective cohort study of 1,45,739 pregnancies from 2009 to 2014 within an integrated healthcare system. Hypertensive pregnancies were identified using the "BP-Inclusive Definition" if at least one of three criteria were met: (1) two elevated outpatient BPs, (2) antihypertensive medication fill plus an outpatient hypertension diagnosis, or (3) hospital discharge diagnosis for preeclampsia or eclampsia. The "Traditional Definition" considered only delivery hospitalization discharge diagnoses. Outcome event analyses compared rates of preterm delivery and small for gestational age (SGA) between the two definitions.

Results: The BP-Inclusive Definition identified 14,225 (9.8%) hypertensive pregnancies while the Traditional Definition identified 13,637 (9.4%); 10,809 women met both definitions. Preterm delivery occurred in 20.9% of BP-Inclusive Definition pregnancies, 21.8% of Traditional Definition pregnancies and 6.6% of non-hypertensive pregnancies; for SGA the numbers were 15.6, 16.3, and 8.6%, respectively ($p < 0.001$ for all events compared to non-hypertensive pregnancies). Analyses in women meeting only one hypertension definition (21–24% of positive cases) found much lower rates of both preterm delivery and SGA.

Conclusion: Prevalence of hypertension in pregnancy was similar between the two study definitions. However, a substantial number of women met only one of the study definitions. Women who met only one of the hypertension definitions had much lower rates of adverse neonatal events than women meeting both definitions.

KEYWORDS

pregnancy, hypertension (chronic and gestational), blood pressures, small for gestational age, preterm delivery

Introduction

Hypertensive disorders of pregnancy are common and a leading cause of maternal and neonatal morbidity (1). These hypertensive disorders include chronic hypertension, gestational hypertension, preeclampsia superimposed on chronic hypertension, and preeclampsia or eclampsia. Retrospective epidemiologic studies are often used to determine the burden of hypertensive diseases of pregnancy and to evaluate trends over time (2–6).

Studies evaluating the burden of hypertensive disorders of pregnancy generally use discharge diagnosis codes from the delivery hospitalization to estimate overall rates of disease. Diagnosis codes, however, have limitations. Studies evaluating diagnosis codes or a combination of diagnosis codes plus antihypertensive medications report low sensitivity for identifying individuals with hypertension (7, 8). The availability of data from electronic medical records (EMRs) allows for expanding the criteria used to identify and track hypertension in pregnancy. EMRs offer the potential to identify hypertensive disorders of pregnancy using recorded blood pressure (BP) values. This is particularly true in pregnancy because BPs are actively monitored and measured at each prenatal visit.

In a preliminary proof of concept study by Chen et al. we evaluated whether measured and EMR-recorded BP values were useful for identifying hypertension in pregnancy and concluded these BPs were helpful (9). Chen's study, however, did not require women to be enrolled in the health-plan for the entire pregnancy. In addition, follow-up was censored at 35 weeks 6 days gestation and adverse neonatal outcome events were not assessed (9).

To address these issues, we compared a Traditional Definition for identifying pregnant women with hypertension (using hospital discharge diagnosis codes) to a definition incorporating recorded BPs, plus antihypertensive prescription dispenses and diagnosis codes. Epidemiologically, the objective was to determine the value of a definition including recorded blood compares to the standard definition for identification of hypertensive diseases of pregnancy. For this study we specified that women needed to be enrolled in the health plan for their entire pregnancy and assessed two neonatal outcome events [preterm delivery and small for gestational age (SGA) infants] associated with hypertension (10–17) to evaluate whether the two definitions identified populations of women with similar risk for adverse pregnancy outcomes.

Materials and methods

Design and setting

This was a retrospective cohort study set within Kaiser Permanente Southern California (KPSC). KPSC is a large integrated healthcare delivery system providing medical care to over 4.4 million members. Medical care is captured in a comprehensive EMR that includes diagnoses, procedures and treatments from inpatient stays and ambulatory visits, pharmacy dispensing records, vital signs, laboratory results, and radiology reports. These data are linked using a unique medical record number that are retained for life. Pregnancy episodes, mother-infant linkage, and pregnancy specific outcome event data are collected and maintained for research purposes. The institutional review board of KPSC approved the study with a waiver of informed consent.

Patients

Women who delivered liveborn or stillborn infant(s) from 2009 to 2014 were eligible for inclusion. The delivery year beginning in 2009 was selected because prior to this time, BP measures were not recorded within discrete fields in the EMR. For pregnancy clinical care, KPSC clinicians use self-reported last menstrual period along with first trimester ultrasound data to determine an estimated delivery date (EDD). The start of pregnancy and gestational age were assigned using the EDD established in the EMR.

We included pregnant women between the ages of 15–49 years on the day of delivery who were continuously

enrolled in the health-plan from 6 months prior to the start of pregnancy through delivery. Women could contribute more than one pregnancy during the study period. We also required gestational age at birth to be between 22 and 43 weeks because live births outside these gestational ages are implausible. Pregnancies meeting these criteria were included in the base cohort used for descriptive comparisons between study definitions. For the singleton cohort, multiple gestation pregnancies were excluded because of their association with hypertensive disorders of pregnancy and the neonatal outcome events under study.

Hypertension definitions

Under the ACOG classification of hypertensive disorders of pregnancy, the threshold BP for defining chronic and gestational hypertension is a systolic BP greater than or equal to 140 and/or a diastolic BP greater than or equal to 90 on two occasions at least 4 h apart (18, 19). Gestational hypertension is generally considered to occur after 20 weeks' gestation. Preeclampsia or eclampsia also occurs after 20 weeks' gestation and can be superimposed on chronic hypertension. Preeclampsia/eclampsia can also occur after the development of gestational hypertension or can be the presenting hypertensive disorder (18, 19).

The "BP-Inclusive Definition" for identifying hypertensive disorders of pregnancy used three criteria. Hypertension was considered to be present if any of the following criteria were met: (1) two elevated outpatient BPs (systolic BP $\geq$ 140 and/or diastolic BP $\geq$ 90) occurring on different days within 30 days of each other from the start of pregnancy through delivery, (2) one or more fills for an antihypertension medication plus one or more hypertension diagnosis codes from the start of pregnancy through delivery (excluding the delivery hospitalization), or (3) one or more hospital discharge diagnosis codes for preeclampsia or eclampsia occurring after 20 weeks' gestation (see **Supplementary Table 1** for a list of diagnosis codes).

The comparison (Traditional) definition for identifying hypertensive disorders of pregnancy used diagnosis codes for chronic hypertension, gestational hypertension, and preeclampsia or eclampsia recorded in the EMR from the delivery hospitalization. As previously noted, this "Traditional Definition" has been used in previous epidemiologic studies evaluating hypertensive disorders in pregnancy (**Supplementary Table 1**).

Women identified using the BP-Inclusive Definition were classified as having chronic hypertension if they met criteria for hypertension prior to 20 weeks gestation and as having gestational hypertension if they did not meet criteria before 20 weeks but did meet criteria after 20 weeks gestation. A woman was classified as having preeclampsia superimposed

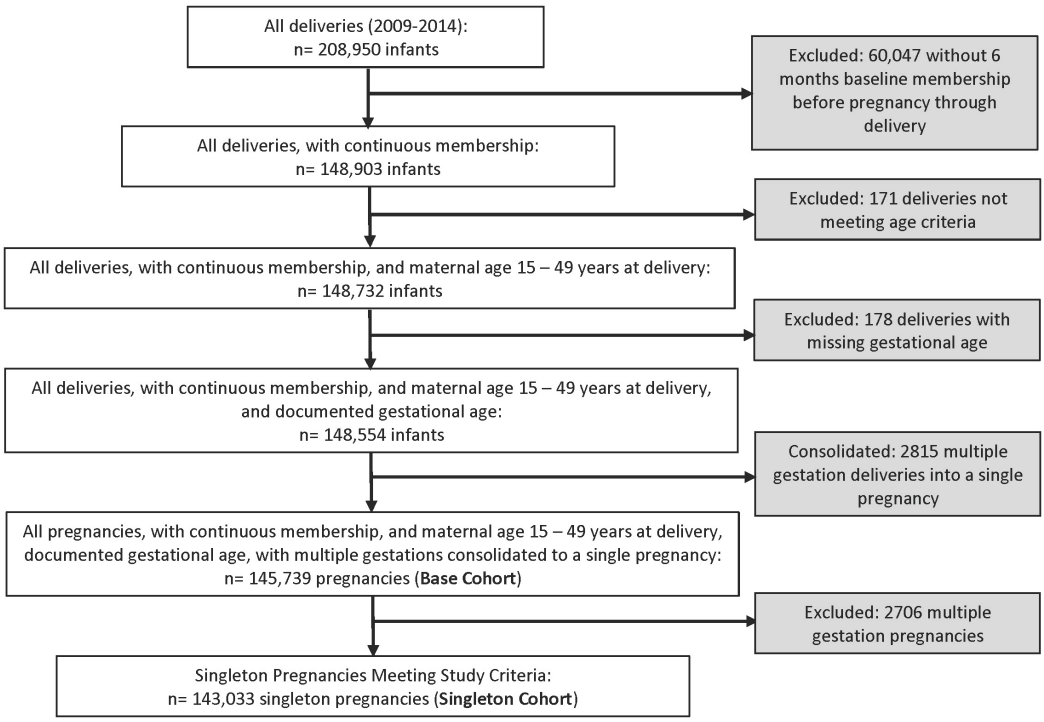


FIGURE 1
Patient disposition.

on chronic hypertension if she was identified as having chronic hypertension and then went on to have a diagnosis of preeclampsia in the EMR or if she received a hospital diagnosis for this condition after 20 weeks gestation. Lastly, women could be classified as preeclampsia or eclampsia based solely on a hospital diagnosis code after 20 weeks gestation. For women identified using the Traditional Definition, their categorization into these four subgroups was based entirely on delivery hospitalization diagnosis codes found in the EMR. Within KPSC hospital diagnosis codes are entered into the EMR by professional coders based on physician admission notes and discharge summaries. Hospital codes were not validated by chart review for this study.

Neonatal events

Two neonatal outcome events were evaluated: (1) preterm birth, defined as a delivery prior to 37 weeks 0 days gestational age and (2) SGA, defined as a birthweight less than the 10th percentile based on gender, race and gestational age using published growth curves (20).

Statistical analysis

The prevalence of hypertensive disorders in pregnancy, overall and by hypertension category (chronic, gestational, etc.,) were determined using the *base cohort* (all pregnancies meeting inclusion criteria between 2009 and 2014). Descriptive comparisons between pregnancies meeting the BP-Inclusive Definition, the Traditional Definition and non-hypertensive pregnancies were conducted using the *singleton cohort* (the base cohort excluding multiple gestation pregnancies). The prevalence of neonatal outcome events were compared between each definition group and the non-hypertensive group from the singleton cohort. Comparisons between these groups were made using Poisson regression with robust variance and p-values < 0.05 indicating statistical significance.

Secondary analyses were conducted to assess differences between pregnancies that met the BP-Inclusive Definition and pregnancies that met the Traditional Definition as these two groups are not mutually exclusive. The secondary analyses separated pregnancies into three mutually exclusive groups: (1) those pregnancies who met both hypertension definitions (BP-Inclusive and Traditional Definitions), (2) those who met the study BP-Inclusive Definition but not the Traditional Definition (BP-Inclusive Definition Only), and (3) those who met the Traditional Definition but not the BP-Inclusive Definition (Traditional Definition Only). Again, comparisons between groups were made using Poisson regression with robust variance and p-values < 0.05 indicating statistical significance. All analyses were conducted using SAS (SAS Enterprise Guide 7.1; SAS Institute Inc).

Results

The Base Cohort, after applying inclusions and exclusions, consisted of 1,45,739 pregnancies (Figure 1). Most pregnancies (1,28,686 or 88.3%) did not meet either hypertension definition. The prevalence of hypertension was similar using the two definitions; 14,225 (9.8%) met the BP-Inclusive Definition and 13,637 (9.4%) pregnancies met the Traditional Definition. There was considerable overlap between the two study definitions with 10,809 pregnancies meeting both hypertension definitions. However, 24.0% of pregnancies (3,416 of 14,225) met the BP-Inclusive Definition Only and 20.7% (2,828 of 13,637) met the Traditional Definition Only (Table 1). The majority of women (94.2%) who met the BP-Inclusive Definition Only were identified based on the two elevated outpatient BP criteria without a diagnosis at delivery or a diagnosis plus prescription during pregnancy. By comparison, 66.8% of women who met the Traditional Definition Only did not have an outpatient hypertension diagnosis or antihypertensive medication dispensed during pregnancy (Table 1).

TABLE 1 Hypertension criteria for non-overlapping hypertensive pregnancies.

Pregnancy met Traditional Definition only	***N* = 2,828**
• Antihypertensive drug dispensed but no diagnosis during pregnancy	55 (1.9%)
• Diagnosis but no antihypertensive drug dispensed during pregnancy	885 (31.3%)
• No drug dispensed or diagnosis during pregnancy, only a discharge code	1,888 (66.8%)
Pregnancy met BP-Inclusive Definition only	***N* = 3,416**
• Met 2 blood pressure and diagnosis plus prescription dispense criteria	96 (2.8%)
• Met diagnosis plus prescription dispense criteria only	101 (3.0%)
• Met 2 blood pressure criteria only	3,219 (94.2%)

TABLE 2 Breakdown of hypertensive disorders of pregnancy in the base cohort for 14,225 women identified using the BP-Inclusive Definition.

Hypertensive disorders of pregnancy	**Percent (N)**
Chronic hypertension (*n* = 4,276)	
Chronic hypertension	22.3% (3,170)
Chronic hypertension who went on to develop preeclampsia	7.8% (1,106)
Gestational hypertension (*n* = 4,776)	
Gestational hypertension	24.3% (3,457)
Gestational hypertension who went on to develop preeclampsia	9.3% (1,319)
Preeclampsia-eclampsia (without evidence of chronic or gestational hypertension)	36.4% (5,173)
Total	100% (14,225)

For the individual criteria used in the BP-Inclusive Definition: 7,990 (56.2%) pregnancies met the two elevated BP criteria, 3,166 (22.3%) pregnancies met the diagnosis plus prescription criteria and 7,598 (53.4%) pregnancies had a hospital diagnosis of preeclampsia/eclampsia. Pregnancies could meet more than one criterion. Additional details regarding the base cohort are provided in Table 2 (Hypertensive Disorders of Pregnancy in women meeting the BP Inclusive Definition) and Supplementary Table 2 (Demographic Characteristics of the Base Cohort).

Demographic information for the singleton cohort by hypertension definition is reported in Table 3. The average age for women with a hypertensive disorder of pregnancy (using either definition) was higher than the age for the

TABLE 3 Baseline characteristics for the singleton cohort by hypertension definition (2009–2014).

Characteristic	Non-hypertensive ($n = 126,682$)	Traditional Definition* ($n = 13,033$)	BP-Inclusive Definition** ($n = 13,592$)
Maternal age at delivery, Mean ± SD	29.9 ± 5.8	31.0 ± 6.3	31.0 ± 6.2
Age at delivery, *N* (%)			
15–19	6,462 (5.1)	599 (4.6)	562 (4.1)
20–24	17,111 (13.5)	1,603 (12.3)	1,645 (12.1)
25–29	33,187 (26.2)	2,824 (21.7)	3,064 (22.5)
30–34	41,967 (33.1)	4,010 (30.8)	4,205 (30.9)
35–50	27,955 (22.1)	3,997 (30.7)	4,116 (30.3)
Race/Ethnicity, *N* (%)			
White	32,232 (25.4)	3,080 (23.6)	3,628 (26.7)
Asian	16,622 (13.1)	1,416 (10.9)	1,444 (10.6)
Black	9,831 (7.8)	1,692 (13)	1,659 (12.2)
Hispanic	65,772 (51.9)	6,566 (50.4)	6,582 (48.4)
Other	2,225 (1.8)	279 (2.1)	279 (2.1)
Maternal education, *N* (%)			
Less than high school	10,377 (8.2)	1,065 (8.2)	1,030 (7.6)
High school	29,770 (23.5)	3,043 (23.3)	3,201 (23.6)
College	67,497 (53.3)	7,187 (55.1)	7,541 (55.5)
Graduate	18,840 (14.9)	1,724 (13.2)	1,806 (13.3)
Unknown	198 (0.2)	14 (0.1)	14 (0.1)
BMI, *N* (%)			
<18.5	8,504 (6.7)	658 (5)	616 (4.5)
18.5–24.9	54,535 (43)	2,952 (22.7)	2,940 (21.6)
25.0–29.9	34,467 (27.2)	3,414 (26.2)	3,444 (25.3)
>30.0	29,174 (23)	6,009 (46.1)	6,591 (48.5)
Missing	2 (0)	0	1 (0)
Parity, *N* (%)			
0	50,824 (40.1)	5,845 (44.8)	6,073 (44.7)
1	40,124 (31.7)	3,662 (28.1)	3,829 (28.2)
2	17,268 (13.6)	1,586 (12.2)	1,677 (12.3)
>3	8,443 (6.7)	832 (6.4)	864 (6.4)
Missing	10,023 (7.9)	1,108 (8.5)	1,149 (8.5)
Co-morbidities, *N* (%)			
Diabetes	1,051 (0.8)	713 (5.5)	715 (5.3)
Heart disease	311 (0.2)	61 (0.5)	57 (0.4)
Renal disease	87 (0.1)	91 (0.7)	92 (0.7)
Outpatient blood pressures, median, (IQR)			
Total blood pressures	14 (11, 17)	19 (14, 28)	18 (14, 28)
Total elevated blood pressures	–	4 (2, 7)	3 (2, 7)
Time between first and last elevated blood pressure, days	–	126 (25, 197)	152 (52, 203)

*"Traditional Definition" is based on discharge diagnosis codes from the delivery hospitalization. **"BP-Inclusive Definition" is based on measured blood pressure values, diagnosis codes and dispensed antihypertensive medications. 10,809 women met both the Traditional and the BP-Inclusive Definition.

non-hypertensive pregnancies, driven primarily by a higher percentage of hypertensive women in the 35–50 years age group. Women whose pregnancy met one of the hypertension definitions were also more likely to be obese (46.1–48.5% versus 23%), to be nulliparous (44.7–44.8% versus 40.1%) and to have co-morbid conditions (diabetes, heart disease or renal disease) than non-hypertensive women. These finding were consistent for both hypertension definitions.

Over 2.24 million outpatient BPs were recorded for the 1,43,033 pregnancies in the singleton cohort. The median number of outpatient BPs recorded during pregnancy in the non-hypertensive cohort was 14 while the median number of BPs ranged between 18 and 19 in pregnancies meeting one of the hypertension definitions (Table 3). As expected, pregnancies meeting the hypertension definitions had more documented elevated BPs than the non-hypertensive pregnancies; pregnancies meeting either one of the two hypertensive definitions had a median of three or four elevated BPs recorded over a 4-to-5-month period of time (126–152 days).

The BP-Inclusive Definition identified more deliveries as having chronic hypertension (22.7%) than the Traditional Definition (18.4%) (Table 4). Preeclampsia superimposed on chronic hypertension was also higher in the BP-Inclusive Definition cohort (10.6% versus 8.3%) for similar reasons; a higher percentage identified with chronic hypertension led to more women being classified as having preeclampsia superimposed on chronic hypertension. The proportion of women with just preeclampsia or eclampsia was lower in pregnancies meeting the BP-Inclusive Definition compared to the Traditional Definition (42.0 versus 46.6%, respectively).

The prevalence of preterm delivery and SGA infants were similar for pregnancies meeting the BP-Inclusive Definition and the Traditional Definition and were significantly higher than for women without evidence of hypertensive disorders of pregnancy (Figure 2).

The secondary analysis separated hypertensive women into three mutually exclusive groups, the baseline characteristics of these three groups were similar to those found in the base cohort (Supplementary Table 3). The highest prevalence of adverse neonatal outcome events were seen in women who met both study definitions (Preterm Delivery = 25.3%, SGA = 17.4%) (Figure 3). The prevalence of neonatal outcome events for women meeting one of the hypertension definitions but not the other were also higher than the prevalence found for non-hypertensive pregnancy but markedly less elevated. Both outcomes for pregnancies meeting the Traditional Definition Only were statistically higher than non-hypertensive pregnancies (Preterm Delivery 8.5% versus 6.6%; SGA 10.6% versus 8.6%). This, however, was not true for pregnancies meeting the BP-Inclusive Definition Only. For the preterm delivery outcome, pregnancies meeting the BP-Inclusive Definition had a prevalence of 7.2% compared to 6.6% in non-hypertensive pregnancies ($p = 0.13$).

TABLE 4 Hypertension subgroups by hypertension definition (singleton cohort).

Hypertension subgroup	Traditional Definition % ($N = 13,033$)	BP-Inclusive Definition % ($N = 13,592$)
Chronic hypertension	18.4% (2,400)	22.7% (3,078)
Gestational hypertension	26.7% (3,483)	24.8% (3,364)
Preeclampsia superimposed on chronic hypertension	8.3% (1,083)	10.6% (1,441)
Preeclampsia/Eclampsia	46.6% (6,067)	42.0% (5,709)

Discussion

In this study, we compared two epidemiologic definitions for identifying hypertensive disorders of pregnancy. Both approaches identified a similar prevalence of hypertensive disorders, and as expected, hypertensive pregnancies identified using these definitions had an increased prevalence of adverse neonatal outcome events compared to pregnancies not identified as hypertensive. Overall, a high percentage of hypertensive pregnancies met both hypertension definitions but there was a significant percentage of pregnancies who met only one of the two hypertension definitions used in this study (i.e., 21–24% of pregnancies met one of the definitions but not the alternative.).

Secondary analyses focused on the three mutually exclusive populations of hypertensive pregnancies. These analyses found that women who met both hypertension definitions had the highest prevalence of adverse neonatal outcome events. Women who met either the BP-Inclusive Definition Only or the Traditional Definition Only had a lower prevalence of adverse fetal outcomes, although these prevalence's were still higher than those seen in non-hypertensive women. In pregnancies identified using the BP-Inclusive definition Only (identified based strictly on the elevated BP criterion) the prevalence of SGA was significantly higher than in non-hypertensive pregnancies, while the prevalence of pre-term delivery was not statistically different.

The significance of these findings is unknown and will require additional study. Specifically, for women who met the Traditional Definition Only, it is worth evaluating their clinical profile to understand why they received a hypertension diagnosis at delivery without other evidence of hypertension during pregnancy and why these women had much lower rates of adverse pregnancy outcomes. Often these women receive no antihypertensive medications during pregnancy because US guidelines do not recommend treatment for moderate

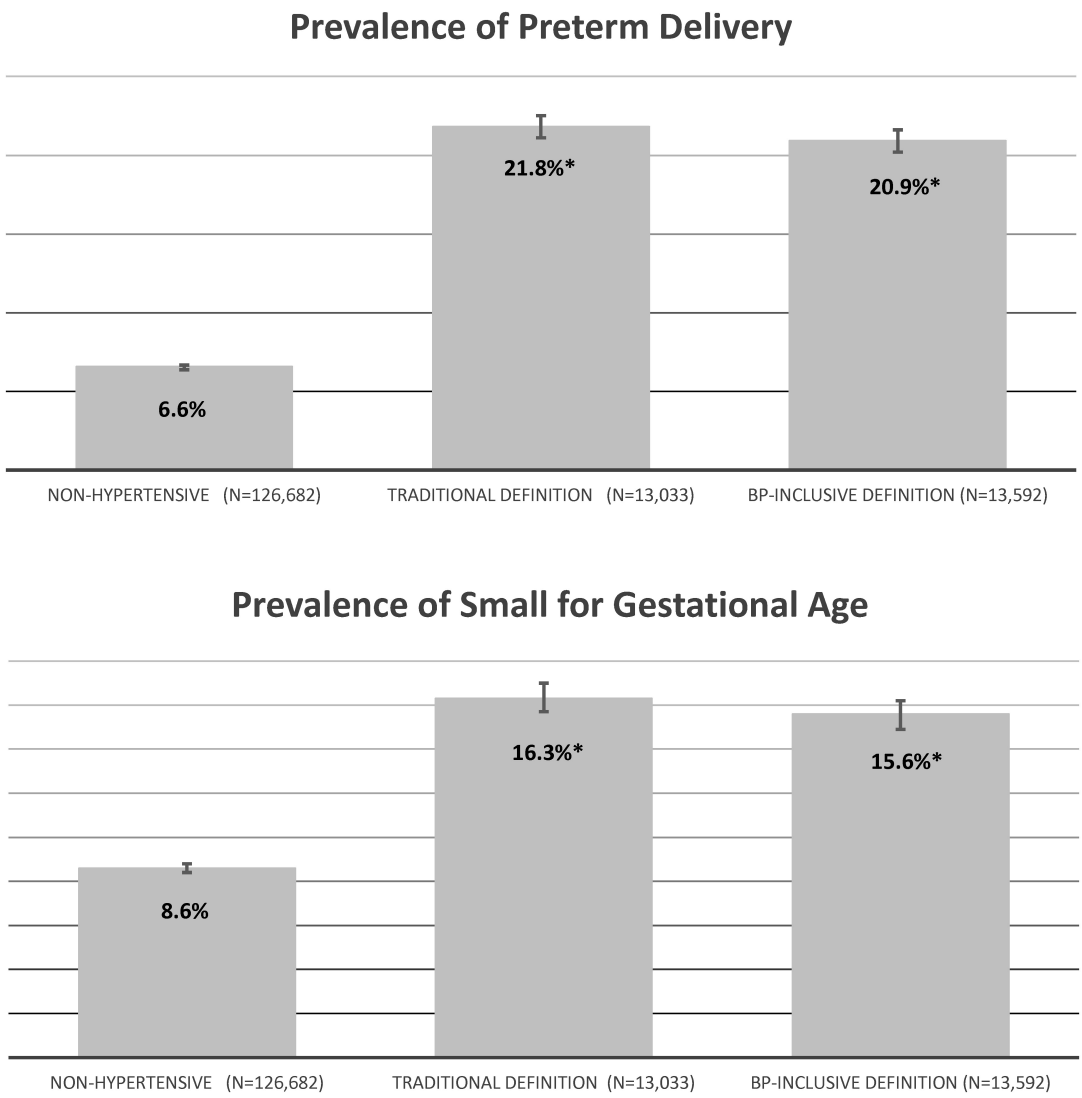


FIGURE 2
Pregnancy outcomes for the singleton cohort by hypertension definition (percent). Non-hypertensive – pregnancies that did not meet either hypertension definition; Traditional Definition – pregnancies who met the Traditional Definition based on delivery hospitalization discharge codes as having hypertension; BP-Inclusive Definition – pregnancies who met the BP-Inclusive Definition based on elevated blood pressures, prescriptions and a diagnosis or delivery diagnoses for eclampsia/preeclampsia as having hypertension. *$P < 0.001$ versus non-hypertensive pregnancies.

hypertension in pregnancy. However, a good percentage received a diagnosis of hypertension during pregnancy without meeting the elevated BP criteria specified in the BP-Inclusive Definition. There are several potential explanations. First, hypertensive women may stop their BP medications to prevent potential harmful exposures to the fetus. Second, BPs are known to decline early in pregnancy with a gradual increase in the second and third trimester; it is possible that the increase in BP during the second and third trimester never reached the threshold BP of ≥140/90 in some of these women. Third, we restricted qualifying BPs to those recorded in an outpatient setting; expanding this criterion to include inpatient BPs could increase the number of women meeting the elevated-BP standard. And lastly, some of these women may have had evidence of hypertension only during their delivery hospitalization.

Most of the women who met the BP-Inclusive Definition Only were identified based on the elevated-BP criteria. It is important to understand why these women did not receive a diagnosis of hypertension. Chart reviews were conducted in our prior study to evaluate discrepancies between various hypertension definitions compared to the definition that incorporated BP values (9). Among a sample of women with elevated BP values but without a diagnosis of hypertension, 58%

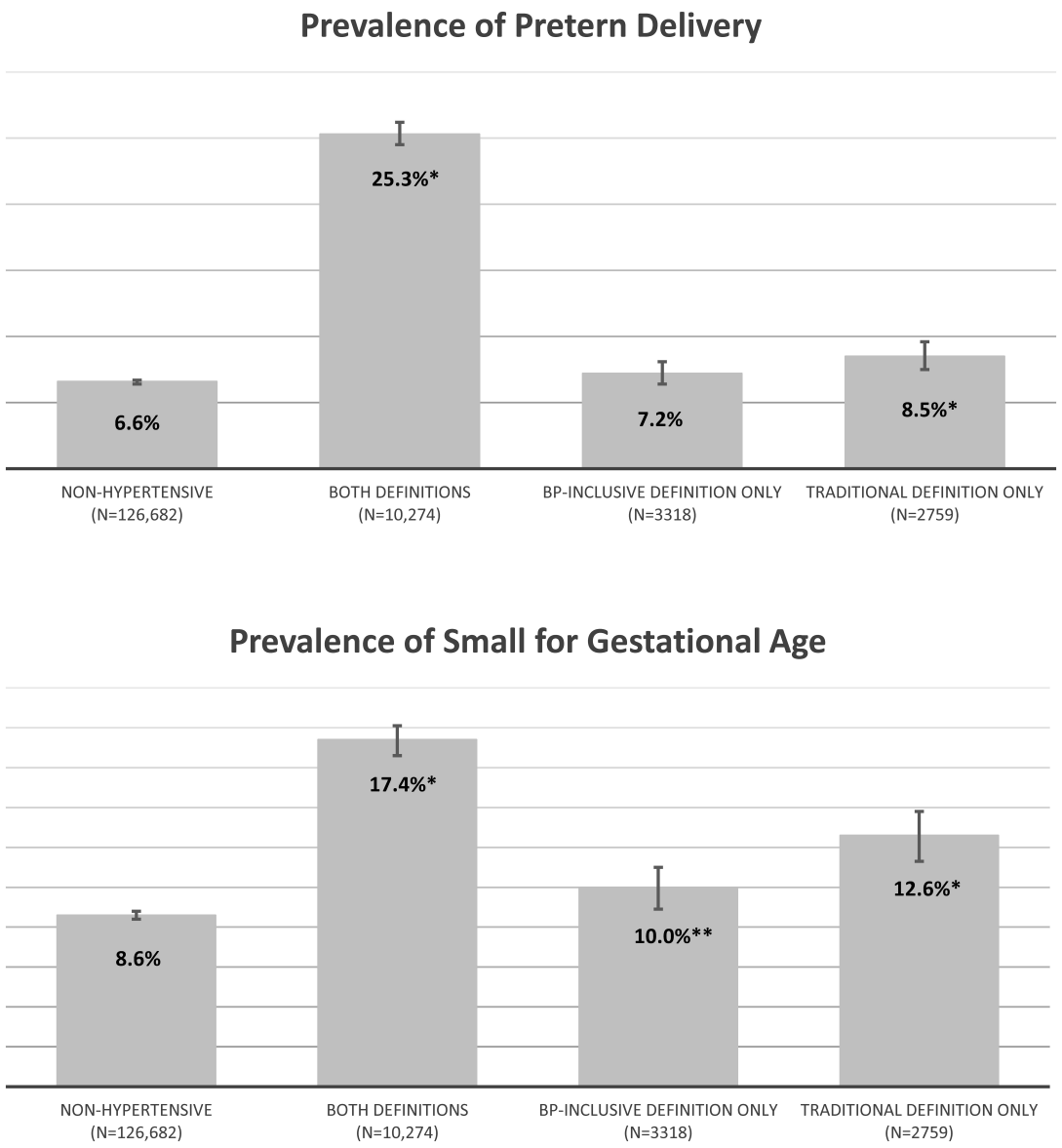


FIGURE 3
Secondary analysis of pregnancy outcomes for the singleton cohort by mutually exclusive hypertension groups (percent). Non-hypertensive – pregnancies that did not meet either hypertension definition; Both Definitions – pregnancies that were identified as hypertensive by both study definitions; Traditional Definition Only – pregnancies that met the Traditional Definition but not the BP-Inclusive Definition; BP-Inclusive Definition Only – pregnancies that met the BP-Inclusive Definition but not the Traditional Definition. *$P < 0.001$ compared to non-hypertensive pregnancies. **$P = 0.006$ compared to non-hypertensive pregnancies.

had evidence in the chart that the elevated BPs were recognized by the provider. Reasons for the lack of a hypertension diagnosis in this previous study could not be determined (9). It is possible that providers are reluctant to assign a diagnosis of hypertension if there is no plan for treatment. It is also possible that if multiple BP values were obtained on a single day, including some that were elevated and others that were not; providers may have given more weight to the values that were not elevated. Additional work needs to be done to understand why hypertension diagnoses are not recorded in the EMR of women with elevated BPs.

This study included a large sample of women and over 2.2 million outpatient BP values recorded during pregnancy. If, as previous studies suggest, diagnosis codes for hypertension have low sensitivity (7, 8) then measured BPs have the potential to identify and support the diagnosis of hypertension. The inclusion of measured BPs is attractive from an epidemiologic standpoint because it allows for quantification of risk based on BP level and BP variability during pregnancy (21). However,

pregnancies identified based only on the BP criterion used in this study were associated with a very small increase in the prevalence of adverse neonatal outcome events compared to pregnancies with no evidence of hypertension. The time between first and last elevated BP was also shorter in the BP only group, 63 days versus 152 days in the full group meeting the BP-Inclusive Definition. Additionally, women meeting the elevated BP only criterion had a median of 4 high BPs out of 21 total measured during pregnancy. These findings support the need for further work in this area.

Several limitations need to be considered when evaluating the results of this study. First, the elevated BP measures used for the BP-Inclusive Definition may not represent true hypertension; elevated BPs can arise in a variety of clinical circumstances (such as white-coat hypertension, pain or stress related conditions and medications like decongestants or non-steroidal anti-inflammatory drugs). Second, the BP criteria used in the study, two elevated BPs on different days but with 30 days of each other, could be flawed. It could be argued that given the observational nature of these data, a higher number of elevated BPs or a different time interval between measurements are necessary to establish hypertension. Our criteria were designed to capture what might reasonably occur in clinical practice where a woman has elevated outpatient BPs on two separate visits before hypertension is diagnosed; the 30-day time frame was designated so that BP elevations were within a relatively short time span and not spread out over a 280 day pregnancy. Future studies could look at changing the required number of BPs and timing of the BP measures needed to define hypertension from electronic health records. Third, we only evaluated two neonatal outcomes; maternal outcomes that could be studied in the future include maternal intensive care unit admissions and cardiovascular or cerebrovascular outcomes.

Conclusion

Both epidemiologic definitions used in this study identified similar prevalences of pregnancies complicated by hypertension. A high number of hypertensive pregnant women met criteria for both definitions, however, there was a significant proportion of pregnancies that met one but not both definitions. The prevalence of neonatal outcome events was different between women who met both definitions versus those meeting only a single definition. Additional work needs to be done understand the reasons and importance of these outcome event differences in hypertensive pregnant women meeting different epidemiologic definitions.

Data availability statement

The datasets presented in this article are not readily available. Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions. Requests to access the datasets should be directed to kristi.reynolds@kp.org.

Ethics statement

This study involving human participants was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board. The board waived the requirement for signed informed consent.

Author contributions

TC, SS, LA, VH, TE, RN, AI, and SD: concept and design of the study. LA, CP, HZ, ZB, and AI: acquisition of study data. SS, VH, HZ, RN, and ZB: analysis of the data. TC, SS, LA, VH, TE, HZ, RN, ZB, AI, and SD: interpretation of the results. TC, SS, VH, and HZ: drafting of the manuscript. TC, SS, LA, KR, VH, TE, CP, HZ, AI, and SD: critical revisions for important intellectual content. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) R01HD082141 (PI: SD).

Acknowledgments

We would like to acknowledge Natalie A. Bello for her editorial review and recommendations in the generation of this manuscript.

Conflict of interest

SS reports receiving research funding from Synoos Health that represents a consortium of pharmaceutical companies. TE has done consulting for DiabetOmics Inc., Alynylam Pharmaceuticals, and Ferring Pharmaceuticals. LA has received research funding from Bausch Health Companies. SD has received research funding from GSK pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial

relationships that could be construed as a potential conflict of interest.

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/fcvm.2022.1006104/full#supplementary-material

References

1. Centers for Disease Control and Prevention, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. *Maternal and Infant Health – Pregnancy Complications*. (2018). Available online at: http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregcomplications.htm (accessed May 5, 2020).

2. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. *Hypertension.* (2019) 74:1089–95. doi: 10.1161/HYPERTENSIONAHA.119.12968

3. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am J Obstet Gynecol.* (2012) 206:134.e1–8. doi: 10.1016/j.ajog.2011.10.878

4. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol.* (2009) 113:1299–306. doi: 10.1097/AOG.0b013e3181a45b25

5. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States 1987 – 2004. *Am J Hypertens.* (2008) 21:521–6. doi: 10.1038/ajh.2008.20

6. Baraban E, McCoy L, Simon P. Increasing prevalence of gestational diabetes and pregnancy-related hypertension in Los Angeles County, California, 1991–2003. *Prev Chronic Dis.* (2008) 5:A77.

7. Rector TS, Wickstrom SL, Shah M, Thomas Greeenlee N, Rheault P, Rogowski J, et al. Specificity and sensitivity of claims-based algorithms for identifying members of medicare+choice health plans that have chronic medical conditions. *Health Serv Res.* (2004) 39:1839–57. doi: 10.1111/j.1475-6773.2004.00321.x

8. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Med.* (2007) 1:e18–26.

9. Chen L, Shortreed SM, Easterling T, Cheetham TC, Reynolds K, Avalos LA, et al. Identifying hypertension in pregnancy using electronic medical records: the importance of blood pressure values. *Pregnancy Hypertens.* (2020) 19:112–8. doi: 10.1016/j.preghy.2020.01.001

10. Fisher SC, Van Zutphen AR, Romitti PA, Browne ML, National Birth Defects Prevention Study. Maternal hypertension, antihypertensive medication use, and small for gestational age births in the national birth defects prevention study, 1997–2011. *Matern Child Health J.* (2018) 22:237–46. doi: 10.1007/s10995-017-2395-8

11. Nzelu D, Dumitrascu-Biris D, Kay P, Nicolaides KH, Kametas NA. Severe hypertension, preeclampsia and small for gestational age in women with chronic hypertension diagnosed before and during pregnancy. *Pregnancy Hypertens.* (2018) 14:200–4. doi: 10.1016/j.preghy.2018.10.006

12. Panaitescu AM, Baschat AA, Akolekar R, Syngelaki A, Nicolaides KH. Association of chronic hypertension with birth of small-for-gestational-age neonate. *Ultrasound Obstet Gynecol.* (2017) 50:361–6. doi: 10.1002/uog.17553

13. Catov JM, Nohr EA, Olsen J, Ness RB. Chronic hypertension related to risk for preterm and term small for gestational age births. *Obstet Gynecol.* (2008) 112:290–6. doi: 10.1097/AOG.0b013e31817f589b

14. Hitti J, Sienas L, Walker S, Benedetti TJ, Easterling T. Contribution of hypertension to severe maternal morbidity. *Am J Obstet Gynecol.* (2018) 219:405.e1–7. doi: 10.1016/j.ajog.2018.07.002

15. Nakanishi S, Aoki S, Nagashima A, Seki K. Incidence and pregnancy outcomes of superimposed preeclampsia with or without proteinuria among women with chronic hypertension. *Pregnancy Hypertens.* (2017) 7:39–43. doi: 10.1016/j.preghy.2017.01.001

16. Premkumar A, Baer RJ, Jelliffe-Pawlowski LL, Norton ME. Hypertensive disorders of pregnancy and preterm birth rates among black women. *Am J Perinatol.* (2019) 36:148–54. doi: 10.1055/s-0038-1660461

17. Premkumar A, Henry DE, Moghadassi M, Nakagawa S, Norton ME. The interaction between maternal race/ethnicity and chronic hypertension on preterm birth. *Am J Obstet Gynecol.* (2016) 215:787.e1–8. doi: 10.1016/j.ajog.2016.08.019

18. The American College of Obstetricians and Gynecologists. APA ACOG practice bulletin No. 202: gestational hypertension and preeclampsia. *Obstet Gynecol.* (2019) 133:e1–25. doi: 10.1097/AOG.0000000000003018

19. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. APA ACOG practice bulletin No. 203: chronic hypertension in pregnancy. *Obstet Gynecol.* (2019) 133:e26–50. doi: 10.1097/AOG.0000000000003020

20. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birthweight for gestational age using a United States national reference. *BMC Pediatr.* (2003) 3:6. doi: 10.1186/1471-2431-3-6

21. Magee LA, Singer J, Lee T, McManus RJ, Lay-Flurrie S, Rey E, et al. Are blood pressure level and variability related to pregnancy outcome? Analysis of control of hypertension in pregnancy study data. *Pregnancy Hypertens.* (2020) 19:87–93. doi: 10.1016/j.preghy.2019.12.002

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 20 January 2023
DOI 10.3389/fcvm.2022.969148

OPEN ACCESS

EDITED BY
Valeria Visco,
University of Salerno, Italy

REVIEWED BY
Ioanina Parlatescu,
Carol Davila University of Medicine and Pharmacy, Romania
Antonio Celentano,
University of Melbourne, Australia

*CORRESPONDENCE
Elena Calabria
✉ calabriaelena92@gmail.com

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

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 14 June 2022
ACCEPTED 27 December 2022
PUBLISHED 20 January 2023

CITATION
Canfora F, Calabria E, Pecoraro G, Leuci S, Coppola N, Mazzaccara C, Spirito F, Aria M, D'Aniello L, Mignogna MD and Adamo D (2023) Prevalence of hypertension and correlation with mental health in women with burning mouth syndrome: A case-control study. *Front. Cardiovasc. Med.* 9:969148. doi: 10.3389/fcvm.2022.969148

Prevalence of hypertension and correlation with mental health in women with burning mouth syndrome: A case-control study

Federica Canfora[1], Elena Calabria[1]*, Giuseppe Pecoraro[1], Stefania Leuci[1], Noemi Coppola[1], Cristina Mazzaccara[2,3], Francesca Spirito[4], Massimo Aria[5], Luca D'Aniello[6], Michele Davide Mignogna[1†] and Daniela Adamo[1†]

[1]Department of Neuroscience, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy, [2]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy, [3]CEINGE Advanced Biotechnologies, Naples, Italy, [4]Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy, [5]Department of Economics and Statistics, University of Naples Federico II, Naples, Italy, [6]Department of Social Sciences, University of Naples Federico II, Naples, Italy

Background: The relationship between hypertension (HTN) and chronic pain is still a matter of debate, and its prevalence in patients with burning mouth syndrome (BMS) has never been evaluated. This study aimed to assess the prevalence of HTN in women with BMS and to evaluate its relationship with potential predictors such as risk factors for cardiovascular diseases, pain, and mental health status analyzing differences with healthy women.

Methods: In total, 250 women with BMS (WBMS) were prospectively recruited and compared with an equal number of healthy women (HW) matched for age. Education, body mass index, smoke and alcohol consumption, intensity and quality of pain, and psychological profile were further investigated to identify the potential predictors of HTN. Specifically, pain assessment [the Numeric Rating Scale (NRS) and Short-Form McGill Pain Questionnaire (SF-MPQ)] and psychological assessment [Hamilton Rating Scale for Depression and Anxiety (HAM-D and HAM-A), Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS)] was carried out for the participants.

Results: HTN was found in 128 (51.2%) WBMS and 76 (30.4%) HW ($p < 0.001$**). The scores of the NRS, SF-MPQ, HAM-D, HAM-A, and PSQI were statistically significantly higher in the WBMS than in the HW ($p < 0.001$**). A strongly linear correlation between HTN and employment status, systemic diseases, and education level ($p < 0.001$**) was found in WBMS, while a strong correlation between HTN and employment status, hypercholesterolemia, systemic diseases, and drug consumption was found in HW ($p < 0.001$**). No statistically significant correlation was found between HTN and pain, anxiety, depression, and sleep disturbances.

Conclusion: These results suggest that WBMS showed a higher prevalence of HTN compared with controls. Unemployed WBMS with lower education and other systemic comorbidities are at an increased risk of developing HTN. HTN is associated with alteration in the vascular structure and function of the brain, and these processes accelerate brain aging, which contributes to a reduction in intracortical connectivity, thus affecting the modulatory system of control of pain in patients with BMS, independently of their mental health assessment. Predictors that may underlie this association remain unclear, taking into account the differences found in HW, and should be further elucidated.

KEYWORDS

burning mouth syndrome (BMS), hypertension, women, chronic orofacial pain, cardiovascular risk factor

Introduction

Hypertension (HTN) is the leading cause of cardiovascular disease, and it is responsible for 8.5 million premature deaths from stroke, ischemic heart disease, and kidney disease worldwide (1–3). In addition, HTN is an evidence-based risk factor for brain aging and dementia (4, 5).

The number of people affected by HTN aged 30–79 years has doubled from 1990 to 2021, reaching 626 and 652 millions of women and men, respectively, in the world (6). Gender disparity in the HTN epidemiology reveals differences in age stratification; indeed, the prevalence of HTN in patients aged between 18 and 29 years is 3% in women vs. 8.5% in men, while in patients aged between 30 and 44 years, it is 7.3% in women vs. 15.8% in men (7). In contrast, this prevalence increases strongly after menopause, and it is more common in women than in men in the elderly population above the age of 75 years, reaching 78% (8).

The mechanisms in which sex interacts with vascular aging and subsequently with an increase in blood pressure are complex, including a multitude of hormonal, chromosomal, or even psychosocial factors (9). Indeed, sex steroids and the receptors through which they act are emerging as important mediators in the promotion and maintenance of sexual divergence in blood pressure regulation across the lifespan (10).

Obesity, dyslipidemia, impaired fasting glucose, and chronic pain are the most frequent comorbidity associated with HTN (11–14).

Burning mouth syndrome (BMS) is a chronic orofacial pain disorder with a strong female predilection; it is characterized by a generalized or localized intraoral burning or dysesthetic sensation or pain of the oral mucosa without any evidence of any specific mucosal lesions and/or laboratory findings (15). The overall prevalence of BMS was 1.73% in the general population and 7.72% in the clinical settings of dental practice with an average of 4%, reaching a prevalence of 18% in postmenopausal women (16). Several studies reported a consistent gender difference associated with BMS (16). Nasri-Heir et al. (17) reported the highest prevalence in women of middle age (>50 years) with a female/male ratio of 7:1, whereas in the recent meta-analysis by Wu et al. (16), the female/male ratio reported was 3:1. Possible factors behind these gender differences could include genetic factors affecting pain vulnerability as well as hormonal and psychosocial factors (18).

The pathophysiology of BMS includes central nervous system dysfunctions, which increase the central pain sensitization processes and reduce the functioning of descending pain inhibitory mechanisms (17). The higher pain sensitivity in women is probably due to biological sex differences in the ascending and descending modulation pathways and also for psychological phenomena that predominantly affect women (19).

While functional interactions between the pain inhibitory mechanism and the cardiovascular system exist (20), blood pressure is consistently and inversely associated with pain perception in chronic pain-free subjects. Indeed, elevated blood pressure may determine the attenuation of acute pain sensitivity (blood pressure-related hypoalgesia), and presumably, a similar phenomenon should be attended also in chronic pain status (20). However, recent studies found that, in patients with chronic pain, the relationship between blood pressure and pain sensitivity is completely reversed, and consequently, higher blood pressure has been associated with increased or higher sensitivity in the perception of chronic pain intensity (14, 20, 21).

Based on the above studies (14, 20, 21) and taking into account the positive relationship between elevated blood pressure and impaired pain perception, we assumed a possible association between HTN and a condition of chronic orofacial pain such as BMS. In addition, several studies underline that changes in hormonal profile and psychological factors during menopause could have a role in the development of both conditions in women (9, 22–24).

No published studies have examined the prevalence of HTN in the BMS population, specifically in women who are the most frequently affected population.

Therefore, this study aimed to investigate the prevalence of HTN in a wide sample of women with BMS (WBMS) compared with a control group of healthy women (HW) matched for age and to identify the potential predictors of HTN in WBMS and HW, analyzing the differences between the two groups and taking in account sociodemographic profile (age, employment, marital status), body mass index (BMI), risk factors (smoking and alcohol use), other systemic comorbidities and drug consumption, pain evaluation, and psychological factors.

Materials and methods

Study design and participants

This was an observational case-control study that was conducted between April 2020 and January 2022 at the Oral Medicine Department of the University of Naples "Federico II" in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. It was approved by the Ethical Committee of the University (Approval Number: 251/19—the date of approval was February 20, 2019). The adopted methods conformed with the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (25).

At the baseline appointment (time 0), 270 patients in the study group and 265 individuals in the control group were considered eligible for this study. However, only 250 individuals in each group met the inclusion and exclusion criteria (Figure 1). All the participants prospectively recruited were women aged at least 18 years. The case group included patients suffering from BMS at the first consultation, which referred to the BMS symptom onset antecedent to any new drugs introduced in their treatment to exclude any causative effect, as described in previous studies (26–28). The control group included healthy subjects presenting at the hospital during the study period for dental treatments. Every subject considered eligible has been included in this study after having provided written informed consent. No payment was provided for participation. The patients and controls were matched by age. First, we recruited the patients and calculated their average age; then, we recruited the controls to obtain a matched sample.

In accordance with the International Classification of Orofacial Pain (ICOP 2020) 1st edition (15), the inclusion criteria of the WBMS group were as follows:

- Female patients aged at least 18 years;
- Patients experiencing an intraoral burning or dysesthetic sensation, recurring daily for more than 2 h per day for more

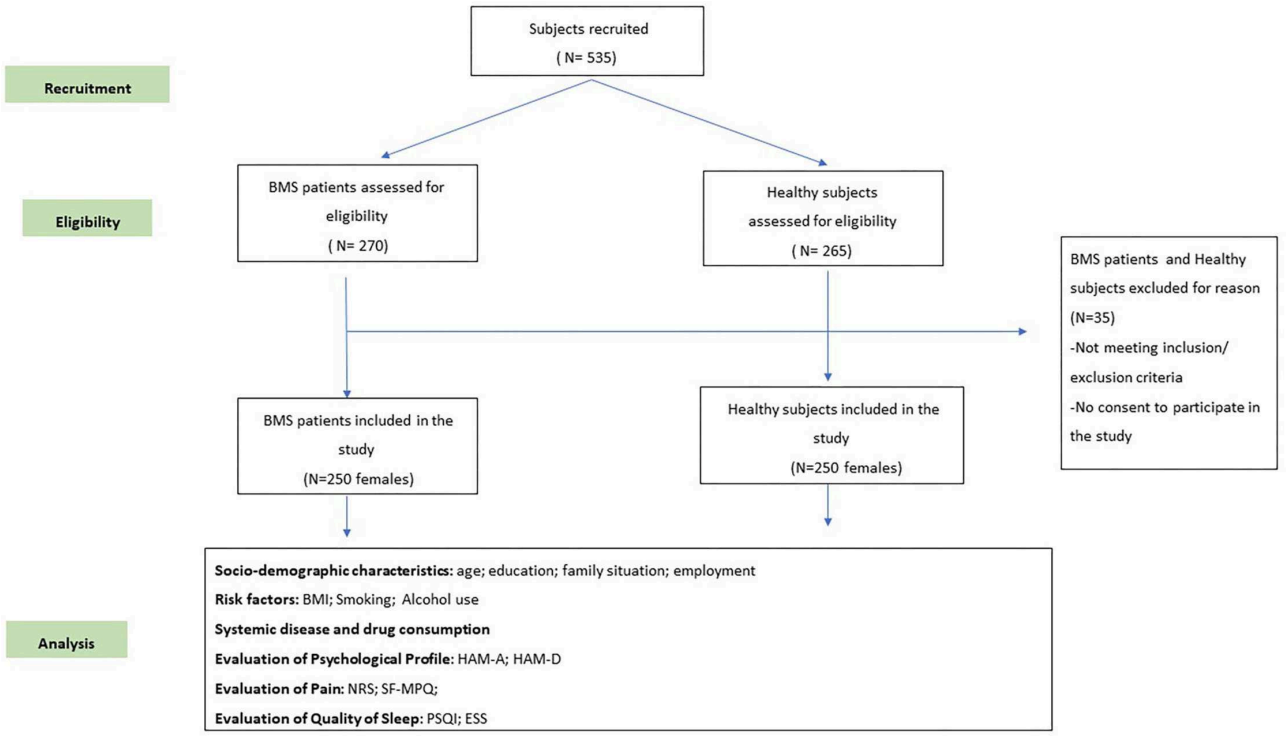


FIGURE 1
A flow chart of the study. BMS, burning mouth syndrome; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SF-MPQ, Short-Form McGill Pain Questionnaire.

than 3 months, without evident causative lesions on clinical examination and investigation; the pain has the characteristics of burning quality and is experienced superficially in the oral mucosa;
- Patients with normal blood test findings (including blood count, blood glucose levels, glycated hemoglobin, serum iron, ferritin, and transferrin); and
- Patients who are not currently in treatment with psychotropic drugs.

The WBMS group exclusion criteria were as follows:

- Patients suffering from diseases that could be recognized as a causative factor of BMS,
- Patients unable to understand or complete the questionnaires,
- Patients having a history of a psychiatric disorder or a neurological or organic brain disorder,
- Patients undergoing treatment with psychotropic drugs or systemic drugs possibly associated with oral symptoms,
- Patients having a history of alcohol or substance abuse, and
- Patients suffering from obstructive sleep apnoea syndrome (OSAS).

The inclusion criteria of the HW were as follows:

- Female subjects aged at least 18 years,
- Subjects without any lesion of the oral mucosa,
- Subjects without psychiatric disorder or a neurological or organic brain disorder,
- Subjects without a history of BMS,
- Subjects with normal blood test findings (including blood count, blood glucose levels, glycated hemoglobin, serum iron, ferritin, and transferrin), and
- Subjects who had not undergone treatment with psychotropic drugs.

The exclusion criteria of the HW were as follows:

- Subjects unable to understand or complete the questionnaires,
- Subjects having a history of alcohol or substance abuse,
- Subjects suffering from OSAS.

Procedure

In the course of routine initial clinical evaluation, all the patients underwent a careful medical analysis, specifically an intra- and extra-oral examination by a board-certified expert clinician in oral medicine (DA). The patients had subsequently been assessed with regard to oral symptoms and the sites involved, age, years of education, family situation, job status, risk factors (current smoking status and alcohol consumption), medical comorbidities, and systemic drugs taken. The blood pressure (BP) has been recorded after the patient was seated for a minimum of 5 min in a standardized fashion during each examination cycle (29). The BP was calculated as the mean of two measurements recorded by a physician. We defined hypertension as having systolic blood pressure of 140 mmHg or

greater, diastolic blood pressure of 90 mmHg or greater, or taking medication for hypertension (30). Moreover, we used measured weight and height to calculate the body mass index (BMI) as weight (kilograms) divided by the square of height (meters) (31). According to the WHO classification, the cutoff values considered were 18.5–24.9 kg/m^2 for normal, 25.0–29.9 kg/m^2 for overweight, and > 30 kg/m^2 for obesity. In particular, obesity class I: BMI of 30–34.9 kg/m^2, obesity class II: BMI of 35–39.9 kg/m^2, obesity class III: BMI of ≥40 kg/m^2 (also referred to as severe, extreme, or massive obesity) (32, 33).

Pain and psychological profile assessment

A set of predefined questionnaires were administered to patients and controls to comprehensively analyze the intensity and quality of pain experienced, psychological profile, and sleep quality.

The Numerical Rating Scale (NRS) (34) and the Short Form of the McGill Pain Questionnaire (SF-MPQ) (35) were administered to evaluate the intensity and quality of pain of the sample group.

The NRS is an 11-point scale where the two endpoints are, respectively, the extremes of no pain and worst pain (34). This could be graphically administered, through a linear 11-box scale, or verbally administered. The SF-MPQ (35) is a multidimensional pain questionnaire that measures the quality of pain. This scale has 15 items considering the sensory, affective, and evaluative aspects of the perceived pain (34). Each item scored from 0 (none) to 3 (severe). There are no established critical cutoff points for the interpretation of the scores, and a higher score indicates worse pain.

The Hamilton Depression Rating Scale (HAM-A) (36) and the Hamilton Rating Scale for Anxiety (HAM-D) (37) were administered to evaluate anxiety and depression symptoms, respectively.

The HAM-A is a clinician-administered anxiety assessment scale containing 14 items, scored from 0 to 4, which evaluate both somatic anxiety and psychic anxiety. A total score of <17 indicates mild severity, a score between 18 and 24 indicates mild to moderate, and a score between 25 and 30 indicates moderate to severe (37).

The HAM-D is a hetero-administered scale containing 21 items that explore the affective field scoring from 0 to 54. The cutoff score considered are as follows: a score between 7 and 17 indicates mild depression, a score between 18 and 24 indicates moderate depression, and a score of >24 indicate severe depression. The HAM-A is a clinician-administered anxiety assessment scale containing 14 items, scored from 0 to 4, which evaluates both somatic anxiety and psychic anxiety. A total score of <17 indicates mild severity, a score between 18 and 24 indicates mild to moderate severity, and a score of 25–30 indicates moderate to severe severity (38).

The daytime sleepiness and the subjective sleep quality were evaluated using the Epworth Sleepiness Scale (ESS) (39) and the pittsburgh sleep quality index (PSQI) (40), respectively. First, the ESS evaluates the sleep propensity in daily life through 8 items, each scored from 0 to 3. On this scale, a higher score corresponds to higher daytime sleepiness (41, 42). Second, the PSQI considers a period of 1 month to evaluate sleep quality, evaluating seven components each scored from 0 to 3: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (43). PSQI total score ranges between 0 and 21, and a higher score corresponds to the worst sleep quality (44).

Statistical analysis

The statistical analysis was performed using the R software (v. 4.2.0 – R Core Team, 2016) (45). Descriptive statistics, including means, standard deviations (SDs), medians, and interquartile ranges (IQRs), were measured to summarize the sociodemographic and clinical characteristics of the WBMS and HW.

Fisher's exact test was used to assess the significant differences between frequencies for systematic diseases, drug consumption, antihypertensive drugs, oral symptoms, sites involved, and clinical parameters (psychological profile, and sleep and pain assessment) between WBMS and HW and between WBMS with and without hypertension, while the Mann–Whitney U test was computed for comparing median values.

Dependence analysis among WBMS and HW with HTN and qualitative predictors was performed. A significant difference between frequencies was measured by Fisher's exact test.

Dependence analysis among WBMS and HW with HTN and quantitative predictors was performed. Differences between groups were tested with the Mann–Whitney U test comparing median values. In all analyses, the Bonferroni correction was used to counteract the multiple comparisons problem.

Results

The demographic variables and the risk factors are shown in Table 1. WBMS reported a statistically significantly lower education level (in years) and a higher level of unemployment compared with the HW ($p < 0.001^{**}$). With respect to the family and marital status, a statistically significantly higher proportion of HW was divorced ($p = 0.013^{*}$) in comparison to the WBMS. Additionally, WBMS presented a statistically significant higher percentage of heavy smokers (>15 cigarettes, 25 subjects-10%; $p = 0.003^{**}$), while, overall, WBMS consumed less alcohol as there were statistically significantly more non-habitual alcohol users ($p = 0.016^{*}$) compared to the control group. The frequency distributions of participants depending on the BMI categories revealed that overall, WBMS showed a considerably higher BMI than HW ($p = 0.001^{**}$), especially with regard to the overweight and class I obesity categories.

The prevalence of systemic disease and drug consumption are summarized in Table 2. A statistically significantly higher proportion of WBMS presented HTN and hypercholesterolemia compared to HW ($p < 0.001^{*}$), while no significant differences were found with respect to all the other comorbidities. In detail, 128 (51.2%) WBMS and 76 (30.4%) HW showed HTN ($p < 0.001^{**}$); similar results were present for hypercholesterolemia affecting 90 (36%) WBMS and 53 HW (21.2%; $p < 0.001^{**}$).

As shown in Figure 2, the bar plot underlines the distribution of HTN considering the age stratification in which the highest percentage of WBMS with HTN (42.9%) is classified between the ages of 65 and 75 years, while for the HW, the highest percentage (38.2%) is between the ages of 55 and 65 years. Moreover, HTN was found in 29 WBMS (22.6%) and 10 HW (13.2%), aged >75 years.

Moreover, considering all the antihypertensive drugs, a statistically significantly higher proportion of WBMS (117; 46.8%) was on antihypertensive therapy compared to the HW (74; 29.6%) ($p < 0.001^{**}$). The frequency distribution of the antihypertensive drugs among the WBMS is shown in Table 2 and Figure 3. In

10.3389/fcvm.2022.969148

TABLE 1 Socio-demographic profile and risk factors of 250 WBMS patients and 250 HW.

Demographic variables	WBMS	HW	*P*-value
Age (in years)	**Mean ± SD** 62.3 ± 11.4	**Mean ± SD** 60.8 ± 11.7	0.146
Education (in years)	**Mean ± SD** 9.2 ± 4.55	**Mean ± SD** 11.4 ± 4.81	<0.001**
Family situation - Single - Married - Divorced - Widowed	**Frequency (%)** 23 (9.2) 195 (78) 8 (3.2) 24 (9.6)	**Frequency (%)** 29 (11.6) 182 (72.8) 22 (8.8) 17 (6.8)	0.367 0.255 0.013* 0.317
Employment - Employed - Unemployed	**Frequency (%)** 68 (27.2) 182 (72.8)	**Frequency (%)** 106 (42.4) 144 (57.6)	<0.001** <0.001**
Risk factors	**Frequency (%)**	**Frequency (%)**	***P*-value**
Smoking			
- Never	186 (74.4)	198 (79.2)	0.244
- <5 cigarettes	10 (4)	18 (7.2)	0.172
- 5–10 cigarettes	11 (4.4)	13 (5.2)	0.835
- 10–15 cigarettes	18 (7.2)	13 (5.2)	0.459
- >15 cigarettes	25 (10)	8 (3.2)	0.003**
Alcohol use			
- Never	223 (89.2)	203 (81.2)	0.016*
- Yes (1 unit)	22 (8.8)	40 (16)	0.020*
- Yes (2 units)	5 (2)	6 (2.4)	1.000
- Yes (>2)	0 (0)	1 (0.4)	1.000
Body Mass Index (kg/m2)			
- BMI<18.5	1 (0.4)	7 (2.8)	<0.001**
- BMI: 18.5-24.9 *normal*	69 (27.6)	133 (53.2)	
- BMI: 25.0-29.9 *overweight*	147 (58.8)	90 (36)	
- BMI: 30-34 *class I obesity*	28 (11.2)	18 (7.2)	
- BMI: 35-39.99 *class II obesity*	2 (0.8)	2 (0.8)	
- BMI>40 *class III obesity*	3 (1.2)	0 (0)	
BMI	**Mean ± SD** 26.8 ± 3.70	**Mean ± SD** 24.5 ± 3.58	

The significance difference between means was measured by the student t-test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$. The significance difference among the percentages was measured by the Fisher's exact test. BMI, Body Mass Index; WBMS, women with burning mouth syndrome; HW, healthy women.

addition, the majority of WBMS (75; 30%) and HW (48; 19.2%) assumed only one antihypertensive drug, 35 WBMS (13.6%) assumed two antihypertensive drugs, 8 WBMS (3.2) assumed three antihypertensive drugs, and no WBMS assumed four antihypertensive drugs. On the contrary, only 11 out of 128 WBMS and 2 out of 76 HW were found to have HTN without assuming antihypertensive medications. A statistically significant difference was found in a higher percentage of WBMS (37; 14.8%) treated with the angiotensin II receptor antagonist (ARB) molecule compared to the HW (14; 5.6%) ($p = 0.001^{**}$).

When comparing sociodemographic variables and risk factors between the subgroup of 128 WBMS with HTN and the subgroup of 122 WBMS without HTN, some differences were also detected (Supplementary Table 1). As expected, WBMS suffering from HTN were statistically older than those without HTN (67.2 ± 9.58 years vs. 51.1 ± 10.9 years) and had a lower education (8.03 ± 4.3 years vs. 10.4 ± 4.49 years) ($p < 0.001^{**}$). In relation to the family status, there was a statistically higher prevalence of widowed (18; 14.1%) among the WBMS with HTN and a lower number of employed (18; 14.1%) ($p < 0.001^{**}$). Differences were also detected with respect to the BMI as a statistically significantly higher proportion of WBMS with HTN (77; 602%) in comparison to the WBMS with no HTN (70; 57.4%) ($p < 0.001$). On the contrary, a higher percentage of WBMS without HTN showed a normal BMI (40; 32.8%) compared to the WBMS with HTN (29; 22.7%) ($p < 0.001$). In addition, as displayed in Supplementary Table 2, a comparison of the prevalence of systemic diseases and drug consumption between WBMS with and without HTN revealed no statistically significant difference, except from the antiplatelets, as a higher number of WBMS with HTN were under this medication (48; 37.5%) ($p < 0.001^{*}$). Further information on the frequency distribution by age ranges of the total WBMS with and without HTN is displayed in Supplementary Figure 1 and Supplementary Table 3.

The type and location of the oral symptoms are shown in Table 3. Statistically significant differences were found between the cases and controls in relation to most of the symptoms. All the WBMS reported a burning sensation (250; 100%), which was the worst symptom reported, followed by xerostomia (151; 60.4%), dysgeusia (115; 46.2%), globus pharyngeus (103; 41.2%), intraoral foreign body sensation (60; 24%), sialorrhea (57; 22.8%), change in the tongue morphology (46; 18.4%), and itching (41; 16.4%). In contrast, halitophobia was the only symptom reported more in HW (19;

10.3389/fcvm.2022.969148

TABLE 2 Prevalence of systemic diseases, drug consumption and antihypertensive drugs evaluation in 250 WBMS patients and 250 HW.

Systemic diseases	WBMS Frequency (%)	HW Frequency (%)	*P*-value
Hypertension	128 (51.2)	76 (30.4)	<0.001**
Hypercholesterolemia	90 (36)	53 (21.2)	<0.001**
Hypothyroidism	46 (18.4)	34 (13.6)	0.179
Gastroesophageal reflux disease	36 (14.4)	28 (11.2)	0.349
Other cardiovascular disease	15 (6)	14 (5.6)	0.851
Neoplastic diseases	11 (4.4)	19 (7.6)	0.187
Asthma	10 (4)	8 (3.2)	0.811
HCV infection	6 (2.4)	4 (1.6)	0.751
Hyperthyroidism	5 (2)	4 (1.6)	1.000
Neurological disorders	5 (2)	3 (1.2)	0.724
Myocardial Infarction	4 (1.6)	6 (2.4)	0.751
Endocrine Disease	3 (1.2)	5 (2)	0.724
HBV infection	1 (0.4)	2 (0.8)	1.000
Others	47 (18.8)	45 (18)	0.908
Drug consumption	**WBMS Frequency (%)**	**HW Frequency (%)**	***P*-value**
Antiplatelets	62 (24.8)	22 (8.8)	<0.001**
Proton pump inhibitors	50 (20)	29 (11.6)	0.014
Simvastatin	48 (19.2)	33 (13.2)	0.089
Beta blockers	42 (16.8)	38 (15.2)	0.715
ACE-inhibitors	41 (16.4)	21 (8.4)	0.009
Angiotensin II receptor antagonists (ARBs)	37 (14.8)	14 (5.6)	0.001**
Levothyroxine sodium	37 (14.8)	30 (12)	0.431
Thiazide Diuretics	28 (11.2)	20 (8)	0.229
Calcium Channel blockers	19 (7.6)	12 (4.8)	0.266
Blood thinner	6 (2.4)	9 (3.6)	0.602
Bisphosphonates	6 (2.4)	7 (2.8)	1.000
Steroids	4 (1.6)	2 (0.8)	0.686
Antihypertensive drugs	**WBMS Frequency (%)**	**HW Frequency (%)**	***P*-value**
Assumption- Yes	117 (46.8)	74 (29.6)	<0.001**
1. Antihypertensive drug	75 (30)	48 (19.2)	0.007
2. Antihypertensive drugs	34 (13.6)	22 (8.8)	0.118
3. Antihypertensive drugs	8 (3.2)	3 (1.2)	0.221
4. Antihypertensive drugs	0 (0)	1 (0.4)	1.000

A significance difference between the percentages was measured by the Fisher's exact test. **Significant with Bonferroni correction 0.002 for the systemic diseases. **Significant with Bonferroni correction 0.003 for the drug consumption. **Significant with Bonferroni correction 0.01 for antihypertensive drugs evaluation. HW, healthy women; WBMS, women with burning mouth syndrome.

7.6%) than in WBMS (16; 6.4%) without any statistically significant difference. The most frequent sites involved were, in order, the tongue (225; 90%), followed by the anterior palate (163; 65.2%), the lips (162; 64.8%), the gums (154; 61.6%), and the cheeks (139; 55.6%).

Comparisons of the clinical parameters between the WBMS and HW are summarized in Table 4. A statistically significant difference was found in the NRS and SF-MPQ score between the two groups ($p < 0.001$**). The majority of WBMS (229; 91.6%) reported severe pain (NRS > 8) and the median and IQR of the SF-MPQ total score were 10 (7–12).

Statistically significant higher percentages of WBMS suffered from anxiety, depression, and sleep disturbances in comparison to the HW ($p < 0.001$**). Precisely, 246 WBMS (98.4%) and 89 HW (35.6%) showed anxiety (HAM-A>7), while 247 WBMS (98.8%)

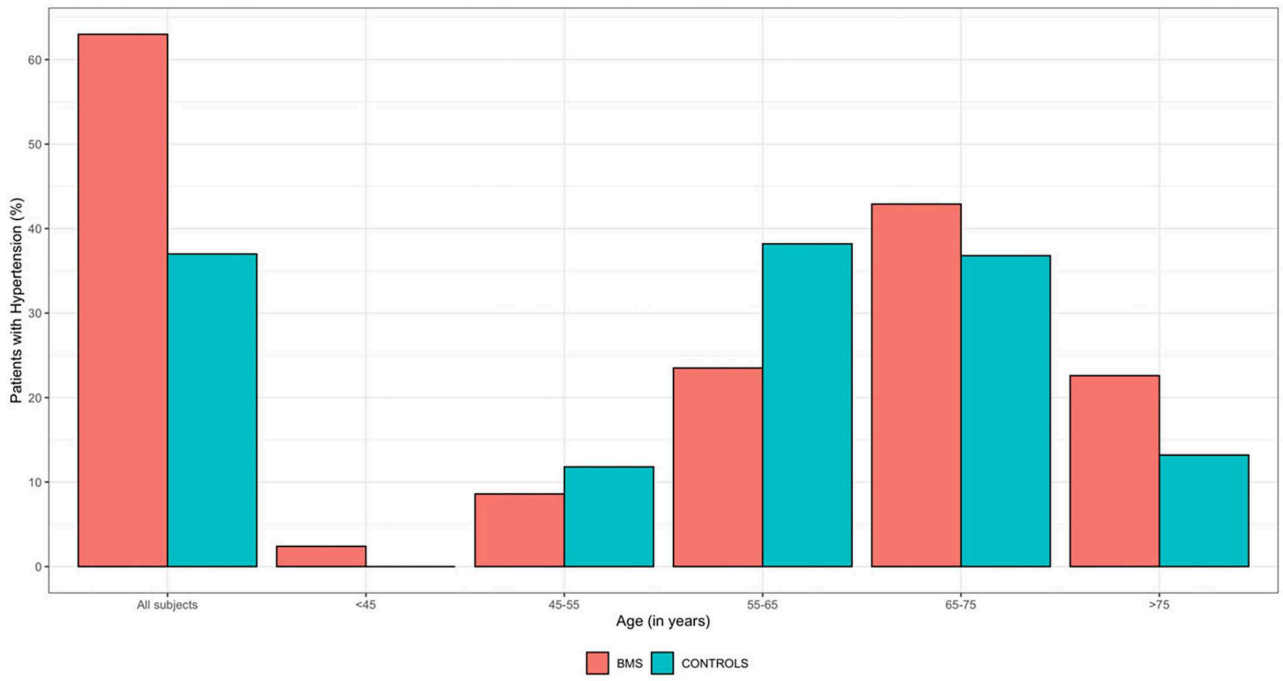


FIGURE 2
Frequency distribution of HTN by age ranges of 250 WBMS and 250 HW. HW, healthy women; WBMS, women with BMS.

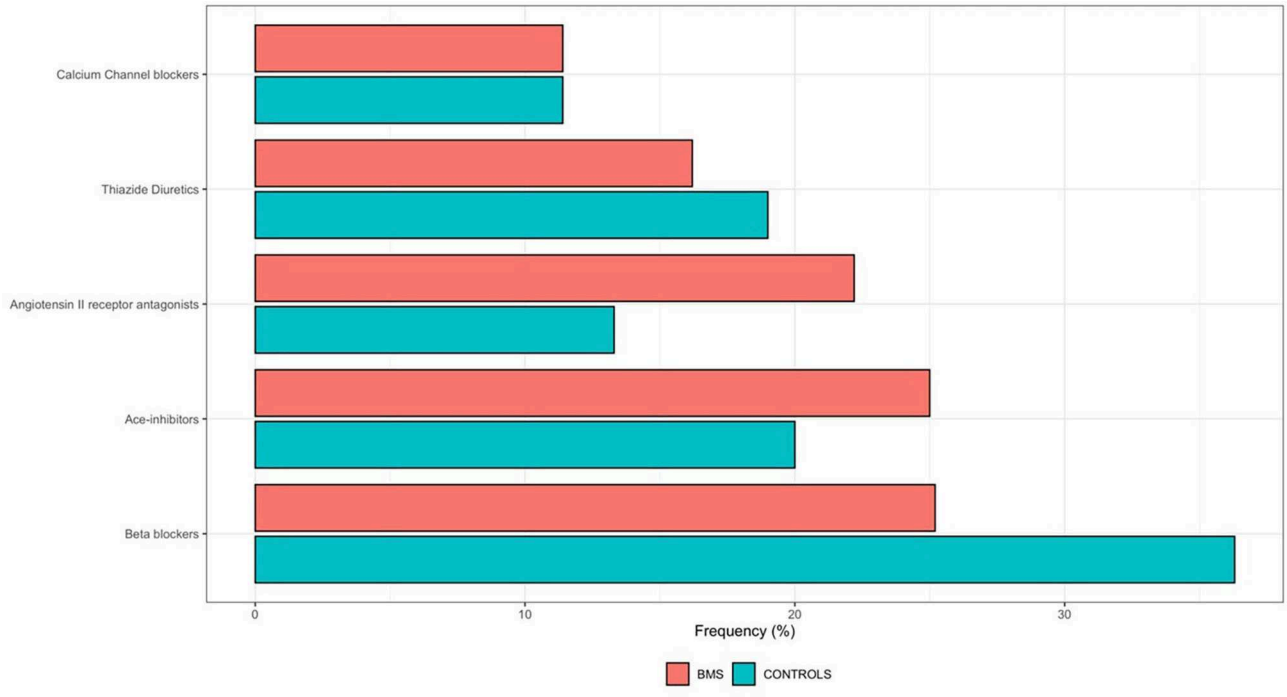


FIGURE 3
Frequency distribution of the antihypertensive drugs among 250 WBMS and 250 HW. HW, healthy women; WBMS, women with BMS.

and 81 HW (32.4%) showed depression (HAM-D>7). In particular, the majority of WBMS (124; 49.6%) showed mild anxiety (HAM-A: 8–17), while 104 WBMS (41.6%) suffered from mild to moderate anxiety (HAM-A: 18–25). Regarding depression, 116 WBMS (46.4%) had mild depression (HAM-D: 8–18) and 102 WBMS (40.8%) had moderate depression (HAM-D: 17–23). Severe anxiety (HAM-A: 25–30) and severe depression (HAM-D>24) were found in 18 WBMS (7.2%) and in 29 WBMS (11.6%), respectively.

10.3389/fcvm.2022.969148

TABLE 3 Prevalence of oral symptoms and sites involved in 250 WBMS patients and 250 HW.

Oral symptoms	WBMS Frequency (%)	HW Frequency (%)	*P*-value
Burning	250 (100)	14 (5.6)	<0.001**
Xerostomia	151 (60.4)	34 (13.6)	<0.001**
Dysgeusia	115 (46.2)	12 (4.8)	<0.001**
Globus pharingeus	103 (41.2)	10 (4)	<0.001**
Intraoral Foreign Body Sensation	60 (24)	14 (5.6)	<0.001**
Sialorrhea	57 (22.8)	11 (4.4)	<0.001**
Change in tongue morphology	46 (18.4)	1 (0.4)	<0.001**
Itching	41 (16.4)	9 (3.6)	<0.001**
Tingling sensation	32 (12.8)	6 (2.4)	<0.001**
Occlusal Dysesthesia	22 (8.8)	5 (2)	0.001**
Diysosmia	17 (6.8)	3 (1.2)	0.002**
Halitophobia	16 (6.4)	19 (7.6)	0.726
Oral Dyskinesia	15 (6)	2 (0.8)	0.002**
Sites involved	**WBMS Frequency (%)**	**HW Frequency (%)**	***P*-value**
Tongue	225 (90.0)	33 (13.2)	<0.001**
Anterior Palate	163 (65.2)	26 (10.4)	<0.001**
Lips	162 (64.8)	31 (12.4)	<0.001**
Gums	154 (61.6)	37 (14.8)	<0.001**
Cheeks	139 (55.6)	32 (12.8)	<0.001**
Floor of the mouth	123 (49.2)	27 (10.8)	<0.001**
Soft Palate	116 (46.4)	25 (10)	<0.001**

A significance difference between the percentages was measured by the Fisher's exact test. **Bonferroni correction 0.004 for Oral Symptoms.**Significant with Bonferroni correction 0.006 for Sites involved. HW, healthy women; WBMS, women with burning mouth syndrome.

With respect to sleep evaluation, the WBMS showed a strongly statistically significant difference in the PSQI total score ($p < 0.001^{**}$), as poor sleep (PSQI > 5) was found in 226 WBMS (90.4%) and in only 133 HW (53.2%), while no statistically significant difference was found in the ESS total score between the two groups ($p = 0.101$).

When comparing oral symptoms, the sites involved and the scores of pain (NRS, T-PRI), anxiety and depression (HAM-A, HAM-D), and sleep quality (PSQI, ESS), no differences were detected between WBMS with and without HTN (Supplementary Tables 4, 5).

A dependence analysis between HTN and qualitative and quantitative predictors was performed separately for WBMS and HW to analyze differences in the predictors of HTN between cases and controls. The results of the dependence analysis between HTN and qualitative and quantitative predictors in WBMS are summarized in Table 5. In detail, employment status was found to correlate with HTN ($p < 0.001^{**}$); in particular, unemployed WBMS in this group were 110 (85.9%), while the employed WBMS suffering from HTN were only 18 (14.1%). Also, the systemic diseases were positively correlated with HTN ($p < 0.001^{**}$), and specifically, WBMS suffering from diseases other than HTN were 124 (96.9%). Among the quantitative predictors, only education level, expressed in years, was found to correlate with HTN ($p < 0.001^{**}$).

The results of the dependence analysis between HTN and qualitative and quantitative predictors in HW are summarized in Table 6. The evaluation of qualitative predictors showed a correlation not only with employment status and systemic diseases ($p < 0.001^{**}$) as in WBMS but also with hypercholesterolemia and drug consumption as in HW ($p < 0.001^{**}$). No correlation was found between HTN and quantitative predictors in HW.

Discussion

Blood pressure and its regulatory systems have been proven to be deeply interconnected with pain modulation (20). For instance, both essential HTN and secondary HTN are effective in reducing acute pain perception throughout a process known as blood pressure-related hypoalgesia (46). On the contrary, in chronic pain sufferers, this mechanism seems to be under-regulated, and as a consequence, elevated blood pressure is associated with greater chronic pain intensity (14).

Nevertheless, the prevalence and role of HTN in chronic pain conditions are poorly understood, especially in women. The female's prevalence of HTN increases after menopause (>40 years), suggesting the pivotal role of sexual hormone imbalance in the pathophysiology of the disease (1, 10, 22). In detail, menopause

TABLE 4 Pain assessment, psychological profile and sleep in 250 WBMS patients and 250 HW.

Clinical parameters	WBMS	HW	*P*-value
NRS	**Frequency (%)**	**Frequency (%)**	<0.001**
- Mild pain 1–5	6 (2.4)	238 (95.2)	
- Moderate pain 6–7	15 (6)	7 (2.8)	
- Severe pain >8	229 (91.6)	5 (2)	
SF-MPQ	**Median; IQR**	**Median; IQR**	<0.001**
	10 [7–12]	0 [0-0]	
HAM-A	**Frequency (%)**	**Frequency (%)**	<0.001**
- Normal 0–7	4 (1.6)	161 (64.4)	
- Mild severity 8–17	124 (49.6)	73 (29.2)	
- Mild to moderate 18–25	104 (41.6)	12 (4.8)	
- Moderate to severe 25–30	18 (7.2)	4 (1.6)	
HAM-D	**Frequency (%)**	**Frequency (%)**	<0.001**
- Normal 0–7	3 (1.2)	169 (67.6)	
- Mild depression 8–16	116 (46.4)	60 (24)	
- Moderate depression 17–23	102 (40.8)	16 (6.4)	
- Severe depression >24	29 (11.6)	5 (2)	
PSQI	**Frequency (%)**	**Frequency (%)**	<0.001**
- PSQI total score <5	24 (9.6)	117 (46.8)	
- PSQI total score >5	226 (90.4)	133 (53.2)	
ESS	**Frequency (%)**	**Frequency (%)**	0.101
- Normal range 0–10	218 (87.2)	220 (88)	
- Mild sleepiness 11–14	30 (12)	23 (9.2)	
- Moderate sleepiness 15–17	2 (0.8)	2 (0.8)	
- Severe sleepiness >18	0 (0)	5 (2)	

A significance difference between the percentages was measured by the Fisher's exact test. ** Significant with Bonferroni correction 0.003. IQR is the interquartile range. The significance difference between medians was measured by the Mann–Whitney test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$. ESS, Epworth Sleepiness Scale; HAM-A, Hamilton rating scale for anxiety; HAM-D, Hamilton rating scale for depression; HW, healthy women; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SF-MPQ, Short-form McGill Pain Questionnaire; WBMS, women with burning mouth syndrome.

promotes a derangement of the cardiocirculatory system with a marked decline in endothelium-dependent vasodilation and also in the emergence of other atherogenic factors (47, 48); in addition, the menopause transition broadly affects health and wellbeing in the midlife woman being associated with decreased physical activity and weight gain, impaired sleep, and negative mood (47, 49). All these aspects are also involved in the chronic pain experience, further causing an increase in blood pressure. Indeed, the fluctuations of estrogen hormones and, subsequently, their reduction influence the development and exacerbation of both HTN and pain (50, 51). This theory is supported by epidemiological studies in which the perimenopausal and postmenopausal women showed a higher prevalence of chronic pain and HTN compared to men (9, 52). Moreover, women showed lower pain threshold and tolerance, resulting in increased pain intensity (53). Additionally, it has been proven that women experiencing pain are less prone to use coping strategies, are predisposed to pain chronicization, and are more likely to seek the help of a pain specialist for treatment (50, 54).

BMS epidemiology highlights that it affects more female subjects, especially after menopause (16). Structural and functional alterations in the peripheral and central nervous system are considered in the etiopathogenesis of the disease, thus affecting the pain perception and predisposition for mood disorders, sleep disturbance, and cognitive impairment (17, 19, 55, 56), as suggested also in a recent study from Canfora et al. (57).

This is the first study that evaluated the prevalence of HTN in a wide sample of WBMS in comparison with an age-matched control group and explored the possible predictors of HTN in this disease. Finally, this study analyzed the potential role of HTN in the disease progression and the mutual interaction between HTN and pain, mood disorders, sleep, and other comorbidities.

The results of the study suggested a statistically significant difference in the prevalence of HTN in the sample with a higher prevalence of HTN in WBMS (51.2%) compared with HW (30.4%). Considering age stratification, the prevalence of HTN was higher in HW until 65 years but it increased in WBMS aged higher than 65 years. Precisely, the prevalence of HTN in HW with age < 65 years was in line with the epidemiological studies that investigate women's HTN in the general population (38.2%), and this percentage was found to be consistently lower in WBMS (23.5%).

Instead, this prevalence increased to 42.9% in WBMS aged between 65 and 75 years, resulting in a higher prevalence compared with the general prevalence of HTN in women and in patients suffering from chronic pain. Indeed, even if this prevalence is slightly higher compared with the study of Bruehl et al. (14) on 300 chronic pain patients (39%), these results support the possibility of the functional and overlapping links of the anti-nociceptive and the cardiovascular systems in which impairment in the mechanism of modulating both pain and blood pressure may increase HTN prevalence in WBMS (58–60).

Indeed, blood pressure is modulated by functional circuitry linking the hypothalamus, the nucleus tractus solitarius, the nucleus raphe magnus, and the rostral ventrolateral medulla in which the activity of central adrenergic fibers and alpha-2 receptors may prolong the activation of anti-nociceptive pathways in patients with BMS (61, 62).

Moreover, the bidirectional relationship between pain and blood pressure may involve the levels of cerebral catecholamine, as a result of changed catechol-O-methyltransferase (COMT)-dependent

10.3389/fcvm.2022.969148

TABLE 5 Dependence analysis among 128 WBMS patients with HTN and qualitative and quantitative predictors.

WBMS-qualitative predictors	HTN Frequency (%)	*P*-value
Marital status		
- Married - not married	97 (75.8) 31 (24.2)	0.545
Employment		
- Employed - Not employed	18 (14.1) 110 (85.9)	<0.001**
Smoking		
- Smoker - No smoker	27 (21.1) 101 (78.9)	0.111
Alcohol use		
- Yes - No	12 (9.4) 116 (90.6)	0.542
Hypercholesterolemia		
- Yes - No	56 (43.8) 72 (56.2)	0.012
Systemic diseases		
- Yes - No	124 (96.9) 4 (3.1)	<0.001**
Drug consumptions		
- Yes - No	96 (75) 32 (25)	0.074
Quantitative Predictors	**HTN Frequency(%)**	***P*-value**
NRS	10 [9.75–10]	0.360
SF-MPQ	10 [7.75–12]	0.339
HAM-A	18 [15–20.2]	0.245
HAM-D	18 [14–20]	0.502
PSQI	8 [8–9.25]	0.882
ESS	6.5 [5–9]	0.149
Education (in years)	8 [5–12.2]	<0.001**
BMI (kg/m^2)	26.9 [25.3–28.8]	0.073

A significance difference between the percentages was measured by the Fisher's exact test. **Significant with Bonferroni correction 0.004 for qualitative predictors. IQR is the interquartile range. The significance difference between medians was measured by the Mann–Whitney test. **Significant with Bonferroni correction 0.006 for quantitative predictors. BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; HAM-A, Hamilton rating scale for anxiety; HAM-D, Hamilton rating scale for depression; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SF-MPQ, Short-form McGill Pain Questionnaire; WBMS, women with burning mouth syndrome.

TABLE 6 Dependence analysis among 122 HW with HTN and qualitative and quantitative predictors.

HWC- Qualitative Predictors	HTN Frequency (%)	*P*-value
Marital status		
- Married - Not married	57 (75) 19 (25)	0.887
Employment		
- Employed - Not employed	23 (30.3) 53 (69.7)	<0.001**
Smoking		
- Smoker - No smoker	13 (17.1) 63 (82.9)	0.117
Alcohol		
- Yes - No	11 (14.5) 65 (85.5)	0.418
Hypercholesterolemia		
- Yes - No	21 (27.6) 55 (72.4)	<0.001**
Systemic diseases		
- Yes - No	76 (100) (0)	<0.001**
Drug consumptions		
- Yes - No	67 (88.2) 9 (11.8)	<0.001**
Quantitative predictors	**HTN Frequency (%)**	***P*-value**
NRS	0 [0–0.25]	0.437
SF-MPQ	0 [0–1.25]	0.128
HAM-D	5 [2.75–9.25]	0.716
HAM-A	6 [3–11.2]	0.110
PSQI	6 (4–9)	0.010
ESS	6 (3–8)	0.149
Education (years)	10 [7.5–13]	0.011
BMI (kg/m^2)	25.4 [22–26.9]	0.223

A significance difference between the percentages was measured by the Fisher's exact test. **Significant with Bonferroni correction 0.003 for Qualitative Predictors. IQR is the interquartile range. The significance difference between medians was measured by the Mann–Whitney test. **Significant with Bonferroni correction 0.006 for quantitative predictors. BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; HAM-A, Hamilton rating scale for anxiety; HAM-D, Hamilton rating scale for depression; HW, healthy women; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; SF-MPQ, Short-form McGill Pain Questionnaire.

metabolism (63–65). Indeed, the gene which codes for this protein activity is highly polymorphic, and some variants contribute to a lower metabolism of norepinephrine to normetanephrine; the increase of these neurotransmitters not only contributes to higher blood pressure but also modifies pain response (66).

The impact of long-term elevated blood pressure on cerebral health involves structural pathological changes of the brain such as WMH, cortical thinning, enlarged Virchow-Robin spaces, and brain atrophy (67), suggesting that HTN can accelerate brain aging in the same areas involved in chronic pain. However, it is difficult to determine if these brain alterations are a direct consequence of HTN but it could explain the previous study results in which a high prevalence of WMH was found in patients with BMS (68, 69).

In this study, a statistically significant difference in years of education was found between WBMS and HW with lower educational attainment found in WBMS compared with HW, and it may be implicated in the impairment of blood pressure control and considered a predictor of HTN. These results are in line with previous studies' results, in which an increase in the year of education leads to an increase in the individual's knowledge and skills about the disease; on the contrary, unschooled patients were at greater risk of developing uncontrolled HTN (70, 71).

In addition, less educational attainment has a significant role also on the limited knowledge about healthcare and disease (72), such as BMS. For this reason, the patient's ability to manage both diseases is strictly dependent on their education (73).

Moreover, in this study, a higher prevalence of unemployment was found in WBMS (72.8%) compared with HW (57.6%), and this condition was a predictor of HTN as suggested from the results of the dependence analysis. This finding was in line with previous reports in which employment status was inversely associated with HTN in women (22, 74), maybe due to the employment's influence on a woman's socioeconomic status (75).

In line with previous studies, the coexistence of other systemic comorbidities represents a predictor of HTN in patients and in controls, and unfortunately, this is a non-modifiable risk factor of HTN (76, 77).

Therefore, unemployed WBMS with few years of education and other systemic comorbidities are at increased risk to develop HTN. Instead, the predictors of HTN are slightly different in HW group, showing that unemployment, systemic comorbidities, hypercholesterolemia, and drug consumption increase the risk of HTN.

In our sample, the common modifiable health risk behaviors of HTN such as tobacco use (78, 79) and alcohol consumption (80, 81) were not predictors of HTN in patients and controls, but probably these results have to be considered in light of the prevalence of non-smokers (74.4 and 79.9%, respectively) and no alcohol consumers (89.2 and 81.2%, respectively) among WBMS and HW.

In addition, in our sample, BMI was not a predictor of HTN but probably because the majority of WBMS and HW were not obese. In addition, disability related to diseases, such as BMS, makes patients more sedentary and prone to develop obesity. Therefore, body weight reduction in overweight women and the promotion of healthy lifestyle behaviors (50) represent an essential part of both HTN and BMS treatment.

From the analysis of the psychological profile, WBMS showed a higher prevalence of anxiety, depression, and sleep disturbance compared with HW, but no differences were found between WBMS with or without HTN.

Moreover, pain, anxiety depression, and sleep disturbances were not predictors of HTN both in WBMS and in HW. Therefore, the association between depression and anxiety and increased HTN risk remains inconsistent in this study in contrast with other studies that found depression associated with an increased (82, 83) or decreased (84) risk of HTN.

Patients receiving the HTN diagnosis could increase their psychological distress, which may further aggravate the adjunctive diagnosis of BMS (85, 86). Indeed, the coexistence of several medical comorbidities may have a labeling effect causing mental distress and a decrease in the quality of life, resulting in increased healthcare utilization (77).

Sleep disturbance (PSQI $>$ 5) was found in 90.4% of WBMS, confirming the results of previous studies in which a high prevalence of poor sleep was found in patients with BMS (55, 87). Despite sleep disturbance not being considered a predictor of HTN in our sample, it is known that sleep disturbance is associated with an independent HTN risk (88, 89). Particularly, a 2016 American Heart Association (AHA) scientific statement concluded that there is strong epidemiological evidence that self-reported short sleep duration ($<$6 h) is a risk factor for HTN where women may be more prone to the effects of short sleep duration on HTN risk (89). This statement was confirmed by a review of 2012 in which higher HTN risk among short sleepers has been reported (90).

Short sleep may increase HTN risk through several physiological mechanisms, including disturbed autonomic balance, hormonal imbalances, inflammation and oxidative stress, greater predisposition to obesity, metabolic syndrome, and unhealthy lifestyle behaviors (88–90). Thus, when present simultaneously, BMS, HTN, mood disorder, and sleep disturbance represent a toxic combination that affects the quality of life of individuals, worsening the outcome of the disease (88, 91).

The results of this study highlight that BMS is a complex disease, with several intertwined comorbidities that may aggravate and prevent the healing of patients if a complete medical and psychological assessment and treatment of all conditions is not carried out. Therefore, despite dental professionals playing a central role in the diagnosis and the management of disease, it is crucial to improve the knowledge about BMS also among medical professionals and promote multidisciplinary collaboration to identify and treat the possible associated comorbidities and reduce the societal burden caused by BMS, further worsening the association with HTN and mood disorder.

Conclusion

WBMS showed a higher prevalence of HTN compared with HW. Unemployed WBMS with lower education and other systemic comorbidities are at an increased risk to develop HTN. The mechanism whereby these phenomena are associated is not completely clear by the results of this study although it is reasonable to consider the interaction of the genetic, environmental, and biological factors that could contribute to both HTN and BMS development. Indeed, the effects of the cardiovascular sympathetic stimulation in response to the failure of pain-regulatory mechanisms may contribute to broadening pain perception and HTN. The association of BMS and HTN may, in turn, accelerate brain aging contributing to the occurrence of WMH, resulting in intracortical connectivity reduction, which further affects pain processing and produces a vicious circle.

Moreover, a higher prevalence of anxiety, depression, and sleep disturbance was found in WBMS compared with HW. Considering the deleterious effects of concomitant HTN and mood disorders, early recognition and proper treatment of both conditions in patients affected by BMS are important.

Healthy lifestyle behaviors, in addition to treatments, are essential in WBMS to promote psychological wellbeing, improve the quality of life, and prevent early brain aging. Further studies will be needed to confirm the association between HTN and BMS.

Limitation

This study has some limitations. First, an important limitation of the study is related to the hypertension diagnosis because it was not possible to verify if hypertension preceded the chronic pain onset or, on the contrary, the chronic pain came first. This could be important in the etiopathogenesis interpretation. Second, the duration of antihypertensive drug assumption and eventual switching

in the therapy could not be reported by the patients; as a consequence, we do not know if there were resistant hypertension among these patients; and consequently, although no correlation has been found with HTN and pain scores, it is not possible to address the question of whether controlling the high pressure may have a role in modulating pain perception.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the University of Naples Federico II (Approval Number: 251/19—the date of approval was February 20, 2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

DA, FC, and MM: conceptualization. DA, FC, EC, GP, and MM: methodology. LD'A and MA: software and formal analysis. MM and DA: validation and supervision. FC, EC, SL, NC, CM, GP, FS, LD'A, MA, and MM: investigation. FC, EC, SL, NC, and MM: resources. FC, EC, CM, SL, NC, FS, LD'A, MA, and MM: data curation. FC, DA, and EC: writing—original draft preparation. FC, EC, LD'A, MA, GP, DA, and MM: writing—review and editing. DA, FC, EC, and MM: visualization. All authors have contributed to the work and are familiar with the primary data, each has read the final version of the manuscript, approved its content, and have agreed to have their name added to the paper.

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/fcvm.2022.969148/full#supplementary-material

References

1. 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

2. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *JACC Heart Fail.* (2017) 5:543–51. doi: 10.1016/j.jchf.2017.04.012

3. Barri YM. Hypertension and kidney disease: a deadly connection. *Curr Hypertens Rep.* (2008) 10:39–45. doi: 10.1007/s11906-008-0009-y

4. Wang J, Sun W, Wells GA Li Z, Li T, Wu J, et al. Differences in prevalence of hypertension and associated risk factors in urban and rural residents of the northeastern region of the People's Republic of China: a cross-sectional study. *PLoS ONE.* (2018) 13:e0195340. doi: 10.1371/journal.pone.0195340

5. Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. *Curr Hypertens Rep.* (2017) 19:24. doi: 10.1007/s11906-017-0724-3

6. 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

7. Reckelhoff JF. Gender differences in hypertension. *Curr Opin Nephrol Hypertens.* (2018) 27:176–81. doi: 10.1097/MNH.0000000000000404

8. Scheidt-Nave C, Kamtsiuris P, Gößwald A, Hölling H, Lange M, Busch MA, et al. German health interview and examination survey for adults (DEGS) - design, objectives and implementation of the first data collection wave. *BMC Public Health.* (2012) 12:730. doi: 10.1186/1471-2458-12-730

9. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovasc Res.* (2002) 53:688–708. doi: 10.1016/S0008-6363(01)00527-2

10. Connelly PJ, Casey H, Montezano AC, Touyz RM, Delles C. Sex steroids receptors, hypertension, and vascular ageing. *J Hum Hypertens.* (2022) 36:120–5. doi: 10.1038/s41371-021-00576-7

11. Seravalle G, Grassi G. Obesity and hypertension. *Pharmacol Res.* (2017) 122:1–7. doi: 10.1016/j.phrs.2017.05.013

12. Robbins CL, Dietz PM, Bombard J, Tregear M, Schmidt SM, Tregear SJ. Lifestyle interventions for hypertension and dyslipidemia among women of reproductive age. *Prev Chronic Dis.* (2011) 8:A123.

13. Ferdinand KC, Kleinpeter MA. Management of hypertension and dyslipidemia. *Curr Hypertens Rep.* (2006) 8:489–96. doi: 10.1007/s11906-006-0028-5

14. Bruehl S, Chung OY, Jirjis JN, Biridepalli S. Prevalence of clinical hypertension in patients with chronic pain compared to nonpain general medical patients. *Clin J Pain.* (2005) 21:147–53. doi: 10.1097/00002508-200503000-00006

15. Orofacial Pain Classification Committee. International classification of orofacial pain (ICOP). *Cephalalgia.* (2020) 40:129–221. doi: 10.1177/0333102419893823

16. Wu S, Zhang W, Yan J, Noma N, Young A, Yan Z. Worldwide prevalence estimates of burning mouth syndrome: a systematic review and meta-analysis. *Oral Dis.* (2021) 28:1431–40. doi: 10.1111/odi.13868

17. Nasri-Heir C, Zagury JG, Thomas D, Ananthan S. Burning mouth syndrome: current concepts. *J Indian Prosthodont Soc.* (2015) 15:300–7. doi: 10.4103/0972-4052.171823

18. Suzuki N, Mashu S, Toyoda M, Nishibori M. Oral burning sensation: prevalence and gender differences in a Japanese population. *Pain Pract.* (2010) 10:306–11. doi: 10.1111/j.1533-2500.2010.00361.x

19. Adamo D, Celentano A, Ruoppo E, Cucciniello C, Pecoraro G, Aria M, et al. The relationship between sociodemographic characteristics and clinical features in burning mouth syndrome. *Pain Med.* (2015) 16:2171–9. doi: 10.1111/pme.12808

20. Saccò M, Meschi M, Regolisti G, Detrenis S, Bianchi L, Bertorelli M, et al. The relationship between blood pressure and pain. *J Clin Hypertens.* (2013) 15:600–5. doi: 10.1111/jch.12145

21. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? *Pain.* (2002) 95:119–24. doi: 10.1016/S0304-3959(01)00387-6

22. Rose KM, Newman B, Tyroler HA, Szklo M, Arnett D, Srivastava N. Women, employment status, and hypertension: cross-sectional and prospective findings from

the atherosclerosis risk in communities (ARIC) Study. *Ann Epidemiol.* (1999) 9:374–82. doi: 10.1016/S1047-2797(99)00015-0

23. Dahiya P, Kamal R, Kumar M. Niti, Gupta R, Chaudhary K. Burning mouth syndrome and menopause. *Int J Prev Med.* (2013) 4:15–20.

24. Yao H, Zhang Q, Song Q, Liu M, Tang G. Characteristics of oral mucosal lesions and their association with socioeconomic status and systemic health: a cross-sectional study of consecutively collected oral medicine clinic data in a remote rural area of China. *Front Public Health.* (2022) 10:897814. doi: 10.3389/fpubh.2022.897814

25. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg.* (2014) 12:1495–9. doi: 10.1016/j.ijsu.2014.07.013

26. Obara T, Naito H, Nojima T, Koga H, Nakao A. Burning mouth syndrome induced by angiotensin-converting enzyme inhibitors. *Cureus.* (2020) 12:e11376. doi: 10.7759/cureus.11376

27. Azzi L, Veronesi G, Tagliabue A, Croveri F, Maurino V, Reguzzoni M, et al. Is there an association between drugs and burning mouth syndrome? A case-control study. *Oral Dis.* (2019) 25:1634–44. doi: 10.1111/odi.13116

28. Jin JQ, Cui HM, Han Y, Su S, Liu HW. Multifactor analysis of patients with oral sensory complaints in a case-control study. *Chin Med J.* (2020) 133:2822–8. doi: 10.1097/CM9.0000000000001190

29. Drawz PE, Beddhu S, Kramer HJ, Rakotz M, Rocco MV, Whelton PK. Blood pressure measurement: a KDOQI perspective. *Am J Kidney Dis.* (2020) 75:426–34. doi: 10.1053/j.ajkd.2019.08.030

30. Brouwers S, Sudano I, Kokubo Y, Sulaica EM. Arterial hypertension. *Lancet.* (2021) 398:249–61. doi: 10.1016/S0140-6736(21)00221-X

31. Landi F, Calvani R, Picca A, Tosato M, Martone AM, Ortolani E, et al. Body mass index is strongly associated with hypertension: results from the longevity check-up 7+ study. *Nutrients.* (2018) 10:E1976. doi: 10.3390/nu10121976

32. Weir CB, Jan A. *BMI Classification Percentile and Cut Off Points. StatPearls. StatPearls Publishing.* (2021). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK541070/ (accessed May 28, 2022).

33. Consultation WH. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* (2000) 894:1–253.

34. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), Mcgill pain questionnaire (MPQ), short-form Mcgill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res.* (2011) 63:S240–252. doi: 10.1002/acr.20543

35. Melzack R. The short-form McGill pain questionnaire. *Pain.* (1987) 30:191–7. doi: 10.1016/0304-3959(87)91074-8

36. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* (1959) 32:50–5. doi: 10.1111/j.2044-8341.1959.tb00467.x

37. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

38. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* (1967) 6:278–96. doi: 10.1111/j.2044-8260.1967.tb00530.x

39. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* (1991) 14:540–5. doi: 10.1093/sleep/14.6.540

40. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

41. Trimmel K, Zebrowska M, Böck M, Stefanic A, Mayer D, Klösch G, et al. Wanted: a better cut-off value for the epworth sleepiness scale. *Wien Klin Wochenschr.* (2018) 130:349–55. doi: 10.1007/s00508-017-1308-6

42. Vignatelli L, Plazzi G, Barbato A, Ferini-Strambi L, Manni R, Pompei F, et al. Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci.* (2003) 23:295–300. doi: 10.1007/s100720300004

43. Curcio G, Tempesta D, Scarlata S, Marzano C, Moroni F, Rossini PM, et al. Validity of the Italian version of the pittsburgh sleep quality index (PSQI). *Neurol Sci.* (2013) 34:511–9. doi: 10.1007/s10072-012-1085-y

44. Carpenter JS, Andrykowski MA. Psychometric evaluation of the pittsburgh sleep quality index. *J Psychosom Res.* (1998) 45:5–13. doi: 10.1016/S0022-3999(97)00298-5

45. Team RC. *Vienna: R Foundation for Statistical Computing* (2016).

46. Olsen RB, Bruehl S, Nielsen CS, Rosseland LA, Eggen AE, Stubhaug A. Hypertension prevalence and diminished blood pressure-related hypoalgesia in individuals reporting chronic pain in a general population: the Tromsø study. *Pain.* (2013) 154:257–62. doi: 10.1016/j.pain.2012.10.020

47. Moreau KL, Hildreth KL. Vascular aging across the menopause transition in healthy women. *Adv Vasc Med.* (2014) 2014:204390. doi: 10.1155/2014/204390

48. Meadows JL, Vaughan DE. Endothelial biology in the post-menopausal obese woman. *Maturitas.* (2011) 69:120–5. doi: 10.1016/j.maturitas.2011.03.012

49. Zhu D, Chung HF, Pandeya N, Dobson AJ, Kuh D, Crawford SL, et al. Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. *Eur J Epidemiol.* (2018) 33:699–710. doi: 10.1007/s10654-018-0367-y

50. Tan MN, Kartal M, Guldal D. The effect of physical activity and body mass index on menopausal symptoms in Turkish women: a cross-sectional study in primary care. *BMC Women's Health.* (2014) 14:38. doi: 10.1186/1472-6874-14-38

51. Maas AHEM, Franke HR. Women's health in menopause with a focus on hypertension. *Neth Heart J.* (2009) 17:68–72. doi: 10.1007/BF03086220

52. Gibson CJ Li Y, Bertenthal D, Huang AJ, Seal KH. Menopause symptoms and chronic pain in a national sample of midlife women veterans. *Menopause.* (2019) 26:708–13. doi: 10.1097/GME.0000000000001312

53. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth.* (2013) 111:52. doi: 10.1093/bja/aet127

54. Arman M, Gebhardt A, Hök Nordberg J, Andermo S. Women's lived experiences of chronic pain: faces of gendered suffering. *Qual Health Res.* (2020) 30:772–82. doi: 10.1177/1049732319888478

55. Adamo D, Sardella A, Varoni E, Lajolo C, Biasotto M, Ottaviani G, et al. The association between burning mouth syndrome and sleep disturbance: a case-control multicentre study. *Oral Dis.* (2018) 24:638–49. doi: 10.1111/odi.12807

56. Adamo D, Pecoraro G, Fortuna G, Amato M, Marenzi G, Aria M, et al. Assessment of oral health-related quality of life, measured by OHIP-14 and GOHAI, and psychological profiling in burning mouth syndrome: a case-control clinical study. *J Oral Rehabil.* (2020) 47:42–52. doi: 10.1111/joor.12864

57. Canfora F, Calabria E, Cuocolo R, Ugga L, Buono G, Marenzi G, et al. Burning fog: cognitive impairment in burning mouth syndrome. *Front Aging Neurosci.* (2021) 13:727417. doi: 10.3389/fnagi.2021.727417

58. Pinto E. Blood pressure and ageing. *Postgrad Med J.* (2007) 83:109–14. doi: 10.1136/pgmj.2006.048371

59. Hackett J, Naugle KE, Naugle KM. The decline of endogenous pain modulation with aging: a meta-analysis of temporal summation and conditioned pain modulation. *J Pain.* (2020) 21:514–28. doi: 10.1016/j.jpain.2019.09.005

60. González-Roldán AM, Terrasa JL, Sitges C, van der Meulen M, Anton F, Montoya P. Age-related changes in pain perception are associated with altered functional connectivity during resting state. *Front Aging Neurosci.* (2020) 12:116. doi: 10.3389/fnagi.2020.00116

61. Sapru HN. Role of the hypothalamic arcuate nucleus in cardiovascular regulation. *Auton Neurosci.* (2013) 175:38–50. doi: 10.1016/j.autneu.2012.10.016

62. Matsushita Y, Manabe M, Kitamura N, Shibuya I. Adrenergic receptors inhibit TRPV1 activity in the dorsal root ganglion neurons of rats. *PLoS One.* (2018) 13:e0191032. doi: 10.1371/journal.pone.0191032

63. Nackley-Neely AG, Tan KS, Fecho K, Flood P, Diatchenko L, Maixner W. Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both β2 and β3 adrenergic receptors. *Pain.* (2007) 128:199–208. doi: 10.1016/j.pain.2006.09.022

64. Xu J, Boström AE, Saeed M, Dubey RK, Waeber G, Vollenweider P, et al. A genetic variant in the catechol-O-methyl transferase (COMT) gene is related to age-dependent differences in the therapeutic effect of calcium-channel blockers. *Medicine.* (2017) 96:e7029. doi: 10.1097/MD.0000000000007029

65. Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain.* (2006) 125:216–24. doi: 10.1016/j.pain.2006.05.024

66. Gonzalez-Lopez E, Vrana KE. Dopamine beta-hydroxylase and its genetic variants in human health and disease. *J Neurochem.* (2020) 152:157–81. doi: 10.1111/jnc.14893

67. Alateeq K, Walsh EI, Cherbuin N. Higher blood pressure is associated with greater white matter lesions and brain atrophy: a systematic review with meta-analysis. *J Clin Med.* (2021) 10:637. doi: 10.3390/jcm10040637

68. Hay M, Barnes C, Huentelman M, Brinton R, Ryan L. Hypertension and age-related cognitive impairment: common risk factors and a role for precision aging. *Curr Hypertens Rep.* (2020) 22:80. doi: 10.1007/s11906-020-01090-w

69. Adamo D, Canfora F, Calabria E, Coppola N, Leuci S, Pecoraro G, et al. White matter hyperintensities in burning mouth syndrome assessed according to the age-related white matter changes scale. *Front Aging Neurosci.* (2022) 14:923720. doi: 10.3389/fnagi.2022.923720

70. Di Chiara T, Scaglione A, Corrao S, Argano C, Pinto A, Scaglione R. Education and hypertension: impact on global cardiovascular risk. *Acta Cardiol.* (2017) 72:507–13. doi: 10.1080/00015385.2017.1297626

71. Babaee Beigi MA, Zibaeenezhad MJ, Aghasadeghi K, Jokar A, Shekarforoush S, Khazraei H. The effect of educational programs on hypertension management. *Int Cardiovasc Res J.* (2014) 8:94–8.

72. Tedesco MA, Di Salvo G, Caputo S, Natale F, Ratti G, Iarussi D, et al. Educational level and hypertension: how socioeconomic differences condition health care. *J Hum Hypertens.* (2001) 15:727–31. doi: 10.1038/sj.jhh.1001249

73. Sorel JE, Ragland DR, Syme SL, Davis WB. Educational status and blood pressure: the second national health and nutrition examination survey, 1976-1980, and the hispanic health and nutrition examination survey, 1982-1984. *Am J Epidemiol.* (1992) 135:1339–48. doi: 10.1093/oxfordjournals.aje.a116245

74. Rumball-Smith J, Nandi A, Kaufman JS. Working and hypertension: gaps in employment not associated with increased risk in 13 European countries, a retrospective cohort study. *BMC Public Health.* (2014) 14:536. doi: 10.1186/1471-2458-14-536

75. Rose KM, Newman B, Bennett T, Tyroler HA. Employment status and high blood pressure in women: variations by time and by sociodemographic characteristics. *Ann Epidemiol.* (1997) 7:107–14. doi: 10.1016/S1047-2797(96)00127-5

76. Noh J, Kim HC, Shin A, Yeom H, Jang SY, Lee JH, et al. Prevalence of Comorbidity among people with hypertension: the Korea national health and nutrition examination survey 2007-2013. *Korean Circ J.* (2016) 46:672–80. doi: 10.4070/kcj.2016.46.5.672

77. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American heart association. *Circulation.* (2016) 134:e535–78. doi: 10.1161/CIR.0000000000000450

78. Primatesta P, Falaschetti E, Gupta S, Marmot MG, Poulter NR. Association between smoking and blood pressure: evidence from the health survey for England. *Hypertension.* (2001) 37:187–93. doi: 10.1161/01.HYP.37.2.187

79. Virdis A, Giannarelli C, Neves MF, Taddei S, Ghiadoni L. Cigarette smoking and hypertension. *Curr Pharm Des.* (2010) 16:2518–25. doi: 10.2174/138161210792062920

80. Husain K, Ansari RA, Ferder L. Alcohol-induced hypertension: Mechanism and prevention. *World J Cardiol.* (2014) 6:245–52. doi: 10.4330/wjc.v6.i5.245

81. Tasnim S, Tang C, Musini VM, Wright JM. *Effect of alcohol on blood pressure. The Cochrane Database of Systematic Reviews*. (2020). Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8130994/ (accessed June 5, 2020). doi: 10.1002/14651858.CD012787.pub2

82. Rubio-Guerra AF, Rodriguez-Lopez L, Vargas-Ayala G, Huerta-Ramirez S, Serna DC, Lozano-Nuevo JJ. Depression increases the risk for uncontrolled hypertension. *Exp Clin Cardiol.* (2013) 18:10–2.

83. DeMoss DS, Teigen KJ, Claassen CA, Fisk MJ, Blair SE, Bakre SA, et al. Association between depression and hypertension using classic and revised blood pressure thresholds. *Fam Pract.* (2020) 37:616–22. doi: 10.1093/fampra/cmaa010

84. Licht CMM, de Geus EJC, Seldenrijk A, van Hout HPJ, Zitman FG, van Dyck R, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertension.* (2009) 53:631–8. doi: 10.1161/HYPERTENSIONAHA.108.126698

85. Hamer M, Batty GD, Stamatakis E, Kivimaki M. Hypertension awareness and psychological distress. *Hypertension.* (2010) 56:547–50. doi: 10.1161/HYPERTENSIONAHA.110.153775

86. Mucci N, Giorgi G, De Pasquale Ceratti S, Fiz-Pérez J, Mucci F, Arcangeli G. Anxiety, stress-related factors, and blood pressure in young adults. *Front Psychol.* (2016) 7:1682. doi: 10.3389/fpsyg.2016.01682

87. Adamo D, Schiavone V, Aria M, Leuci S, Ruoppo E. Dell'Aversana G, et al. Sleep disturbance in patients with burning mouth syndrome: a case-control study. *J Orofac Pain.* (2013) 27:304–13. doi: 10.11607/jop.1109

88. Makarem N, Alcántara C, Williams N, Bello NA, Abdalla M. Effect of sleep disturbances on blood pressure. *Hypertension.* (2021) 77:1036–46. doi: 10.1161/HYPERTENSIONAHA.120.14479

89. Gangwisch JE, Feskanich D, Malaspina D, Shen S, Forman JP. Sleep duration and risk for hypertension in women: results from the nurses' health study. *Am J Hypertens.* (2013) 26:903–11. doi: 10.1093/ajh/hpt044

90. Wang Q, Xi B, Liu M, Zhang Y, Fu M. Short sleep duration is associated with hypertension risk among adults: a systematic review and meta-analysis. *Hypertens Res.* (2012) 35:1012–8. doi: 10.1038/hr.2012.91

91. Mazza A, Ravenni R, Armigliato M, Rossetti C, Schiavon L, Fiorini F, et al. Mood disorders in uncontrolled hypertension despite multiple anti-hypertensive medications: searching for a link. *High Blood Press Cardiovasc Prev.* (2016) 23:41–6. doi: 10.1007/s40292-015-0128-x

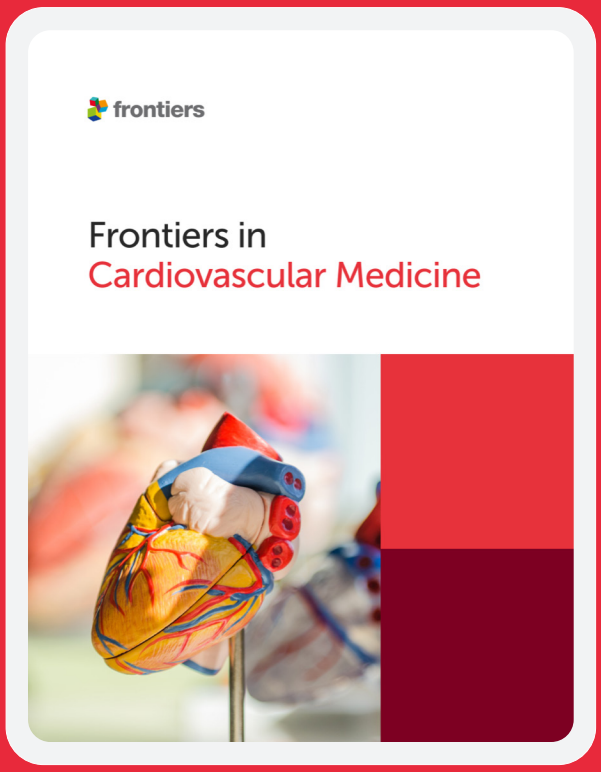
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact