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Dietary strategies for managing hypertension and hypotension: insights and mechanisms

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Dietary strategies for managing hypertension and hypotension: insights and mechanisms

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Table of contents

05 Editorial: Dietary strategies for managing hypertension and hypotension: insights and mechanisms
Agnieszka Kujawska, Claire Elizabeth Robertson, Fadi J. Charchar, Nicholas McMahon and José Augusto Simões

08 Relationship between serum iron, zinc, calcium, and HIF-1a—comparative analysis of 2 regions and 4 ethnic groups in China
Yan Guo, Zhong-Sheng Lu, Xue-Cheng Zhang, Qiang Zhang, Xiao Liu, Jie Chen and Meng-Lan Zhang

21 Association between copper intake and essential hypertension: dual evidence from Mendelian randomization analysis and the NHANES database
Qing Miao, Jingtao Zhang, Yingjie Yun, Wei Wu and Chuanjin Luo

35 The effect of cumulative exposure with unhealthy lifestyles on the H-type hypertension among Chinese adults: a community-based, propensity-score-matched, and case–control study
Ling Li, Jia Wang, Jing Li, Minqi Li, Tianyao Long, Yangyi Zhengliu, Yuan Lv and Xiuqin Hong

47 Circulating fatty acids, genetic susceptibility and hypertension: a prospective cohort study
Lingling Lu, Xiaoli Gu, Daheng Yang, Bingjian Wang and Guangfeng Long

59 Dietary antioxidant index and hypertension in the Iranian population: a nested case–control study within the Fasa adults cohort study
Mohammad amin Firooznia, Mehran Rahimlou, Eghbal Sekhavati, Mohammadreza Motazedian and Reza Tabrizi

67 Effects of salt substitute on urinary electrolytes and blood pressure in a real-world setting—cohort study in Hunan, China
Hao Wu, Wenbin Ouyang, Jing Deng, Yongmei He, Lu Yin, Xia Cao, Zhiheng Chen, Pingting Yang, Yaqin Wang, Ying Li and Xin Huang

76 Effect of plasma homocysteine on cardiometabolic multimorbidity among Chinese adults: a population-based and real-world evidence study
Ling Li, Jia Wang, Jing Li, Minqi Li, Jie Wang, Tianyao Long, Yangyi Zhengliu, Xuan Tan, Yiwei Peng and Xiuqin Hong

87 Association between fat-soluble vitamin co-exposure patterns and blood pressure in people with hypertension: a cross-sectional study
Suming Dai, Ping Wang, Sijia Wang, Hong Chen, Zhixin Cui, Wenhai Lu, Ziyi Zhou, Nan Zhang, Zhuo Wang, Tengfei Lin, Yun Song, Lishun Liu, Xiao Huang, Ping Chen, Genfu Tang, Yong Duan, Hao Zhang, Binyan Wang, Yan Yang and Zezhong Tian

98 Sex differences in the associations of water, coffee and tea consumption with cardiovascular diseases: a prospective cohort study
Dandan Ke, Yueqing Wang, Yabing Hou, Weihao Shao, Jiawen Ke, Xiaoxuan Zhang, Hongxi Yang, Zhong He and Zuolin Lu

108 Association of dietary patterns with hypertension among adults residing in Tibetan China: findings from a population-based study
Xinran Li, Xin Zhang, Qiling Gou, Qingtao Meng and Xiaoping Chen

118 Interactive effect between Selenium and Vitamin C levels on risk of hypertension among adult women in the United States: evidence from NHANES 2011 to 2020
Dongfang Wu, Ping Fan and Sze Wan Ching

125 A retrospective cohort study of H-type hypertension and its influence on the prognostic effect in patients with non-dialysis CKD
Xiaoyu Cai, Menglei Ju, Xinying Jiang, Shengnan Ge, Yuzhang Han, Shumin Lin, Hui Peng, Man Li and Cheng Wang

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Editorial: Dietary strategies for managing hypertension and hypotension: insights and mechanisms

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Editorial on the Research Topic
Dietary strategies for managing hypertension and hypotension: insights and mechanisms

1 Introduction

The relationship between diet and health has been observed for thousands of years, as evidenced in the works of Galen (1). Galen wrote: "Many of the finest physicians have written about the properties of foods, taking the subject very seriously since it is about the most valuable of any in medicine. (…) But since by holding differing views they have raised suspicions about one another (for they cannot all be speaking the truth!) we must become impartial judges and put what they have said to the test. For without demonstration it is wrong to put one's confidence in one more than the others" (2). Despite the centuries that have passed since Galen's observations, nutrition science still lacks robust data and, consequently, evidence-based consensus in many subfields. With this Research Topic, we aim to extend the current understanding of dietary factors in hypertension (HTN) and cardiovascular health.

2 Diet-related factors for hypertension

Diet could be analyzed based on multiple levels, with one of the top layers being dietary patterns. Among the Tibetan population, three predominant dietary patterns were identified (Li X. et al.). Adherence to the "Tsamba-red meat-tuber" pattern was linked to

an elevated risk of HTN, whereas the "Rice-vegetable-fruit" and "Dairy products" patterns were associated with a reduced HTN risk. Based on these results, the efficacy of a targeted dietary intervention might be examined among Tibetans residing in the Garze Tibetan Autonomous Prefecture of Sichuan Province (Li et al.).

In the nested case–control study within the Fasa Adult Cohort Study (FACS), involving 975 participants aged 35–70 years, higher antioxidant intake is linked to a lower likelihood of developing HTN, emphasizing the valuable role of antioxidant-rich diets as an adjunctive measure in HTN prevention and management (Firooznia et al.).

A comprehensive study involving 195,250 participants from the UK Biobank cohort investigated the interplay between genetic predisposition and plasma fatty acid (FA) profiles in relation to HTN risk (Lu et al.). Higher plasma levels of polyunsaturated (PUFAs) and n-3 PUFAs were inversely associated with HTN risk, whereas elevated monounsaturated fatty acids (MUFAs) and saturated fatty acids (SFAs) were related to an increased risk (Lu et al.). Notably, a significant additive interaction between genetic risk and plasma FA levels was observed, contributing to a 10%−18% increased HTN risk (Lu et al.).

Another level of diet analysis is based on intake and the level of vitamins and their relationship with health indicators. Wu D. et al. showed that sufficient intake of both Vitamin C and Selenium is linked to a reduced risk of HTN among U.S. women. In a study by Dai et al., participants with higher overall vitamin levels did not exhibit significantly different blood pressure compared to those with lower levels. Nevertheless, plasma 25-hydroxyvitamin D3 demonstrated a modest inverse relationship with systolic blood pressure, whereas elevated α-tocopherol (vitamin E) levels correlated with a slight increase in systolic pressure (Dai et al.). These findings suggest that α-tocopherol may counterbalance the potential protective effect of vitamin D3 on blood pressure, highlighting the complex interplay among fat-soluble vitamins in hypertensive individuals (Dai et al.).

Diet can also be analyzed in terms of specific micronutrient intakes, though such studies are complicated by potential interactions between nutrients. For instance, in comparison to salt restriction, the use of salt substitutes leads to a more pronounced reduction in sodium intake alongside a significant increase in potassium consumption (Wu H. et al.). However, these changes do not translate into superior blood pressure control, particularly among individuals using salt substitutes with 13% potassium chloride content. Notably, only the group exposed to the higher 25% potassium chloride formulation demonstrated a meaningful reduction in systolic blood pressure, underscoring the importance of potassium concentration in the efficacy of salt substitutes for blood pressure management (Wu H. et al.).

Miao et al. sought to clarify the relationship between various human trace elements and essential HTN. Employing two-sample, multivariate, and inverse Mendelian randomization analyses, the investigation focused on 15 trace elements identified through comprehensive database searches (Miao et al.). The analyses revealed a significant link between copper intake and the risk of developing essential HTN. This association was further substantiated by analysis of data from the National Health and Nutrition Examination Survey (NHANES), which revealed higher copper intake to be associated with increased HTN risk (Miao et al.).

It is important to note that hypertension is now recognized as a cluster of disorders with various mechanisms underlying pathology, including genetic, environmental, neurohormonal, renal, vascular, and metabolic factors contributing to its pathogenesis (3). Diet could be used to influence the level of particular risk factors, including homocysteine (Hcy) level (4). The coexistence of hyperhomocysteinemia (HTH) and HTN, termed H-type hypertension, is significantly associated with accelerated renal decline and an increased risk of major adverse cardiovascular and cerebrovascular events in patients with chronic kidney disease not requiring dialysis (Cai et al.).

Among Chinese adults in Hunan Province, the combination of heavy alcohol use, unhealthy diet, and elevated BMI showed the strongest association with HTH, with risk further amplified by the addition of smoking (Li, Wang, Li, Li, Long, et al.). The relationship between the number of unhealthy lifestyle factors and HTH risk followed a J-shaped dose–response curve, underscoring the compounding effect of multiple behaviors (Li, Wang, Li, Li, Long, et al.).

Emerging evidence robustly underscores elevated plasma Hcy levels as a significant independent predictor of cardiometabolic multimorbidity (CMM) (Li, Wang, Li, Li, Wang, et al.). Notably, the synergistic coexistence of diabetes, HTN, and coronary heart disease amplifies this risk, revealing Hcy as a critical modifiable biomarker in CMM pathogenesis (Li, Wang, Li, Li, Wang, et al.).

3 Diet-related factors for cardiovascular health

Sato et al. (5) described the relationship between hypoxia-inducible factor 1-alpha (HIF-1α) and cardiovascular health. Guo et al. investigated the relationship between blood concentrations of zinc, iron, and calcium and HIF-1α among individuals residing at different altitudes and belonging to diverse ethnic groups, aiming to deepen understanding of altitude illness mechanisms. Based on serum samples from 400 from Xining and Sanya analysis, significant differences in zinc, calcium, and HIF-1α levels were observed between low- and high-altitude populations, while iron levels remained consistent (Guo et al.). Variations in microelements and HIF-1α blood levels were found to be related to altitude and ethnicity, potentially influencing the onset and progression of altitude-related illnesses (Guo et al.).

A comprehensive analysis of over 460,000 UK Biobank participants examined the associations between hydration sources, including water, coffee, and tea, with cardiovascular disease (CVD) risk over a median follow-up of 8.7 years (Ke et al.). Higher water intake was related to a reduced risk of heart failure, coronary heart disease, and stroke in both men and women. Conversely, high consumption of coffee (six or more cups daily) and tea was associated with an elevated risk of these cardiovascular outcomes (Ke et al.). In addition, an excessive coffee and tea intake appeared to diminish the protective effects of water consumption on CVD risk (Ke et al.).

Author contributions

AK: Writing – review & editing, Writing – original draft. CR: Writing – review & editing. FC: Writing – review & editing. NM: Writing – review & editing. JS: Writing – review & editing.

Conflict of interest

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

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Relationship between serum iron, zinc, calcium, and HIF-1a—comparative analysis of 2 regions and 4 ethnic groups in China

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Background: Altitude illness has serious effects on individuals who are not adequately acclimatized to high-altitude areas and may even lead to death. However, the individualized mechanisms of onset and preventive measures are not fully elucidated at present, especially the relationship between altitude illness and elements, which requires further in-depth research.

Methods: Fresh serum samples were collected from individuals who underwent health examinations at the two hospitals in Xining and Sanya between November 2021 and December 2021. The blood zinc (Zn), iron (Fe), and calcium (Ca) concentrations, as well as hypoxia-inducible factor 1-alpha (HIF-1α) concentrations, were measured. This study conducted effective sample size estimation, repeated experiments, and used GraphPad Prism 9.0 and IBM SPSS version 19.0 software for comparative analysis of differences in the expression of elements and HIF-1α among different ethnic groups, altitudes, and concentration groups. Linear regression and multiple linear regression were employed to explore the relationships among elements and their correlation with HIF-1α.

Results: This study included a total of 400 participants. The results from the repeated measurements indicated that the consistency of the laboratory test results was satisfactory. In terms of altitude differences, except for Fe ($p = 0.767$), which did not show significant variance between low and high altitude regions, Zn, Ca, and HIF-1α elements all exhibited notable differences between these areas ($p < 0.0001$, $p = 0.004$, and $p < 0.0001$). When grouping by the concentrations of elements and HIF-1α, the results revealed significant variations in the distribution of zinc among different levels of iron and HIF-1α ($p < 0.05$). The outcomes of the linear regression analysis demonstrated that calcium and zinc, iron and HIF-1α, calcium and HIF-1α, and zinc and HIF-1α displayed substantial overall explanatory power across different subgroups ($p < 0.05$). Finally, the results of the multiple linear regression analysis indicated that within the high-altitude population, the Li ethnic group in Sanya, and the Han ethnic group in Sanya, the multiple linear regression model with HIF-1αas the dependent variable and elements as the independent variables exhibited noteworthy overall explanatory power ($p < 0.05$).

Conclusion: The levels of typical elements and HIF-1α in the blood differ among various altitudes and ethnic groups, and these distinctions may be linked to the occurrence and progression of high-altitude illness.

KEYWORDS

high-altitude illness, iron, zinc, calcium, HIF-1α, altitude, race, linear regression analysis

1 Background

High altitude illness is caused by prolonged exposure to high altitude/low oxygen environments (1). At altitudes of 2,500 meters or higher, anyone who ascends may develop one of three types of acute high altitude illnesses within 1–5 days (2). These include acute mountain sickness (AMS), which is a non-specific symptom complex including headache, fatigue, dizziness, and nausea (3); high altitude cerebral edema (HACE), a potentially fatal condition characterized by ataxia, altered mental status, and characteristic changes on magnetic resonance imaging (4); and high altitude pulmonary edema (HAPE), a non-cardiogenic pulmonary edema caused by excessive hypoxic pulmonary vasoconstriction, which can be fatal if not promptly recognized and treated (5). These illnesses can develop at any time between a few hours and 5 days after ascent, with severity ranging from mild inconvenience to life-threatening conditions (1). The most important factors in the treatment of acute mountain sickness are acclimatization, stopping further ascent and resting, or beginning descent; supplemental oxygen and medication intervention, and, if conditions allow, the use of portable hyperbaric chambers (6). With the increasing popularity of mountain sports and tourism, better education for at-risk populations is crucial (7). Therefore, identifying the risk factors and high-risk populations for high altitude illness and targeted prevention are particularly important.

The pathogenesis of high-altitude illness is characterized by intricate regulation of various physiological systems (8). Prolonged exposure to high-altitude environments leads to a series of adaptive alterations in response to reduced oxygen levels in the atmosphere (9). In terms of adjustments in the respiratory system, an increased respiratory rate and depth help to enhance oxygen uptake to compensate for reduced oxygen availability at high altitudes (10). As for modifications in the cardiovascular system, a heightened heart rate and cardiac output optimize oxygen delivery in the blood, meeting the oxygen needs of tissues and organs. Additionally, prolonged exposure to high altitudes stimulates an increase in red blood cell count, enhancing the capacity for oxygen transport. Enhanced vasodilation also promotes improved blood flow, thereby enhancing the efficiency of oxygen delivery (11). Failure to adapt to the body's oxygen demands may result in symptoms of high-altitude illness, such as headache, nausea, vomiting, and fatigue. While the systemic physiological responses to acute hypoxia and the adaptive changes have been extensively documented, the molecular mechanisms underpinning these physiological adjustments remain incompletely elucidated (12, 13). Further investigation is warranted to comprehensively unravel factors including hypoxia tolerance, oxidative stress, inflammatory responses, trace elements, and other pertinent aspects.

Hypoxia-inducible factor 1-alpha (HIF-1α), as an important transcription factor, regulates the expression of multiple genes under low-oxygen conditions, promoting cellular adaptation to low-oxygen environments, and serving as a significant marker for high-altitude illness (14). Currently, it is believed that the regulation of HIF-1α may be linked to the onset and progression of high-altitude illness, but the specific mechanisms and impacts require further research for comprehensive understanding (15, 16). Additionally, abundant research indicates the potential pivotal role of elements in the occurrence and development of high-altitude illness (17, 18). Prolonged residence in high-altitude areas may elevate the body's demand for certain elements due to their critical involvement in regulating internal physiological processes. Furthermore, iron is a component of hemoglobin, aiding in the transportation of oxygen to various parts of the body, maintaining the body's energy levels, and participating in cellular respiration and energy metabolism processes. Zinc is crucial for the normal functioning of the immune system, promoting wound healing, DNA synthesis, and cell division. Calcium is a key element in maintaining the health of bones and teeth, participating in physiological processes such as nerve conduction, muscle contraction, and blood clotting. These three elements interact synergistically in the human body to maintain normal function and health (19–21). However, the correlation between elements and hypoxia tolerance has not been reported and requires further in-depth exploration.

Xining, the capital of Qinghai Province, is located on the northeastern edge of the Tibetan Plateau, at an altitude of approximately 2,275 meters (7,464 feet), with a cold semi-arid climate. Sanya, a coastal city at the southern tip of Hainan Island in China, was chosen for a low-altitude comparison with Xining, known for its warm and humid tropical monsoon climate year-round. Contrasting climates and altitudes between Sanya and Xining provide insights into how environmental factors influence the levels of elements and HIF-1α concentrations in different populations. Additionally, the Han Chinese, accounting for about 92% of China's population, live across various altitudes. The Li ethnic group, one of the oldest indigenous groups on Hainan Island, resides in mountainous areas with unique customs and traditions. The Tibetan people, living in the high-altitude Tibetan Plateau, possess unique physiological traits to cope with low oxygen levels. These three ethnic groups offer insights into genetic and environmental adaptations to high-altitude living, particularly in terms of elements and HIF-1α regulation. In this study, 383 healthy young men of Tibetan, Han, and Li ethnicities from Xining and Sanya were included to investigate the levels and relationships of the hypoxia tolerance marker HIF-1α, and three elements, including zinc (Zn), iron (Fe), and calcium (Ca), in different altitudes and ethnic groups, aiming to provide reference value for the prevention, treatment, and pathogenesis exploration of high-altitude illness.

2 Materials and methods

2.1 Patients and sample

This study was approved by the ethics committee of Hainan Hospital of the General Hospital of the People's Liberation Army and

Qinghai Provincial People's Hospital (2021-41) and was conducted in compliance with the Declaration of Helsinki (22). Fresh serum samples were collected from individuals who underwent health examinations at the two hospitals between November 2021 and December 2021, and the blood biochemical tests were conducted in the aforementioned hospitals. The information on Xining and Sanya, as well as details on different ethnic groups, are labeled in Supplementary Figure S1.

The inclusion criteria were as follows:

(1) Male, 18–45 years old.
(2) Li, Tibetan, or Han ethnicity.
(3) Have resided in Sanya or Xining for more than 3 years.
(4) Have not left their place of residence in the six months prior to blood sample collection.
(5) Self-reported absence of physical discomfort.

The exclusion criteria were:

(1) Remaining serum sample after clinical test is less than 1.5 mL.
(2) Clinically diagnosed patients with malignant tumors, cor pulmonale, hepatitis, nephritis, immune diseases, severe infections, and other illnesses.
(3) All participants included in the study have good physical condition, balanced diet, good digestion, normal bowel movements, healthy lifestyle, and have not suffered from chronic or debilitating diseases recently, nor have they taken any medication.

2.2 Sample size calculation

The study estimated the minimum sample size required based on the sample size estimation method described in the literature, as well as the data on serum Zn, Fe, Ca, and HIF-1 reported in previous study (23). The significance level (α) was set at 0.05, and the power (β) at 0.80. By using the values of $\mu\alpha = 1.96$ (bilateral) and $\mu\beta = 1.28$ (one side), and incorporating the standard deviation (σ) and the effect size (δ) into the formula ($n = 2(\mu\alpha + \mu\beta)^2\ \sigma^2/\delta^2$), the minimum sample size was calculated. Subsequently, the minimum sample size for this study was determined *a priori* based on preliminary data and expected effect sizes, ensuring adequate power to detect significant differences. Using GPower[1] to conduct post-hoc power analysis was based on the actual collected data to ensure that the sample size was adequate for detecting significant differences. The power for between-group comparisons was calculated and reported in section.

2.3 Elimination of data deviation

The blood zinc (bc2815), blood iron (bc1735), and blood calcium (bc0725) concentration detection kits were procured from Beijing Solebao Technology Co., Ltd. (China), while the human HIF-1α ELISA Kit (ft-p36684r) was obtained from Shanghai FanTai Biotechnology Co., Ltd. (China). To mitigate potential discrepancies arising from differences in instruments, equipment, testing personnel, and testing environment between the two laboratories, a pre-formal test phase involved collecting 10 remaining serum samples from clinical tests conducted at two hospitals. Each sample was then divided into two portions, with one stored in cold storage and the other transported to a different laboratory under cold storage conditions. Subsequently, both laboratories conducted simultaneous testing on the same day upon receiving the samples. The resulting test data was compared and analyzed to assess the consistency of the laboratories' test results. In cases where significant differences were observed, mean calculations were utilized to ensure result consistency prior to further analysis.

2.4 Statistical analysis

All statistical analyses were performed using GraphPad Prism 9.0 and IBM SPSS version 19.0 software. Prior to conducting statistical analysis, normality tests were conducted, and when the data met the normal distribution criteria, repeated measurement paired sample *t*-tests was employed to assess the consistency of blood routine test results from the two laboratories. One-way ANOVA was utilized to evaluate differences in serum Zn, Fe, Ca, and HIF-1α content, in cases where the data did not conform to normal distribution, non-parametric Mann–Whitney *U* tests were applied for analysis. A significance level of $p < 0.05$ was used to determine statistical significance. Linear regression analysis was used to explore the relationships between Zn, Fe, Ca, and HIF-1α. In a regression model, if the tolerance is less than 0.01, the variance inflation factor (VIF) value is greater than 10, and the condition index (CI) value is greater than 30, it indicates that there is multicollinearity among the independent variables.

3 Results

3.1 Sample size estimation

Based on the calculation results from Table 1 and in consideration of the actual circumstances, it is proposed to include the four groups of Sanya Li ethnic group (SL), Sanya Han ethnic group (SH), Xining Han ethnic group (XH), and Xining Tibetan ethnic group (XZ) in this study, with a total of 400 cases. A total of 400 subjects were enrolled in the study. Among them, 17 patients were excluded from the clinical diagnosis of hepatitis, nephritis, thalassemia, leukemia, severe infection and other diseases. A total of 383 patients were actually included in the study, including 97 cases in the Sanya Li ethnic group, 93 cases in the Sanya Han ethnic group, 95 cases in the Xining Han ethnic group, and 98 cases in the Xining Tibetan ethnic group. The result of post-hoc power analysis indicated that our study had a power of 0.85 for detecting between-group differences, meeting statistical requirements.

3.2 Repeated test

To avoid measurement errors caused by different trial centers, paired sample *t*-tests were used to test the measurement data of 20

1 http://www.gpower.hhu.de/

TABLE 1 Sample size estimation table for this study.

Index		Ethnic 1		Ethnic 2		δ	σ	n
		$\bar{x}$	$s1$	$\bar{x}$	$s2$			
Zn	($\mu g\,mL^{-1}$)	0.943	0.031	0.783	0.195	0.16	0.14	16
Fe	($\mu g\,mL^{-1}$)	1.637	1.612	1.739	0.623	0.102	1.222	3014.3
Ca	($\mu g\,mL^{-1}$)	85.299	1.119	92.578	2.536	7.279	1.96	1.5
HIF-1α	($ng\,L^{-1}$)	343.35	45.32	326.51	23.4	16.84	36.066	96.3

x, mean value; s, standard deviation; allowable error $\delta = |x1 - x2|$, overall standard deviation $\sigma = [(s1^2 + s2^2)/2]^{1/2}$. HIF-1α, hypoxia-inducible factor 1-alpha.

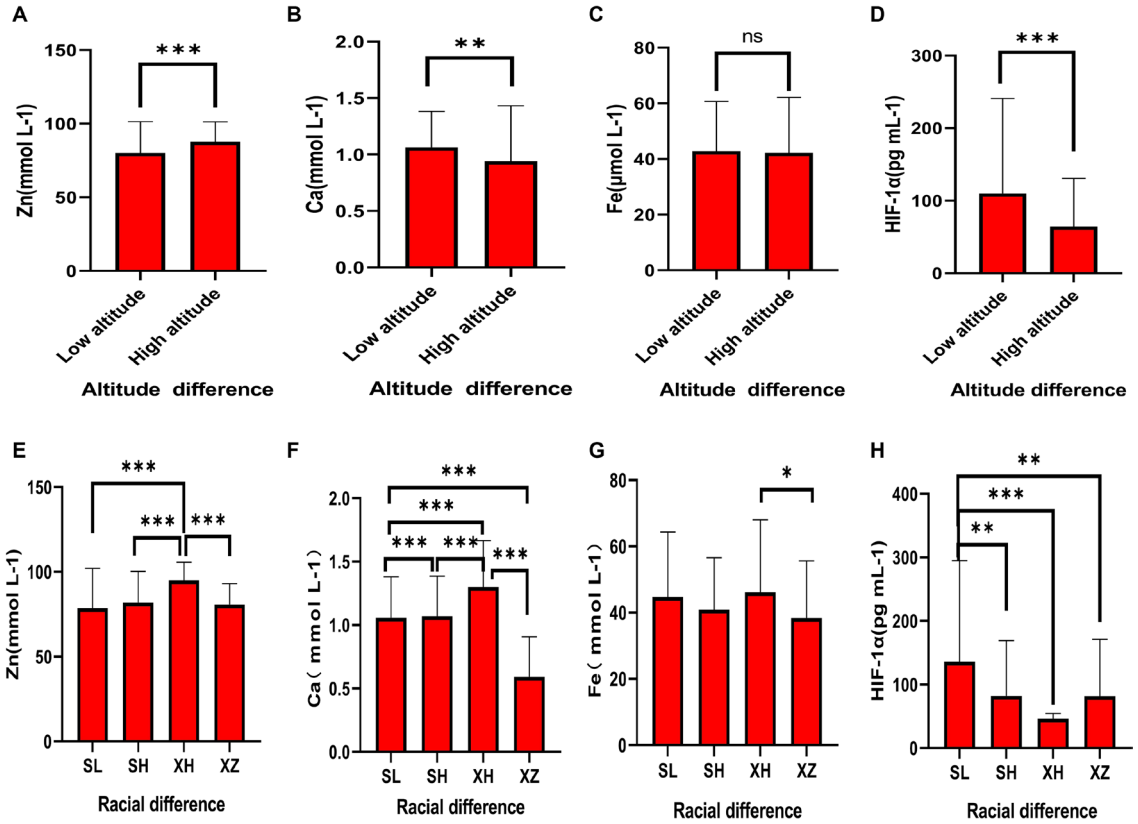

FIGURE 1
Expression levels of common elements (Zn, Fe, Ca) and HIF-1α in different altitudes and ethnicities. **(A)** Differential expression of Zn in different altitude regions. **(B)** Differential expression of Ca in different altitude regions. **(C)** Differential expression of Fe in different altitude regions. **(D)** Differential expression of HIF-1α in different altitude regions. **(E)** Differential expression of Zn in different ethnicities. **(F)** Differential expression of Ca in different ethnicities. **(G)** Differential expression of Fe in different ethnicities. **(H)** Differential expression of HIF-1α in different ethnicities. "*" indicates a p-value less than 0.05, "**" indicates a p-value less than 0.01, "***" indicates a p-value less than 0.001, and "ns" indicates no statistical significance.

patients. The results indicated that the two laboratories tested 20 samples for Zn ($t = 1.558$, $p = 0.136$), Fe ($t = 1.613$, $p = 0.123$), Ca ($t = 0.458$, $p = 0.652$), and HIF-1 α ($t = 1.197$, $p = 0.246$). These findings suggest that the blood routine test results from the two laboratories are consistent, allowing for further data analysis. The consistency of test results from two laboratories was shown in Supplementary Table S1.

3.3 Altitude and radial difference analysis

As shown in Figures 1A–D and Table 2, in terms of altitude difference, apart from Fe showing no significant difference between low and high altitude areas, Zn, Ca, and HIF-1α elements all exhibit significant differences between low and high altitude areas. Specifically, Zn content is higher in high-altitude areas, while Ca and HIF-1α content is higher in low-altitude areas. As shown in Figures 1E–H and Table 3, in terms of ethnic differences, there are significant differences in Zn and Ca concentrations among the four ethnic groups, with the highest levels of Zn and Ca found in the high-altitude Xining Han ethnic group and the lowest levels found in the high-altitude Xining Tibetan ethnic group. The Fe concentration in the Xining Han ethnic group is higher than that in the Xining Tibetan ethnic group, and the difference is statistically significant. The HIF-1α concentration in the Sanya Li ethnic group is significantly higher than in the other three groups, with the Xining Han ethnic group having the lowest concentration. The consistency of test results from two laboratories

TABLE 2 Expression levels of common elements (Zn, Fe, Ca) and HIF-1α in different altitudes and ethnicities.

	Low altitude		High altitude		*F*-value	*p*-value
	SL (*n* = 97)	SH (*n* = 95)	XH (*n* = 97)	SH (*n* = 98)		
Zn	78.61 ± 23.51	81.94 ± 18.33	94.95 ± 10.78	80.65 ± 12.36	18.09	<0.0001
Fe	1.058 ± 0.32	1.070 ± 0.32	1.301 ± 0.37	0.593 ± 0.32	78.12	<0.0001
Ca	44.68 ± 1.99	40.88 ± 1.63	46.19 ± 2.24	38.43 ± 1.74	3.433	0.017
HIF-1α	136.20 ± 16.11	82.30 ± 9.011	46.25 ± 0.85	81.90 ± 9.02	12.89	<0.0001

SL, Sanya Li ethnic group; SH, Sanya Han ethnic group; XH, Xining Han ethnic group; XZ, Xining Tibetan ethnic group; HIF-1α, hypoxia-inducible factor 1-alpha.

was shown in Supplementary Table S1. The map of the locations of Xining and Sanya, as well as information on different ethnic groups was shown in Supplementary Figure S1.

3.4 Trace element difference analysis

To further explore the relationship between elements and HIF-1α, when all populations were grouped by the average concentration of zinc, it was found that calcium concentration significantly increased in the high zinc concentration group, while the differences in iron and HIF-1α concentrations between the high and low zinc concentration groups were not statistically significant (Figures 2A–C and Table 4). Similarly, when all populations were grouped by the average concentration of calcium, the differences in zinc, iron, and HIF-1α concentrations between the two groups were not statistically significant (Figures 2D–F and Table 5). After grouping all populations by the average concentration of iron, it was observed that zinc concentration significantly increased in the high iron concentration group, while the differences in calcium and HIF-1α concentrations between the two groups were not statistically significant (Figures 2G–I and Table 6). Finally, when all populations were grouped by the average concentration of HIF-1α, it was noted that zinc concentration was significantly higher in the low HIF-1α concentration group than in the high HIF-1α concentration group, while the differences in calcium and iron concentrations between the two groups were not statistically significant (Figures 2J–L and Table 7).

3.5 Linear regression analysis

In Table 8, pairwise linear regression analyses were conducted for Zn, Fe, Ca, and HIF-1α content at the overall level. The results indicated a linear correlation between Ca and Zn, with a determination coefficient R^2 of 0.96. However, these relationships were not statistically significant (Figure 3). For low-altitude areas, linear regression analysis was performed for Zn, Ca, Fe, and HIF-1α. The analysis revealed that only the overall explanatory power of the linear regression model between Fe and HIF-1α reached statistical significance ($R^2 = 0.02$, $p = 0.04$) (Figure 4). In high-altitude areas, the linear regression models for Ca and HIF-1α, as well as Fe and HIF-1α, both demonstrated a significant overall explanatory power ($R^2 = 0.03$, $p = 0.02$ and $R^2 = 0.02$, $p = 0.04$, respectively) (Figure 4). When considering regional and ethnic groupings, in the Sanya Li ethnic group, the linear regression models for Zn and HIF-1α, as well as Fe and HIF-1α, both exhibited significant overall explanatory power, with regression equations of ($R^2 = 0.06$, p = 0.02) and ($R^2 = 0.07$, $p = 0.01$), respectively. In the Sanya Han ethnic group, only the linear regression model for Zn and HIF-1α showed significant overall explanatory power, with a regression equation of ($R^2 = 0.09$, $p = 0.00$). For the Xining Han ethnic group, only the linear regression model for Fe and HIF-1α demonstrated significant overall explanatory power, with a regression equation of ($R^2 = 0.05$, $p = 0.03$). No regression model showed significant overall explanatory power in the Xining Tibetan ethnic group (Figure 5).

TABLE 3 Expression levels of common elements (Zn, Fe, Ca) and HIF-1α in different altitudes.

	Low altitude	High altitude	*T*-value	*p*-value
	n = 190	*n* = 193		
Zn	80.24 ± 21.14	87.69 ± 13.62	4.108	<0.0001
Ca	1.06 ± 0.32	0.94 ± 0.49	2.983	0.004
Fe	42.82 ± 17.88	42.25 ± 19.95	0.296	0.767
HIF-1α	109.8 ± 9.51	64.35 ± 4.64	4.293	<0.0001

HIF-1α, hypoxia-inducible factor 1-alpha.

TABLE 4 Expression levels of common elements (Fe, Ca) and HIF-1α in the high Zn concentration group and the low Zn concentration group.

	Zn		*T*-value	*p*-value
	Low (*n* = 207)	High (*n* = 176)		
Fe	42.30 ± 18.93	42.81 ± 18.97	0.7937	0.262
Ca	0.71 ± 0.24	1.34 ± 0.31	22.19	<0.0001
HIF-1α	91.35 ± 104.8	81.67 ± 107.4	0.891	0.373

HIF-1α, hypoxia-inducible factor 1-alpha.

3.6 Multiple linear regression analysis

As shown in Table 9, using HIF-1α content as the dependent variable and Zn, Fe, and Ca content as the independent variables, multiple linear regression analysis was conducted. The results indicate that there is no issue of multicollinearity in the multiple linear regression models constructed based on data from different altitudes and ethnic groups. However, at the overall level, in low-altitude areas, and in the Xining Han ethnic and Xining Tibetan ethnic groups, the multiple linear regression models did not show a significant overall explanatory power. In high-altitude areas, the multiple linear regression model demonstrated a significant overall

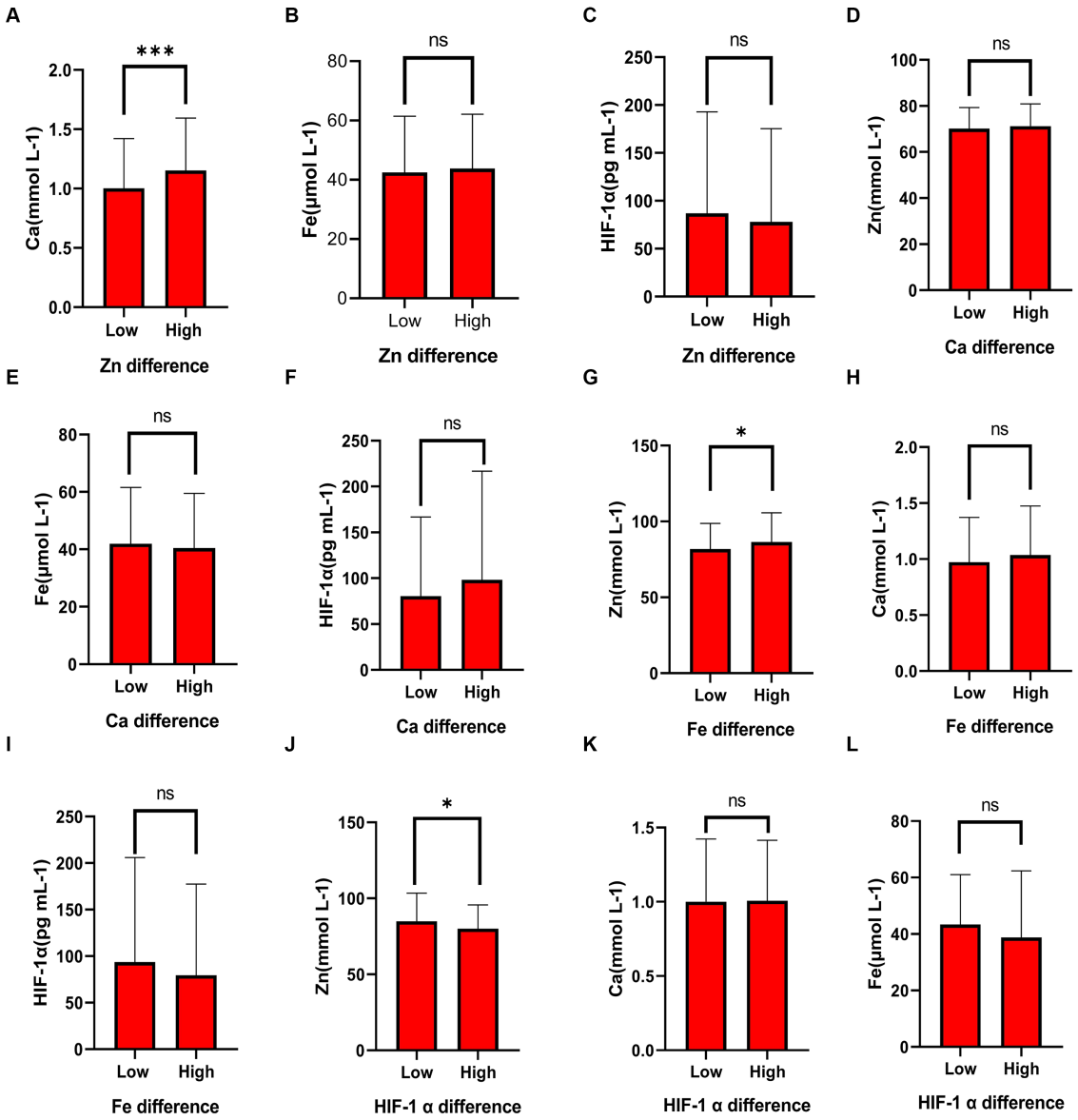

FIGURE 2
The differential expression of common elements (Zn, Fe, Ca) and HIF-1α in different concentration groups. **(A)** The expression of Ca in the high Zn concentration group and the low Zn concentration group. **(B)** The expression of Fe in the high Zn concentration group and the low Zn concentration group. **(C)** The expression of HIF-1α in the high Zn concentration group and the low Zn concentration group. **(D)** The expression of Zn in the high Ca concentration group and the low Ca concentration group. **(E)** The expression of Fe in the high Ca concentration group and the low Ca concentration group. **(F)** The expression of HIF-1α in the high Ca concentration group and the low Ca concentration group. **(G)** The expression of Zn in the high Fe concentration group and the low Fe concentration group. **(H)** The expression of Ca in the high Fe concentration group and the low Fe concentration group. **(I)** The expression of HIF-1α in the high Fe concentration group and the low Fe concentration group. **(J)** The expression of Zn in the high HIF-1α concentration group and the low HIF-1α concentration group. **(K)** The expression of Ca in the high HIF-1α concentration group and the low HIF-1α concentration group. **(L)** The expression of Fe in the high HIF-1α concentration group and the low HIF-1α concentration group. "*" indicates a p-value less than 0.05, "**" indicates a p-value less than 0.01, "***" indicates a p-value less than 0.001, and "ns" indicates no statistical significance.

explanatory power, with determination coefficients R^2 of 0.04. The coefficients for Zn, Ca, and Fe were −0.19, −17.61, and −0.43, respectively. In the Sanya Li ethnic group, the multiple linear regression model showed a significant overall explanatory power, with determination coefficients R^2 of 0.12. The coefficients for Zn, Ca, and Fe were 1.90, −57.13, and 1.75, respectively. In the Sanya Han ethnic group, the multiple linear regression model demonstrated a significant overall explanatory power, with determination coefficients R^2 of 0.16. The coefficients for Zn, Ca, and Fe were −1.61, 32.04, and −1.21, respectively.

4 Discussion

This study comprehensively analyzed the differences in elements (Zn, Fe, Ca) and HIF-1α expression among different ethnic groups

TABLE 5 Expression levels of common elements (Zn, Fe) and HIF-1α in the high Ca concentration group and the low Ca concentration group.

	Ca		*T*-value	*p*-value
	Low (*n* = 200)	High (*n* = 183)		
Fe	42.57 ± 19.10	42.49 ± 18.79	0.039	0.969
Zn	77.20 ± 14.38	91.42 ± 18.88	8.333	$p < 0.0001$
HIF-1α	89.62 ± 104.2	83.94 ± 108.0	0.523	0.601

HIF-1α, hypoxia-inducible factor 1-alpha.

TABLE 6 Expression levels of common elements (Zn, Fe) and HIF-1α in the high Fe concentration group and the low Fe concentration group.

	Fe		*T*-value	*p*-value
	Low (*n* = 202)	High (*n* = 181)		
Zn	81.79 ± 16.86	84.46 ± 19.17	2.537	0.012
Ca	0.97 ± 0.40	1.04 ± 0.44	1.467	0.143
HIF-1α	93.64 ± 112.4	79.39 ± 98.04	1.315	0.189

HIF-1α, hypoxia-inducible factor 1-alpha.

TABLE 7 Expression levels of common elements (Zn, Fe, Ca) in the high HIF-1α concentration group and the low HIF-1α concentration group.

	HIF-1α		*T*-value	*p*-value
	Low (*n* = 313)	High (*n* = 70)		
Fe	43.37 ± 17.66	38.80 ± 23.56	1.831	0.068
Zn	84.88 ± 18.54	80.03 ± 15.61	2.034	0.043
Ca	1.00 ± 0.42	1.01 ± 0.41	0.104	0.917

HIF-1α, hypoxia-inducible factor 1-alpha.

(Tibetan, Li, Han) under different environmental conditions (altitude), revealing the complex interaction of environmental and genetic factors in the regulation of elements in the human body. The significant differences between ethnic groups and altitudes highlight the impact of geographical and sociocultural backgrounds on nutritional status and the potential mechanisms of high-altitude illness. The study found that, apart from Fe showing no significant difference between low and high altitude areas, Zn, Ca, and HIF-1α levels all exhibit significant differences between low and high altitude areas, and there are significant differences in Zn and Ca concentrations among the four ethnic groups. Furthermore, the analysis of trace element differences revealed significant distribution differences in Zn among different concentrations of Fe and HIF-1α. In addition, linear regression suggested that Ca and Zn, Zn and HIF-1α, and Fe and HIF-1α may be linearly correlated in specific populations. Multiple linear regression analysis indicated that in high-altitude areas, specific ethnic groups in Sanya (low altitude) may exhibit multiple linear correlations between elements Zn, Ca, Fe, and HIF-1α. These research findings will provide theoretical support for the role of elements in the occurrence of high-altitude illness.

Fe is an essential constituent of hemoglobin and plays a pivotal role in the genesis and operation of red blood cells, a well-established fact (24). Anemia is widely recognized as a prominent manifestation of iron insufficiency, leading to the synonymous use of iron-deficiency anemia with iron deficiency (21). Furthermore, iron is intricately involved in DNA synthesis, cellular respiration, electron transfer, and overall metabolic processes (25). Recently, the discovery of iron death, a regulated form of cell demise characterized by iron-dependent accumulation of lipid peroxides reaching lethal levels, has been associated with numerous neurodegenerative diseases (26). The significant elevation of human hemoglobin levels with increased altitude of habitation, representing a noteworthy physiological adaptation to enhance oxygen metabolism and acclimate to low-oxygen environments at high altitudes, is well documented (27). However, this study revealed no substantial variance in serum iron concentration between low-altitude and high-altitude cohorts. Notably, among different ethnicities, only the Xining Han ethnic group exhibited significantly higher serum iron levels compared to the Xining Tibetan ethnic group. Investigations have substantiated the substantial iron supply required for augmented red blood cells, while highlighting the potential cytotoxic effects of iron overload, resulting in damage and afflictions in liver, pancreas, and cardiac tissues (27–30). Hepcidin, a hepatic-synthesized small peptide, serves as a critical regulator of iron absorption and internal equilibrium in mammals. Studies have demonstrated a notable decrease in hepcidin in the liver in a murine model of iron deficiency, accompanied by a significant increase in HIF-1α levels (31). Transgenic mice lacking HIF-1α no longer exhibit down-regulation of hepcidin in the liver following iron deficiency, indicating the pivotal role of HIF-1α in governing iron homeostasis and hepcidin regulation (32). This association has been further corroborated in the elegant roundworm, suggesting a potential linear correlation between iron and HIF-1α in specific populations. The adaptive physiological alterations observed in the Han population subsequent to migration to high altitudes due to environmental shifts appear fundamentally distinct from the genetic physiological disparities in minority ethnic groups such as the Li/Tibetan people, who have inhabited diverse altitudes across generations. Consequently, comprehensive consideration of ethnic and geographical factors is imperative in the study of human physiological indicators.

Zn is one of the second most abundant elements in the human body, participating in various important biological processes (33). For example, as a co-factor for 3,000 different proteins, it is involved in the structure and catalytic activity of over 300 enzymes (34). Zinc deficiency can lead to increased oxidative stress, causing damage to DNA, proteins, and lipids (35). Research has also found that young mice deficient in zinc have higher blood-brain barrier permeability after exposure to high levels of oxygen compared to normal zinc levels in young mice (36). Additionally, excessive accumulation of zinc can lead to the loss of tight junction proteins in brain endothelial cells, inducing damage to the blood-brain barrier (37). Zinc plays an important regulatory role in the cell for HIF-1α (38). HIF-1α is an important transcription factor that is activated in cells

TABLE 8 Linear regression between HIF-1α and common elements (Zn, Fe, Ca).

Variable		Person analysis	Model	ANOVA			
X	Y	*R*	*R*2	Regression	Residual	*F* value	*p* value
Overall							
Ca	Zn	0.98	0.96	120803.632	4596.40	10013.52	0.00
Ca	Fe	0.05	0.00	379.13	136450.31	1.06	0.30
Ca	HIF-1a	0.00	0.00	53.57	4288563.61	0.00	0.95
Fe	Zn	0.05	0.00	292.47	125107.56	0.89	0.35
HIF-1a	Zn	0.00	0.00	9.09	4288608.10	0.00	0.98
HIF-1a	Fe	0.04	0.00	6416.08	4282201.11	0.57	0.45
Low altitude areas							
Zn	HIF-1a	0.07	0.00	14203.96	3235376.10	0.83	0.36
Ca	HIF-1a	0.05	0.00	9241.72	3240338.34	0.54	0.46
Fe	HIF-1a	0.15	0.02	69540.76	3180039.30	4.11	0.04
High altitude areas							
Zn	HIF-1a	0.11	0.01	10294.12	830883.20	2.37	0.13
Ca	HIF-1a	0.16	0.03	22254.97	818922.35	5.19	0.02
Fe	HIF-1a	0.15	0.02	18587.39	822589.93	4.32	0.04
SL group							
Zn	HIF-1a	0.24	0.06	143947.88	2272238.74	6.02	0.02
Ca	HIF-1a	0.04	0.00	4090.33	2412096.29	0.16	0.69
Fe	HIF-1a	0.26	0.07	167212.23	2248974.39	7.06	0.01
SH group							
Zn	HIF-1a	0.30	0.09	63277.64	632194.39	9.11	0.00
Ca	HIF-1a	0.10	0.01	6688.48	688783.54	0.88	0.35
Fe	HIF-1a	0.19	0.04	24832.60	670639.42	3.37	0.07
XH group							
Zn	HIF-1a	0.08	0.01	43.45	6374.95	0.63	0.43
Ca	HIF-1a	0.06	0.00	25.23	6393.17	0.37	0.55
Fe	HIF-1a	0.23	0.05	329.56	6088.84	5.03	0.03
XZ group							
Zn	HIF-1a	0.04	0.00	1529.28	771904.64	0.19	0.66
Ca	HIF-1a	0.07	0.00	3503.11	769930.80	0.44	0.51
Fe	HIF-1a	0.14	0.02	14645.65	758788.26	1.85	0.18

SL, Sanya Li ethnic group; SH, Sanya Han ethnic group; XH, Xining Han ethnic group; XZ, Xining Tibetan ethnic group; HIF-1α, hypoxia-inducible factor 1-alpha.

under low oxygen conditions, promoting the expression of a series of genes to help cells adapt to low oxygen pressure (39). Research indicates that zinc can affect the activity of HIF-1α in multiple ways, including its stability and transcriptional activity. This suggests that the content and homeostasis of zinc in cells are crucial for maintaining the normal function of HIF-1α (38). Therefore, zinc plays an important role in regulating the HIF-1α signaling pathway, which is significant for cellular adaptation to low oxygen environments (40). Our study also found significant differences in the levels of Zn among different altitudes and ethnicities, with higher serum concentrations of Zn observed in high-altitude areas. Additionally, linear regression analysis revealed a linear correlation between Zn and HIF-1α, suggesting that Zn may be closely associated with the occurrence and development of high-altitude illness.

Ca plays an important role in the human body. It is not only a major component of bones and teeth, but also participates in many biological processes, including nerve transmission, muscle contraction, cell signaling, and blood clotting (20). In addition, calcium also plays a crucial role in maintaining the stability and permeability of cell membranes, which is essential for normal cell function (41). Calcium ions (Ca^{2+}) can affect the HIF-1α signaling pathway through multiple pathways. Firstly, calcium ions can influence the activity of HIF-1α by regulating its stability. Studies have shown that changes in calcium ion concentration can affect the protein degradation rate of HIF-1α, thereby regulating its level in

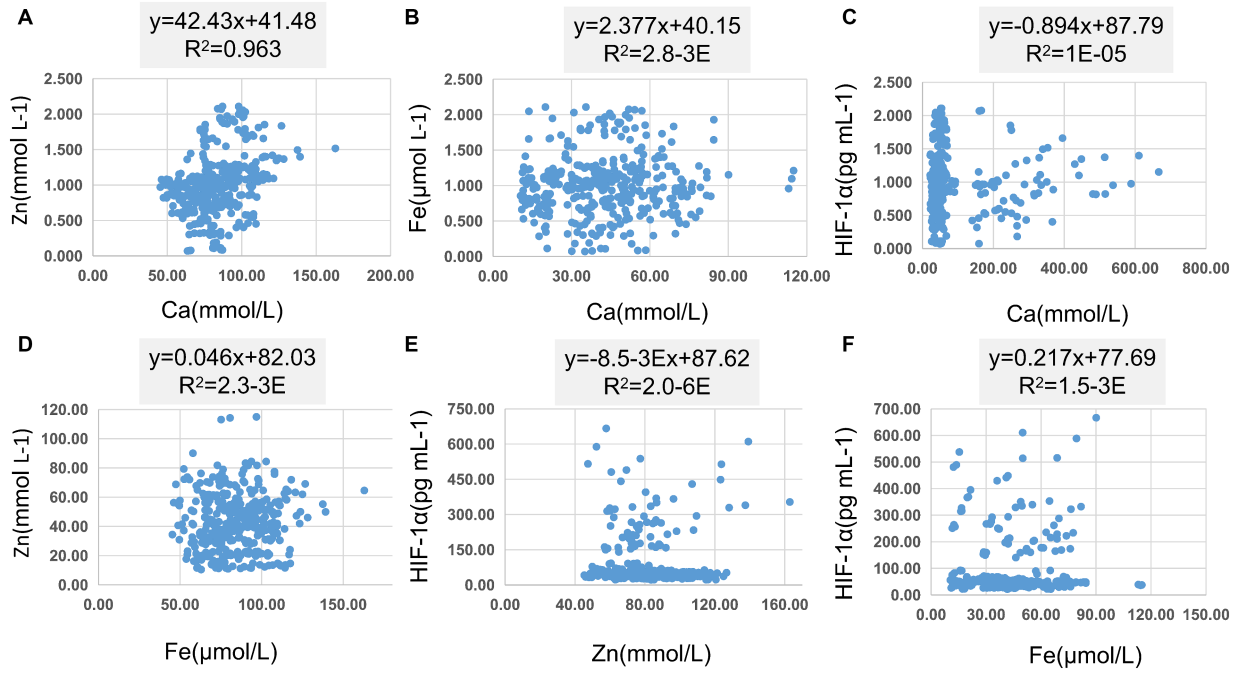

FIGURE 3
Scatter plot of linear regression between common elements (Zn, Fe, Ca) and HIF-1α. **(A)** Scatter plot of linear regression between Zn and Ca. **(B)** Scatter plot of linear regression between Fe and Ca. **(C)** Scatter plot of linear regression between HIF-1α and Ca. **(D)** Scatter plot of linear regression between Zn and Fe. **(E)** Scatter plot of linear regression between HIF-1α and Zn. **(F)** Scatter plot of linear regression between HIF-1α and Fe.

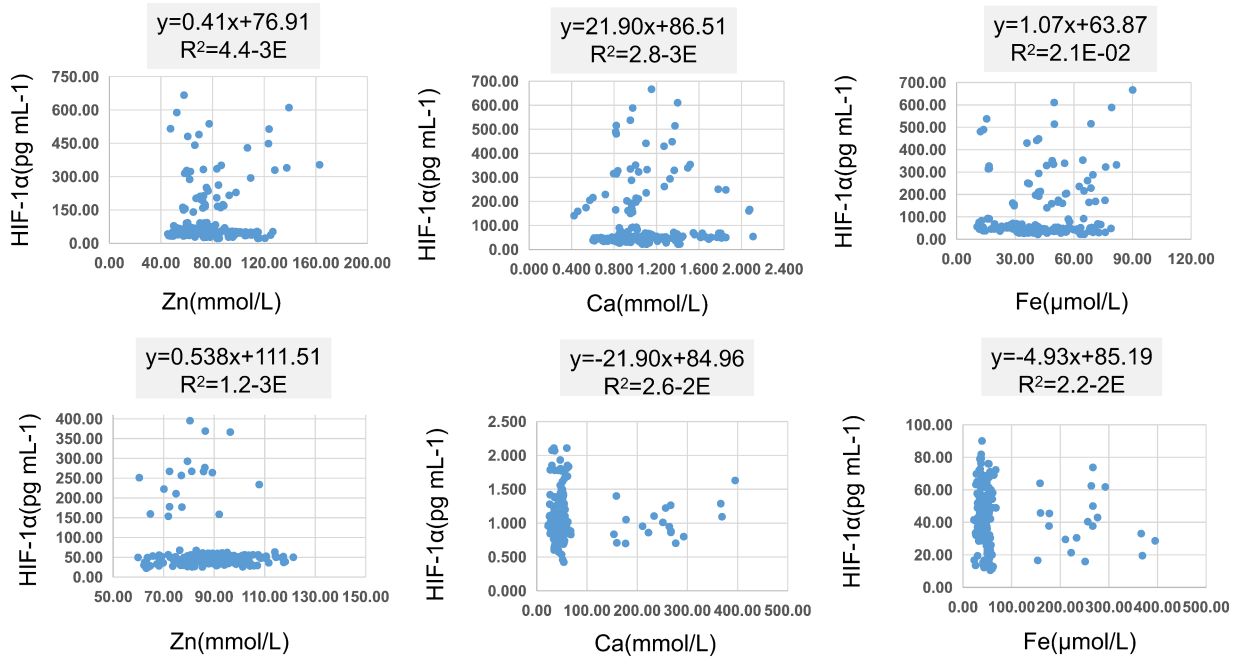

FIGURE 4
Scatter plot of linear regression between HIF-1α and common elements (Zn, Fe, Ca) in different altitudes. **(A)** Scatter plot of linear regression between HIF-1α and Zn in low-altitude areas. **(B)** Scatter plot of linear regression between HIF-1α and Ca in low-altitude areas. **(C)** Scatter plot of linear regression between HIF-1α and Fe in low-altitude areas. **(D)** Scatter plot of linear regression between HIF-1α and Zn in high-altitude areas. **(E)** Scatter plot of linear regression between HIF-1α and Ca in high-altitude areas. **(F)** Scatter plot of linear regression between HIF-1α and Fe in high-altitude areas.

cells (42). Secondly, calcium ions can also affect the function of HIF-1α by regulating its transcriptional activity. Calcium ions regulate the activity of transcription factors or co-activators associated with HIF-1α, affecting the gene transcription process

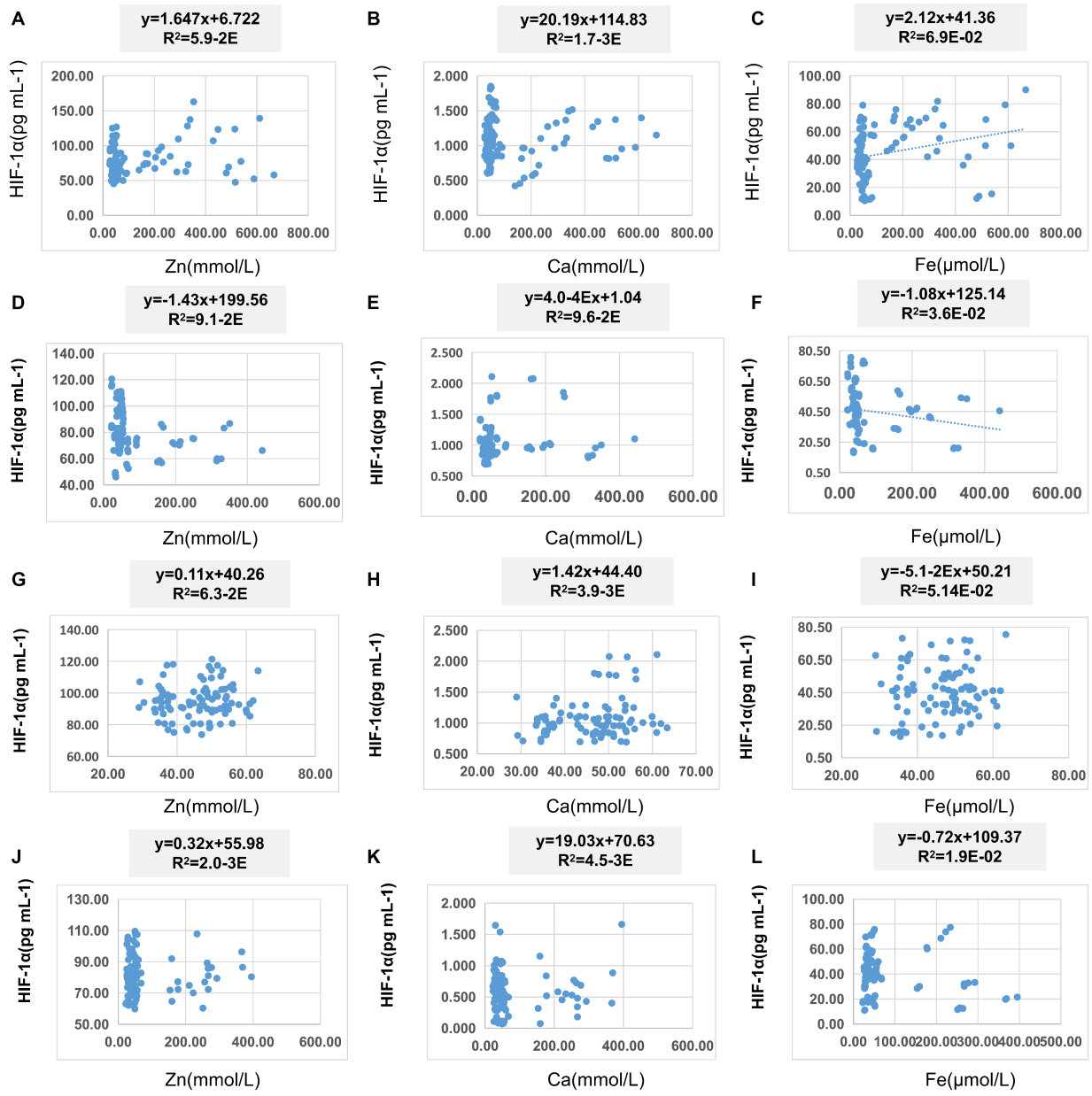

FIGURE 5
Scatter plot of linear regression between HIF-1α and common elements (Zn, Fe, Ca) in different ethnic groups. **(A)** Scatter plot of linear regression between HIF-1α and Zn in Sanya Li ethnic group. **(B)** Scatter plot of linear regression between HIF-1α and Ca in Sanya Li ethnic group. **(C)** Scatter plot of linear regression between HIF-1α and Fe in Sanya Li ethnic group. **(D)** Scatter plot of linear regression between HIF-1α and Zn in Sanya Han ethnic group. **(E)** Scatter plot of linear regression between HIF-1α and Ca in Sanya Han ethnic group. **(F)** Scatter plot of linear regression between HIF-1α and Fe in Sanya Han ethnic group. **(G)** Scatter plot of linear regression between HIF-1α and Zn in Xining Han ethnic group. **(H)** Scatter plot of linear regression between HIF-1α and Ca in Xining Han ethnic group. **(I)** Scatter plot of linear regression between HIF-1α and Fe in Xining Han ethnic group. **(J)** Scatter plot of linear regression between HIF-1α and Zn in Xining Tibetan ethnic group. **(K)** Scatter plot of linear regression between HIF-1α and Ca in Xining Tibetan ethnic group. **(L)** Scatter plot of linear regression between HIF-1α and Fe in Xining Tibetan ethnic group.

mediated by HIF-1α (43). These mechanisms make calcium ions play an important role in regulating the ability of cells to adapt to low oxygen environments, thereby affecting cell survival and function (44). Our research has found significant differences in calcium levels among different altitudes and ethnic groups, and there is a significant linear correlation between zinc and calcium. However, further exploration may be needed to understand the involvement of calcium in the pathogenesis of high-altitude illness.

The current study demonstrates several notable strengths. Firstly, a comprehensive analysis was conducted on four ethnic groups residing at two distinct altitudes. The Li nationality, with a population of approximately 1.6 million, has been established on Hainan Island for generations, residing at an average altitude of 3–120 m. Meanwhile, Tibetans, totaling about 4.6 million, have inhabited Qinghai, Tibet, and other plateau regions for centuries, with an average altitude of approximately 4,000 m. Secondly, rigorous measures were implemented

TABLE 9 Multiple linear regression between HIF-1α and common elements (Zn, Fe, Ca).

Variable	Person analysis	Model		ANOVA			Coefficients		Collinearity Statistics		
X	*r*	*R*	*R2*	Regression	*F* value	*p*-value	*B*	Std. Error	Tolerance	VIF	Condition index
Overall											
Zn	−0.02	0.05	0.00	9297.41	0.27	0.84	−0.16	0.32	0.89	1.12	4.97
Ca	0.00	0.05	0.00	9297.41	0.27	0.84	0.80	13.74	0.89	1.12	6.90
Fe	0.04	0.05	0.00	9297.41	0.27	0.84	0.23	0.29	0.99	1.01	13.20
Low altitude areas											
Zn	0.07	0.16	0.03	87265.51	1.71	0.17	0.26	0.49	0.85	1.18	5.25
Ca	0.05	0.16	0.03	87265.51	1.71	0.17	19.02	32.34	0.84	1.19	9.24
Fe	0.15	0.16	0.03	87265.51	1.71	0.17	1.08	0.53	0.99	1.01	11.52
High altitude areas											
Zn	−0.11	0.21	0.04	37626.30	2.95	0.03	−0.19	0.38	0.81	1.23	4.60
Ca	−0.16	0.21	0.04	37626.30	2.95	0.03	−17.61	10.61	0.82	1.23	5.94
Fe	−0.15	0.21	0.04	37626.30	2.95	0.03	−0.43	0.24	0.98	1.02	18.66
SL group											
Zn	0.24	0.35	0.12	292325.99	4.27	0.01	1.90	0.84	0.62	1.62	5.08
Ca	0.04	0.35	0.12	292325.99	4.27	0.01	−57.13	60.19	0.63	1.59	9.78
Fe	0.26	0.35	0.12	292325.99	4.27	0.01	1.75	0.80	0.95	1.05	11.05
SH group											
Zn	−0.30	0.39	0.16	107806.84	5.44	0.00	−1.61	0.47	0.98	1.02	0.12
Ca	0.10	0.39	0.16	107806.84	5.44	0.00	32.04	26.98	0.98	1.02	0.06
Fe	−0.19	0.39	0.16	107806.84	5.44	0.00	−1.21	0.55	0.98	1.02	0.02
XH group											
Zn	0.08	0.24	0.06	359.93	1.80	0.15	0.03	0.08	0.96	1.04	0.16
Ca	0.06	0.24	0.06	359.93	1.80	0.15	1.10	2.33	0.98	1.02	0.05
Fe	−0.23	0.24	0.06	359.93	1.80	0.15	−0.08	0.04	0.98	1.02	0.01
XZ group											
Zn	0.04	0.17	0.03	21883.55	0.91	0.44	0.54	0.75	0.96	1.05	0.21
Ca	0.07	0.17	0.03	21883.55	0.91	0.44	1.54	1.75	1.00	1.00	0.09
Fe	−0.14	0.17	0.03	21883.55	0.91	0.44	2.54	2.75	0.96	1.05	0.01

SL, Sanya Li ethnic group; SH, Sanya Han ethnic group; XH, Xining Han ethnic group; XZ, Xining Tibetan ethnic group; HIF-1α, hypoxia-inducible factor 1-alpha.

to mitigate potential confounding variables. Given the influence of gender, age, and health conditions on serum elements and HIF-1α content, stringent entry criteria were enforced, restricting participation to men who had resided in a specific area for over 3 years, had not traveled to different locations in the 6 months prior to sampling, were aged 18–45 and free from physical discomfort. Additionally, all participants exhibited good physical condition, maintained a balanced diet, normal digestion, regular bowel movements, and a healthy lifestyle, and had not recently suffered from chronic or debilitating illnesses or taken medication, thereby minimizing result deviation. Thirdly, robust statistical analyses were employed, encompassing sample size estimation, repeated experiments, subgroup analysis, linear regression analysis, and thorough validation of results. Nevertheless, our study is subject to certain inherent limitations. Firstly, the study design was based on a cohort study, resulting in a relatively low level of evidence. Secondly, some analytical processes did not undergo further exploration through nonlinear analysis. Lastly, the study solely revealed the correlation between common elements and HIF-1α, without delving into causality and specific mechanisms. It would be beneficial to consider conducting more extensive longitudinal studies to establish causal relationships and explore the underlying mechanisms between common elements and HIF-1α. Additionally, incorporating nonlinear analytical methods could provide further insights into the complex interactions observed in our study.

5 Conclusion

In summary, this research identified variations in the concentrations of common elements (e.g., zinc, calcium, and iron) as well as HIF-1α in the serum across diverse altitudes and ethnicities. These variances may be associated with the onset of high-altitude

sickness. Through a comprehensive examination of the associations between ethnicity, altitude, and other sociobiological factors on trace element levels, this study provides valuable insights into the nutritional status across different populations. Nevertheless, further investigation is warranted to elucidate the causal correlation and specific mechanisms linking elements to high-altitude illness.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Hainan Hospital of the General Hospital of the People's Liberation Army and Qinghai Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YG: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing. Z-SL: Conceptualization, Formal analysis, Resources, Writing – review & editing. X-CZ: Conceptualization, Formal analysis, Resources, Writing – review & editing. QZ: Conceptualization, Data curation, Project administration, Visualization, Writing – original draft, Writing – review & editing. XL: Data curation, Investigation, Resources, Validation, Writing – original draft. JC: Investigation, Methodology, Project administration, Visualization, Writing – original draft. M-LZ: Data curation, Project administration, Resources, Software, Writing – original draft.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1433640/full#supplementary-material

SUPPLEMENTARY FIGURE S1
The map of Xining and Sanya, as well as information on different ethnic groups. Xining, the capital of Qing Province, is located on the northeastern edge of the Tibetan Plateau, at an altitude of approximately 2,275 meters, with cold semi-arid climate. Sanya is a coastal city at the southern tip of Hainan Island in China, with an average altitude of 7 meters. It was selected for a low-altitude comparison with Xining, known for its warm and humid tropical monsoon climate throughout the year.

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Association between copper intake and essential hypertension: dual evidence from Mendelian randomization analysis and the NHANES database

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Background: Although previous studies have identified an association between trace elements and essential hypertension, the specific trace elements involved and the mechanisms of their association remain unclear. This study aimed to elucidate the relationship between various human trace elements and essential hypertension, thereby addressing existing gaps in the research.

Methods: This study employed two-sample, multivariate, and inverse Mendelian randomization (MR) analyses to investigate the causal relationship between 15 human trace elements as exposure factors and essential hypertension as the outcome. The analysis revealed a statistically significant association between copper intake and essential hypertension. Further validation was conducted using logistic regression models based on data from the National Health and Nutrition Examination Survey (NHANES).

Results: Eighteen trace elements were initially identified through searches in the GWAS database and PubMed. After screening, 15 trace elements were selected as potential exposure factors. MR analysis, utilizing the 2021 genome-wide dataset for essential hypertension, identified copper as a risk factor, showing a positive association with hypertension. Subsequent logistic regression analyses based on NHANES data further confirmed a significant association between dietary copper intake and the risk of essential hypertension, except for the 0.80–1.08 mg/d group in model 3 ($p < 0.05$). Restricted cubic spline (RCS) analysis indicated a nonlinear relationship between copper intake and the risk of developing essential hypertension.

Conclusion: This study demonstrates a significant association between copper intake and the development of essential hypertension. The findings suggest that higher copper intake is linked to an increased risk of hypertension, underscoring the need to monitor copper intake levels in the prevention and management of this condition.

KEYWORDS

copper intake, essential hypertension, Mendelian Randomization, National Health and Nutritional Examination Survey, trace elements

1 Introduction

Essential hypertension is a cardiovascular disease characterized by elevated arterial pressure within the systemic circulation. Persistent hypertension can lead to significant damage to target organs, including blood vessels, the heart, brain, kidneys, and retina, ultimately resulting in severe cardiovascular and cerebrovascular events such as congestive heart failure, stroke, and chronic renal failure. It is a major contributor to mortality from cardiovascular and cerebrovascular diseases (1). Recent surveys indicate that the global prevalence of hypertension is rising steadily, with an increasingly younger age of onset, posing a significant societal burden (2–4). Despite extensive research, the etiology and pathogenesis of hypertension, particularly essential hypertension, remain incompletely understood (5, 6). Consequently, identifying the pathogenic factors underlying essential hypertension is crucial for its prevention and treatment.

Trace elements, although present in the human body in minute quantities (typically less than 0.01% of body weight) are vital for maintaining normal physiological functions and overall health. These elements play essential roles in enzyme catalysis, hormone synthesis and secretion, antioxidant defense, DNA synthesis and repair, and cell signaling (7, 8). Recent studies have increasingly linked trace elements to the development of various diseases, including essential hypertension. For instance, selenium, a key antioxidant, is involved in protecting the cardiovascular system from oxidative stress and may contribute to cardiovascular disease prevention (9). Zinc is implicated in blood pressure regulation through its effects on immune function and angiotensin-converting enzyme activity (10, 11). Organic germanium has been observed to exert a sustained hypotensive effect, effectively reducing both systolic and diastolic blood pressure and alleviating hypertension symptoms (12). Copper, similarly, has been associated with blood pressure regulation, influencing it through its role in norepinephrine synthesis (13, 14). Several other trace elements have also been found to have associations with essential hypertension (15, 16).

The Mendelian randomization (MR) method is a powerful tool for evaluating potential causal relationships between risk factors and diseases. This approach uses genetic variation as an instrumental variable to assess the impact of specific risk factors. Since genotypes are randomly assigned at conception, the observed genetic variations are free from confounding factors such as environmental exposures and are unaffected by disease onset. In this study, a two-sample, multivariate, inverse Mendelian randomization analysis was conducted using 15 micronutrients as exposures and essential hypertension as the outcome. The findings revealed a positive association between copper, one of the micronutrients, and essential hypertension. To further investigate this relationship, we conducted a detailed clinical data analysis using the National Health and Nutrition Examination Survey (NHANES) database, aiming to clarify both the quantitative and qualitative relationships between dietary copper intake and essential hypertension.

2 Materials and methods

2.1 Data sources for Mendelian randomization

2.1.1 Genetic epidemiologic data on micronutrients

This study searched the Genome-Wide Association Studies (GWAS) catalog[1] and Pubmed[2] (last checked April 2024) for published data on mineral and vitamin circulating concentrations in published GWAS data. A total of 18 trace minerals were retrieved, including Copper, Calcium, Carotene, Folate, Iron, Magnesium, Potassium, Selenium, Retinol, Vitamin A, Vitamin B1, Vitamin B2, Vitamin B6, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, and Zinc. of these, Vitamin B1 and Vitamin B2 were excluded because genome-wide significant results were not reported or GWAS studies were not performed. Retinol was also excluded because its data were adjusted for body mass index (BMI) which could lead to biased Mendelian randomization (MR) estimates. GWAS data for 15 micronutrients were finally screened for Copper (ieu-a-1073), Calcium (ukb-b-8951), Carotene (ukb-b-16202), Folate (ukb-b-11349), and Iron (ukb-b-20447), Magnesium (ukb-b-7372), Potassium (ukb-b-17881), Selenium (ieu-a-1077), Vitamin A (ukb-b-9596), Vitamin B12 (ukb-b-19524), Vitamin B6 (ukb-b- 7864), Vitamin C (ukb-b-19390), Vitamin D (ukb-b-18593), Vitamin E (ukb-b-6888), and Zinc (ieu-a-1079). These data were used as exposure factors in a subsequent two-sample Mendelian randomization study.

2.1.2 Genetic epidemiologic data on essential hypertension

We searched the FinnGen Research Program (FINNGEN)[3] database for genetic epidemiology data on essential hypertension. Considering sample size, sequencing depth, ethnicity, and data update time, we selected a genome-wide genetic dataset on essential hypertension uploaded in 2023[4]. This dataset included 102,864 cases and 289,117 control individuals, totaling 16,380,466 SNPs. All studies included in FINNGEN were approved by the relevant ethical review boards and participants provided informed consent. The current study used only publicly available summary-level data and therefore did not require additional ethical review.

2.2 Mendelian randomization analysis

2.2.1 Removal of weak instrumental variables

To satisfy the association assumption, SNPs had to be strongly correlated with exposure factors, and to ensure independence among SNPs and to remove result bias due to chain imbalance. In this study, SNP data were screened by R software, and the filtering criteria were

1 https://www.ebi.ac.uk/gwas
2 https://www.ncbi.nlm.nih.gov/pubmed
3 https://r10.finngen.fi/
4 https://risteys.finregistry.fi/endpoints/I9_HYPTENSESS

(1) SNPs included in the instrumental variables were correlated with exposure factors ($p < 1 \times 10^{-5}$), and due to the fact that the number of SNPs that could reach the genome-wide significance level ($p < 5 \times 10^{-8}$) of the SNPs are fewer in number, a single or very small number of SNPs may not capture enough genetic variation, so using a looser p-value threshold increases the number of SNPs available for MR analyses and enhances the overall instrumental variable strength; (2) exclude SNPs that have an $R^2 > 0.001$ with the most significant SNP in the 10,000 kb range, with R^2 being the proportion of the variability in the risk factors explained by the SNPs, $R^2 = 2 \times (1 - \text{MAF}) \times \text{MAF} \times (\beta_1/\text{SD})^2$, where MAF is the minor allele frequency of exposure, β_1 is the allele effect value of exposure, and SD is the standard deviation; (3) SNPs with an F-statistic >10, $F = (N-2) \times R^2/(1-R^2)$, and N is the sample size to obtain SNPs that were strongly correlated with the exposure factors and were independent of each other as effective Instrumental variables. To ensure that each instrumental variable was associated with the same effector allele, this study harmonized the summary statistics and eliminated palindromic SNPs (17).

2.2.2 Two-sample Mendelian randomization analysis

Instrumental variable data for the outcome were obtained using R, and effect sizes were combined. The exposure and outcome data were then preprocessed to ensure consistent formatting. Subsequently, two-sample Mendelian randomization (MR) analyses were conducted to assess the causal relationship between the exposure factor and the outcome variable, using odds ratios (OR) as the measure of association. The inverse variance weighted (IVW) method, a commonly used statistical approach in two-sample MR analysis, was employed. This method is characterized by excluding the intercept term in the regression and using the inverse of the outcome variance as the weighting factor. The reliability of IVW results depends on the absence of heterogeneity and horizontal pleiotropy in the instrumental variables (18). Additionally, the MR-Egger method was utilized, as it can provide valid estimates even in the presence of horizontal pleiotropy among instrumental variables. The weighted median method was also applied, offering the advantage of producing reliable MR estimates as long as more than half of the instrumental variables are valid. This method allows for the inference of causal relationships based on the majority of valid instrumental variables (19). When heterogeneity is present without horizontal pleiotropy, the weighted model approach is preferred, and the IVW random effects model can be employed. Conversely, the simple model approach can be used as a methodological complement to assess the robustness of MR analysis results.

2.2.3 Sensitivity analysis

To ensure the reliability of the causal effect assessment, sensitivity analyses were conducted. The robustness of the causal findings was evaluated using the leave-one-out method, which tests the influence of each instrumental variable on the overall results. If excluding a particular instrumental variable significantly alters the overall results, it suggests that this variable may be a key component in the MR analysis or that there may be issues such as genetic bias. Heterogeneity tests were also performed as part of the two-sample MR analyses to determine whether there were differences among the instrumental variables. Cochran's Q test was employed to assess heterogeneity; a p-value greater than 0.05 indicates the absence of heterogeneity, whereas a p-value less than 0.05 suggests its presence. Furthermore, the presence of horizontal pleiotropy was evaluated, which occurs when instrumental variables directly affect the outcome variables independently of the exposure factor, thereby violating the exclusivity assumption of MR. If horizontal pleiotropy is detected in the MR analysis results, it indicates that the findings may not be reliable (20).

2.2.4 Multivariate Mendelian randomization analysis

As an extension of two-sample MR, multivariate MR can be employed to estimate the collective causal effects of multiple risk factors on essential hypertension. By incorporating all exposures into a single model, multivariate MR allows for the assessment of the independent direct effects of individual micronutrients on essential hypertension, free from mediation by other exposure factors. In this study, we identified SNPs that were significantly associated with the exposures of interest and combined them with existing instrumental variables. After removing duplicate SNPs, we calculated the effect size and corresponding standard error for each SNP from both the exposure and outcome datasets. The inverse variance weighted (IVW) method, based on weighted linear regression, was then applied to infer causality in the multivariate MR analyses (21).

2.2.5 Reverse Mendelian randomization analysis

Reverse Mendelian randomization is a method used to assess causal relationships by treating disease states as exposure variables and potential risk factors as outcome variables. This approach is particularly effective in investigating scenarios where reverse causality may be present—situations in which the disease could influence the exposure factor. In this study, essential hypertension was used as the exposure variable, while the trace elements identified through Mendelian randomization, as previously described, served as the outcome variables. A reverse Mendelian randomization analysis was then conducted to explore and confirm the potential reverse causality between trace elements and essential hypertension. Figure 1A illustrates the schematic diagram and workflow of the Mendelian randomization study.

2.3 Analysis of the NHANES database

2.3.1 Sources of information and study populations

The National Health and Nutrition Examination Survey (NHANES) is an ongoing, large-scale, representative, national survey of health and nutrition status conducted by the National Center for Health Statistics (NCHS), a division of the Centers for Disease Control and Prevention (CDC) (22). The protocol for NHANES was approved by the NCHS Research Ethics Review Board (23), and informed written consent was obtained from all participants; therefore, ethical approval for this study was waived. A total of 59,842 participants were surveyed in this cross-sectional study that included data from six cycles from 2007–2018, and the detailed NHANES study design and data are publicly available on the[5] website.

5 https://www.cdc.gov/nchs/nhanes/index.Htm

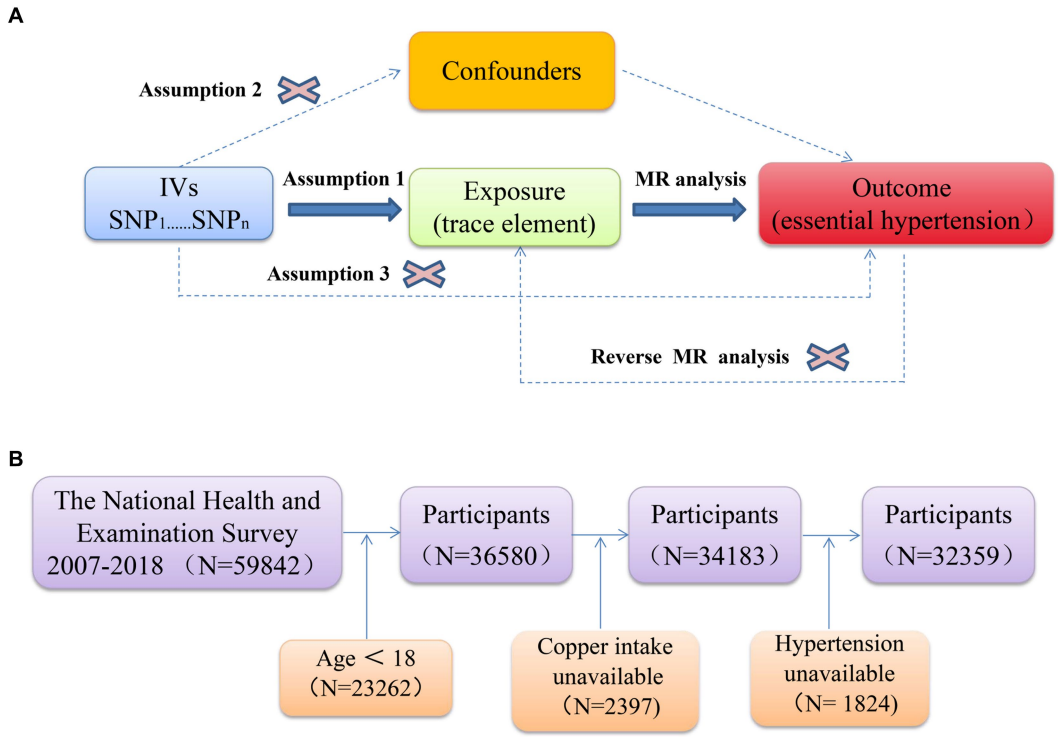

FIGURE 1
(A) Schematic of Mendelian randomization; **(B)** flowchart depicting the participants' selection.

2.3.2 Definitions of copper intake

Data on dietary copper were extracted from the "Dietary Interview—Total Nutrient Intakes, First Day," "Dietary Interview—Total Nutrient Intakes, Second Day," and "Dietary Supplement Use 30-Day—Total Dietary Supplements" datasets within the Dietary Data module. To ensure data completeness, the average dietary copper intake from Day 1 and Day 2 was calculated and combined with the amount of dietary copper from supplements to obtain the total dietary copper intake. This approach assumed that data were not missing for either day. If copper intake data were available only for Day 1 or Day 2, the intake for that day was combined with the dietary supplement data to estimate total copper intake. Following the Joint FAO/WHO Expert Committee on Food Additives (JECFA) guidelines, which set the upper limit (UL) of copper intake for adults at 10 mg/day, any data indicating a copper intake greater than 20 mg/day were excluded to avoid the influence of extreme values.

2.3.3 Essential hypertension ascertainment

The diagnosis of essential hypertension requires a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg, measured on three separate occasions on the same day, without the use of antihypertensive medication. Blood pressure data from the NHANES database were obtained from three consecutive measurements taken on the same day. To identify individuals with hypertension, we utilized responses to the question "BPQ 020" ("Have you ever been told you have high blood pressure?"), as previous studies have demonstrated a strong correlation between self-reported hypertension and clinical confirmation. Additional health conditions were identified using relevant questions from the NHANES database (24). For instance, sleep apnea syndrome was diagnosed using the question "How often do you snort/stop breathing?" Thyroid disease was identified through the question "Do you still have a thyroid problem?" and kidney disease was diagnosed with "Ever told you had weak/failing kidneys?" Family history of hypertension or stroke was determined using the question "Blood relatives w/hypertension/stroke. "Heart valve disease was diagnosed based on the question "Had heart valve problem?" and chronic obstructive pulmonary disease (COPD) was identified with the question "Ever told you had COPD?" Pregnancy-related hypertension was assessed using the pregnancy test results in the laboratory panel, and current use of painkillers, hormones, and contraceptives was determined by questions such as "Ever taken prednisone or cortisone daily?," "Drugs injected - Steroids," and "Taking estrogen/progestin now?" Individuals with a diagnosis suggestive of secondary hypertension were excluded, resulting in a final cohort of participants with essential hypertension.

2.3.4 Assessment of covariates

The study collected data on various demographic, socioeconomic, and health-related variables, including age, gender, ethnicity, education level, marital status, household poverty-to-income ratio, smoking status, alcohol consumption, physical activity, and disease status (e.g., diabetes, cardiovascular health, high cholesterol levels, sleep disorders, and mental health). This information was gathered through standardized questionnaires. Additionally, participants' body weight and body mass index (BMI, kg/m^2) were measured at a mobile health check-up center and included as covariates in the analysis.

Age, weight, BMI, and household poverty-to-income ratio were treated as continuous variables, while ethnicity, education level,

marital status, smoking status, alcohol consumption, physical activity, and disease status (e. g. diabetes, cardiovascular health, high cholesterol levels, and sleep disorders) were categorized as categorical variables. Ethnicity was classified as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other races. Education level was categorized into less than high school, high school or equivalent, and college or above. Alcohol consumption was defined as consuming ≥4 drinks per day, and smoking status was determined by whether participants had smoked more than 100 cigarettes in their lifetime. Marital status was classified as living with a partner or living alone, and physical activity was assessed by asking, "In a typical week, do you do any moderate-intensity exercise?" Self-reported disease status, including cardiovascular and other conditions, was obtained through personal interviews using standardized medical condition questionnaires, such as "Have you ever been told you have a sleep disorder?," "Have you ever been told you have diabetes?," and "Have you ever been told you have high cholesterol levels?" Participants answered these questions with "yes" or "no." Previous research has shown a good correlation between self-reported conditions and clinical diagnoses (25). Further details regarding the covariates are available on the NHANES website.

2.3.5 Statistical analysis

Data from this study were analyzed following CDC guidelines. Participant characteristics were presented as means with 95% confidence intervals (CIs) for continuous variables and as counts with percentages for categorical variables. Baseline characteristics between groups were compared using analysis of variance (ANOVA) for normally distributed continuous data, the chi-square test for categorical variables, and the Kruskal–Wallis H test for non-normally distributed continuous data. The U. S. Institute of Medicine (IOM) of the National Academy of Sciences provides a Recommended Dietary Allowance (RDA) for copper, which is 0.9 mg/day for adults (26). Based on quartiles of dietary copper intake, the study population was divided into five groups: <0.80 mg/d, 0.80–1.08 mg/d, 1.08–1.45 mg/d, 1.45–2.29 mg/d, and >2.29 mg/d. Baseline characteristics were plotted accordingly. To enhance data visualization, forest plots were created for dichotomous variables, using a dietary copper intake of 0.8 mg/d as the cut-off, and subgroup analyses were conducted for covariates.

Logistic regression was then employed to examine the association between dietary copper intake and the development of hypertensive disorders, adjusting for potential confounders. Odds ratios (ORs) and their 95%CIs were calculated to assess the relationship between dietary copper intake and hypertensive outcomes, with four models being constructed: Model 1 was unadjusted; Model 2 adjusted for age, sex, race, education level, and marital status; Model 3 further adjusted for household poverty-to-income ratio (PIR), alcohol intake, smoking status, body mass index (BMI), and physical activity; and Model 4 additionally adjusted for hypercholesterolemia, diabetes cardiovascular disease, and sleep disorders. The group with the lowest copper intake served as the reference group in all models.

Finally, the non-linear relationship between copper intake and essential hypertension was analyzed using a restricted cubic spline (RCS) with three knots at the 10th, 50th, and 90th percentiles. All statistical analyses were performed using SPSS Statistics version 26 and R version 4.3.2. Statistical significance was determined by a two-sided test, with $p < 0.05$ indicating a statistically significant difference. Figure 1B illustrates the study flow for the NHANES analysis.

3 Results

3.1 Instrumental variable filtering results

The results of Mendelian randomization between 15 trace elements and essential hypertension were visualized based on the IVW method, as shown in Figure 2A. Two micronutrients were screened out from the 15 micronutrients that were associated with essential hypertension ($p < 0.05$), Copper (6 SNPs) and Potassium (13 SNPs). A total of 181 SNPs were included in the analyses, all of which had F values >10.

3.2 Results of the MR analysis

The results of MR analysis showed that Copper and Potassium were significantly associated with essential hypertension. The results of the analyses for Copper were MR-Egger $\beta = 0.032$, $p = 0.049$; IVW $\beta = 0.024$, $p = 0.003$, indicating that when Copper was used as an exposure factor, the composite effect value β was greater than 0, suggesting that it is a risk factor for essential hypertension, and the risk of developing the outcome increased with increased exposure. Potassium the results of the analyses were MR-Egger $\beta = -0.081$, $p = 0.704$; IVW $\beta = -0.152$, $p = 0.038$, indicating that when Potassium was used as an exposure factor, the composite effect values β were all less than 0, suggesting that it is a protective factor and that the risk of developing the outcome decreases with increasing exposure. Copper and Potassium and Essential Hypertension the Mendelian randomised forest plot of Copper and Potassium is shown in Figure 2B.

3.3 Effect of exposure factors on outcome variables

The MR analysis results of the 2 micronutrients that showed a causal effect of exposure and outcome were visualized concerning the MR analysis results of essential hypertension. As shown by the scatter plot (Figures 3A,B), the black dots were distributed in a concentrated manner, suggesting a causal relationship between exposure and outcome, and the overall direction of the lines obtained by different methods was consistent. The slopes of the lines corresponding to Copper were all >0, indicating a positive correlation between exposure and outcome, while the slopes of the lines corresponding to Potassium were all <0, indicating a negative correlation between exposure and outcome. Based on the IVW method, the OR of Copper [OR = 1.024, 95%CI (1.008, 1.041), $p = 0.003$] was greater than 1, indicating that it was a risk factor, and the OR of Potassium [OR = 0.085, 95%CI (0.743, 0.092), $p = 0.039$] was less than 1, indicating that it was a protective factor.

3.4 Results of sensitivity analysis

3.4.1 Heterogeneity test

Instrumental variables were tested for heterogeneity using MR-Egger and IVW methods. Copper (MR-Egger $Q = 1.349$, $p = 0.852$; IVW $Q = 2.305$, $p = 0.805$) and Potassium (MR-Egger $Q = 13.924$, $p = 0.237$; IVW $Q = 14.096$, $p = 0.294$) had p-values >0.05, indicating that there was no heterogeneity in the SNPs of the instrumental variables.

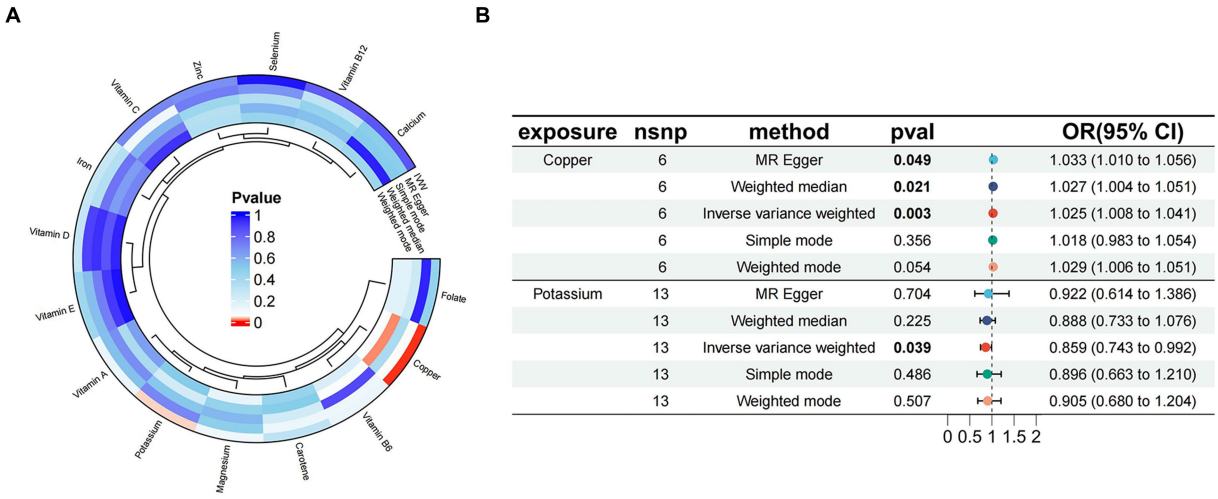

FIGURE 2
(A) Circle plot visualizing the results of Mendelian randomization between 15 micronutrients and essential hypertension; **(B)** Mendelian randomized forest plot of copper, potassium, and essential hypertension.

3.4.2 Horizontal multiple validity test

Horizontal multiple validity test of instrumental variables using both MR-Egger intercept test and MR-PRESSO global test showed that Copper (intercept tended to be 0; RSSobs = 0.631, $p = 0.704$), Potassium (intercept tended to be 0; RSSobs = 16.760, $p = 0.291$), and the results obtained by The intercept terms obtained by MR-Egger intercept test converged to 0 and p-value >0.05, while the p-values obtained by the MR-PRESSO global test were all >0.05, suggesting that there is no horizontal multiplicity in the instrumental variables of the exposure factors.

3.4.3 Leave-one-out test

When any one SNP was removed and the MR analysis was repeated, no significant difference in overall causality was found, indicating that the results were not due to a single SNP. As shown in Figures 3C,D.

3.5 Multivariate Mendelian randomisation

Multivariate MR analyses were performed separately to correct for the interaction between various micronutrients and essential hypertension. The results showed that Potassium was not a protective factor for essential hypertension (OR = 0.798, 95%CI: 0.067–1.049, $p = 0.105$), while Copper remained a risk factor for essential hypertension (OR = 1.025, 95%CI:1.008–1.449, $p = 0.003$).

3.6 Reverse MR analysis

The results for MR Egger, Weighted Median Estimator, IVW, Simple Mode, and Weighted Mode were (OR = 1.090, 95%CI: 0.911–1.303, $p = 0.416$), (OR = 1.018, 95%CI:0.990–1.046, $p = 0.219$), (OR = 1.006, 95%CI: 0.971–1.042, $p = 0.757$), (OR = 1.025, 95%CI: 0.992–1.060, $p = 0.215$), (OR = 1.020, 95%CI: 0.990–1.052, $p = 0.264$). The p-values of the above 5 research results are all greater than 0.05, the results suggest that essential hypertension is not a causal factor for copper intake and there is no significant causal relationship between the two.

3.7 Baseline characteristics of study participants

After the exclusion of age less than 18 years, invalid dietary copper intake data, and hypertension data, 32,359 subjects were finally included in this study. Five observation groups (<0.8 mg/d, 0.80–1.08 mg/d, 1.08–1.45 mg/d, 1.45–2.29 mg/d, >2.29 mg/d) were divided according to dietary copper intake and a table of baseline characteristics of the population was produced (Table 1). The results showed a higher proportion of females in the lower copper intake group compared to the normal copper intake group ($p < 0.001$), with a decreasing proportion of the female population as copper intake increased; the lower copper intake group also had a higher proportion of sleep disorders ($p < 0.001$). There was no statistically significant difference in alcohol consumption levels between groups ($p = 0.292$).

3.8 Subgroup analysis of copper intake with essential hypertension

Figure 4 depicts the correlation between dietary copper intake and the prevalence of essential hypertension, accounting for various confounding factors. Across a wide range of subgroups defined by age, sex, race, marital status, smoking status, sleep patterns, cardiovascular disease, history of diabetes mellitus, and history of hyperlipidemia, higher dietary copper intake was consistently associated with an increased prevalence of essential hypertension, with p-values of less than 0.05 in each subgroup, indicating statistical significance. In stratified analyses, significant interactions were observed between dietary copper intake and factors such as smoking status, household income-to-poverty ratio, and the presence of hyperlipidemia with the risk of developing essential hypertension. The primary findings remained robust across several sensitivity analyses.

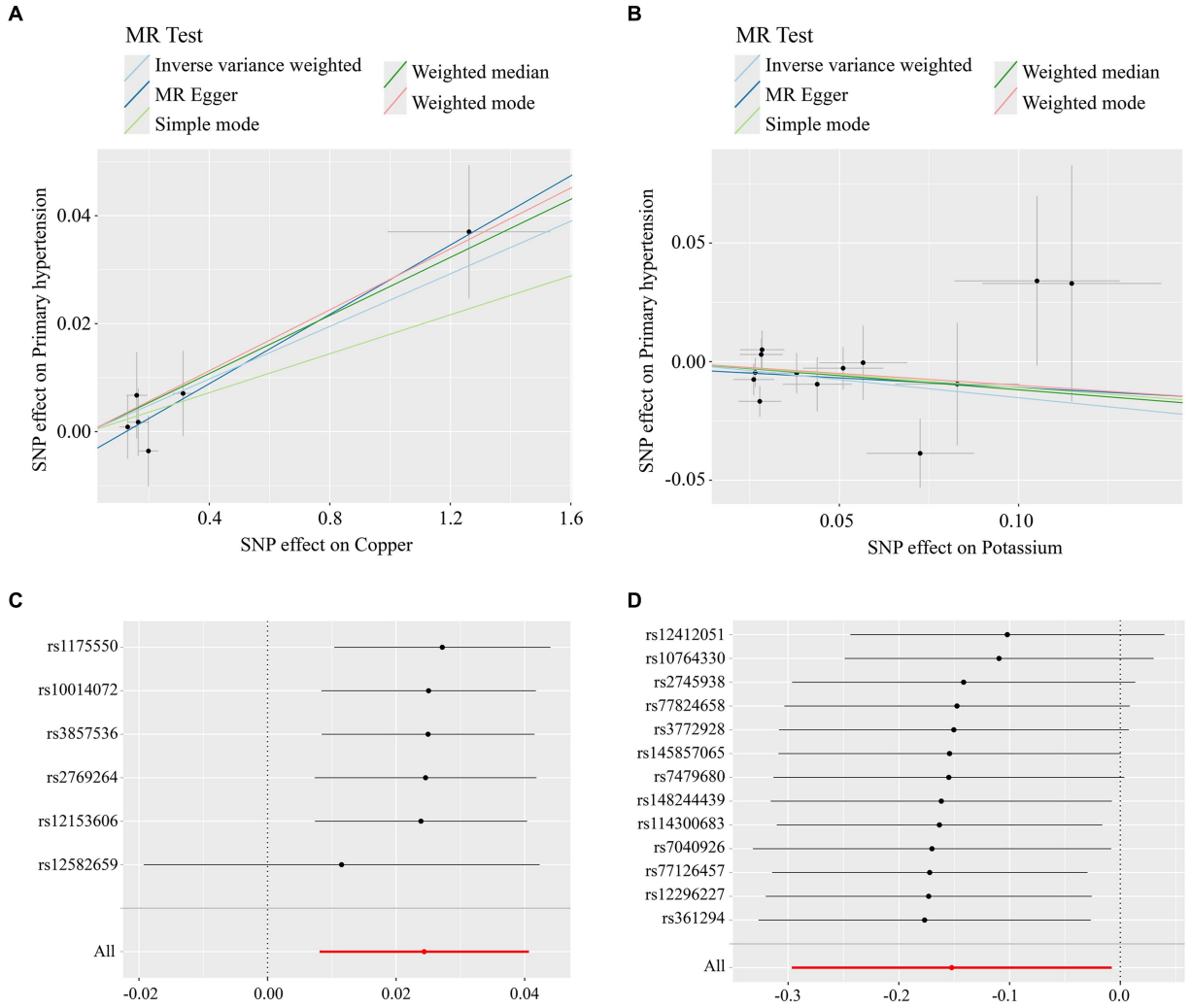

FIGURE 3
(A) Scatterplot of Mendelian randomisation results for copper; **(B)** scatterplot of Mendelian randomisation results for trace element Potassium; **(C)** Mendelian randomisation of leave-one-out graphs for elemental copper; **(D)** Mendelian randomisation of leave-one-out graphs for elemental potassium.

3.9 Binomial logistic regression analysis of copper intake with essential hypertension

As demonstrated in Table 2, in Model 1, which was not adjusted for any covariates, four high copper intake groups exhibited an elevated risk of developing essential hypertension in comparison to the normal copper intake group. Furthermore, all of these associations were statistically significant. The results indicated a statistically significant association between high copper intake and essential hypertension, with an odds ratio of 1.10 ($p = 0.001$, 95%CI:1.041–1.183), 1.186 ($p < 0.001$, 95% CI: 1.112–1.264), 1.384 ($p < 0.001$, 95%CI:1.292–1.483), and 1.465 ($p < 0.001$, 95%CI:1.305–1.645). After adjusting for sex, race, age, education level, and marital status, the risk of developing essential hypertension remained higher in the high copper intake group compared to the normal copper intake group (1.120, $p = 0.003$, 95% CI:1.040–1.206; 1.168, $p < 0.001$, 95%CI:1.084–1.259; 1.312, $p < 0.001$, 95%CI:1.211–1.422; and 1.292, $p < 0.001$, 95%CI:1.132–1.473). Model 3, which was adjusted for PIR, alcohol intake, smoking status, BMI, and physical activity, demonstrated statistical significance in all three groups, except for the high copper intake group, where the difference was 0.80–1.08 mg and was not statistically significant ($p = 0.271$, greater than 0). Model 4, which was adjusted for hypercholesterolemia, diabetes, cardiovascular disease, sleep disorders, and depressive state data, demonstrated a consistently higher incidence of essential hypertension in the high copper intake group compared to the normal copper intake group. The results were all statistically significant with odds ratios of 1.156 ($p = 0.015$, 95% CI: 1.029-1.298), 1.398 ($p < 0.001$, 95% CI: 1.243-1.572), 1.496 ($p < 0.001$, 95% CI: 1.320-1.695) and 1.469 ($p < 0.001$, 95% CI. 95% CI: 1.196-1.804).

3.10 Restricted cubic spline of copper intake with essential hypertension

As shown in Figure 5, analyses of the RCS without adjustment for covariates revealed an "L"-shaped nonlinear relationship between

TABLE 1 Baseline characteristics of patients with essential hypertension according to the amount of copper intake.

Characteristics	Copper intake (mg/d) (32359)					*p*
	<0.80	0.80–1.08	1.08–1.45	1.45–2.29	>2.29	
	N = 7,934	*N* = 8,143	*N* = 8,119	*N* = 6,556	*N* = 1,607	
Age (years)	48 (30–65)	49 (32–64)	48 (33–63)	47 (33–61)	46 (32–59)	<0.001
Gender						<0.000
Male	2.809 (35.40%)	3.530 (43.40%)	4.260 (52.50%)	4.019 (62.30%)	1.166 (72.60%)	<0.001
Female	5.125 (64.60%)	4.613 (56.60%)	3.859 (47.50%)	2.537 (38.70%)	441 (27.40%)	
Race						<0.001
Mexican American	1.086 (13.69%)	1.341 (16.47%)	1.298 (15.99%)	1.052 (16.05%)	206 (12.82%)	
Other Hispanic	927 (11.68%)	855 (10.50%)	844 (10.40%)	603 (9.20%)	145 (9.02%)	
Non-Hispanic Blake	2.903 (36.59%)	3.279 (40.27%)	3.438 (42.35%)	2.939 (44.83%)	696 (43.31%)	
Non-Hispanic White	2.353 (29.66%)	1830 (22.47%)	1.562 (19.24%)	998 (15.22%)	277 (17.24%)	
Other Race	665 (8.38%)	838 (10.29%)	977 (12.03%)	964 (14.70%)	283 (17.61%)	
Education level						<0.001
Less than high school	2.550 (32.25%)	2.117 (26.07%)	1780 (21.97%)	1.249 (19.10%)	247 (15.40%)	
High school or equivalent	2.186 (27.65%)	2044 (25.17%)	1833 (22.62%)	1.300 (19.88%)	289 (18.02%)	
College or above	3.160 (39.96%)	3.951 (48.65%)	4.479 (55.28%)	3.986 (60.97%)	1.068 (66.58%)	
Not recorded	11 (0.14%)	9 (0.11%)	11 (0.14%)	3 (0.05%)	0 (0.00%)	
Marital status						
Living with partner	3.765 (50.41%)	4.498 (58.32%)	4.853 (62.40%)	4.082 (64.59%)	978 (63.14%)	
Living alone	3.604 (48.91%)	3.214 (41.68%)	2.924 (37.60%)	2.238 (35.41%)	571 (36.86%)	
FPIR	2.02 (0.86–2.90)	2.38 (1.07–3.70)	2.60 (1.16–4.25)	2.80 (1.26–4.84)	2.93 (1.29–5.00)	<0.001
BMI(kg/m^2)	29.65 (24.40–33.50)	29.40 (24.30–33.00)	28.99 (24.00–32.40)	28.37 (23.70–31.70)	27.55 (23.40–30.50)	<0.001
Weight(kg)	80.46 (65.00–92.00)	81.41 (65.88–93.20)	81.64 (66.20–93.00)	81.86 (66.60–92.50)	81.22 (66.98–91.70)	0.039
Smoking status						<0.001
Yes	1724 (45.15%)	1.598 (41.09%)	1.546 (40.30%)	1.277 (41.62%)	323 (41.62%)	
No	2094 (54.85%)	2.291 (58.91%)	2.290 (59.70%)	1791 (58.38%)	453 (58.38%)	
Alcoholic ≥ 4 drinks/day (%)						0.292
Yes	508 (17.09%)	485 (15.66%)	502 (16.20%)	407 (16.20%)	121 (18.70%)	
No	2.464 (82.91%)	2.613 (84.34%)	2.597 (83.80%)	2.106 (83.80%)	526 (81.30%)	
Physical activity						<0.001
moderate activity/week	1.296 (33.10%)	1.617 (40.80%)	1710 (43.90%)	1.509 (48.50%)	445 (56.70%)	

(Continued)

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TABLE 1 (Continued)

Characteristics	Copper intake (mg/d) (32359)					*p*
	<0.80	0.80–1.08	1.08–1.45	1.45–2.29	>2.29	
	N = 7,934	*N* = 8,143	*N* = 8,119	*N* = 6,556	*N* = 1,607	
others	2.619 (66.90%)	2.347 (59.20%)	2.186 (56.10%)	1.603 (51.50%)	340 (43.30%)	
Sleep disorder						0.038
Yes	1.090 (27.80%)	1.012 (25.50%)	985 (25.30%)	782 (25.10%)	178 (22.70%)	
No	2.828 (72.20%)	2.952 (74.50%)	2.910 (74.70%)	2.330 (74.80%)	607 (77.30%)	
Essential hypertension						<0.001
Yes	3.054 (38.49%)	2.936 (36.06%)	2.805 (34.55%)	2041 (31.13%)	481 (29.93%)	
No	4.880 (61.51%)	5.207 (63.94%)	5.314 (65.45%)	4.515 (68.87%)	1.126 (70.07%)	
Diabetes						<0.001
Yes	550 (14.36%)	542 (14.03%)	490 (12.92%)	326 (10.72%)	81 (10.09%)	
No	3.281 (85.64%)	3.321 (85.97%)	3.302 (87.08%)	2.714 (89.28%)	684 (89.41%)	
Hypercholesterolemia						0.04
Yes	2.447 (35.75%)	2.578 (36.52%)	2.699 (37.92%)	2.157 (38.17%)	480 (34.29%)	
No	4.398 (64.25%)	4.481 (63.48%)	4.418 (62.08%)	3.494 (61.83%)	920 (65.71%)	
Cardiovascular health						<0.001
Yes	640 (26.88%)	627 (25.20%)	625 (25.68%)	479 (24.93%)	121 (25.60%)	
No	1741 (73.12%)	1861 (74.80%)	1809 (74.32%)	1.442 (75.07%)	351 (74.40%)	
Depression status						<0.001
Yes	1.697 (27.30%)	1.670 (25.47%)	1.680 (25.30%)	1.370 (25.56%)	285 (21.56%)	
No	4.520 (72.70%)	4.887 (74.53%)	4.960 (74.70%)	3.990 (74.44%)	1.037 (78.44%)	

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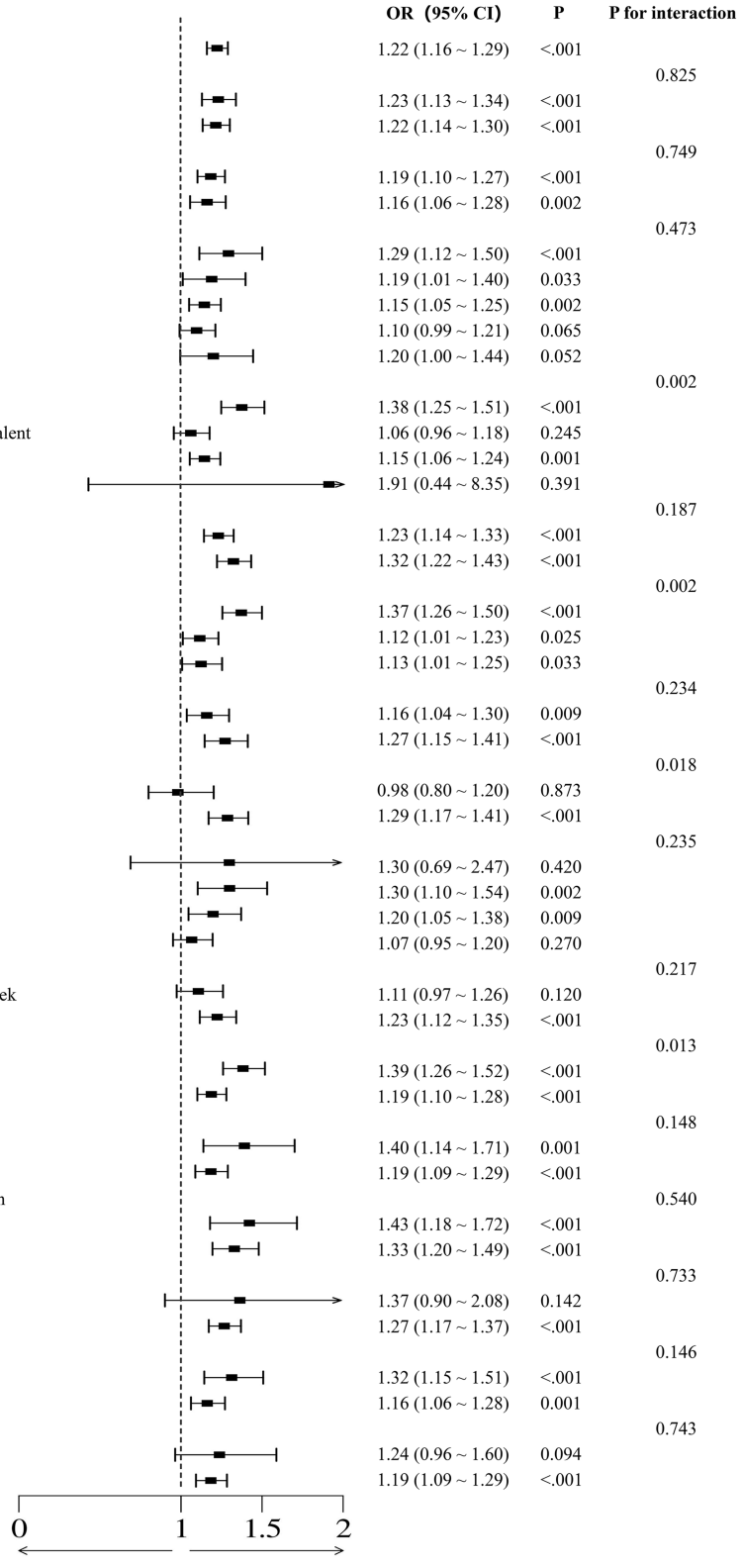

FIGURE 4
The association between normal and high copper intake and essential hypertension was evaluated using binomial logistic regression models, which were employed to calculate forest plots. The adjustments were made with reference to the covariates selected in the full binomial logistic regression model.

TABLE 2 The risk of essential hypertension was analyzed by multivariable-adjusted logistic regression for different levels of copper intake.

Variable	Model 1		Model 2		Model 3		Model 4	
Hypertension	OR (95% CIs)	*p*-value	OR (95% CIs)	*p*-value	OR (95% CIs)	*p*-value	OR (95% CIs)	*p*-value
Copper intake								
<0.80 mg	1		1		1		1	
0.80–1.08 mg	1.110 (1.041–1.183)	0.001	1.120 (1.040–1.206)	0.003	1.063 (0.954–1.184)	0.271	1.156 (1.029–1.298)	0.015
1.08–1.45 mg	1.186 (1.112–1.264)	<0.001	1.168 (1.084–1.259)	<0.001	1.231 (1.103–1.374)	<0.001	1.398 (1.243–1.572)	<0.001
1.45–2.29 mg	1.384 (1.292–1.483)	<0.001	1.312 (1.211–1.422)	<0.001	1.317 (1.172–1.480)	<0.001	1.496 (1.320–1.695)	<0.001
>2.29 mg	1.465 (1.305–1.645)	<0.001	1.292 (1.132–1.473)	<0.001	1.237 (1.025–1.491)	0.026	1.469 (1.196–1.804)	<0.001

hypertension and copper intake (p for overall <0.001, p for nonlinear <0.001). In models 2 and 4, the "L"-shaped relationship was still present (p for overall <0.001, p for nonlinear = 0.038; p for overall <0.001, p for nonlinear <0.001), whereas a "U"-shaped relationship was shown in model 3 (p for overall = 0.014, p for nonlinear = 0.022).

4 Discussion

After screening 15 micronutrients and removing weak instrumental variables, a two-sample Mendelian randomization analysis identified copper and potassium as being associated with essential hypertension. Sensitivity analyses further supported these findings (27). To account for potential interactions between trace elements, a multivariate Mendelian randomization analysis was conducted, which revealed that potassium was not associated with essential hypertension, while copper remained a significant risk factor. To validate these results, a logistic regression analysis using data from the NHANES database was performed. The findings confirmed that copper intake is associated with the prevalence of essential hypertension, consistent with the results obtained from Mendelian randomization.

The study data revealed that women and individuals with sleep disorders represented a larger proportion of those with low dietary copper intake. This finding may be explained by the unique physiological characteristics of women, such as cyclical blood loss, which can lead to copper depletion, and specific conditions like pregnancy and lactation, where increased copper requirements may result in insufficient intake if not adequately supplemented through diet or additional sources. Additionally, certain dietary habits or restrictions, such as vegetarianism, can further impact copper intake. The observed correlation between sleep disorders and low copper intake may be due to copper deficiency's direct or indirect effects on the brain's regulatory processes of excitation and inhibition, potentially leading to disrupted sleep and insomnia (28). Moreover, research has shown that sleep fragmentation can exacerbate myocardial ischemia–reperfusion injury by promoting copper overload in cardiomyocytes (29).

In clinical studies, Karolina Kedzierska et al. demonstrated a negative correlation between Na+/K+/Cl\—cotransport activity and plasma copper concentration in hypertensive patients (Rs = −0.579, $p < 0.05$). Similarly, ex-Na+/Li + activity was also negatively correlated with plasma copper concentration (Rs = −0.508, $p < 0.05$). These findings suggest that plasma copper concentration may increase the risk of essential hypertension by affecting sodium transport activity in the erythrocyte membrane (30). Using data from the NHANES database, Liu et al. observed a nonlinear relationship between serum copper concentration and elevated blood pressure in U. S. children and adolescents, finding that higher serum copper levels were significantly associated with hypertension in this population (31). Furthermore, a study found that the logarithmic transformation of dietary copper intake in hypertensive patients was significantly associated with longer telomere length, indicating that copper may contribute to the development and progression of essential hypertension by influencing telomere length (32). In another study, Pan He et al. identified a U-shaped relationship between dietary copper intake and new-onset hypertension, with an inflection point at approximately 1.57 mg/day among Chinese adults (14). The difference in our findings may be attributed to the use of different databases and the study populations, as Pan He's research focused on a Chinese cohort, whereas our study analyzed a U. S. population. Several other clinical studies have also explored the relationship between copper and cardiovascular diseases, including hypertension. For example, Muñoz-Bravo et al. found that elevated serum copper levels were associated with an increased risk of cardiovascular events (33). Zhou et al. identified blood copper as a novel risk factor for subclinical carotid atherosclerosis and demonstrated that mixtures of copper, cadmium, and lead may exert a synergistic pro-atherosclerotic effect (34). Additionally, Zhang et al. reported that baseline plasma copper levels were significantly and positively associated with the risk of first stroke in Chinese hypertensive patients (35).

Experimental animal studies suggest that copper levels may directly regulate blood pressure by influencing angiotensin, the nervous system, or kidney function. For instance, in angiotensin II (Ang II)-induced hypertension, the antioxidant 1 copper chaperone (Atox1) raises blood pressure by reducing extracellular oxygen anions and increasing the expression and activity of vascular superoxide dismutase 3 (SOD3) (36). Additionally, angiotensin-converting enzyme II (ACE2) significantly reduces copper levels in the vasculature of Atox1-deficient rats, likely due to an Ang II-induced

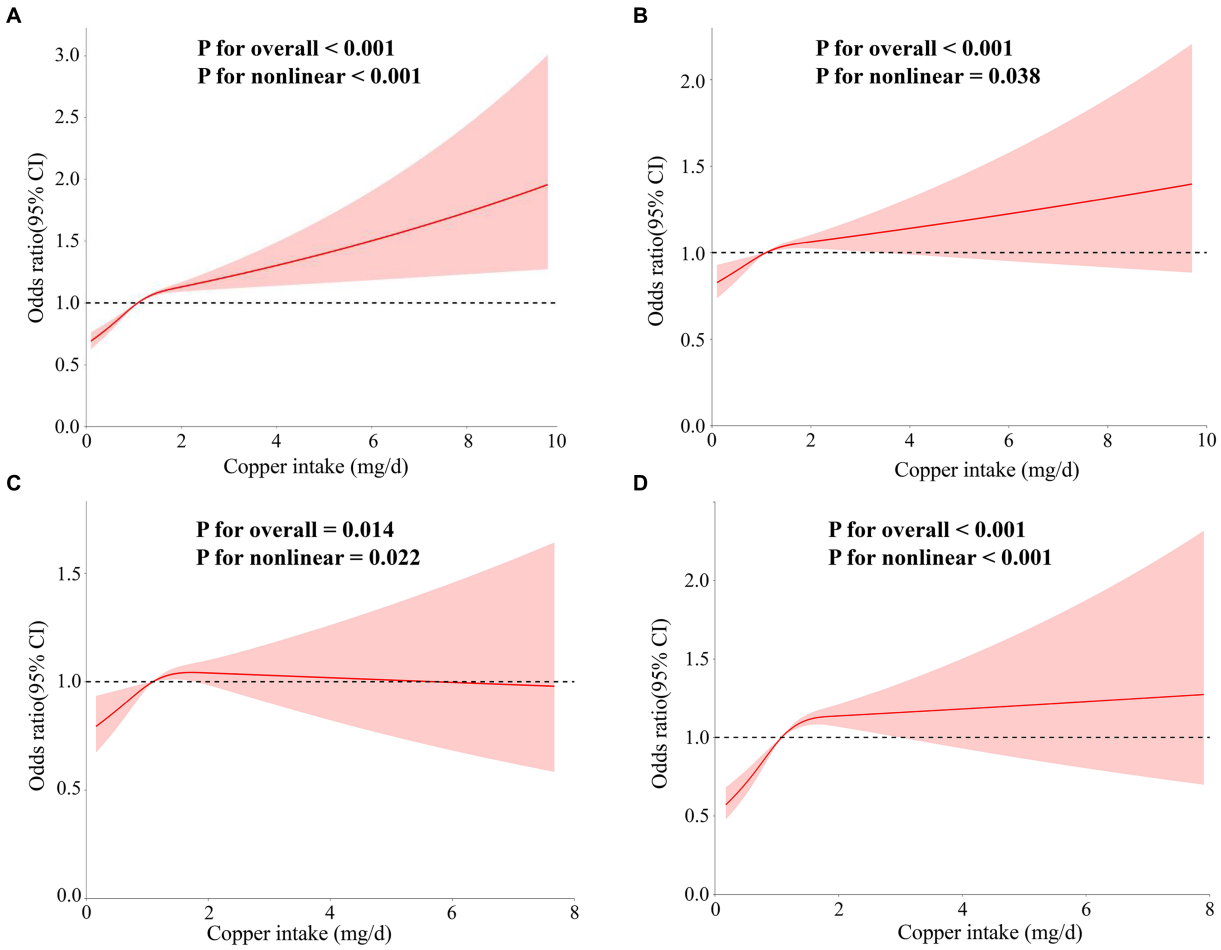

FIGURE 5
The correlation between copper intake and essential hypertension was assessed using RCS curves. The models were as follows: **(A)** Model 1 without adjustment for covariates; **(B)** Model 2 adjusted for age, sex, race, education, and marital status variables; **(C)** Model 3 adjusted for PIR, alcohol intake, smoking status, body mass index (BMI), and physical activity variables; **(D)** models adjusted for hypercholesterolemia, diabetes, cardiovascular disease, renal failure, and sleep disorder variables.

increase in circulating SOD3, which aligns with the observed reduction in copper levels in tissues such as the liver and kidneys of hypertensive rodents (36). It has been demonstrated that ATP7A, a copper-transporting protein, plays a critical role in Ang II-induced hypertension and the regulation of endothelial function by modulating SOD3 activity and vascular superoxide anion production (37). Conversely, in norepinephrine-induced hypertension, the generation of vascular oxygen anions was unaffected in ATP7A mutant mice with impaired copper transport, a finding consistent with observations in SOD3 knockout mice (38). Furthermore, the basal and Ang II-induced increases in vascular SOD3-specific activity were significantly inhibited in ATP7A mutant mice. In cultured vascular smooth muscle cells and mouse aorta, Ang II stimulation promoted the binding of ATP7A to SOD3, potentially enhancing SOD3-specific activity by facilitating copper delivery from ATP7A to SOD3. Copper transport proteins in the kidney and central nervous system also play roles in blood pressure regulation. Atox1 expression has been observed in several brain regions, including the choroid plexus, which is part of the circumventricular organs (CVOs), and ATP7A is also expressed in the choroid plexus (39). Deficiency of SOD3 in the CVO has been reported to elevate both basal and post-Ang II injection blood pressure, partly by modulating sympathetic outflow (40). It is speculated that brain-expressed Atox1 may regulate blood pressure by modulating SOD3 activity or its copper chaperone function, potentially affecting other secreted copper enzymes (41). Additionally, SOD3 gene transfer has been shown to reduce renal sodium retention in hypertensive rats (42). Therefore, Atox1 and ATP7A likely play significant roles in hypertension by regulating both kidney and brain functions.

Multiple lines of evidence support the role of vascular copper transporter proteins in regulating both the activity of copper-dependent enzymes, such as SOD1 and SOD3, and the overall intracellular copper content. For instance, Clegg MS et al. found that copper levels were altered in the tissues of hypertensive rats compared to healthy controls, with the degree of alteration correlating with the severity of hypertension (43). While the current study suggests that copper may have an interventional effect on hypertension, the precise mechanisms remain unclear. This study is notable as the first cross-sectional analysis to utilize the NHANES database, encompassing a 12 year cohort of over 50,000 subjects, to identify copper intake as a

risk factor for essential hypertension. By combining Mendelian randomization with NHANES data, we were able to assess causality, thereby overcoming the limitations of traditional observational studies, which often struggle to distinguish between causality and correlation. This approach enhances causal inference (44, 45). The National Health and Nutrition Examination Survey (NHANES) is a comprehensive database offering a vast array of epidemiological data, which significantly bolsters the statistical reliability of our findings. This study confirms a dose–response relationship between copper intake and the risk of essential hypertension. The results can inform the development of targeted hypertension prevention strategies and dietary interventions in high-risk populations, as well as provide a foundation for future laboratory studies aimed at elucidating the underlying biological mechanisms.

Our study has several limitations. Individual differences in food selection, digestive processes, and absorptive capacity may influence actual copper intake, introducing variability that is difficult to control. Additionally, the database lacks renal ultrasound, CT, or MRI assessments of renal structure and function, as well as imaging of the adrenal glands, which could help rule out conditions such as adrenal adenomas or hyperplasia. This absence of detailed diagnostic testing limits our ability to accurately diagnose conditions like primary aldosteronism and Cushing's syndrome, leading to some imprecision in distinguishing primary hypertension from secondary forms. However, given the low prevalence of secondary hypertension in the hypertensive population, our study remains feasible and relevant. Another limitation involves the assumptions inherent in Mendelian randomization (MR). MR presumes that gene effects are consistent across all individuals, but in reality, gene effects may vary depending on environmental factors or other contextual influences. Such gene-environment interactions could complicate MR results, potentially affecting the accuracy of causal inferences (46).

Data availability statement

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

Ethics statement

All participants provided informed consent before enrollment.

Author contributions

QM: Conceptualization, Data curation, Methodology, Software, Writing – original draft, Writing – review & editing. JZ: Conceptualization, Data curation, Writing – original draft. YY: Conceptualization, Data curation, Methodology, Writing – original draft. WW: Writing – review & editing. CL: Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1454669/full#supplementary-material

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The effect of cumulative exposure with unhealthy lifestyles on the H-type hypertension among Chinese adults: a community-based, propensity-score-matched, and case–control study

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Objective: To assess whether cumulative exposure of unhealthy lifestyles is associated with HTH in Chinese adults and to explore the combination of unhealthy lifestyles.

Methods: This study combined a community-based cross-sectional study with a 1:1 matched case–control study using propensity scores among adults in six randomly selected districts from Hunan Province, China. We recruited 5,258 people, of whom 4,012 met the criteria. Lifestyles and personal characteristics were collected by a questionnaire. Lifestyle score was calculated using cigarette smoking, heavy alcohol consumption, inactive exercise, unhealthy diet and abnormal BMI. HTH was defined as having a diagnosis of essential hypertension with Hcy ≥ 15 umol/L. Logistic regression models and multivariate analyses were used to explore the associations. We calculated odds ratios (ORs) and attributable risk proportion (ARP) for the association of HTH with lifestyle score. The dose–response relationship was evaluated using restricted cubic splines method.

Results: Of the 4,012 adults, 793 had HTH, with a population prevalence of 19.8%. In the propensity-score-matched case–control study, 1,228 (614 cases and 614 controls) were included, and those with at least four unhealthy lifestyle factors had a higher risk of HTH than those with 0 unhealthy lifestyle factor (adjusted OR = 2.60, 95%CI:1.42–4.78), with an ARP of the cumulative exposure of unhealthy lifestyle was 28.23% (95% CI: 6.34–37.86%). For three unhealthy lifestyles group, the combination of heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2 was most associated with HTH (OR = 7.49, 95%CI: 1.12–50.08). For four unhealthy lifestyles group, the combination of smoking, heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2 had the greatest correlation with HTH (OR = 3.75, 95%CI: 1.24–7.38). Notably, there was a monotonically increasing curve (J-shaped) relationship between unhealthy lifestyles and the risk of HTH (p = 0.014).

Conclusion: Our findings suggest that there was a significant cumulative exposure effect of unhealthy lifestyles on the risk of HTH, with the largest effect combination being heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2. Targeted interventions that reducing heavy alcohol consumption, quitting smoking, promoting physical activity and a healthy diet, and keep a normal BMI could substantially reduce the burden of HTH.

KEYWORDS

cumulative exposure effect, unhealthy lifestyles, H-type hypertension (HTH), Chinese community population, propensity score matching, case–control study

Introduction

Globally, cardiovascular diseases (CVDs) have collectively remained the leading causes of death and substantially caused to loss of health and excess health economic burden (1). Hypertension is the leading and modifiable risk factor for CVD, accounting for one-third of the total global deaths and 1.56 billion adult cases (2). Currently, scientists became interested in new risk factors for CVDs, such as serum homocysteine (Hcy) levels, which has been identified as a potential risk factor for hypertension (3). Previous study revealed that hyper-Hcy (HHcy) were associated with 75% of the hypertension cases (4). In 2008, the concept of H-type hypertension (HTH) proposing essential hypertension combined with HHcy was first introduced by Chinese researchers (5). Notably, the risk of CVDs in patients with HTH was approximately 5 times that of single-hypertension and 12 times that of healthy people (6), and HTH was independently associated with atherosclerotic plaques and stroke (7). Thus, the prevention strategies of HTH are the major global public health issue and challenges today.

Numerous epidemiological studies have established that unhealthy lifestyles, such as long-term heavy drinking, smoking, unhealthy diet, and lack of exercise, May lead to an increase in plasma Hcy levels and ultimately HHcy (8, 9). Detailly, current smoking but not quitting smoking was associated with higher risk of HHcy (10). Additionally, increasing evidence suggests that strict dietary control is highly important for blood pressure control and was one of the means to reduce plasma Hcy levels in hypertensive patient. A diet with rich in fruits and vegetables can lower plasma Hcy levels, thereby reducing the risk of CVD by 7 ~ 9% (11). However, it is worth noting that from the perspective of life course theory (12), there is a cumulative effect of risk factors in the pathogenesis of chronic diseases. Therefore, the study of a single behavioral lifestyle may underestimate its overall risk to health, while the establishment of behavioral lifestyle score can comprehensively reflect the impact of an individual's cumulative exposure to behavioral lifestyle on population health. For example, behavioral lifestyle score was associated with morbidity and mortality of cancer (13) or cardiovascular diseases (14). However, there was limit study conducted unhealthy lifestyle score so far to assess the its cumulative exposure effect on the HTH. Here, the association between unhealthy lifestyles and HTH will be differed by confounders level (such as age, sex and comorbidity status, etc.) in different directions and magnitudes. Therefore, we conducted a case–control study based on propensity score matching, which adopted a semi-parametric method to increase the possibility of reasonable matching between the case group and the control group, and dealt with multiple confounding factors or stratification, which greatly improved the reliability of the results (15).

Notably, the prevalence of HHcy is much higher among adults in China than in other countries (16–18). Additionally, most of epidemiological studies only focused on hospital-based populations, with few based on general community populations, which May limit interpretation of these data. And, those were mainly concentrated in North China and rare in South China (17). Thus, in this study, we conducted a community-based study design to achieve the following aims: (1) to assess whether cumulative exposure of unhealthy lifestyles is associated with the HTH in Chinese adults; and (2) if such association exists, to explore the combination of unhealthy lifestyles in it.

Materials and methods

Study design and population

In this study, we used a study design which combined a population-based cross-sectional study with a 1:1 matched case–control study using propensity scores in Hunan Province (including 14 districts and a population of more than 66 million), China. Detailed information on study design of this population has been described in our previous study (10). Briefly, a multistage cluster random sampling design was carried out to obtain a representative sample from July 2013 to March 2014. First, six districts were randomly selected from the 14 districts. Second, one urban and one rural community were randomly selected from each selected district. Our study included adults over 30 years old, and subjects who lived in the community less than 5 years, suffered from any type of cancer or had a major surgery within the last 6 months were excluded. Those met the inclusion and exclusion criteria signed written informed consent. After obtaining informed consent, eligible participants were asked to complete a questionnaire. Accordingly, 4,012 participants were included in the population-based cross-sectional study to determine the relationship between cumulative exposure and HTH. Furtherly, a 1:1 matched case–control study based on the propensity score matching method (614 healthy participants and 614 HTH) was conducted to verify these cumulative effects (Figure 1).

Data collection

Demographic characteristics (including age, sex, family income, education, marital status, occupation status and self-reported

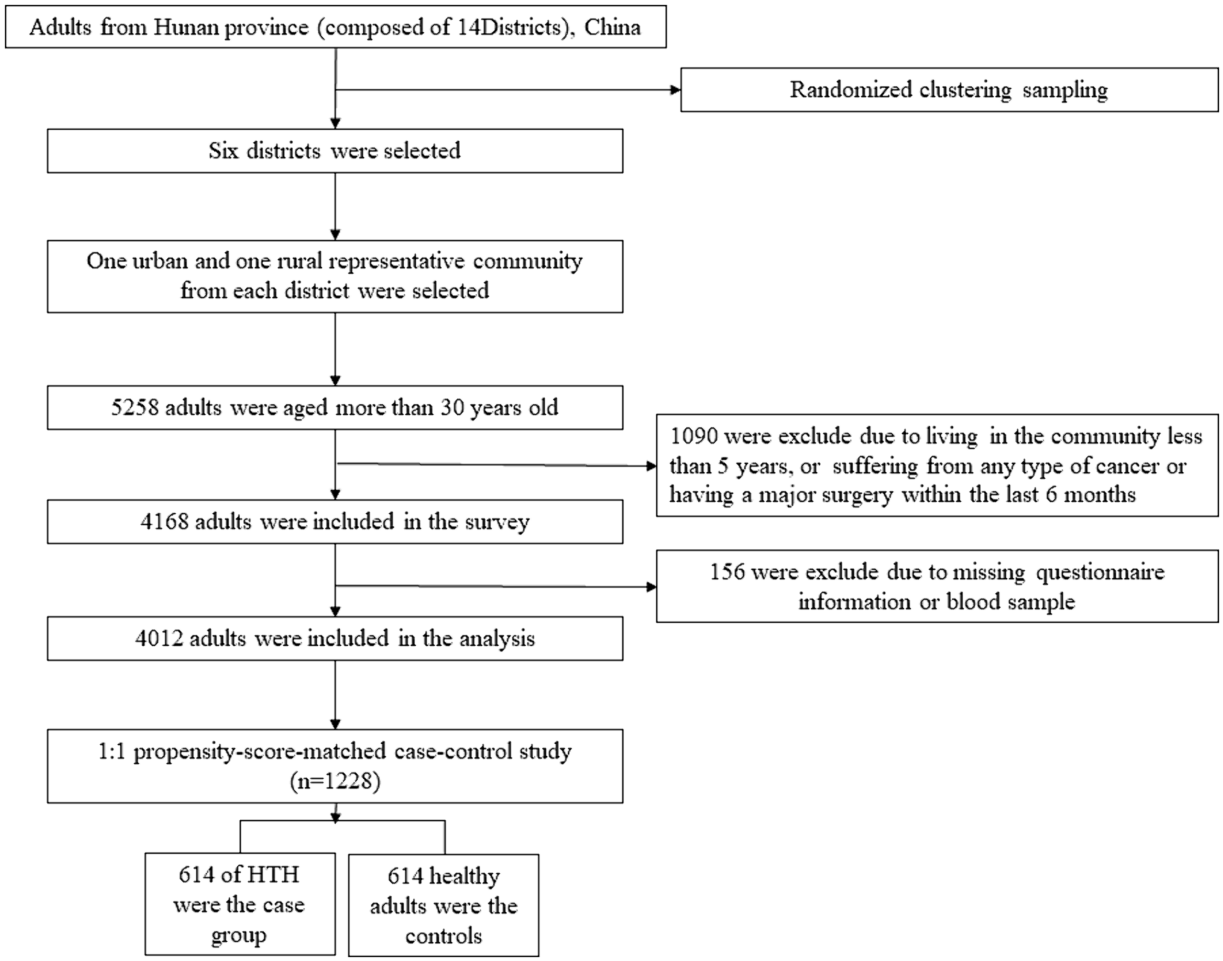

FIGURE 1
Flowchart of the study.

comorbidities) and lifestyles factor (including smoking, alcohol drinking, exercise and diet) were collected by trained researchers through face-to-face and one-to-one questionnaires, which was referred the questionnaire of the China Health and Retirement Longitudinal Study (CHARLS) (19). A test–retest reliability test was performed on the questionnaire, with a Cronbach's α coefficient in this sample being 0.778. Family income per year was asked for every participant, and further divided into three groups: low, medium and high. Educational attainment was classified as follows: below of high school, ordinary/vocational high school and undergraduate/college degree. Marital status was classified into three groups: unmarried, married/cohabitation and divorce/widow. Occupation included four types: wage-laborer, white-collar worker, farmer and retiree. Self-reported comorbidities included ischemic heart disease, stroke or diabetes.

Height, bodyweight and diastolic/systolic blood pressure were measured by professionally trained nurses using the calibrated electronic automatic tester. Each participant had their blood pressure measured three times with at least 5 min of rest each time. The average of the 3 values was calculated and documented as the final blood pressure value.

Blood samples were collected at 07:30–10:00 after a fasting period of 12 h. The plasma Hcy was measured by trained laboratory technicians using the microplate enzyme immunoassay method, with homocysteine Detection Kit of MedicalSystem Biotechnology Co., Ningbo, China (Reagent batch number, 13082408). Other laboratory indicators included fasting blood-glucose (FPG), plasma total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP) were detected using a Hitachi 7,600 Automatic Biochemistry Analyzer (Hitachi).

Assessment of behavioral lifestyle factors and unhealthy lifestyle score

Smoking was defined in the questionnaire as smoking more than 100 cigarettes in life. Here, a set of simple and easy-to-understand photos to measure the drinks of different kinds of drinks (see in Supplementary Figure S1), and the drink frequency (days) and amounts (drinks) in the past week were reported. The average daily alcohol drinks were estimated as follows: average daily alcohol drinks = (frequency [days] × (amounts [drinks] in each of those days))/7 (10). Heavy alcohol consumption level was defined as average daily alcohol drinks ≥2. For physical activity, the number of days per week that the participants did physical activities (such as weightlifting,

stair climbing, fast cycling, aerobics, running, etc.) and the time of each exercise were obtained through the questionnaires. Inactive exercise was defined as having lasting for less than 10 continuous minutes per week (20). We evaluated dietary status using food frequency questionnaire according to a more recent dietary recommendation for blood pressure and combining with traditional Chinese eating habits, which considered adequate consumption of fresh fruit, fresh vegetables, unprocessed meats (including red meat, fish or shellfish), reduced consumption of high-fat, high-salt and sugar-sweetened food. We defined an unhealthy diet as meeting less than four items of the recommendations (see Supplementary methods for details). Body-mass index (BMI) was calculated as bodyweight in kg divided by the square of height in meters, and a value more than or equal to 24 was defined as an abnormal BMI. Additionally, we constructed a composite score of unhealthy lifestyles including cigarette smoking, alcohol consumption, inactive physical exercise, unhealthy diet and abnormal BMI ($\geq$24 Kg/m^2) on the basis of earlier evidence of these factors' contribution to HTH or because of their potential role as a risk factor for CVD (11). For the above unhealthy lifestyles, we scored 1 for an unhealthy level and 0 for none. Thus, the unhealthy lifestyle score was the total of the points ranging from 0 to 5, with higher scores showing unhealthier lifestyles.

Assessment of HTH

Single-hypertension is defined as a diastolic/systolic blood pressure $\geq$ 90/140 mm/Hg or clinically diagnosed with hypertension or taking antihypertensive drugs, but Hcy < 15 μmol/L. Single-HHcy was defined as plasma Hcy $\geq$ 15 μmol/L with a normal blood pressure. HTH was defined as having a diagnosis of essential hypertension with Hcy $\geq$ 15 μmol/L.

Covariates

Demographic characteristics including age, sex, marital status, family income, education and occupation status, and self-reported comorbidities (ischemic heart disease, stroke or diabetes), and laboratory indicators including fasting FPG, TC, TG, LDL-C, HDL-C, and CRP were analyzed in our models as covariates, based on previous research (10).

Statistical analysis

The mean and standard deviation were used to describe the normal distribution of quantitative variables, and the *t*-test was used to compare the differences. The median and quartile intervals were used to represent the quantitative variables that did not follow the normal distribution, and the *Wilcoxon rank sum* test was used to compare the differences. Categorical variables were expressed as counts and percentages (%), and differences were compared using *Chi-square* test or *Fisher exact probability* method.

Multiple logistic regression models were applied to examine the associations of each lifestyle factor and the overall lifestyle score with health states (including single-HHcy, single-hypertension and HTH) risk. The results were reported as odds ratios (ORs) with 95% CIs. We assigned a median value to each lifestyle score category to test the linear trend. The dose–response relationship between cumulative exposure of behavioral lifestyle and HTH was estimated using a restricted cubic spline (RCS) function. Here, a 1:1 matched case–control study was established using propensity score matching method to further validate the exposure effects of unhealthy lifestyles. The data before and after matching were, respectively, compared to see whether the patients were balanced in important covariates. The difference of the covariates in the two groups before matching was less than 0.05, and the difference of the covariates after matching was greater than 0.06, indicating that the covariates after matching were balanced among groups (see Supplementary Table S1 for details). In this case–control study, to examine the proportion of HTH in the exposed population that theoretically would not have occurred if all participants had adhered to 5 low-risk lifestyle factors (lifestyle score was zero), we calculated the attributable risk proportion (ARP) under the assumption of a causal relationship between lifestyle and HTH risk. The formula for calculating ARP was as follows: $AF = (\mathrm{OR} - 1) / \mathrm{OR} \times 100\%$

To verify the robustness of the results, four models were constructed in the sensitivity analysis based on previous researches (10, 21). In model 1, no covariate was adjusted. In model 2, we adjusted for age, sex, education, family income, marital status and occupational status. In model 3, history of prevalent comorbidities (including ischemic heart disease, stroke and diabetes) was further adjusted. In model 4, additionally included the serum FPG, TC, TG, LDL-C and HDL-C and CRP. Meanwhile, we tested the robustness and potential variations in different subgroups stratified by sex (male and female), age groups (<45 years, and $\geq$45 years) and prevalent comorbidities (yes, and no). Statistical analyses were conducted using STATA version 18.0 (Institute, Gary, NC, United States). A two-sided $p < 0.05$ was considered statistically significant.

Results

Population characteristics

Table 1 shows baseline characteristics of participants. A total of 4,012 participants were included, with an average age of 54.6 years (Standard Deviation [SD]: 12.6) and 59.0% female. Among them, 312 (7.8%), 1,072 (26.7%), 1,364 (34.02%), 776 (19.3), 365 (9.1%) and 123 (3.1%) had zero, one, two, three, four and five unhealthy lifestyle factors, respectively. The prevalence rates of single-HHCy, single-hypertension and HTH were 15.6% (627/4012), 15.0% (601/4012) and 19.8% (793/4012), respectively. Those of HTH were more likely to be older, male, to have low family income, less educated, married or cohabitation, farmer, and a higher prevalence of self-reported comorbidities (including ischemic heart disease, stroke and diabetes) than those among healthy group. Additionally, the participants in HTH group have higher levels of serum FPG, TC, TG, LD-C, HDL-C, and CRP. Among the 4,012 participants, 962 (24.0%) were non-current smokers, 1,079 (26.9%) were heavy alcohol drinker, 1974(49.2%) maintained an unhealthy diet, 2,610(65.1) were inactive in exercise and 1,578 (39.3%) had an abnormal BMI. Those unhealthy lifestyles were more prevalent among participants with HTH. Notably, those with HTH were more likely to be exposed to a variety of unhealthy behaviors than healthy population. Supplementary Table S2 provides details about the cumulative exposure of lifestyle factors and includes 32 combinations in total. The most two frequent combinations were

TABLE 1 Baseline characteristics of participants according to health status (single-HHcy, single-hypertension and HTH)*.

Characteristics	Total	Healthy group	Single-HHcy	Single-hypertension	HTH	*p*-value
N	4,012	1991 (49.6)	627 (15.6)	601 (15.0)	793 (19.8)	
Age (years, SD)	54.6 (12.6)	52.7 (12.4)	52.1 (12.6)	56.9 (10.8)	59.6 (12.7)	<0.001
Sex						<0.001
Male	2,368 (59.0)	636 (31.9)	302 (48.2)	262 (43.6)	444 (56.0)	
Female	1,644 (41.0)	1,355 (68.1)	325 (51.8)	339 (56.4)	349 (44.0)	
Family income†						0.005
Low	1,559 (38.8)	763 (38.3)	235 (37.5)	217 (36.1)	344 (43.4)	
Medium	1,439 (35.9)	710 (35.7)	237 (37.8)	247 (41.1)	245 (30.9)	
High	1,014 (35.3)	518 (26.0)	155 (24.7)	137 (22.8)	204 (25.7)	
Education						<0.001
Below of high school	2033 (50.7)	1,018 (51.3)	267 (42.6)	287 (47.6)	461 (58.1)	
Ordinary or vocational high school	1,154 (58.7)	543 (27.3)	203 (32.4)	201 (33.4)	207 (26.1)	
Undergraduate or college degree	825 (20.6)	430 (21.6)	157 (25.0)	113 (18.8)	125 (15.8)	
Occupation status						
Wage-laborer	595 (14.8)	318 (16.0)	119 (19.0)	65 (10.8)	93 (11.7)	<0.001
White-collar worker	1,102 (27.5)	606 (30.4)	199 (31.7)	130 (21.6)	167 (21.1)	
Farmer	714 (17.8)	381 (19.1)	71 (11.3)	76 (12.6)	186 (23.5)	
Retiree	1,601 (39.9)	686 (34.5)	238 (38.0)	330 (54.9)	347 (43.8)	
Marital status						
Unmarried	65 (1.6)	24 (1.2)	12 (1.9)	13 (2.2)	16 (2.0)	0.002
Married/cohabitation	3,808 (94.9)	1881 (94.5)	594 (94.7)	571 (95.0)	762 (96.1)	
Divorce/widow	139 (3.5)	86 (4.3)	21 (3.4)	17 (2.8)	15 (1.9)	
Self-reported comorbidities						
Ischemic heart disease	310 (7.7)	117 (5.9)	44 (7.0)	60 (10.0)	89 (11.2)	<0.001
Stroke	114 (2.8)	56 (2.8)	7 (1.1)	17 (2.8)	34 (4.3)	0.005
Diabetes	210 (5.2)	80 (4.0)	19 (3.0)	43 (7.2)	95 (8.6)	<0.001
GLU, mean (SD)	5.7 (1.6)	5.6 (1.7)	5.5 (1.1)	5.6 (1.4)	6.0 (1.5)	<0.001
TC, mean (SD)	4.8 (0.9)	4.7 (0.9)	5.2 (1.0)	4.8 (0.9)	5.0 (1.0)	<0.001
TG, mean (SD)	2.0 (16)	1.7 (1.3)	2.4 (1.7)	1.9 (1.6)	2.5 (2.1)	<0.001

(Continued)

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TABLE 1 (Continued)

Characteristics	Total	Healthy group	Single-HHcy	Single-hypertension	HTH	*p*-value
LDL, mean (SD)	2.6 (0.8)	2.6 (0.8)	2.8 (1.0)	2.7 (0.8)	2.6 (0.9)	<0.001
HDL, mean (SD)	1.3 (0.3)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)	<0.001
CRP, mean (SD)	5.5 (1.6)	5.5 (1.5)	5.6 (1.4)	5.4 (1.5)	5.7 (2.0)	<0.001
Current smoking	1,079 (26.9)	435 (21.8)	186 (29.7)	140 (23.3)	318 (40.1)	<0.001
Heavy alcohol drinking	962 (24.0)	403 (20.2)	188 (30.0)	135 (22.5)	236 (29.8)	<0.001
Unhealthy diet	1974 (49.2)	864 (43.4)	324 (51.7)	327 (54.4)	459 (57.9)	<0.001
Inactive exercise	2,610 (65.1)	1,260 (63.3)	393 (62.7)	420 (69.9)	537 (67.7)	0.005
BMI ≥24 Kg/m^2	1,578 (39.3)	632 (31.7)	212 (33.8)	316 (52.6)	418 (52.7)	<0.001
Unhealthy lifestyles score (point)						
0	312 (7.8)	189 (9.5)	48 (7.7)	39 (6.5)	36 (4.6)	<0.001
1	1,072 (26.7)	629 (31.6)	174 (27.7)	119 (19.8)	150 (18.9)	
2	1,364 (34.0)	722 (36.3)	196 (31.3)	219 (36.4)	227 (28.6)	
3	776 (19.3)	307 (15.4)	116 (18.5)	146 (24.3)	207 (26.1)	
4	365 (9.1)	120 (6.0)	76 (12.1)	47 (7.8)	122 (15.4)	
5	123 (3.1)	24 (1.2)	17 (2.7)	31 (5.2)	51 (6.4)	

HHcy, hyper-homocysteine; HTH, H-type hypertension; SD, standard deviation; BMI, body mass index; HTH, H-type hypertension. FPG, fasting blood-glucose; TC, plasma total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CRP, C-reactive protein. *Continuous variables were expressed as mean (95% confidence interval), and categorical variables were expressed as number (percentage). *p*-values were calculated using analysis of variance for continuous variables, and Pearson chi-squared test or Fisher's exact for categorical variables. †Family income was divided into high, medium, and low level according to triquartile method.

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TABLE 2 The effect of cumulative exposure with unhealthy lifestyles on HTH based on 4,012 community population.

Unhealthy lifestyles score (point)	Odd Ratio	95%CI	*p*-value
Model 1			
0	1.00		
1	1.25	0.84–1.86	0.269
2	1.65	1.12–2.43	0.011
3	3.54	2.38–5.27	<0.001
4	5.34	3.45–8.26	<0.001
5	11.16	6.11–20.37	<0.001
Trend for per score point	1.63	1.52–1.75	<0.001
Model 2			
0	1.00		
1	1.11	0.74–1.67	0.611
2	1.26	0.84–1.88	0.259
3	2.52	1.66–3.84	<0.001
4	3.45	2.14–5.58	<0.001
5	8.82	4.65–16.71	<0.001
Trend for per score point	1.50	1.38–1.64	<0.001
Model 3			
0	1.00		
1	1.08	0.72–1.62	0.718
2	1.22	0.81–1.82	0.338
3	2.40	1.57–3.66	<0.001
4	3.27	2.02–5.29	<0.001
5	8.46	4.46–16.04	<0.001
Trend for per score point	1.49	1.37–1.63	<0.001
Model 4			
0	1.00		
1	1.02	0.67–1.55	0.930
2	1.07	0.71–1.62	0.757
3	2.12	1.37–3.27	0.001
4	2.64	1.61–4.33	<0.001
5	5.08	2.62–9.84	<0.001
Trend for per score point	1.40	1.28–1.53	<0.001

the unhealthy diet and inactive exercise group and inactive exercise group, corresponding to 15.7 and 10.2%, respectively.

Associations of unhealthy lifestyle factors with HTH

The associations of single unhealthy lifestyle factors with the risk of three health status were displayed in Supplementary Table S3. The univariate logistic analysis found that, smoking, heavy alcohol drinking, inactive exercise, unhealthy diet and BMI ($\geq$24 Kg/m^2) were positively associated with HTH. After adjusting for age, sex, marital status, family income, education and occupation status, self-reported comorbidities (including ischemic heart disease, stroke or diabetes), serum FPG, TC, TG LDL-C, HDL-C and CRP, we found the similar positive results, for details, those with HTH had corresponding ORs of 1.29 (for smoking, 95% CI: 1.00–1.66, $p = 0.046$), 1.52 (for unhealthy diet, 95% CI: 1.27–1.82, $p < 0.001$), 1.29 (for inactive exercise, 95% CI: 1.06–1.59, $p = 0.013$), and 2.16 (for BMI, 95% CI: 1.79–2.61, $p < 0.001$), respectively. Additionally, after adjusted for above covariables, only unhealthy diet (OR = 1.49, 95% CI:1.23–1.80) and BMI (OR = 2.38, 95% CI: 1.95–2.90) were positively associated with single-hypertension, while no lifestyles were found associated with Single-HHcy (Supplementary Table S3).

Effects of cumulative exposure with unhealthy lifestyles on HTH

Multiple logistic regression models were carried out to examine the effect of cumulative exposure with unhealthy lifestyles on the risk of HTH (Table 2). In the cross-sectional study based on 4,012 participants, after adjusted for the covariables (including age, sex,

marital status, family income, education and occupation status, self-reported comorbidities, serum FPG, TC, TG LDL-C, HDL-C and CRP), when compared with those living favorable lifestyles among healthy group (zero unhealthy lifestyle factors), those with three (OR = 2.12, 95% CI: 1.37–3.27, $p = 0.001$), four (OR = 2.64, 95% CI: 1.61–4.33, $p < 0.001$), or five (OR = 5.08, 95% CI: 2.62–9.84, $p < 0.001$), unhealthy lifestyle factors had higher risk of HTH. Notably, RCS analysis showed that there was a monotonically increasing curve (J-shaped) relationship between unhealthy lifestyle scores and the risk of HTH ($p = 0.001$) (Figure 2A), suggesting that the more the number of unhealthy lifestyle factors, the greater the risk of HTH.

In the propensity-score-matched case–control study 1 (614 healthy controls vs. 614 HTH cases), 1,228 participants were included. We confirmed the results of the above cross-sectional study that unhealthy lifestyles had positive cumulative exposure on risk of HTH (Table 3). For details, compared with those living favorable lifestyles, the risk of HTH was increased by 82% (OR = 1.82, 95% CI: 1.03–3.22, $p = 0.038$) and 160% (OR = 2.60, 95% CI: 1.42–4.78, $p = 0.002$) in the groups with three and at least four unhealthy lifestyle factors, respectively. For three unhealthy lifestyle factors group, we found the combination of heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2 was most associated with HTH (OR = 7.49, 95%CI:1.12–50.08, $p = 0.038$, Table 4). For four unhealthy lifestyle factors group, the combination of smoking, heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2 had the greatest correlation with HTH (OR = 3.75, 95%CI: 1.24–7.38, $p = 0.015$, Table 4). Additionally, trend test analysis prompted that the risk of HTH increased as the number of combined healthy lifestyle factors increased, with participants with four or five unhealthy lifestyle factors having the highest risk of HTH ($P_{trend} < 0.001$). We also noticed a significant monotonically increasing (characterized by J-shaped curve) relationship between unhealthy lifestyle scores and the risk of HTH by RCS analysis ($p = 0.014$) (Figure 2B). Table 3 also summarized the ARP for lifestyle score. In case–control study 1, the multivariate ARP of combination of the four/five unhealthy lifestyle factors was 28.23% (95% CI: 6.34–37.86%).

Sensitivity and subgroup analysis

In sensitivity analyses, we constructed several models, and found the results remained similar in all sensitivity analyses (Table 2). Then, we conducted subgroup analysis. Supplementary Table S4 shows the

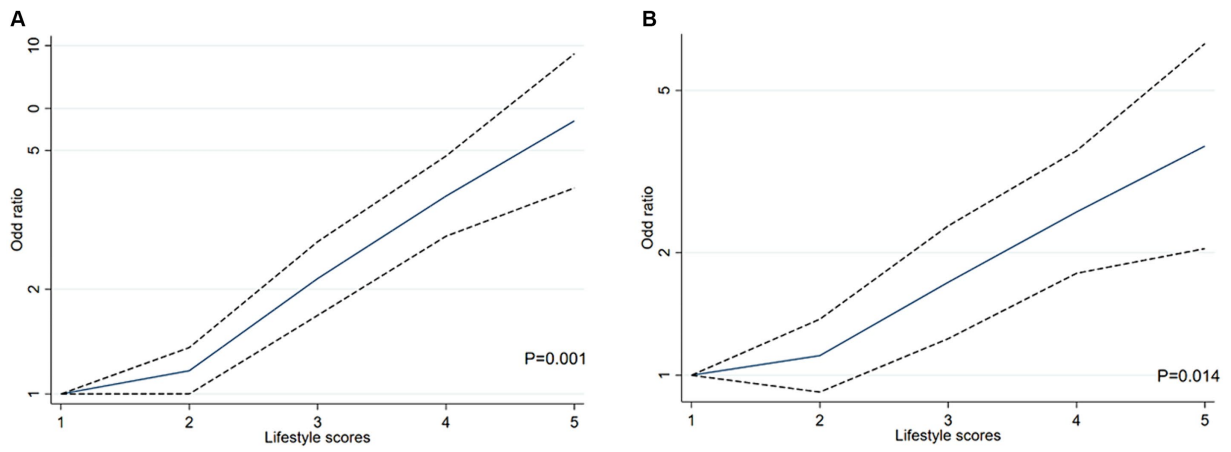

FIGURE 2
The restricted cubic spline (RCS) for the relationship between unhealthy lifestyle score and H-type hypertension in Chinses adults. The reference value for scores was set as a cut-off value for the first quartile. Three nodes were selected for all models. All models adjusted for age, sex, marital status, family income, education and occupation status, self-reported comorbidities (including ischemic heart disease, stroke or diabetes), serum FPG, TC, TG LDL-C, HDL-C and CRP. **(A)** RCS analysis between unhealthy lifestyle scores and the risk of HTH in cross-sectional study based on 4,012 participants. **(B)** RCS analysis between unhealthy lifestyle scores and the risk of HTH in propensity-score-matched case–control study.

TABLE 3 **Cumulative effect of unhealthy lifestyles on HTH based on 1:1 matching case–control studies.**

Unhealthy lifestyles score (point)	Healthy group vs. HTH		
	OR	95%CI	*P*-value
0	1.00		
1	1.42	0.81–2.50	0.224
2	1.23	0.71–2.14	0.463
3	1.82	1.03–3.22	0.038
4/5	2.60	1.42–4.78	0.002
Trend for per score point	1.24	1.12–1.37	<0.001
ARP (%, 95CI)	28.23	6.34–37.86	

TABLE 4 Effects of cumulative exposure combination of unhealthy lifestyle on HTH.

Combination of lifestyle factors	OR	95%CI	*p*-value
Score=3			
Heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2	7.49	1.12–50.08	0.038
Unhealthy diet, inactive exercise and BMI ≥24	3.58	1.66–7.69	0.001
Smoking, unhealthy diet and BMI ≥24 Kg/m^2	3.38	1.22–9.41	0.020
Smoking, heavy alcohol consumption and unhealthy diet	1.71	0.11–26.41	0.702
Smoking, heavy alcohol consumption and inactive exercise	0.23	0.03–1.98	0.196
Smoking, heavy alcohol consumption and BMI ≥24 Kg/m^2	1.00	1.00–1.00	1.000
Smoking, unhealthy diet and inactive exercise	1.48	0.71–3.07	0.292
Smoking, inactive exercise and BMI ≥24 Kg/m^2	3.11	0.89–14.63	0.651
Heavy alcohol consumption, unhealthy diet and inactive exercise	1.48	0.59–3.72	0.404
Heavy alcohol consumption, inactive exercise and BMI ≥24 Kg/m^2	1.00	1.00–1.00	1.000
Score=4			
Smoking, heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2	3.75	1.24–7.38	0.015
Smoking, heavy alcohol consumption, inactive exercise and BMI ≥24 Kg/m^2	3.26	1.01–10.51	0.048
Heavy alcohol consumption, unhealthy diet, inactive exercise and BMI ≥24 Kg/m^2	3.17	1.13–8.89	0.028
Smoking, unhealthy diet, inactive exercise and BMI ≥24 Kg/m^2	3.03	0.79–17.90	0.097
Smoking, heavy alcohol consumption, unhealthy diet and inactive exercise	1.18	0.54–2.57	0.670
Score=5			
Smoking, heavy alcohol consumption, unhealthy diet, inactive exercise and BMI ≥24 Kg/m^2	3.41	1.50–7.80	0.004

results stratified by sex, age group, and self-reported comorbidity groups, which were not materially changed with those of the main analyses. For instance, compared with those of zero unhealthy lifestyle factor, the cumulative exposure effect of unhealthy lifestyle (five unhealthy lifestyle factors) on risk of HTH were stronger in males (OR = 4.69, 95%CI: 1.60–8.38) than in females, and in older (OR = 4.86, 95%CI: 2.30–10.30) than younger adults. Cumulative exposure effect was more pronounced in those with comorbidities than those without, with an adjusted OR of 2.52 (95% CI: 1.41–4.52 $p = 0.002$) obtained for three unhealthy lifestyle factors, 3.57 (95% CI: 1.89–6.73, $p < 0.001$) for four unhealthy lifestyle factors and 6.81 (95% CI: 3.19–14.57, $p < 0.001$) for five unhealthy lifestyle factors, respectively (Supplementary Table S4).

Discussion

In this study, we found that an unhealthy lifestyle score defined by five high-risk lifestyle factors (including smoking, heavy alcohol drinking, unhealthy diet, inactive exercise and high BMI) was significantly associated with a higher risk of HTH, suggesting that there was a positive cumulative exposure of unhealthy lifestyle on HTH among Chinese adults, with the largest effect combination being heavy alcohol consumption, unhealthy diet and BMI ≥24 Kg/m^2. Participants who had three or more unhealthy lifestyle factors exhibited an increase in their risk of HTH, ranging from 82 to 408%, compared to those having no unhealthy lifestyles (0 unhealthy lifestyle factor). These unhealthy lifestyle factors explained about 28.23% of the HTH risk.

In our study, we found that smokers had a higher risk of developing H-hypertension than non-smokers. Epidemiological studies have shown that smokers tend to have lower levels of the B-vitamins, such as folate, vitamin B6 and vitamin B12, which affect homocysteine levels by controlling co-factors or co-substrates of homocysteine metabolizing enzymes (22, 23). And, smoking has been shown to increase the risk of vascular damage by increasing sympathetic tone, platelet viscosity and reactivity, free radical production, endothelial damage, or elevated arterial pressure (24). Data from eight prospective cohort studies involving 70,130 participants and 21,238 cases of hypertension, suggested that smoking cessation did not increase the risk of hypertension (25). Therefore, there is an urgent need to provide effective strategies to encourage smokers to quit, especially those with H-type hypertension, and thus reduce their risk of developing CVD. Additionally, alcohol consumption is an important preventable and modifiable cause of non-communicable disease, and increased the risk of hypertension in a positive dose-dependent manner (26). In present study, univariate analysis showed that heavy alcohol consumption level (average daily alcohol drinks ≥2) was associated with increased risk of HTH (OR = 1.67, 95% CI: 1.38–2.01). However, after adjustment for potential confounders (sex and age, etc.), no significant increase in HTH prevalence risk was observed (OR = 1.06, 95% CI: 0.85–1.33). Gender is an important modifier of the alcohol threshold level for harm. The Physicians' Health study reported a definite protective effect on hypertension in women who drank 2 ~ 4 drinks per week up to one drink per day, but the relationship was linear in men (27). In our study, the proportion of male population in HTH group (56.0%) was significantly lower than that in control group (31.9%). This sex difference May be due to differences in testosterone regulation, which results in higher renal cysteine beta-synthetase (CBS) activity in men than in women, and CBS catalyzes an important pathway for

intracellular homocysteine metabolism (28). Thus, as there is no safe amount of alcohol to drink, it is best to aim for abstinence in the first instance, especially for males with HTH.

Our present study found that the unhealthy diet did not differ statistically between the HHcy group and the normal Hcy group after adjusted for other potential confounders, which was contrary to some studies showing that higher fruit and vegetable intake was associated with lower Hcy levels (29, 30). However, other studies have shown that vegetarians were at much higher risk of HHcy than non-vegetarians (31, 32). As is well-known, the intake of a variety of foods is more in line with human physiological characteristics. In addition, foods rich in B vitamins are not only vegetables and fruits, but also unprocessed meats, animal livers, and fish (33). Therefore, appropriately increasing the intake of vegetables and fruits, as part of a balanced diet, can benefit healthy people, while B vitamin supplementation may have a more direct effect on HHcy patients. In addition, greater daily physical activity is associated with lower homocysteine levels and that active exercise programs could positively control homocysteine level (34). However, our study found no relationship of inactive exercise with HHcy, which was similar with another study (35). These conflicting conclusions May be due to differences and flaws in study design, which require further validation in prospective studies. In fact, exercise training prevents the development of atherosclerosis through SIRT1 activation and oxidative stress inhibition under HHcy situation (36). In this study, we found inactive exercise increased the risk of HTH, further validating the results of previous study from another region in China (37). Thus, in the prevention and treatment of HTH and CVD, active physical exercise, especially aerobic exercise, should be put on the agenda. Besides, high BMI has been associated with HTH, and being obese or overweight (BMI $\geq$24 Kg/m^2) was a potential risk factor for HTH (38). Our research supports this view.

Previous observational studies have demonstrated that individual lifestyle factors are of critical importance in the progression of HTH (11, 39). However, it is worth noting that from the perspective of life course theory (12), there is a cumulative effect of risk factors in the pathogenesis of chronic diseases. For instance, a systematic review and meta-analysis of 142 prospective cohort showed that those with the healthiest lifestyles had lower risks of morbidity and mortality of CVD, compared with the participants with the least-healthy lifestyles (including cigarette smoking, alcohol consumption, physical activity, diet, and BMI) (14). Another study from Netherlands Cohort Study found that a significant healthy lifestyle score (smoking, BMI, physical activity, Mediterranean diet adherence, and alcohol intake) was significantly inversely associated with risk of esophageal and gastric cancer, in a linear fashion (13). A 12.2-year follow-up study of UK Biobank indicated that compared with the very unhealthy group (smoking, alcohol consumption, diet, and physical activity), the very healthy group had a 41% reduction in the risk for cardiometabolic multimorbidity in hypertensive patients and a 32–50% reduction in the risk for specific cardiometabolic disease (40). Therefore, it is of great importance to consider multiple healthy lifestyle factors when investigating the relationship of lifestyles with HTH because different behaviors tend to promote each other. For instance, most people who drink also smoke (41). To the best of our knowledge, however, little research has looked the relationship between cumulative exposures of lifestyle factors and HTH. Notably, our study provides important and new information on this issue, in which having a combination of unhealthy lifestyles (involving smoking, heavy alcohol consumption, inactive exercise, unhealthy diet and abnormal BMI) May higher the risk of HTH among the general population in China. Critically, these unhealthy lifestyle factors explained about 28.23% for the HTH risk, suggesting that avoiding these unhealthy lifestyle factors can reduce the risk of HTH by28.23%. Thus, lifestyle modifications, such as smoking cessation, reducing heavy alcohol drinking, regular physical activity, complement the nutritional approach and keeping a normal BMI to enhance Hcy metabolism (42), has great potential in the primary prevention of HTH.

In this study, we included baseline sex (males vs. female), age (<45 years vs. $\geq$45 years) and self-reported comorbidity groups (yes vs. no) in a subgroup analysis, which were not materially changed with those of the main analyses. For instance, cumulative exposure effect if unhealthy lifestyles were more pronounced in females than males, in elders than youngers and in those with comorbidities than those without. Gender roles and social norms lead to different lifestyle risk factors for males and females, for example, males are more likely to have unhealthy lifestyles like cigarettes smoking, heavy alcohol consumption, eating poorly and not exercising (43). And, Hcy levels increased with age, and total HHcy prevalence has been reported to be higher in the elderly than in youngers, due to nutritional causes or metabolic changes common to old age and poor nutritional absorption (44). In general, patients under comorbidity status have insufficient awareness of the risk of unhealthy lifestyles (45). Thus, these findings suggest that we should also take unhealthy behaviors change into account, especially in the males, elder and those with comorbidities, when preventing and screening for the HTH, thereby preventing the development of cardiovascular disease.

The study we conducted has a number of strengths. To the best of our knowledge, our study is the first to explore the effect of cumulative exposure with unhealthy lifestyles on HTH using a combined unhealthy lifestyle enabled us to comprehensively characterize an individual's profile, and confirmed that the combination of heavy alcohol consumption, unhealthy diet and BMI $\geq$24 Kg/m^2 was the most associated with HTH. Furthermore, we use a PSM case–control study to verify the positive association between lifestyle score and HTH, which can ensure the objectivity of the study, using similar covariate distributions to construct treatment and control groups without affecting study outcomes (15). As a semi-parametric method, PSM has fewer formal restrictions on the processing of model functions and fewer distribution assumptions for error terms, which increases the possibility of reasonable matching between the treatment group and the control group. Compared with the traditional method, when dealing with the problems such as multiple confounding factors or stratification, the matching has the possibility, and the calculation amount is greatly reduced, which provides an efficient and appropriate matching for the research (15). However, there were still some potential limitations that should be considered in interpretation of results. Firstly, many variables were self-reported and only evaluated at a point in time, so there May be recall or evaluation biases. For example, we used a composite index that included a variety of foods to assess unhealthy diet, however, it was not possible to completely avoid recall bias. Thus, the generalisability of our findings should be interpreted with caution. Besides, the lifestyle was only assessed by questionnaire at baseline. Future studies with repeated and objective assessment, such as wearables to assess individual exercise metabolism (46), will be necessary. Additionally, although lifestyle score was evaluated as a composite index (including smoking, heavy alcohol

drinking, unhealthy diet, inactive exercise, and high BMI) in our study, other possible lifestyles (e.g., sitting/sedentary behaviors) associated with risk of HTH were not considered. Second, participants in our study were from Hunan province, China, although the sample of this special population is considered large, the generalizability of our findings May be constrained in other regions of China. Thus, future multi-province or multinational monitoring studies are necessary to confirm our findings. Additionally, due to the case–control design of this study, causality cannot be inferred. Therefore, larger prospective investigations are required in the future to confirm the current findings. Finally, in present study, we focused on the association of unhealthy lifestyles with H-type hypertension, rather than with other clinical phenotypes such as ventricular hypertrophy in hypertension, which is a direct effect on the heart. In the next studies, we will consider using echocardiography to evaluate ventricular hypertrophy and explore the influence of unhealthy lifestyles on its occurrence.

In conclusion, our findings add new evidence to this field that cumulative exposure of unhealthy lifestyles (including smoking, heavy alcohol drinking, unhealthy diet, inactive exercise and high BMI) is consistently associated with higher risk of HTH among Chinses adults, with the largest effect combination being heavy alcohol consumption, unhealthy diet and BMI $\geq$24 Kg/m^2. These findings highlight that the effectiveness of comprehensive lifestyle modification in the prevention of HTH could be adopted to and reduce the risk of developing long-term CVD. Further long-term longitudinal studies are needed to evaluate the potential benefits of other lifestyles within this population to reduce the burden of disease.

Data availability statement

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

Ethics statement

The studies involving humans were approved by The Ethics Committee of Hunan Normal University (No. 034/2017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LL: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. JW: Formal analysis, Writing – review & editing. JL: Formal analysis, Writing – review & editing. ML: Data curation, Writing – review & editing. TL: Investigation, Writing – review & editing. YZ: Investigation, Writing – review & editing. YL: Writing – review & editing. XH: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1470788/full#supplementary-material

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Circulating fatty acids, genetic susceptibility and hypertension: a prospective cohort study

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Background: Combining genetic risk factors and plasma fatty acids (FAs) can be used as an effective method of precision medicine to prevent hypertension risk.

Methods: A total of 195,250 participants in the UK Biobank cohort were included in this study from 2006–2010. Polygenic risk scores (PRSs) were calculated for hypertension using single-nucleotide polymorphisms (SNPs). Concentrations of plasma FAs, including polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs) and saturated fatty acids (SFAs), were tested by nuclear magnetic resonance. The Cox model was used to test for the main effects of PRS, different plasma FAs and their joint effects on hypertension. Relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) were used to test the additive interaction.

Results: Plasma PUFAs, n-3 PUFAs, MUFAs and SFAs were related to the risk of hypertension (PUFAs: HR, 0.878; 95% CI, 0.868–0.888; MUFAs: HR, 1.13; 95% CI, 1.123–1.150; SFAs: HR, 1.086; 95% CI, 1.074–1.098; n-3 PUFAs: HR, 0.984; 95% CI, 0.973–0.995). Moreover, an additive interaction was found between PRS and plasma FAs, which could contribute to an approximately 10–18% risk of hypertension, and the associations between high plasma MUFAs and a high PRS of hypertension were the strongest positive [RERI: 0.178 (95% CI: 0.062, 0.294), AP: 0.079 (95% CI: 0.027, 0.130)].

Conclusion: Increased plasma MUFAs or SFAs and decreased plasma PUFAs or n-3 PUFAs were associated with hypertension risk, especially among people at high genetic risk.

KEYWORDS

plasma fatty acids, hypertension, polygenic risk score, additive interaction, cohort study

Introduction

Hypertension is the single contributing factor for the incidence rate and mortality of cardiovascular disease (CVD), including coronary artery disease (CAD), stroke, heart failure (HF), atrial fibrillation (AF), chronic kidney disease (CKD) and end-stage renal disease (ESRD), worldwide (1, 2), and more than one billion individuals are afflicted by hypertension. By 2025, the proportion of individuals with hypertension in the global adult population will reach approximately 29% (3). SBP is the main risk factor when it is ranked by disability-adjusted life

years (DALYs) attributable to risk globally, resulting in 10.4 million (95% CI: 9.39–11.5) deaths and 2.18 million (95% CI: 1.98–2.37) DALYs (3).

Recently, the Lancet Hypertension Committee proposed that a healthy environment and healthy lifestyle can effectively prevent hypertension (4). Recommendations of blood pressure guidelines, proposed by the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC)/European Society of Hypertension (ESH), mention that changing unhealthy lifestyles can be an effective measure to prevent hypertension, including healthy diets (5, 6). Prevailing dietary guidelines, such as the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets, emphasize reducing total fat and saturated fatty acids (SFAs) and increasing fish and olive oil with monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) (7–11). However, evidence on the associations of circulating fatty acid (FA) with hypertension risk is inconclusive and insufficient (12–15).

On the basis of a previous study, the inconclusive and inconsistent relationship between dietary FAs and hypertension may be explained by gene-nutrient interactions and gene polymorphisms (16–18), and individuals' genetic makeup may constitute a varied relationship between dietary FAs and hypertension. Large-scale genome-wide association studies (GWASs) have revealed that genetic polymorphisms also play a significant role in the development of hypertension (19–21) and have identified some genomic loci associated with hypertension, in which single nucleotide polymorphisms (SNPs) are aggregated into polygenetic risk scores (PRSs) that can sharply discriminate hypertension risk (21–24). However, because of the distinction between dietary FAs and plasma FAs, little is known about whether genetic variants could modify the specific role of plasma FAs in hypertension development.

Using large-scale sample data from the UK Biobank, to fill this gap, we conducted a prospective cohort study to reveal the relationship between plasma FA levels and hypertension. Furthermore, to evaluate the interaction between plasma FAs and genetic predisposition to hypertension, we calculated the PRS of hypertension and explored the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) between plasma FAs and PRS. To our knowledge, the present study is the first to discuss the relationship between plasma FA levels and genetic predispositions.

Patients and methods

Study design and population

The UK Biobank was a prospective cohort study whose research design and population details were as described above (25). A total of approximately 500,000 adults aged 40–69 years were included through multiple assessment centers from 2006–2010 (26). At baseline, participants provided electronic signatures, completed a touch-screen questionnaire, were asked about their medical history and health status by trained professionals and further collected data after a follow-up interval of 6 months to 3 years (25, 27). A flow chart of the details of participant inclusion is shown in Figure 1.

Assessment of plasma fatty acids

The detailed scheme for sample collection and quantification of the metabolic biomarker profiling platform on the basis of high-throughput nuclear magnetic resonance (NMR) was described in a previous study (28–30) and is available at https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=220. The plasma FAs were among the 249 metabolic biomarkers. The concentrations of plasma FAs were measured repeatedly in approximately 155,000 participants and were moderately correlated with the concentrations measured at baseline, indicating the stability of the measurements. The present study included a total of six fatty acid indicators, including PUFAs, MUFAs, SFAs, n-3 PUFAs, n-6 PUFAs, and n-3/n-6 PUFAs.

Assessment of hypertension

The outcome measured in this study was the occurrence of hypertension. As previously described (31, 32), the UK Biobank collected data from health episode statistics and death certificates according to the International Classification of Diseases 10th and 9th Revision (ICD-10). Specifically, the relevant ICD-10 codes include I10, I11, I12, I13, I15, and O10, whereas the ICD-9 codes include 401 through 405. In the population excluding baseline hypertension, we also omitted participants who were diagnosed with hypertension and those on antihypertensive medications.

Construction of the PRS for hypertension

Approximately 480,000 participants were genotyped in the UK Biobank (23, 33), and the details of the quality control and imputation procedures were performed as previously described (23, 33, 34). The PRS for hypertension was derived from single-nucleotide polymorphisms (SNPs) reported in a previous study (21, 32, 35). PRS calculations for hypertension were performed in this study via standard PRS (Category 301) data obtained from the UK Biobank, specifically field ID 26244 for hypertension, as per previous studies (32, 35). The participants were categorized as having low, intermediate, or high genetic risk of hypertension in noncases by tertiles, as described previously (31, 36, 37).

Assessment of covariates

In accordance with previous studies (6, 23, 38–41), we determined the covariates that were considered in this analysis, including age, sex (male/female), race (white/Asian/black/other/missing), towns deprivation index (TDI), healthy diet (unhealthy/healthy/missing), body mass index (BMI)

Abbreviations: FAs, Fatty acids; PRS, Polygenic risk score; SNP, Single-nucleotide polymorphism; PUFA, Polyunsaturated fatty acid; MUFA, Monounsaturated fatty acid; SFA, Saturated fatty acid; RERI, Relative excess risk due to interaction; AP, Attributable proportion; CVD, Cardiovascular disease; HF, Heart failure; AF, Atrial fibrillation; CKD, Chronic kidney disease; ESRD, End-stage renal disease; DALY, Disability-adjusted life years; GWAS, Genome wide association studies; ICD-10, International Classification of Diseases; TDI, Townsend deprivation index; MET, Metallic equivalent task; BMI, Body mass index; HR, Hazard ratio; CI, Confidence interval; RCS, Restricted cubic spline.

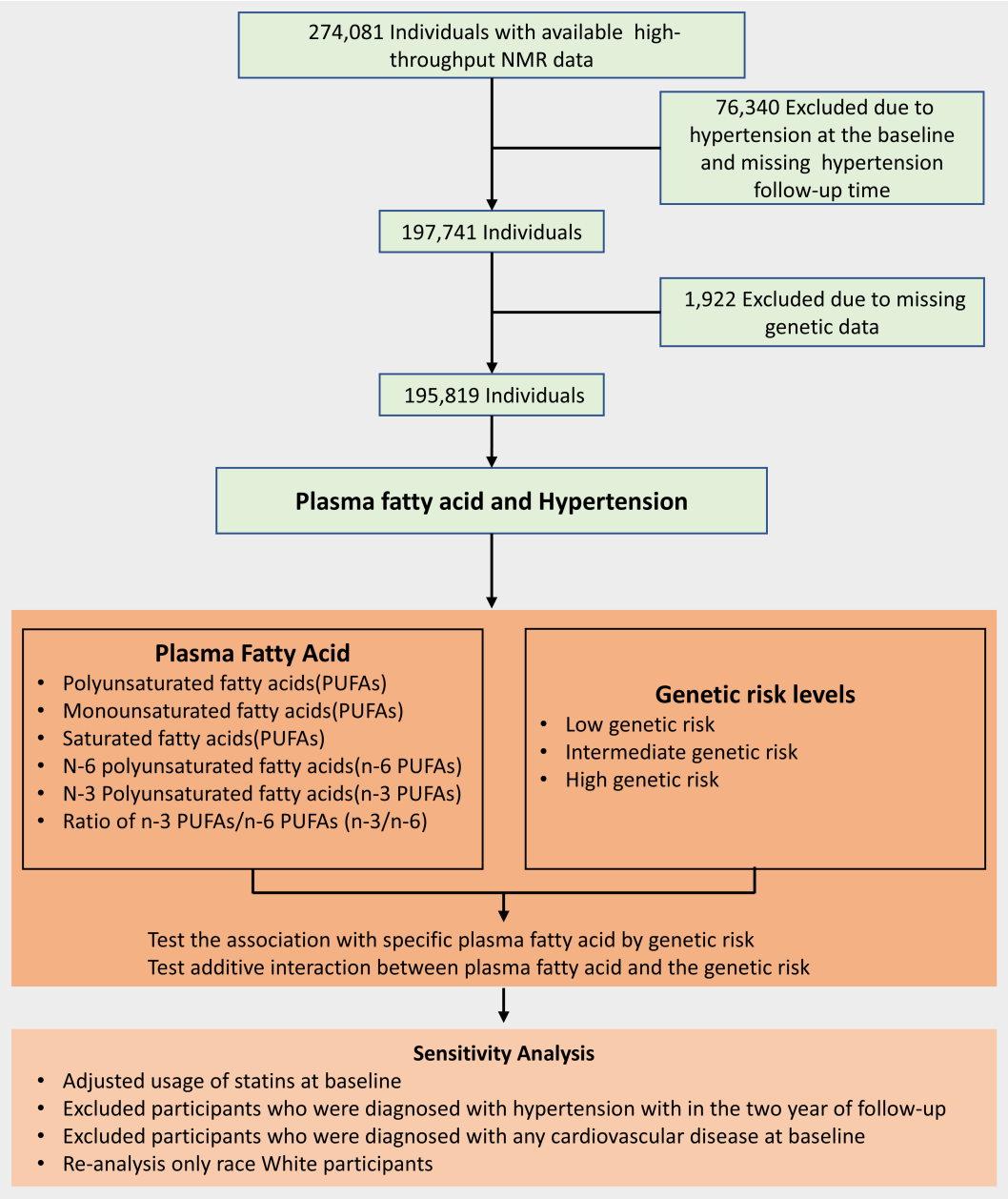

FIGURE 1
Flow diagram for the inclusion of participants.

(<25 kg/m^2/25 to 29.9 kg/m^2/≥30 kg/m^2, missing), alcohol consumption (daily or almost daily/three or four times a week/once or twice a week/one to three times a month/special occasion only/never/missing), smoking status (never/before/current/missing), diabetes status (yes/no/missing) and family history of disease (CVD/other diseases/missing). The authors adhered to the 2017 UK Physical Activity Guidelines to assess physical activity, which was determined by meeting the criteria of engaging in 150 min of walking or moderate activity or 75 min of vigorous activity per week (42). In accordance with a previous study (32), using recent dietary recommendations for cardiovascular health, we evaluated dietary quality, and the healthy level was defined as the intake of more than 5 dietary components (Supplementary Table S1). Weight data were collected from participants using a Tanita BC418MA body composition analyzer, and height measurements were obtained with a Seca 240 cm height measure. BMI was calculated using the formula: weight (kg)/height (m^2). The diagnosis of diabetes was determined using the touchscreen questionnaire, which asked participants, "Has a doctor ever told you that you have diabetes?" The first 10 genetic principal components were further adjusted while the genetic data were analysed. Missing data for continuous variables and categorical variables were substituted by the mean values and missing indicator categories, respectively. Information

about the covariates, including demographic characteristics and socioeconomic conditions, was obtained from the touchscreen questionnaire as described previously (25).

Statistical analysis

Continuous variables and categorical variables are presented as the mean combined standard deviation and the number of cases combined percentage, respectively. For covariates, missing values for continuous variables were replaced with mean values, whereas missing data for categorical variables were addressed via dummy variables. A Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for hypertension according to quartiles or 1-SD increments of specific plasma FAs, which were included in the present study as percentages of total plasma FAs, which were more meaningful than absolute concentrations with regard to metabolic relationships, as previously described (43). Schoenfeld residuals were used to test the proportional hazard assumption. In the multivariate analysis of hypertension, we constructed Model 1 and Model 2, in which Model 1 was adjusted for age and sex, and Model 2 was adjusted for other confounding factors according to previous studies (6, 38–41), including race, TDI, physical activity, BMI, alcohol consumption, smoking status, diet score, diabetes status and family history of disease. We conducted restricted cubic spline (RCS) regression to evaluate the dose-response relationship between plasma FA levels and hypertension risk. A total of 195,250 participants were included in this study. The interaction between plasma fatty acids (FAs) and genetic risk factors was evaluated via two statistical measures: the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP). To identify subgroups susceptible to plasma FAs, we conducted stratified analyses by age (<60/≥60 years), sex (male vs. female), BMI (<25 kg/m^2/25 to 29.9 kg/m^2/≥30 kg/m^2), physical activity (yes/no/unknown), smoking status (current/before/never), alcohol consumption (daily or almost daily/three or four times a week/once or twice a week/one to three times a month/special occasions only/never/missing) and economic level (Townsend deprivation index (TDI) <−3.22/−3.22 to −0.78/≥−0.78). Effect modification by these factors was tested via the heterogeneity test. In the sensitivity analyses, we additionally adjusted the usage of statins and excluded participants with a follow-up time of less than 2 years, those with CVD at baseline and nonwhite participants. Statistical analyses were performed via R software (version 4.2.1), and the *p*-values of all tests were two-sided, with values less than 0.05 considered statistically significant.

Results

Analysis of patient characteristics

A total of 195,250 participants were ultimately included in the present study. Table 1 and Supplementary Table S2 summarize the baseline characteristics of the participants and present the results stratified on the basis of the quantiles of PUFAs, MUFAs and SFAs. As shown in Table 1 and Supplementary Table S2, individuals with lower concentrations of PUFAs tended to be male, be current smokers, have higher BMIs, and have lower diet scores, whereas individuals with lower concentrations of MUFAs and SFAs tended to be female, never smokers, have lower BMIs, and have higher diet scores.

Associations between plasma FA levels and hypertension

The average follow-up time for this study was 12.48 years. Table 2 shows the associations between plasma fatty acid concentrations and hypertension. In Model 1, higher concentrations of SFAs and MUFAs were related to higher hypertension risk, and higher concentrations of PUFAs, n-6 PUFAs, n-3 PUFAs and the ratio of n-3 PUFAs to n-6 PUFAs were associated with lower hypertension risk. When all covariates were adjusted, the difference was still statistically significant (PUFAs: HR, 0.878; 95% CI, 0.868–0.888; MUFAs: HR, 1.137; 95% CI, 1.123–1.150; SFAs: HR, 1.086; 95% CI, 1.074–1.098; n-3 PUFAs: HR, 0.984; 95% CI, 0.973–0.995), which included race, physical activity, smoking status, alcohol consumption, BMI, TDI and diabetes, family history of CVD and diet score except n-3 PUFAs. RCS regression revealed similar results, except for the ratio of n-6 PUFAs to n-3 PUFAs, which was not statistically significant (Figure 1). Stratified analyses revealed that the effects of plasma FAs (per 1-SD) on hypertension were generally similar across different subgroups in terms of physical activity, TDI, smoking status and alcohol consumption. We detected heterogeneity among the subgroups according to sex, age and BMI, but the trends within the groups were consistent (Supplementary Table S3), and the female subgroup, nonelderly subgroup and normal-BMI subgroup seemed to be more sensitive to the effect of plasma FA levels on hypertension risk.

Associations of genetic risk with plasma FA levels and hypertension

We evaluated whether genetic risk factors affect the association between plasma FA and hypertension. A significant increase in hypertension risk across the deciles of the PRS was observed (*p* trend <0.001; Supplementary Table S4), and when the low PRS was used as the reference, hypertension risk was greater for those with intermediate genetic risk and high genetic risk (Model 1, intermediate HR, 1.334; 95% CI, 1.297–1.372; high HR, 1.751; 95% CI, 1.705–1.798; Model 2, intermediate HR, 1.356; 95% CI, 1.289–1.427; high HR, 1.329; 95% CI, 1.301–1.358) (Supplementary Table S5).

We observed a significant joint association between plasma FA levels and genetic risk factors for hypertension, which exhibited a dose-response relationship. As shown in Figure 2, we investigated only the plasma FAs associated with a statistically significant risk of hypertension, including PUFAs, MUFAs, and SFAs. Compared with individuals with a low PRS and low plasma FA risk (quantile 4 as the reference for PUFAs and n-6 PUFAs, quantile 1 as the reference for MUFAs and SFAs), individuals with high genetic risk and high plasma FA risk had the highest risk of hypertension, as shown in Figure 3, in which the HR of the plasma MUFAs was 2.25 (95% CI: 2.12, 2.38), that of the PUFAs was 2.33 (95% CI: 2.20, 2.47) and that of the SFAs was 2.12 (95% CI: 2.01, 2.25). In addition, the RERIs and APs due to the additive interaction of genetic risk factors and plasma FAs were calculated (Table 3). Individuals with high genetic risk and high MUFA risk had the highest RERIs and APs [RERIs: 0.178 (95% CI:

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TABLE 1 Clinical characteristics by quantile of PUFAs (n = 195,819).

	PUFAs			
	Quantile 1	Quantile 2	Quantile 3	Quantile 4
	(N = 48,825)	(N = 48,817)	(N = 48,795)	(N = 48,813)
Age (years), mean (SD)	56.0 (8.05)	56.0 (8.10)	55.3 (8.14)	54.4 (8.23)
Sex, %				
Female	19,663 (40.3%)	27,212 (55.7%)	31,121 (63.8%)	31,826 (65.2%)
Male	29,162 (59.7%)	21,605 (44.3%)	17,674 (36.2%)	16,987 (34.8%)
Race, %				
White	47,355 (97.0%)	47,127 (96.5%)	46,627 (95.6%)	44,021 (90.2%)
Asian or Asian British	555 (1.1%)	631 (1.3%)	744 (1.5%)	1,443 (3.0%)
Black or Black British	128 (0.3%)	233 (0.5%)	410 (0.8%)	1,596 (3.3%)
Chinese	76 (0.2%)	91 (0.2%)	132 (0.3%)	346 (0.7%)
Mixed	232 (0.5%)	237 (0.5%)	305 (0.6%)	382 (0.8%)
Other ethnic group	262 (0.5%)	304 (0.6%)	369 (0.8%)	741 (1.5%)
Missing value	217 (0.4%)	194 (0.4%)	208 (0.4%)	284 (0.6%)
BMI, %				
Normal (<25 kg/m^2)	8,983 (18.4%)	15,759 (32.3%)	21,814 (44.7%)	27,900 (57.2%)
Overweight (25 to 29.9 kg/m^2)	23,375 (47.9%)	22,548 (46.2%)	20,436 (41.9%)	16,920 (34.7%)
Obesity (≥30 kg/m^2)	16,295 (33.4%)	10,352 (21.2%)	6,414 (13.1%)	3,844 (7.9%)
Missing value	172 (0.4%)	158 (0.3%)	131 (0.3%)	149 (0.3%)
Smoke status, %				
Never	22,743 (46.6%)	26,400 (54.1%)	28,899 (59.2%)	31,565 (64.7%)
Previous	17,503 (35.8%)	16,184 (33.2%)	15,444 (31.7%)	14,325 (29.3%)
Current	8,305 (17.0%)	6,007 (12.3%)	4,247 (8.7%)	2,706 (5.5%)
Missing value	274 (0.6%)	226 (0.5%)	205 (0.4%)	217 (0.4%)
Alcohol consumption, %				
Daily or almost daily	10,842 (22.2%)	10,229 (21.0%)	9,537 (19.5%)	7,840 (16.1%)
Three or four times a week	11,161 (22.9%)	11,746 (24.1%)	12,121 (24.8%)	11,663 (23.9%)
Once or twice a week	12,444 (25.5%)	13,025 (26.7%)	13,328 (27.3%)	13,310 (27.3%)
One to three times a month	5,444 (11.2%)	5,290 (10.8%)	5,569 (11.4%)	5,885 (12.1%)
Special occasions only	5,326 (10.9%)	5,120 (10.5%)	4,958 (10.2%)	5,587 (11.4%)
Never	3,488 (7.1%)	3,315 (6.8%)	3,212 (6.6%)	4,400 (9.0%)
Missing value	120 (0.2%)	92 (0.2%)	70 (0.1%)	128 (0.3%)
Townsend deprivation index	−1.22 (3.11)	−1.49 (2.98)	−1.61 (2.92)	−1.50 (3.04)
Family history, %				
CVD	35,327 (72.4%)	35,492 (72.7%)	35,555 (72.9%)	35,327 (72.4%)
Other	12,849 (26.3%)	12,700 (26.0%)	12,647 (25.9%)	12,922 (26.5%)
No disease	649 (1.3%)	625 (1.3%)	593 (1.2%)	564 (1.2%)
Diet score				
Unhealthy	35,836 (73.4%)	33,979 (69.6%)	32,402 (66.4%)	29,645 (60.7%)
Healthy	10,236 (21.0%)	12,191 (25.0%)	13,814 (28.3%)	16,126 (33.0%)
Missing	2,753 (5.6%)	2,647 (5.4%)	2,579 (5.3%)	3,042 (6.2%)
Physical activity, %				
No	7,949 (16.3%)	6,861 (14.1%)	6,095 (12.5%)	5,862 (12.0%)

(Continued)

TABLE 1 (Continued)

	PUFAs			
	Quantile 1	Quantile 2	Quantile 3	Quantile 4
	(*N* = 48,825)	(*N* = 48,817)	(*N* = 48,795)	(*N* = 48,813)
Yes	29,489 (60.4%)	30,950 (63.4%)	32,239 (66.1%)	33,379 (68.4%)
Unknown	11,387 (23.3%)	11,006 (22.5%)	10,461 (21.4%)	9,572 (19.6%)

TABLE 2 Adjusted hazard ratio (HR) and 95% confidence interval (95% CI) of hypertension according to plasma FA exposure.

	Quartiles of plasma FA (% of total fatty acids)				*p* trend	HR (95% CI)[a]
	Quantile 1	Quantile 2	Quantile 3	Quantile 4		
PUFAs						
Model 1	1.00	0.753 (0.733, 0.774)	0.618 (0.600, 0.637)	0.541 (0.525, 0.559)	<0.001	0.789 (0.781, 0.797)
Model 2	1.00	0.864 (0.840, 0.888)	0.780 (0.757, 0.805)	0.720 (0.696, 0.745)	<0.001	0.878 (0.868, 0.888)
MUFAs						
Model 1	1.00	1.177 (1.137, 1.218)	1.452 (1.404, 1.500)	1.913 (1.852, 1.975)	<0.001	1.293 (1.279, 1.306)
Model 2	1.00	1.071 (1.034, 1.109)	1.195 (1.155, 1.237)	1.367 (1.320, 1.415)	<0.001	1.137 (1.123, 1.150)
SFAs						
Model 1	1.00	0.996 (0.965, 1.029)	1.100 (1.066, 1.135)	1.341 (1.301, 1.381)	<0.001	1.135 (1.123, 1.147)
Model 2	1.00	1.007 (0.975, 1.040)	1.086 (1.052, 1.121)	1.208 (1.171, 1.246)	<0.001	1.086 (1.074, 1.098)
n-6 PUFAs						
Model 1	1.00	1.009 (0.980, 1.039)	1.022 (0.992, 1.053)	1.001 (0.971, 1.033)	0.202	1.016 (1.004, 1.027)
Model 2	1.00	0.982 (0.954, 1.011)	0.978 (0.949, 1.008)	0.942 (0.912, 0.972)	0.018	0.991 (0.980, 1.003)
n-3 PUFAs						
Model 1	1.00	0.954 (0.925, 0.983)	0.915 (0.888, 0.943)	0.834 (0.808, 0.860)	0.002	0.931 (0.921, 0.941)
Model 2	1.00	0.988 (0.958, 1.019)	0.988 (0.958, 1.019)	0.968 (0.938, 0.999)	0.439	0.984 (0.973, 0.995)
n-3/n-6 ratio						
Model 1	1.00	0.991 (0.961, 1.022)	0.962 (0.933, 0.993)	0.917 (0.889, 0.946)	0.581	0.966 (0.956, 0.977)
Model 2	1.00	1.014 (0.983, 1.046)	1.016 (0.984, 1.048)	1.019 (0.988, 1.052)	0.394	0.999 (0.989, 1.010)

Model 1 was adjusted for age and sex (male/female). Model 2 included Model 1 plus race (white/Asian/black/other/missing), the TDI, a healthy diet (unhealthy/healthy/missing), physical activity (no/yes/unknown), body mass index (BMI) (<25 kg/m^2, 25 to 29.9 kg/m^2, ≥30 kg/m^2, missing), alcohol consumption (daily or almost daily/three or four times a week/once or twice a week/one to three times a month/special occasion only/never/missing), smoking status (never/before/current/missing), diabetes status (yes/no/missing) and family history of disease (CVD/other diseases/missing).

[a]Per-SD of exposure.

0.062, 0.294), AP: 0.079 (95% CI: 0.027, 0.130)]. Therefore, we suggest that there would be 0.178 relative excess risk due to the additive interaction, accounting for 7.9% (95% CI: 2.7, 13.0%) of the hypertension risk. Moreover, significant interactions between other plasma FAs and genetic risk factors for hypertension were observed. Because of heterogeneity among subgroups according to sex, age and BMI for plasma FAs (per 1-SD) in hypertension patients, stratified analyses were also performed and revealed similar tendencies among

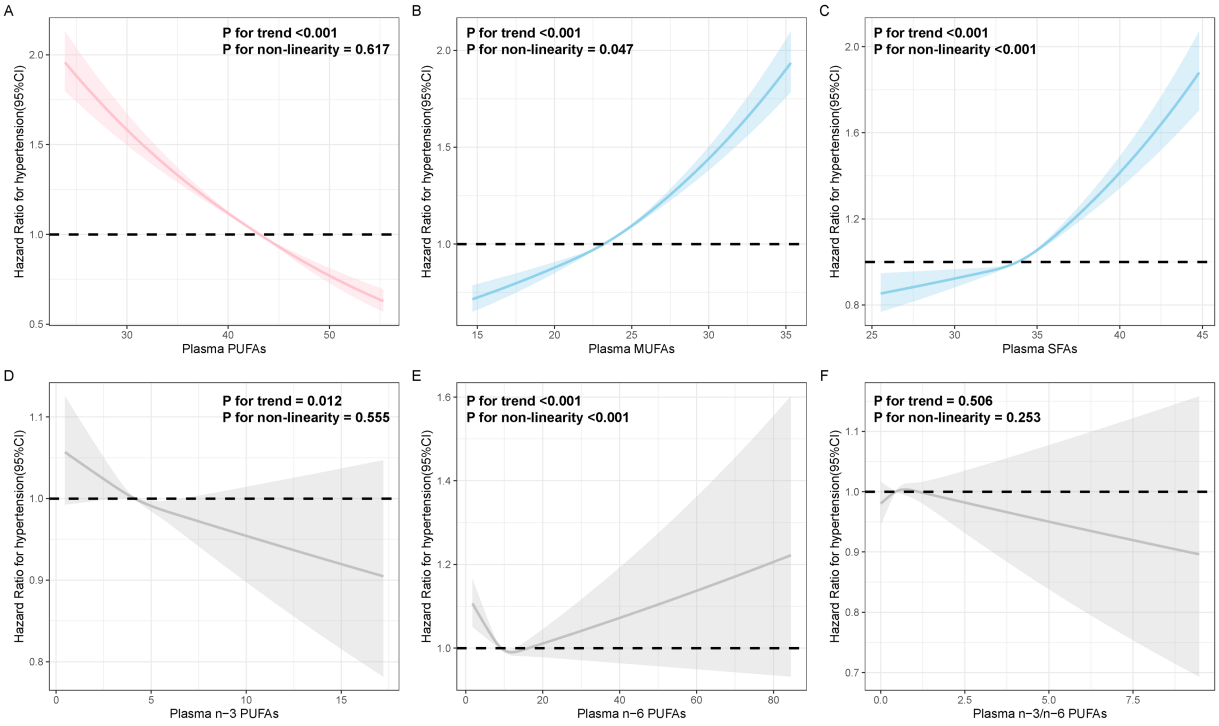
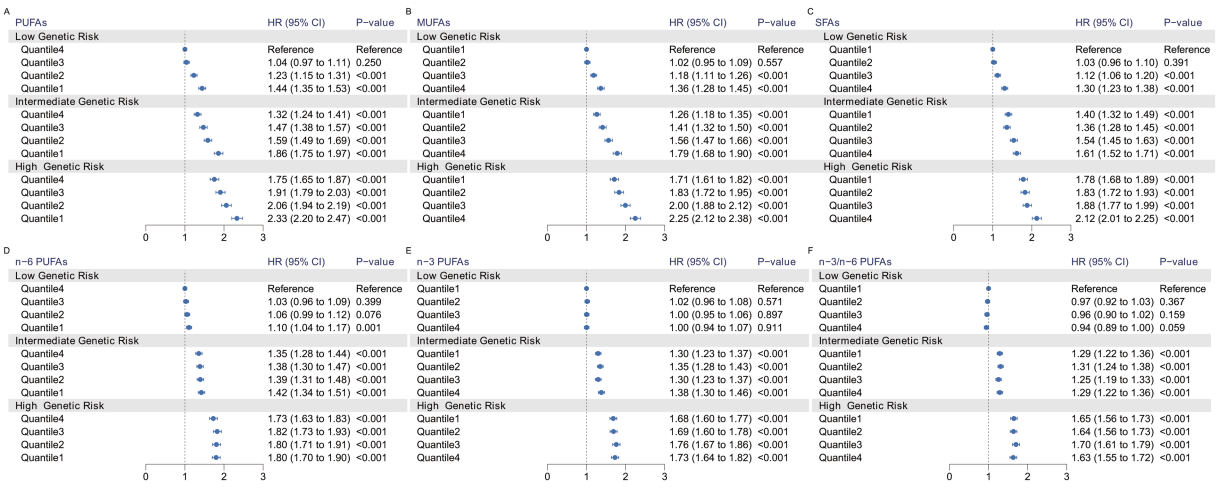


FIGURE 2
Dose-response relationships between plasma FA and hypertension risk. HRs for hypertension associated with plasma PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-3 PUFAs **(D)**, n-6 PUFAs **(E)**, and the n-6/n-3 ratio **(F)** were estimated via restricted cubic-spline regression via Model 2.



A

PUFAs	HR (95% CI)	P−value
Low Genetic Risk		
Quantile4	Reference	Reference
Quantile3	1.04 (0.97 to 1.11)	0.250
Quantile2	1.23 (1.15 to 1.31)	<0.001
Quantile1	1.44 (1.35 to 1.53)	<0.001
Intermediate Genetic Risk		
Quantile4	1.32 (1.24 to 1.41)	<0.001
Quantile3	1.47 (1.38 to 1.57)	<0.001
Quantile2	1.59 (1.49 to 1.69)	<0.001
Quantile1	1.86 (1.75 to 1.97)	<0.001
High Genetic Risk		
Quantile4	1.75 (1.65 to 1.87)	<0.001
Quantile3	1.91 (1.79 to 2.03)	<0.001
Quantile2	2.06 (1.94 to 2.19)	<0.001
Quantile1	2.33 (2.20 to 2.47)	<0.001

B

MUFAs	HR (95% CI)	P−value
Low Genetic Risk		
Quantile1	Reference	Reference
Quantile2	1.02 (0.95 to 1.09)	0.557
Quantile3	1.18 (1.11 to 1.26)	<0.001
Quantile4	1.36 (1.28 to 1.45)	<0.001
Intermediate Genetic Risk		
Quantile1	1.26 (1.18 to 1.35)	<0.001
Quantile2	1.41 (1.32 to 1.50)	<0.001
Quantile3	1.56 (1.47 to 1.66)	<0.001
Quantile4	1.79 (1.68 to 1.90)	<0.001
High Genetic Risk		
Quantile1	1.71 (1.61 to 1.82)	<0.001
Quantile2	1.83 (1.72 to 1.95)	<0.001
Quantile3	2.00 (1.88 to 2.12)	<0.001
Quantile4	2.25 (2.12 to 2.38)	<0.001

C

SFAs	HR (95% CI)	P−value
Low Genetic Risk		
Quantile1	Reference	Reference
Quantile2	1.03 (0.96 to 1.10)	0.391
Quantile3	1.12 (1.06 to 1.20)	<0.001
Quantile4	1.30 (1.23 to 1.38)	<0.001
Intermediate Genetic Risk		
Quantile1	1.40 (1.32 to 1.49)	<0.001
Quantile2	1.36 (1.28 to 1.45)	<0.001
Quantile3	1.54 (1.45 to 1.63)	<0.001
Quantile4	1.61 (1.52 to 1.71)	<0.001
High Genetic Risk		
Quantile1	1.78 (1.68 to 1.89)	<0.001
Quantile2	1.83 (1.72 to 1.93)	<0.001
Quantile3	1.88 (1.77 to 1.99)	<0.001
Quantile4	2.12 (2.01 to 2.25)	<0.001

D

n−6 PUFAs	HR (95% CI)	P−value
Low Genetic Risk		
Quantile4	Reference	Reference
Quantile3	1.03 (0.96 to 1.09)	0.399
Quantile2	1.06 (0.99 to 1.12)	0.076
Quantile1	1.10 (1.04 to 1.17)	0.001
Intermediate Genetic Risk		
Quantile4	1.35 (1.28 to 1.44)	<0.001
Quantile3	1.38 (1.30 to 1.47)	<0.001
Quantile2	1.39 (1.31 to 1.48)	<0.001
Quantile1	1.42 (1.34 to 1.51)	<0.001
High Genetic Risk		
Quantile4	1.73 (1.63 to 1.83)	<0.001
Quantile3	1.82 (1.73 to 1.93)	<0.001
Quantile2	1.80 (1.71 to 1.91)	<0.001
Quantile1	1.80 (1.70 to 1.90)	<0.001

E

n−3 PUFAs	HR (95% CI)	P−value
Low Genetic Risk		
Quantile1	Reference	Reference
Quantile2	1.02 (0.96 to 1.08)	0.571
Quantile3	1.00 (0.95 to 1.06)	0.897
Quantile4	1.00 (0.94 to 1.07)	0.911
Intermediate Genetic Risk		
Quantile1	1.30 (1.23 to 1.37)	<0.001
Quantile2	1.35 (1.28 to 1.43)	<0.001
Quantile3	1.30 (1.23 to 1.37)	<0.001
Quantile4	1.38 (1.30 to 1.46)	<0.001
High Genetic Risk		
Quantile1	1.68 (1.60 to 1.77)	<0.001
Quantile2	1.69 (1.60 to 1.78)	<0.001
Quantile3	1.76 (1.67 to 1.86)	<0.001
Quantile4	1.73 (1.64 to 1.82)	<0.001

F

n−3/n−6 PUFAs	HR (95% CI)	P−value
Low Genetic Risk		
Quantile1	Reference	Reference
Quantile2	0.97 (0.92 to 1.03)	0.367
Quantile3	0.96 (0.90 to 1.02)	0.159
Quantile4	0.94 (0.89 to 1.00)	0.059
Intermediate Genetic Risk		
Quantile1	1.29 (1.22 to 1.36)	<0.001
Quantile2	1.31 (1.24 to 1.38)	<0.001
Quantile3	1.25 (1.19 to 1.33)	<0.001
Quantile4	1.29 (1.22 to 1.36)	<0.001
High Genetic Risk		
Quantile1	1.65 (1.56 to 1.73)	<0.001
Quantile2	1.64 (1.56 to 1.73)	<0.001
Quantile3	1.70 (1.61 to 1.79)	<0.001
Quantile4	1.63 (1.55 to 1.72)	<0.001

FIGURE 3
Risk of incident hypertension according to the concentration of plasma fatty acids and genetic risk categories. The HRs for hypertension according to PUFAs (A), MUFAs (B), SFAs (C), n-6 PUFAs (D), n-3 PUFAs (E), n-3/n-6 PUFAs (F) and polygenic risk score categories were estimated via Model 2 plus the genotyping batch and the first 4 genetic principal components.

the female subgroup, nonelderly subgroup and normal-BMI subgroup (Supplementary Figures S1–S6).

Sensitivity analyses

After further adjusting for the covariates of statin use at baseline and excluding participants with CVD at baseline, those with a follow-up time of less than 2 years and nonwhite participants, we conducted a sensitivity analysis. The analyses revealed that the observed associations between genetic risk, plasma FA concentration and hypertension risk were robust (Supplementary Figures S7–S14 and Supplementary Tables S6–S13). Restricted cubic spline regression and forest plots were used to visualize the relationships among genetic risk factors, plasma FA levels and hypertension (see Figure 2).

TABLE 3 RERIs and APs for additive interactions between shift work exposure and genetic categories.

		Intermediate risk		High risk		*p* for multiplicative interactions
		RERI (95% CI)	AP (95% CI)	RERI (95% CI)	AP (95% CI)	
PUFAs	Quantile 3	0.115 (0.008, 0.221)	0.077 (0.006, 0.149)	0.112 (−0.007, 0.230)	0.058 (−0.003, 0.120)	0.011
	Quantile 2	0.037 (−0.071, 0.144)	0.023 (−0.044, 0.091)	0.075 (−0.043, 0.194)	0.037 (−0.021, 0.094)	
	Quantile 1	0.098 (−0.010, 0.206)	0.052 (−0.005, 0.110)	0.146 (0.027, 0.265)	0.062 (0.012, 0.113)	
MUFAs	Quantile 1	0.118 (0.015, 0.221)	0.084 (0.010, 0.157)	0.092 (−0.024, 0.207)	0.050 (−0.013, 0.113)	0.034
	Quantile 2	0.116 (0.013, 0.219)	0.074 (0.008, 0.141)	0.096 (−0.019, 0.211)	0.048 (−0.010, 0.106)	
	Quantile 3	0.157 (0.053, 0.262)	0.087 (0.029, 0.145)	0.178 (0.062, 0.294)	0.079 (0.027, 0.130)	
SFAs	Quantile 1	−0.067 (−0.170, 0.036)	−0.049 (−0.124, 0.026)	0.018 (−0.093, 0.129)	0.010 (−0.050, 0.070)	0.038
	Quantile 2	0.013 (−0.090, 0.116)	0.009 (−0.058, 0.075)	−0.024 (−0.136, 0.087)	−0.013 (−0.072, 0.046)	
	Quantile 3	−0.093 (−0.197, 0.011)	−0.058 (−0.123, 0.007)	0.040 (−0.071, 0.151)	0.019 (−0.034, 0.071)	
n-6 PUFAs	Quantile 3	0.002 (−0.096, 0.100)	0.002 (−0.070, 0.073)	0.074 (−0.031, 0.179)	0.041 (−0.017, 0.099)	0.769
	Quantile 2	−0.024 (−0.122, 0.073)	−0.018 (−0.088, 0.053)	0.028 (−0.077, 0.133)	0.016 (−0.043, 0.074)	
	Quantile 1	−0.038 (−0.135, 0.059)	−0.027 (−0.095, 0.042)	−0.022 (−0.128, 0.083)	−0.012 (−0.071, 0.046)	
n-3 PUFAs	Quantile 3	0.037 (−0.054, 0.128)	0.027 (−0.039, 0.093)	−0.000 (−0.100, 0.099)	−0.000 (−0.058, 0.058)	0.364
	Quantile 2	0.003 (−0.088, 0.095)	0.002 (−0.067, 0.072)	0.081 (−0.018, 0.181)	0.046 (−0.010, 0.102)	
	Quantile 1	0.085 (−0.007, 0.177)	0.060 (−0.005, 0.125)	0.040 (−0.061, 0.141)	0.023 (−0.035, 0.081)	
n-3/n-6 PUFAs	Quantile 3	0.047 (−0.040, 0.134)	0.035 (−0.030, 0.101)	0.022 (−0.073, 0.117)	0.013 (−0.044, 0.071)	0.183
	Quantile 2	0.014 (−0.075, 0.102)	0.011 (−0.059, 0.080)	0.103 (0.008, 0.198)	0.060 (0.005, 0.116)	
	Quantile 1	0.061 (−0.028, 0.150)	0.047 (−0.021, 0.115)	0.037 (−0.060, 0.134)	0.023 (−0.037, 0.082)	

RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction. PUFAs, n-6 PUFAs, n-3 PUFAs, and the n-3/n-6 PUFA ratio, with the fourth quartile serving as the reference group. For MUFAs and SFAs, the first quartile served as the reference group. Adjusted for age and sex (male/female), race (white/Asian/black/other/missing), Townsend deprivation index (TDI), healthy diet (unhealthy/healthy/missing), physical activity (no/yes/unknown), body mass index (BMI) (<25 kg/m^2, 25 to 29.9 kg/m^2, ≥30 kg/m^2, missing), alcohol consumption (daily or almost daily/three or four times a week/once or twice a week/one to three times a month/special occasions only/never/missing), smoking status (never/before/current/missing), diabetes (yes/no/missing), family history of disease (CVD/other diseases/missing), and the first 10 genetic principal components.

Discussion

In the present study, on the basis of a prospective study of approximately 100,000 participants, we found that plasma FAs, including plasma PUFAs, MUFAs and SFAs, were associated with hypertension risk, in which concentrations of plasma PUFAs were related to a lower risk of hypertension, and plasma SFAs and MUFAs were related to a higher risk of hypertension. Importantly, interaction effects between plasma FA levels and genetic risk factors for hypertension were found, indicating that the relationship between plasma FA levels and the risk of hypertension could be modified by genetic risk factors. Among individuals with intermediate genetic risk, the associations between quantile 3 plasma MUFAs and high genetic risk of hypertension were the strongest positive. The present study, which used a large-scale sample prospective cohort study, provides remarkable insight into additive interactions between plasma FAs and hypertension PRS with respect to hypertension risk.

Previous work has confirmed the relationship between plasma FA exposure and hypertension. However, the conclusions have not been consistent. The Atherosclerosis Risk in Communities (ARIC) study (12) showed that the odds ratio (OR) estimates and 95% CI of incident hypertension for an interquartile increment of a fatty acid were MUFAs [1.11 (0.96, 1.28)], PUFAs [0.88 (0.75, 1.02)], SFAs [1.15 (0.97, 1.36)], 22:6n-3 [1.20 (1.04, 1.37)] and 20:5n-3 [1.16 (1.04, 1.28)], whereas the genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors (GAPP) (13) showed that higher docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3) were correlated with lower blood pressure, and a similar result was observed among Black South African adults (14). In addition, conflicts have also been reported among other plasma FAs, such as SFAs and MUFAs. Yang et al. (15) reported that lower proportions of 14:0, 16:0 and 16:1n-7 were beneficial for increasing blood pressure, and Zheng et al. (12) reported that the risk of hypertension and SFAs was 2.01 (1.05, 2.98), whereas the ARIC reported a negative relationship with hypertension. The present study, which used a large prospective cohort study, strengthened the association with hypertension risk. Metabolic exposure to MUFAs had the strongest relationship with increased hypertension risk, followed by SFAs, and PUFAs and n-6 PUFAs had similar associations with decreased hypertension risk. However, as one of the limitations of this study, we cannot estimate the similarities and differences in the metabonomic components of different plasma FAs, such as EPA.

Some studies have previously explored the relationships between plasma FA levels and hypertension or between genetic risk factors and hypertension; however, to our knowledge, the present study is the first to explore additive interactions between plasma FA levels and genetic risk factors for hypertension. We revealed that the risk of hypertension associated with plasma FAs was increased by genetic risk factors, which indicated that approximately 15–55% of the risk of hypertension could be attributed to additive interactions, and the additive interaction between quantile 1 MUFAs and intermediate risk was the most significant. In light of these findings, the possibility that plasma FAs modify the influence of genetic susceptibility on hypertension risk could be speculated.

Moreover, our findings have highlighted the public health implications for the prevention of hypertension. Hypertension constitutes a major disease burden worldwide, and the recommendations of blood pressure guidelines mention that changing unhealthy lifestyles, such as weekly aerobic exercise, a DASH diet, ideal weight and moderate alcohol consumption, can be effective measures for preventing hypertension (5, 44). However, the success of maintaining a healthy lifestyle depends mostly on the compliance of participants, and many factors may affect persistence, including biological, behavioral, psychosocial and environmental factors (45–47). In addition, previous studies reported that genetic risk, such as variants of the AGT gene encoding angiotensinogen, which plays a role in the renin-angiotensin system (48–50), may vary across ethnicities, indicating the need for tailored prevention programs and precision medicine. To date, the combined preventive effects of plasma FAs in individuals at high genetic risk for hypertension have not been investigated. To fill this gap, our study may provide new evidence that combining plasma FA levels and the genetic risk of hypertension could identify individuals with high hypertension risk and reduce the control cost.

Previous experimental mechanism studies have corroborated our findings. Oleic acid, a MUFA, has been shown in earlier studies to generate mitochondrial reactive oxygen species (51) and decrease cellular nitric oxide synthase activity, which contributes to vascular endothelial cell dysfunction. Similarly, palmitic acid, a saturated fatty acid, has been demonstrated to activate the p38/JNK pathway through the promotion of reactive oxygen species production, leading to the aging and dysfunction of vascular endothelial cells (52). This dysfunction is significantly associated with the onset and progression of hypertension. Additionally, EPA, a PUFA, has been reported in prior studies to mitigate renal oxidative stress by stimulating Nrf-2 and regulating interleukin (IL)-6 to enhance the anti-inflammatory response, thereby influencing systolic blood pressure (53).

The strengths of the study are as follows. First, and most importantly, we included a large sample size that was obtained from multiple centers and used uniform data collection protocols, including detailed demographic and lifestyle information. In addition, the biochemistry assays and assessment of metabolomics were performed in accordance with the internationally recognized standards for testing.

Limitations of the study

The present study is not without limitations. First, the UK Biobank used NMR to analyse the metabolomics characteristics of participants. Although NMR can qualitatively measure known and unknown compounds, with only a small portion of the sample having the characteristics of noninvasive, nondestructive, highly repeatable and quantitative capabilities (54–56), the number of serum/plasma metabolites analysed by NMR is much lower than the actual number of metabolites in the actual sample (57), and the relative sensitivity is low (56). The attenuation caused by the combination of metabolites with serum/plasma may cause the concentration of many metabolites detected to be seriously underestimated (58, 59), thus affecting the analysis of plasma FAs and hypertension. Additionally, most participants in the UK Biobank were Europeans, which limits the applicability to those who are European white. The low participation rate of only 5.5% for the UK Biobank may lead to selection bias (60). Finally, selection bias, referred to as "healthy volunteers," may also limit the representativeness of the present study (60).

Conclusion

In this cohort of adults from the United Kingdom, plasma FA levels were associated with hypertension risk in a dose-response manner. These findings also suggest that the relationship between plasma FA levels and the risk of hypertension could be modified by genetic risk factors, which provides new insight into the relationships of plasma FA levels and hypertension PRS with hypertension risk.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: all UK Biobank information is available online on the webpage www.ukbiobank.ac.uk/. Data access is available through applications.

Ethics statement

The studies involving humans were approved by Northwest Multicentre Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LL: Writing – original draft. XG: Writing – original draft. DY: Writing – original draft. BW: Writing – review & editing. GL: Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1454364/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories of female subgroup. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S2
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories of male subgroup. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S3
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories of <60 subgroup. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S4
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories of ≥60 subgroup. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S5
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories of normal-BMI subgroup. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S6
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories of overweight-obesity BMI subgroup. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S7
Dose-response relationships between plasma FA and hypertension risk. HRs for hypertension associated with plasma PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-3 PUFAs **(D)**, n-6 PUFAs **(E)**, and n-3/n-6 ratio **(F)** were estimated by restricted cubic-spline regression using model 2 additionally adjusted stains.

SUPPLEMENTARY FIGURE S8
Dose-response relationships between plasma FA and hypertension risk. HRs for hypertension associated with plasma PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-3 PUFAs **(D)**, n-6 PUFAs **(E)**, and n-3/n-6 ratio **(F)** were estimated by restricted cubic-spline regression using model 2 excluding participants with were any type of cardiovascular disease at baseline in the UK Biobank.

SUPPLEMENTARY FIGURE S9
Dose-response relationships between plasma FA and hypertension risk. HRs for hypertension associated with plasma PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-3 PUFAs **(D)**, n-6 PUFAs **(E)**, and n-3/n-6 ratio **(F)** were estimated by restricted cubic-spline regression using model 2 excluding participants with follow-up time of less than 2 years in the UK Biobank.

SUPPLEMENTARY FIGURE S10
Dose-response relationships between plasma FA and hypertension risk. HRs for hypertension associated with plasma PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-3 PUFAs **(D)**, n-6 PUFAs **(E)**, and n-3/n-6 ratio **(F)** were estimated by restricted cubic-spline regression using model 2 only race White participants in the UK Biobank.

SUPPLEMENTARY FIGURE S11
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, and polygenic risk score categories were estimated by using model 2 additionally adjusted stains plus the first 10 genetic principal components.

SUPPLEMENTARY FIGURE S12
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components excluding participants with were any type of cardiovascular disease at baseline in the UK Biobank.

SUPPLEMENTARY FIGURE S13
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components excluding participants with follow-up time of less than 2 years in the UK Biobank.

SUPPLEMENTARY FIGURE S14
Risk of incident hypertension according to concentration of plasma fatty acids and genetic risk categories. The HRs for hypertension according to PUFAs **(A)**, MUFAs **(B)**, SFAs **(C)**, n-6 PUFAs **(D)**, n-3 PUFAs **(E)**, n-3/n-6 PUFAs **(F)**, and polygenic risk score categories were estimated by using model 2 plus the first 10 genetic principal components only race White participants in the UK Biobank.

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Dietary antioxidant index and hypertension in the Iranian population: a nested case–control study within the Fasa adults cohort study

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Introduction: Hypertension (HTN) is a prevalent condition associated with numerous cardiovascular and non-cardiac complications. Lifestyle interventions, including dietary adjustments, offer promising avenues for hypertension management. However, the precise relationship between dietary antioxidants and hypertension risk necessitates further investigation. This study aimed to elucidate the association between the Dietary Antioxidant Index (DAI) and hypertension risk using a nested case–control design.

Method: A matched nested case–control study was conducted within the Fasa Adult Cohort Study (FACS), comprising 975 participants aged 35–70 years. Cases (n = 325) were hypertensive patients, while controls (n = 650) were individuals without hypertension, matched for sex and age. Dietary intake was assessed using a validated food frequency questionnaire, and DAI was computed based on standardized intake of antioxidants. Conditional logistic regression models were employed to evaluate the association between DAI and hypertension risk, adjusting for confounding variables.

Results: A significant inverse correlation was observed between DAI and hypertension risk across all models (OR = 0.89; 95% CI = 0.86–0.93, $p < 0.001$). This association remained robust after adjusting for potential confounders, including BMI, smoking, lipid profile, blood glucose levels, and educational status. In conclusion, higher DAI values were associated with a reduced risk of hypertension, highlighting the potential benefits of antioxidant-rich diets in hypertension prevention.

Conclusion: These findings underscore the importance of dietary interventions as a complementary approach to hypertension management.

KEYWORDS

dietary antioxidant index, hypertension, oxidative stress, cardiovascular, diet

Introduction

Hypertension (HTN), a condition that affects over 1 billion adults globally, is both a disease in itself and a significant contributing factor to other disorders (1, 2). The occurrence of hypertension increases dramatically around the world (3). HTN causes a substantial risk for a range of cardiovascular and several non-cardiac diseases (4, 5).

Treatment with antihypertensive medicines that lower blood pressure (BP) and related target organ damage can significantly minimize the heightened risk associated with BP elevation. However, despite the wide range of available treatment choices, nonadherence, intolerance, and resistant hypertension remain significant problems in pharmacological therapy (6). Antihypertensive medications are related to many side effects such as cough, edema, flushing, headache, increased urine output, rapid heart rate, wheezing, shortness of breath, and dizziness (7).

Conversely, there is increasing evidence that endorses the utilization of lifestyle strategies for both the prevention and complementary treatment of hypertension (8). Experimental evidence has shown that reactive oxygen species play a crucial role in the occurrence of hypertension (9). Therefore, adopting antioxidant-rich diets into lifestyle adjustments can be considered as a potential treatment option for high blood pressure (10). This process is explained by the imbalance between the production of reactive oxygen species and reactive nitrogen species, and the antioxidant defense systems, leading to oxidative and nitrosative stress in the cell. These mechanisms play a role in the arterial damage seen in chronic conditions like hypertension (11).

A previous study found that increasing the intake of fruits and vegetables in persons with hypertension for 6 months improved blood antioxidant capacity and lowered both systolic and diastolic blood pressure (12). Another study conducted by Waśkiewicz found a correlation between the total antioxidant capacity of the diet and polyphenol intake with a reduced risk of developing arterial hypertension in the Polish population (13).

However, there is a lack of comprehensive evaluations that thoroughly examine the complex connection between dietary antioxidant consumption and the risk of hypertension. This study aimed to clarify the association between the dietary antioxidant index (DAI) and hypertension through a nested case–control approach. The findings of this study could be offering valuable information for developing preventative measures and dietary guidelines for managing hypertension.

Methods

Study design and population

Information for this matched nested case–control study within the Fasa Adult Cohort Study (FACS) was collected from November 2014 to June 2019. The FACS is a comprehensive, population-based study conducted over an extended period. FACS included 10,035 individuals between the ages of 35 and 70 who did not have any physical or mental disabilities. These individuals were chosen randomly from the Sheshdeh rural area, with a total population of 41,000 people, and had been residents for a minimum of 9 months. This cohort study aimed to identify the risk variables linked to noncommunicable diseases in this particular population (14). This study was a matched nested case–control study. Cases were 325 patients that diagnosed with hypertension. Controls were 650 participants without hypertension. Controls were frequency-matched to cases by sex and age (±5 years), with a control: case ratio of 2:1. In the hypertensive group, hypertension stages were classified according to the standard guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA), which define hypertension as follows: Stage 1 (systolic BP of 130–139 mmHg or diastolic BP of 80–89 mmHg) and Stage 2 (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg). Additionally, the hypertension group was assessed for common hypertension-related complications. Data on left ventricular hypertrophy (LVH) and kidney function status were recorded, and chronic kidney disease (CKD) was identified based on estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, where available. This additional information provides a more detailed clinical profile of the hypertensive participants and supports understanding of the overall cardiovascular risk in this group.

Inclusion and exclusion criteria

The criteria for inclusion were as follows: a permanent residency in the area for a minimum of 2 years and willingness to participate in the study by providing informed consent through a signed agreement and to be in the age range of 20–80 years. Participants were not included in the analysis if they: suffering from autoimmune diseases, types of cancers, consumption of nutritional supplements with antioxidant properties such as vitamin E, selenium, vitamin A, zinc, vitamin C, omega 3, pregnancy and lactation, strict diet and gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and celiac. Also, people whose nutritional intake questionnaires were incompletely filled or whose caloric intake was abnormal (more than 4,500 kcal or less than 700 kcal) were excluded from the study.

Assessment of dietary intake

The evaluation of patients' dietary intake was conducted using a semi-quantitative food frequency questionnaire (FFQ) known for its validity and reliability, the questionnaire consisted of 168 popular food items consumed by Iranians, with standard serving sizes. The participants were asked about the frequency of consuming each food item, with responses categorized as daily, weekly, or monthly, and then converted to daily intakes. The gathered data underwent analysis through Nutritionist IV (First Databank, Hearst Corp., San Bruno, CA, USA). Participants who had not completed more than 10% of the dietary questionnaire items were eliminated from the study.

Assessment of other variables

Enzymatic colorimetric method (Pars Azmoon, Tehran, Iran) was used to assess serum glucose, total cholesterol, triglyceride, and HDL cholesterol concentrations. Additionally, LDL cholesterol levels were determined using the Friedewald algorithm. Body weight was measured using a digital body mass scale and bioelectrical impedance with a precision of 0.01 kg using the Omron Karada Scan HBF-375 from Osaka, Japan. The BMI of each person was determined using the following formula: BMI = weight (in kg)/height (in m2).

Blood pressure was measured using the Omron HEM 7120 Automatic Blood Pressure (Omron, Japan). The measurement occurred after a resting interval of at least 10 min following recent activity. Participants were directed to sit comfortably with their left arm fully

exposed and resting on a supported surface at heart level. Blood pressure measurements were taken on the left arm using the appropriate cuff size. Hypertension was described as having a systolic blood pressure (SBP) of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, or taking blood pressure drugs regularly.

Assessment of DAI

DAI for all study participants was determined using the data obtained from the FFQ. We employed databases that were published earlier and included the most frequently consumed foods to compute the DAI (15). For DAI computation, we standardized the intake of vitamin A, C, E, and selenium, manganese, and zinc by subtracting the global mean and dividing by the global standard deviation. The DAI was then determined by summing the standardized intakes, following the description provided below (16):

$$DAI = \sum_{i=1}^{N=6} \frac{\text{Individual intake} - \text{Mean}}{SD}.$$

Finally, to eliminate the effect of energy, the DAI score was adjusted to energy.

Statistical analysis

We utilized SPSS software version 16 for the data analysis. The continuous variables were presented as mean ± standard deviation, whereas categorical data were presented as frequency (percentage).To examine whether the variables are normally distributed, we used from the Kolmogorov–Smirnov test. In order to analyze the demographic variables, we used independent t test. Participants were categorized into quartiles according to their DAI score. Differences in general characteristics among dietary DAI quartiles and between cases and controls were evaluated using analysis of covariance (ANCOVA) for continuous variables and the Chi-square test for categorical variables. Lineaar regression was used to adjusted DAI score in term of total energy intake. Conditional logistic regression was employed in various models to explore the link between DAC and the risk of hypertension, with adjustments made for the most significant clinical variables. Initially, following control for BMI and smoking, the second model incorporated adjustments for educational levels and serum levels of TG, LDL, HDL and total cholestrol. In another model, supplementary adjustments involved FBS, SFA and PUFA. Confounding variables were chosen based on established relationships with both dietary antioxidant intake and hypertension risk, including BMI, smoking status, lipid profile, blood glucose levels, and educational status. These adjustments were made to control for potential confounding effects, although we acknowledge that certain variables, such as BMI and lipid profile, may act as mediators in the relationship between dietary antioxidants and hypertension.

Statistically significant values were defined as p-values less than 0.05.

Results

In this matched case–control study, 975 participants (325 patients in case group and 650 people in control group) were included. The participants had a mean age of 51.24 ± 8.78 years Table 1 summarizes the demographic details of the study participants. The mean weight of the participants in the case group was 69.52 ± 13.95 kg and in the control group was 63.09 ± 12.68, and A statistically significant difference was found between the two groups ($p < 0.001$). Additionally, the mean systolic blood pressure (SBP) in the case group was 123.7 ± 18.52 mmHg, whereas it was 106.58 ± 15.24 mmHg in the control group, showing a significant disparity ($p < 0.001$). Furthermore, the diastolic blood pressure (DBP) level in the case group was 80.98 ± 12.43 mmHg, compared to 71.60 ± 10.97 mmHg in the control group, indicating a significant difference ($p < 0.001$). Regarding dietary intake, participants in the case group had a mean calorie consumption of 2737.52 ± 804.84 kcal/day, while the control group had a mean calorie intake of 2743.83 ± 860.78 kcal/day, with no significant differences ($p = 0.91$). Additionally, significant differences were observed between the case and control groups in terms of dietary vitamin E and zinc intake ($p < 0.05$). DAI value in hypertensive patients was −0.73 ± 4.18, whereas in the control group, it was 0.98 ± 4.48, indicating a diet with higher antioxidant content among controls (p-value <0.001). Table 2 showed differences in biochemical and nutritional variables among DAI quartiles. We found a significant differenes between DAI quartiles in term of age. Also, participants in the higher quartile of DAI compared to the subjects in the lower quartile consumed significantly higher amounts of enery, fat, carbohydrate, protein, sodium, satuarated fatty acid (SFA), mono and poly unsaturated fatty acid, dietary cholestrol, potassium, vitamin A, vitamin C,vitamin E, zinc, selenium and manganese ($p < 0.001$). However, we could not find any significant differences between DAI quartiles in term of lipid profile, blood sugar, SBP, DBP, weight and BMI ($p > 0.05$).

ORs and 95% CIs for the odds of hypertension according to the DAI value are shown in Table 3. It has been reported that there was a significant inverse correlation between DAI and odds of hypertension in the crude model (OR = 0.91;95%CI = 0.88–0.94, $p < 0.001$). Also, in all of the adjusted models and after adjustment for confounding factors including BMI, smoking, LDL, FBS, HDL, TG, total cholestrol, educational degree, SFA and PUFA, a reverse and significant association were seen (OR = 0.89;95%CI = 0.86–0.93, $p < 0.001$).

Discussion

This study aimed to investigate the potential relationship among DAI and hypertension. The importance of investigating this connection resides in the wider framework of public health, due to the increasing incidence of hypertension and the potential influence of dietary determinants on its onset. The study's findings revealed fascinating patterns that warrant additional discussion, elucidating the complex interaction between dietary habits and hypertension incidence.

The observed odds ratio (OR = 0.89) indicates that each unit increase in DAI is associated with an 11% reduction in hypertension risk. In our study, DAI range was wide. This suggests that individuals moving from a lower to a higher DAI category could potentially reduce their hypertension risk by 11%. Translating these findings into practical dietary changes, an increase in DAI can be achieved through a higher intake of antioxidant-rich foods, including fruits, vegetables, whole grains, and legumes, which are known to

TABLE 1 General characteristics of the study population[a].

Variables	Total (*n* = 975)	Case (*n* = 325)	Control (*n* = 650)	*P*_value[b]
DAI	0.41 ± 4.46	−0.73 ± 4.18	0.98 ± 4.48	<0.001
Age (y)	51.24 ± 8.78	51.24 ± 8.79	51.24 ± 8.78	1.00
Male (%)	288(29.5%)	96(29.5%)	192(29.5%)	1.00
Weight (kg)	65.23 ± 13.46	69.52 ± 13.95	63.09 ± 12.68	<0.001
BMI (kg/m^2)	25.77 ± 4.92	27.28 ± 4.98	25.02 ± 4.71	<0.001
SBP (mmHg)	112.29 ± 18.28	123.7 ± 18.52	106.58 ± 15.24	<0.001
DBP (mmHg)	74.73 ± 12.29	80.98 ± 12.43	71.60 ± 10.97	<0.001
TG (mg/dl)	127.07 ± 70.39	144.94 ± 84.33	118.11 ± 60.34	<0.001
LDL (mg/dl)	112.37 ± 34.07	112.96 ± 34.64	112.07 ± 33.81	0.71
HDL (mg/dl)	50.37 ± 13.30	52.38 ± 15.90	49.36 ± 11.66	0.003
TC (mg/dl)	188.31 ± 40.32	194.82 ± 39.25	185.05 ± 40.49	<0.001
FBS (mg/dl)	94.08 ± 30.87	99.37 ± 39.28	91.36 ± 25.16	0.001
Smoking, no. (%)	234(25%)	85(26.15%)	149(23%)	0.38
Urban residence, *n* (%)	263 (27%)	80 (24.6%)	183 (28.2%)	0.23
Self-report diabetes, no, (%) (%)	146(14.97%)	71 (21.8%)	75 (11.5%)	<0.001
Education, no. (%)				0.38
High school or less	683(70%)	220(67.70%)	463(71.23%)	
College education (%)	292(30%)	105 (32.30%)	187 (28.77%)	
Dietary intake				
Energy, Kcal/day	2741.74 ± 842.14	2737.52 ± 804.84	2743.83 ± 860.78	0.91
Fat, g/day	68.24 ± 25.66	68.64 ± 26.05	68.03 ± 25.47	0.73
Carbohydrate, g/day	389.68 ± 93.37	390.96 ± 91.66	395.04 ± 94.28	0.76
Protein, g/day	86.25 ± 28.83	85.02 ± 26.44	86.86 ± 29.94	0.33
Cholesterol intake, mg/day	258.94 ± 146.97	252.12 ± 148.95	262.35 ± 145.97	0.31
Na (mg/day)	4389.44 ± 1428.41	4451.44 ± 1398.22	4358.48 ± 1443.32	0.34
SFA (g/day)	23.91 ± 10.33	85.57 ± 8.17	85.01 ± 8.00	0.55
MUFA (g/day)	18.29 ± 8.30	18.29 ± 8.35	18.30 ± 8.29	0.99
PUFA(g/day)	10.06 ± 67.37	9.86 ± 4.62	10.15 ± 5.36	0.663
Potassium (mg/day)	3811.88 ± 1569.89	3874.67 ± 1545.49	3780.54 ± 1582.19	0.38
Vitamin A (mcg/day)	744.11 ± 351.32	740.45 ± 364.46	745.01 ± 344.83	0.81
Vitamin C (mg/day)	141.38 ± 87.70	139.94 ± 83.54	142.11 ± 89.76	0.71
Vitamin E(mg/day)	7.84 ± 3.46	7.45 ± 3.38	8.04 ± 3.48	0.01
Zinc(mg/day)	10.76 ± 4.02	10.08 ± 3.97	11.11 ± 4.01	<0.001
Manganese(mg/day)	4.51 ± 2.53	4.21 ± 2.66	4.66 ± 2.44	0.41
Selenium(mcg/day)	132.14 ± 59.57	120.93 ± 49.21	137.75 ± 63.42	0.001

[a] All data are means ± standard deviations unless indicated. [b] Calculated by independent *t* test. BMI, Body mass index; DBP, diastolic blood pressure; DAI, Dietary Antioxidant Inde; mg/dl, milligram/deciliter; FBS, Fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; Na, Sodium; SFA, saturated fatty acid; MUFA, mono unsaturated fatty acid; PUFA, poly unsaturated fatty acid; TG, triglyceride; TC, total cholesterol.

contribute to oxidative stress reduction and blood pressure management. For instance, increasing daily servings of vegetables and fruits by five servings could significantly increase DAI, aligning with observed reductions in hypertension risk. Such dietary adjustments not only promote general cardiovascular health but may also serve as accessible strategies for hypertension prevention, with particular relevance for individuals at higher risk of hypertension.

The results indicated that in all models of multiple adjusted ORs, there was a significant and negative correlation between hypertension and the DAI. This finding aligns with the outcomes of prior research. In a cross-sectional investigation, Fateh et al. (17) examined the correlation between greater total antioxidant capacity in the diet and a lower risk of hypertension in pre/perimenopausal women. Their modeling using logistic regression analysis revealed a decreased hypertension risk in women with

TABLE 2 Distribution of characteristics and dietary intakes across tertiles of the DAI (n = 975) [a].

Variables	Q 1 (n = 243)	Q 2 (n = 244)	Q3 (n = 244)	Q 4 (n = 244)	P-value[b]
Age (y)	51.62 ± 8.72	52.24 ± 8.89	50.22 ± 8.70	50.90 ± 8.73	0.06
Weight (kg)	66.15 ± 14.37	65.53 ± 13.91	64.50 ± 12.67	64.75 ± 12.82	0.51
BMI (kg/m^2)	26.23 ± 5.18	25.81 ± 4.86	25.53 ± 4.69	25.77 ± 4.92	0.35
SBP (mmHg)	112.87 ± 18.52	113.44 ± 19.10	111.68 ± 18.09	111.17 ± 17.37	0.22
DBP (mmHg)	74.70 ± 12.66	74.62 ± 12.54	74.93 ± 12.47	74.67 ± 11.55	0.32
TG (mg/dl)	133.27 ± 73.39	128.91 ± 75.30	124.07 ± 67.89	122.00 ± 64.30	0.29
LDL (mg/dl)	112.47 ± 37.46	117.11 ± 35.10	108.50 ± 29.64	111.36 ± 33.23	0.04
HDL (mg/dl)	49.70 ± 14.55	50.31 ± 12.81	50.63 ± 12.38	50.80 ± 13.48	0.59
TC (mg/dl)	189.06 ± 41.92	192.61 ± 40.79	184.20 ± 38.96	187.40 ± 39.35	0.12
FBS (mg/dl)	93.83 ± 33.36	92.08 ± 24.08	93.91 ± 29.93	96.29 ± 34.80	0.68
Energy, Kcal/day	2974.70 ± 873.12	2499.53 ± 739.22	2593.23 ± 831.05	2900.47 ± 828.07	<0.001
Fat, g/day	71.59 ± 24.29	60.60 ± 21.84	61.77 ± 22.47	79.24 ± 29.07	<0.001
Carbohydrate, g/day	400.12 ± 85.05	385.30 ± 97.45	366.07 ± 96.18	407.18 ± 89.51	<0.001
Protein, g/day	87.45 ± 29.29	78.92 ± 25.92	83.40 ± 28.18	95.32 ± 29.42	<0.001
Cholesterol intake, mg/day	218.90 ± 114.51	230.83 ± 124.38	250.64 ± 134.97	337.00 ± 177.79	<0.001
Na (mg/day)	4699.03 ± 1519.81	4047.25 ± 1280.16	4212.08 ± 1370.89	4601.21 ± 1438.33	<0.001
SFA (g/day)	25.24 ± 10.56	21.71 ± 9.22	21.77 ± 9.35	26.91 ± 11.16	<0.001
MUFA (g/day)	17.55 ± 7.77	16.24 ± 7.17	17.01 ± 6.84	22.45 ± 9.76	<0.001
PUFA (g/day)	8.29 ± 3.59	8.47 ± 3.50	9.73 ± 3.94	13.82 ± 6.74	<0.001
Potassium (mg/day)	3142.99 ± 1052.87	3207.59 ± 1020.54	3692.77 ± 1198.85	5222.62 ± 1871.33	<0.001
Vitamin A (mcg/day)	555.06 ± 259.59	615.52 ± 264.74	771 ± 316.85	1034.06 ± 345.90	<0.001
Vitamin C (mg/day)	86.41 ± 49.10	107.38 ± 53.50	138.78 ± 57.17	232.75 ± 98.63	<0.001
Vitamin E (mg/day)	5.90 ± 2.28	6.38 ± 2.22	7.88 ± 2.61	11.21 ± 3.70	<0.001
Zinc (mg/day)	10.13 ± 3.62	9.39 ± 3.31	10.56 ± 3.78	12.98 ± 4.39	<0.001
Manganese (mg/day)	4.09 ± 2.21	3.95 ± 1.93	4.32 ± 2.30	5.67 ± 3.13	<0.001
Selenium (mcg/day)	134.80 ± 51.16	118.98 ± 49.90	127.95 ± 57.89	146.85 ± 73.25	<0.001

[a] All data are means ± standard deviations unless indicated. [b] One-way ANOVA was used for continuous variables. BMI, Body mass index; DBP, diastolic blood pressure; DAI, Dietary Antioxidant Inde; mg/dl, milligram/deciliter; FBS, Fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; Na, Sodium; SFA, saturated fatty acid; MUFA, mono unsaturated fatty acid; PUFA, poly unsaturated fatty acid; TG, triglyceride; TC, total cholesterol.

TABLE 3 Multivariate-adjusted ORs and 95% CIs for hypertension in relation to dietary antioxidant index.

	OR (CI)	P
Crude	0.91 (0.88, 0.94)	<0.001
Model 1	0.92(0.88,0.944)	<0.001
Model 2	0.9(0.87,0.93)	<0.001
Model 3	0.89(0.86,0.93)	<0.001

Model 1: Adjusted for BMI, smoking. Model 2: Further adjusted for educational degree, LDL, HDL, cholesterol. Model 3: Further adjusted for FBS, SFA and PUFA.

elevated dietary total antioxidant capacity (17). Moreover, the study conducted by Peng et al. (18) suggested a negative link between dietary antioxidants and hypertension risk among the Chinese middle-aged and older adults (18, 19). Another research has identified a potential link between diet and blood pressure in Iranian Kurdish women indicates that consuming a diet filled with antioxidants may be linked to a reduced likelihood to develop hypertension. (20). Similar results were seen in French women (21). Moreover, data from the National Health and Nutrition Examination Survey (NHANES) showed a potential link between higher intakes of dietary carotenoids, a type of antioxidant, and lower prevalence of hypertension in American adults (22).

The inverse association between DAI and hypertension risk observed in this study may be partly explained by several biological mechanisms through which antioxidants affect blood pressure regulation. Antioxidants play a crucial role in neutralizing reactive oxygen species (ROS), thereby reducing oxidative stress, which is known to contribute to vascular damage and hypertension (23). High levels of oxidative stress can impair endothelial function by decreasing the availability of nitric oxide (NO), a critical molecule that promotes vasodilation and regulates blood pressure. By reducing oxidative stress, dietary antioxidants may enhance endothelial function and improve NO bioavailability, thus aiding in blood pressure control. Additionally, dietary antioxidants have been

associated with anti-inflammatory effects, which may also contribute to blood pressure regulation (24, 25). Chronic low-grade inflammation is increasingly recognized as a factor in hypertension pathogenesis. Antioxidant nutrients, such as vitamins C and E and polyphenols, have been shown to decrease inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6), which are elevated in hypertensive individuals. By mitigating inflammation, antioxidants may further reduce the risk of hypertension development (26, 27).

When free radicals accumulate in cells and tissues, exceeding the body's natural antioxidant defenses, an imbalance called "oxidative stress" occurs (28). This stress damages cells and contributes to the development of CVD (29). Fortunately, antioxidants can counteract this process by donating electrons to free radicals, neutralizing their harmful potential and shielding the organism from harmful consequences of oxidative stress (30). Some researchers have suggested that part of the beneficial effects of diets with a high DAI on blood pressure is due to the high consumption of vitamin E and manganese in these diets (31). Research suggests a complex relationship between specific nutrients and hypertension. While vitamins E and manganese showed promise in some studies, findings were mixed across populations. Vitamin E intake exhibited a reverse J-shaped association with hypertension in Chinese adults (cohort study) (32), but no link was found in a Spanish study (33). This highlights the potential influence of ethnicity on such interactions. Conversely, meta-analyses consistently support the benefit of magnesium supplementation in lowering blood pressure (34–36).

Extensive research suggests that consuming foods rich in antioxidants might lower the likelihood of developing hypertension. The DASH (Dietary Approaches to Stop Hypertension) diet, which emphasizes fruits, vegetables, low-fat dairy, and whole grains, has consistently been proven to lower blood pressure in both healthy and hypertensive patients (37). This diet has also been linked to a decrease in cardiovascular complications like stroke, which are often associated with hypertension (38). While several studies suggest a link between antioxidant-rich diets and lower blood pressure risk, findings on supplementing with antioxidants are less conclusive, particularly when considering gender differences. In the Linxian trial, for example, men receiving antioxidant supplements had a decreased risk of developing hypertension after 6 years, while no such benefit was observed in women (39). While some studies suggest potential benefits of antioxidant supplements for blood pressure, others, like the SUVIMAX trial, have found no significant association with preventing hypertension (40). This raises the question of whether the naturally balanced mix of antioxidants found in whole foods might be more effective than isolated supplements, which could potentially disrupt the body's delicate antioxidant system by providing an excess of specific antioxidants.

Multiple studies across humans and animal models show clear differences between genders or sexes in both how often high blood pressure occurs and how the body regulates it (41). Existing evidence suggests a sex-based disparity in Male spontaneous hypertension rat (SHR), with males exhibiting higher oxidative stress levels contributing to their hypertensive state compared to females. Consequently, this implies a potential for greater blood pressure reduction in males upon antioxidant administration compared to females (42). Although prior research suggests a gender-dependent relationship between the variables, our findings revealed a consistently inverse correlation regardless of participant gender.

The observed phenomenon might share a close link with oxidative stress. Existing literature (43, 44) indicates elevated oxidative stress and inflammation in hypertensive individuals. Manganese and zinc are essential elements in antioxidant mitochondrial metalloenzymes (MnSOD, ZnSOD) (45), Selenium, present in selenoproteins, helps prevent lipid peroxidation and oxidative cellular damage. This indicates a possible function for these micronutrients in lessening the observed effects (46). The crucial role of non-enzymatic antioxidants like vitamins A, C, and E in counteracting stress-induced oxidant alterations is emphasized in previous studies. This underscores the potential application of dietary antioxidant sources for the prevention of hypertension triggered by oxidative stress (31, 47).

In this study, we observed notably lower blood pressure values in the control group, which could reflect specific characteristics of the Iranian rural population sampled in the Fasa Adult Cohort Study (FACS). Several factors may account for these findings. First, rural populations in Iran, including the FACS cohort, often engage in traditional lifestyles that include higher physical activity levels and diets rich in fruits, vegetables, and whole grains. These foods contribute to higher DAI values, which are known to mitigate oxidative stress, a factor closely linked to hypertension development (48). Additionally, dietary patterns in rural Iranian settings may provide a variety of antioxidants naturally present in local foods, potentially explaining the observed lower baseline blood pressure in controls. The relationship between antioxidants and blood pressure has been documented, and diets rich in these compounds may support vascular health and reduce hypertension risk (49). Furthermore, unique genetic and environmental interactions specific to this region may also play a role in maintaining lower blood pressure. Previous studies have suggested that Iranian populations may exhibit distinct genetic profiles that, when combined with rural environmental influences, contribute to lower baseline blood pressure values (50).

The present study employs a nested case–control design within a large cohort study, allowing for a robust evaluation of the association between DAI and hypertension. This design helps control for potential confounding factors and provides valuable insights into the relationship being studied.

Limitations

This study has several limitations. First, dietary intake was assessed using a validated FFQ, which is prone to recall bias and measurement error. Although the FFQ provides valuable insights into dietary patterns, its reliance on self-reported data may have affected the accuracy of the DAI calculation. Second, some variables included as confounders in the analysis, such as BMI and lipid profile, may act as mediators rather than confounders, potentially leading to over-adjustment and attenuation of the observed association. Third, the absence of objective biomarkers of antioxidant intake limits the ability to validate self-reported dietary data, which future studies should address. Finally, the generalizability of our findings may be restricted by the specific rural population studied, as dietary habits and genetic

factors may differ across populations. Despite these limitations, the study provides valuable evidence on the relationship between dietary antioxidants and hypertension risk.

Conclusion

In conclusion, our study offers supportive evidence for a significant inverse association between the DAI and hypertension risk, highlighting the potential benefits of antioxidant-rich diets in managing hypertension. Future studies employing more precise dietary assessment methods and interventional designs are warranted to confirm these associations and strengthen the basis for dietary recommendations in hypertension prevention.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Fasa University of Medical Sciences. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MF: Writing – original draft, Writing – review & editing. MR: Writing – review & editing. ES: Writing – review & editing. MM: Writing – review & editing. RT: Writing – review & editing.

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Conflict of interest

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

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Effects of salt substitute on urinary electrolytes and blood pressure in a real-world setting—cohort study in Hunan, China

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Background and aims: Salt substitute is considered an effective strategy to reduce sodium and increase potassium intake and thereby lower blood pressure in China, but its benefits and risks are uncertain in real-world data. This study is designed to compare the difference in the 1-year efficacy of salt substitute and salt restriction on urinary electrolytes and blood pressure.

Methods and results: A total of 2,929 and 2,071 participants with the 24-h estimated urinary sodium excretion (eUNaE) above 2.36 g/d using salt substitute (SS) and salt restriction (SR) strategies, respectively, were followed for 1 year. Salt substitute users were further divided by potassium chloride (KCl) content (13% vs 25%) and duration (9–11 vs 12 months). The 24-h eUNaE and estimated urinary potassium excretion (eUKE) levels were calculated using the Kawasaki formula from spot urine sample. The SS group (n = 1,897) had lower eUNaE (3.82 ± 1.03 vs 4.05 ± 1.01 g/day, $p < 0.01$) than the SR group (n = 1,897) after 1 year. Both 13 and 25% KCl substitutes reduced eUNaE versus restriction ($p < 0.05$).The SS group had a higher eUKE than the SR group (2.09 ± 0.43 vs 1.71 ± 0.62 g/day, $p < 0.01$). The eUKE was higher with 25% versus 13% KCl substitutes, while the Na/K was lower with 25% versus 13% KCl substitutes ($p < 0.05$). No significant blood pressure differences occurred between the SS and SR groups ($p > 0.05$), whereas 25% KCl exposure was related to a lower level of SBP, regardless of whether it was compared with SR or 13% KCl.

Conclusion: Compared with salt restriction, salt substitute results in more sodium reduction and greater potassium increase. In spite of this, it does not result in better control of blood pressure, especially for the group receiving 13% KCl.

KEYWORDS

salt substitute, real-world, salt restriction, cohort, China

Introduction

Elevated dietary sodium consumption, as well as low levels of dietary potassium intake, is associated with hypertension, cardiovascular disease, and premature death (1–3). Sodium consumption in China is high. In recent years, we found high sodium and low potassium intake levels in the Hunan population based on spot urinary analysis (4).

There is empirical evidence that replacing sodium chloride with a potassium-enriched salt substitute can significantly reduce blood pressure. Recently, a randomized trial named the SSaSS study proved that salt substitute could reduce the rates of stroke, major cardiovascular events, and death compared with regular salt among persons who had a history of stroke or over 60 years old and had high blood pressure (5). Moreover, a cluster-randomized trial conducted in elderly care facilities showed that using salt substitute instead of regular salt can lower systolic blood pressure by 7.1 mmHg. In contrast, restricting the supply of regular salt had no effect on systolic blood pressure6. Meanwhile, no apparent serious adverse effects were found in the salt substitute group (5, 6). These results indicated that salt substitute hold great potential for the control of blood pressure and prevention of chronic disease.

However, most salt substitute studies have been carried out in rural or closed areas to reduce the possibility of participants consuming regular salt (5–7). Thus, these studies may maximize the effect of the salt substitute. In fact, data from the China Health and Nutrition Survey showed that the contribution of added salt to total sodium intake dropped from 81% in 1991 to 70% in 20,098. The proportion of sodium intake from packaged food is gradually increasing among the Chinese population, especially in urban areas. Additionally, the salt substitute commonly available on the market usually contains 13% potassium chloride, rather than the 25% cited in the abovementioned research. Therefore, it is essential to evaluate the public health effects of salt substitute in the real world for the general population.

In the current study, we conducted a prospective cohort study and compared the effects of salt substitute usage to salt restriction on urinary electrolytes and blood pressure in the real world of urban China.

Methods

Participants

The study was conducted at the Third Xiangya Hospital of Central South University in Changsha, a city in South China. All the subjects participating in annual health check-ups between January 2021 and December 2021 who had the 24-h estimated urinary sodium excretion (eUNaE) exceeding 2.36 grams/day (approximately equivalent to salt intake above 6 grams/day, which surpasses the recommended level stipulated by the Chinese Dietary Guidelines) and were advised by their physicians to reduce sodium intake. The suggestions included raising awareness about salt reduction, reducing dining out, reading food nutrition labels, decreasing the intake of high-salt foods, changing cooking methods, recommending the use of measuring tools such as salt restriction spoons, and salt substitute. In the first month following baseline sodium screening, all selected subjects were interviewed by skilled physicians through telephone, and those who reported that they had already consumed salt substitute or adopted salt reduction strategy without salt substitute were enrolled in our study. Participants who met the following criteria were further excluded: aged < 18 years; not suitable for salt substitute usage, including those working in a high-temperature or labor-intensive environment, or having chronic kidney disease, stroke, coronary heart disease, or who took drugs that affect sodium and potassium excretion, such as ACEIs or ARBs and diuretics; implemented salt substitute before baseline screening or implemented salt substitute for less than 9 months during the follow-up period; neither followed the recommendation to replace salt with salt substitutes nor to restrict salt by consuming salt restriction spoons or salt-reduced seasonings; and did not agree to be followed and attended physical examination at 12 months after baseline screening. All participants provided written informed consent to participate in the study, and the enrollment process is described in Figure 1.

Follow-up and exposure assessment

After baseline screening, the participants were followed up at months 1 and 12. At the first follow-up visit, the subjects were interviewed through telephone to determine their salt exposure. During follow-up visits at month 12, participants were required to attend the annual health check-up and to complete an online questionnaire regarding their salt consumption behavior, including whether they followed the physician's recommendations to reduce salt intake, and avoid high salt foods, especially the duration of using SS. In this check-up, each participant had to report their medical visits and symptoms in the previous year and received urine sodium and potassium, serum potassium, and electrocardiogram tests.

In our study, all enrolled participants were advised by physicians to limit sodium intake by using salt substitute. Salt substitute, however, had to be purchased directly from the market by themselves. The Chinese market offers two types of salt substitute with different potassium chloride (KCl) contents. The main product contains 13% KCl, which contains 6,556 mg of potassium per 100 grams, whereas the other type of product contains 25% KCl, which contains 13,110 mg of potassium per 100 grams (these data may vary slightly among products from different manufacturers). For individuals suitable for salt substitute usage, physicians in our health management department only recommended the substitute strategy but not the type of product. Our study consisted of two groups of participants based on reported salt consumption: (1) The salt substitute (SS) group refers to participants who cook at home using salt substitutes they have already purchased; (2) the salt restriction (SR) group comprises those who did not use SS at any time point during follow up and had other salt restriction action such as consumed salt-restricted spoons. At the last follow-up, the cumulative duration of SS exposure was collected and those who used SS but had less than 9 months of exposure been excluded. Over 2,134 subjects reported exposure to SS and 97% of whom had been exposed for more than 9 months, and they could be further classified into two subgroups: 12 months and 9–11 months.

Outcome and covariate measures

The National Physical Examination Questionnaire was used to collect sociodemographic characteristics, alcohol usage, cigarette smoking, and medical history. Physical examinations were conducted by trained physicians with the same methods described in our previous studies (4, 8–10). The definitions of chronic diseases are detailed in the

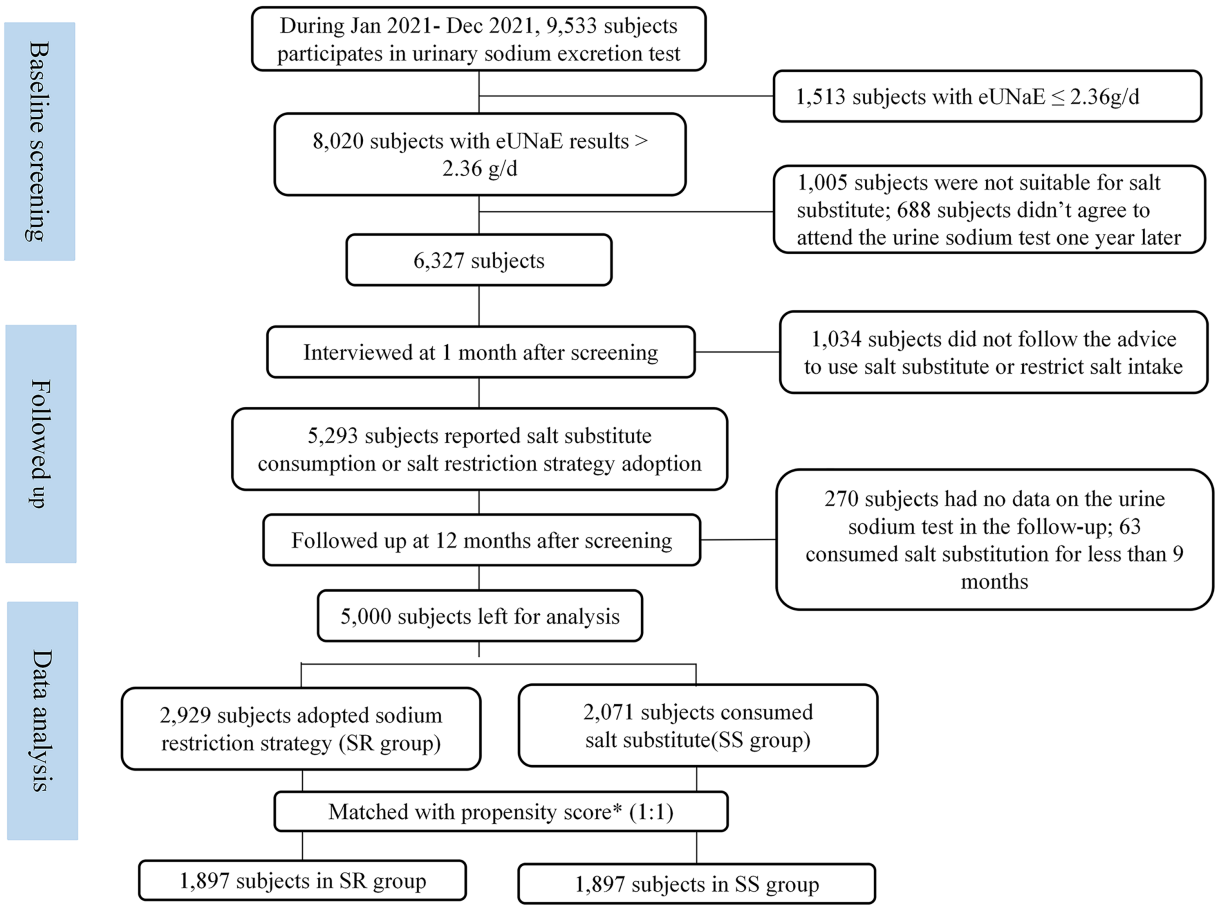

FIGURE 1
Propensity score matched subjects enrollment flowchart. Propensity score was calculated based on age, sex, BMI category, alcohol usage, smoking, hypertension, diabetes, dyslipidemia, level of eUNaE and eUKE at baseline screening. SR, salt restriction; SS, substitute salt.

references (11–16). According to the "Dietary Guidelines for Chinese Residents (2016) (13)," the recommended daily salt intake of Chinese adults over the age of 18 does not exceed 6 grams (approximately equivalent to the sodium intake not exceed 2.36 grams/day), and the daily potassium intake is more than 3.6 grams, respectively (17). Based on these reference amounts, we determined whether an individual's intake of sodium and potassium met the recommended levels.

As described in our previous studies, fasting venous blood samples were collected and analyzed immediately at the clinical laboratory. Meanwhile, mid-stream urine samples were tested for sodium, potassium, and creatinine within 2 h of collection. Sodium and potassium were measured by the ion selective electrode method, and creatinine was measured by the dynamic enzymatic method. In the present study, 24-h urinary sodium (eUNaE) and potassium (eUKE) excretion were determined using the Kawasaki approach (18) as a proxy for average daily sodium and potassium intake. One gram of urine sodium is calculated to equal 2.55 grams of salt intake.

Statistical analyses

It was determined that 5,283 subjects met the inclusion and exclusion criteria. Among them, 5,000 (94.64%) had complete data on the urine sodium test at the last follow-up and were analyzed. However, most of the medical characteristics at baseline were found to be significantly different between the SS and SR groups (Table 1), and a propensity score matching (PSM) approach was used to obtain comparable groups. In particular, a logistic regression model based on age, gender, BMI category, alcohol consumption, smoking, hypertension, diabetes, dyslipidemia, and levels of eUNaE and eUKE at baseline was applied to determine propensity scores for each subject. Using a caliper set at 0.02, participants in the SS group were matched with participants in the SR group using the nearest neighbor matching method. Finally, a total of 3,794 participants were successfully matched and used for effect and safety analysis. As shown in Table 1, the implementation of PSM significantly reduced baseline differences between SR and SS groups, with standardized mean differences (SMDs) for all covariates within 10%, indicating a high degree of baseline balance.

Continuous variables are expressed as the means and standard deviation (SD), whereas categorical variables are expressed as counts (n) and percentages (%), and differences between the SS and SR groups were tested by ANOVA (analysis of variance) and the chi-square test, respectively. A change in eUNaE, eUKE, Na/K ratio, systolic blood pressure (SBP) or diastolic blood pressure (DBP) was calculated by subtracting baseline levels from 1 year after. The effects of salt substitute on eUNaE, eUKE, and the Na/K ratio 1 year after sodium restriction and changes in those three parameters were assessed using linear regression and expressed with standardized coefficients (β) and 95% confidence intervals (CIs). Meanwhile, the effects of using salt

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TABLE 1 Distribution of social demographic and clinical characteristics at baseline in unmatched overall and propensity score matched cohort.

Characteristics at baseline	Unmatched overall cohort				Propensity score matched cohort			
	SR (*n* = 2,929)	SS (*n* = 2,071)	SMD	*p*	SR (*n* = 1,897)	SS (*n* = 1,897)	SMD	*p*
Age (years), *n* (%)								
18–34	536 (18.30)	380 (18.35)	−0.01	0.73	346 (18.24)	354 (18.66)	0.01	0.90
35–49	1,466 (50.05)	10,415 (49.62)			936 (49.34)	923 (48.66)		
≥ 50	927 (31.65)	676 (32.64)			615 (32.42)	620 (32.68)		
Sex, *n* (%)								
Female	848 (28.95)	763 (36.84)	0.17	< 0.01	655 (34.53)	689 (36.32)	−0.04	0.25
Male	2081 (71.05)	1,308 (63.16)			1,242 (65.47)	1,208 (63.68)		
Alcohol usage, *n* (%)	1,656 (56.54)	1,223 (59.05)	0.06	0.08	1,019 (53.72)	1,058 (55.77)	0.03	0.20
Smoking, *n* (%)	903 (30.83)	525 (25.35)	0.12	< 0.01	441 (23.25)	420 (22.14)	0.01	0.42
BMI category, *n* (%)								
Underweight	53 (1.81)	42 (2.03)	0.11	< 0.01	46 (2.42)	36 (1.90)	0.02	0.56
Normal weight	1,261 (43.05)	1,001 (48.33)			888 (46.81)	920 (48.50)		
Overweight	1,286 (43.91)	827 (39.93)			779 (41.06)	759 (40.01)		
Obese	329 (11.23)	201 (9.71)			184 (9.70)	182 (9.59)		
SBP (mmHg), mean (SD)	120.90 (14.58)	121.12 (14.92)	0.03	0.60	120.42 (14.98)	120.80 (14.76)	−0.02	0.95
DBP (mmHg), mean (SD)	75.00 (10.69)	74.51 (10.77)	0.04	0.11	74.51 (10.76)	74.53 (10.79)	−0.00	0.43
Normal BP (mmHg), *n* (%)	2,569 (87.71)	1827 (88.22)	−0.01	0.59	1,678 (88.46)	1,668 (87.93)	−0.03	0.62
Hypertension, *n* (%)	458 (15.64)	297 (14.34)	0.05	0.21	282 (14.87)	280 (14.76)	0.01	0.93
Diabetes, *n* (%)	206 (7.03)	121 (5.84)	0.04	0.09	116 (6.11)	109 (5.75)	−0.03	0.63
Dyslipidemia, *n* (%)	1,064 (36.33)	679 (32.79)	0.08	0.01	621 (32.74)	617 (32.53)	−0.02	0.89
eUNaE (g/day), mean (SD)	4.43 (1.08)	4.51 (1.01)	−0.15	< 0.01	4.48 (1.12)	4.51 (1.01)	0.03	0.36
eUKE (g/day), mean (SD)	2.27 (0.47)	1.98 (0.54)	−0.51	< 0.01	2.11 (0.43)	2.08 (0.52)	−0.06	0.06
Na/K ratio, mean (SD)	2.03 (0.74)	2.57 (1.47)	0.51	< 0.01	2.21 (1.10)	2.28 (1.12)	0.07	0.06

SR, salt restriction; SS, salt substitute; SMD, standardized mean difference; SD, standard deviance; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; eUNaE, estimated urinary sodium excretions; eUKE, estimated urinary potassium excretions; BMI, body mass index.

substitute on the risk of normal blood pressure (BP) and salt intake ≤ 6 g/d were assessed separately with logistic regression and expressed with odds ratios (ORs) and 95% CIs. Potential confounding variables in linear and logistic regression models included age (18–34, 35–49, and ≥ 50), sex (female or male), alcohol usage (yes or no), smoking (yes or no), BMI category (underweight, normal weight, overweight and obese), hypertension (yes or no), diabetes (yes or no), hyperglycemia (yes or no), and dyslipidemia (yes or no). We also analyzed the effect of SS in the unmatched cohort population, in populations with different exposure dosages and in populations with different cumulative exposure durations. The effect of SS among the hypertension subgroup was analyzed through stratification analysis. SAS version 9.4 (SAS Institute Inc.) was used for analyses.

Results

Characteristics of the enrolled participants at baseline

During 2021, 9,533 participants participated in sodium excretion screening, and of them, 8,020 participants showed eUNaE > 2.36 g/d, with a prevalence of 84.13% (95% CI: 83.38, 84.86%). A total of 5,000 participants met the inclusion criteria of our study and had tested sodium excretion at the 12-month follow-up. Among this unmatched population, participants in the SS group were more likely to be female, smokers, normal weight, diabetes, and dyslipidemia, with lower eUKE and higher eUNaE and Na/K ratios ($p < 0.05$) than participants in the SR group (Table 1). After PSM, these differences became insignificant ($p > 0.05$), and both groups were comparable in terms of those characteristics (Table 1). In the PS-matched SS group, 417 participants (21.98%) consumed SS with 25% KCl, and 264 participants (13.92%) started consuming SS between 1 and 3 months after using the SR strategy.

Effects of SS on the level of eUNaE

As shown in Table 2, compared to the baseline, the level of eUNaE decreased in both groups after 1 year of salt intake restriction, and the change level in the SS group was − 0.68 (SD 1.03) g/day, which was significantly greater than that in the SR group (−0.42 (SD 1.16) g/day) ($p < 0.01$). Therefore, the level of eUNaE 1 year later in the SS group

TABLE 2 Comparison on level of urinary sodium and potassium excretion, blood pressure, and BMI at 1 year after the implementation of different salt restriction strategies (N = 3,794).

Level of outcomes after 1 year of strategies implementation	SR (n = 1,897)	SS (n = 1,897)	p
eUNaE (g/day), mean (SD)	4.05 (1.01)	3.82 (1.03)	< 0.01
eUKE (g/day), mean (SD)	1.71 (0.62)	2.09 (0.43)	< 0.01
Na/K ratio, mean (SD)	3.02 (2.12)	1.90 (0.75)	< 0.01
Change in eUNaE (g/day)*, mean (SD)	−0.42 (1.16)	−0.68 (1.03)	< 0.01
Change in eUKE (g/day)*, mean (SD)	−0.40 (0.64)	0.01 (0.46)	< 0.01
Change in Na/K ratio*, mean (SD)	0.81 (2.09)	−0.38 (1.00)	< 0.01
BMI (kg/m2), mean (SD)	24.12(3.01)	24.14(3.07)	0.86
Change in BMI (kg/m2)*, mean (SD)	0.06 (0.95)	0.02 (0.95)	0.16
SBP (mmHg), mean (SD)	120.42 (14.98)	120.80 (14.76)	0.43
DBP (mmHg), mean (SD)	74.51 (10.76)	74.53 (10.79)	0.95
Change in SBP (mmHg)*, mean (SD)	−0.18 (11.42)	−0.51(11.33)	0.38
Change in DBP (mmHg)*, mean (SD)	−0.05 (8.09)	0.01 (7.87)	0.86
Salt intake ≤ 6g/d, n (%)	65 (3.43)	124 (6.54)	< 0.01
Potassium intake ≥ 3.6g/d, n (%)	0 (0.00)	1 (0.05)	0.32
Normal BP, n (%)	1,541 (81.23)	1,515 (79.86)	0.29

*Calculated by subtracting baseline levels from 1 year after.
SR, salt restriction; SS, salt substitute; SD, standard deviance; eUNaE, estimated urinary sodium excretions; eUKE, estimated urinary potassium excretions; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; BMI, body mass index.

(3.82 (SD 1.03) g/day) was substantially lower than that in the SR group (4.05 (SD 1.01) g/day) ($p < 0.01$), and the incidence of daily salt intake ≤ 6 g in the SS group [6.54% (95% CI: 5.47, 7.74%)] was higher than that in the SR group [3.43% (95% CI: 2.65, 4.35%)] ($p < 0.01$). After adjusting for confounding factors, SS was still significantly associated with a decreased level of eUNaE [$\beta = -0.11$, 95% (−0.14, −0.08)], a negative change in eUNaE [$\beta = -0.12$, 95% (−0.15, −0.09)] and a higher risk of salt intake ≤ 6 g/d [OR = 1.96, 95% (1.44, 2.67)] (Table 3). Compared to SR, either exposure to SS with 13% or 25% KCl or the use of SS for 12 months or 9–11 months may lead to lower levels of eUNaE (Figure 2; Supplementary Tables S1–S4). However, the eUNaE levels between the 13 and 25% KCl groups did not differ significantly ($p > 0.05$) (Supplementary Tables S1, S2). Using SS for 12 months or for 9–11 months also produced similar levels of eUNaE (Supplementary Tables S3, S4).

Effects of SS on the level of eUKE and Na/K ratio

One year after salt intake restriction, the changes in eUKE levels in the two groups were opposite ($p < 0.01$), with the SR group showing a negative change (−0.40 (SD 0.64) g/day) and the SS group showing a positive change (0.01 (SD 0.46) g/day) (Table 2). Therefore, the SS group had a significantly higher level of eUKE after 1 year (2.09 (SD 0.43) g/day) than the SR group (1.71 (SD 0.62) g/day) ($p < 0.01$). Similarly, the Na/K ratio changed differently in the two groups ($p < 0.01$), with a positive change in the SR group [0.81 (SD 2.09)] and a negative change in the SS group [−0.38 (SD 1.00)]. The adjustment of confounding factors did not change the significance or direction of the association between SS and eUKE [$\beta = 0.34$, 95% (0.31, 0.37)], Na/K ratio [$\beta = -0.33$, 95% (−0.36, −0.30)], change in eUKE [$\beta = 0.34$, 95% (0.31, 0.37)] or change in Na/K ratio [$\beta = -0.34$, 95% (−0.37, −0.31)] (Table 3). However, despite consuming potassium-enriched salt substitute, only one participant in the SS group showed daily potassium intake ≥ 3.6 g, which was not significantly different from the SR group ($p = 0.32$) (Table 2). The effect of SS with 25% KCl on eUKE and Na/K ratio levels was slightly greater than that of SS with 13% KCl ($p < 0.05$) (Supplementary Tables S1, S2; Figure 2). The eUKE and Na/K ratio levels were similar between subjects exposed to SS for 9–11 and 12 months ($p > 0.05$) (Supplementary Tables S3, S4; Figure 2).

Effects of SS on BP levels and BMI

Table 2 shows that after 1 year of restriction, both groups experienced an insignificant and subtle decrease in the levels of SBP, DBP, or BMI when compared to the baseline ($p > 0.05$). However, SR and SS showed no significant differences in SBP, DBP, BMI, or the risk of normal BP. The different dosages of KCl or duration of SS exposure were also not related to DBP or BMI. However, 25% KCl exposure was related to a lower level of SBP, regardless of whether it was compared with SR or 13% KCl (Supplementary Tables S1–S4; Figure 2).

Sensitivity analyses

A sensitivity analysis was conducted in the unmatched overall cohort population, where SS had similar effects on eUNaE, eUKE, Na/K ratio, BP, and BMI, as observed in the PSM population (Figure 2;

TABLE 3 Effects of salt substitute usage on urinary sodium and potassium excretion, blood pressure, and BMI compared to a regular salt restriction strategy 1 year after implementation of the strategy (N = 3,794).

Outcome at 1 year after implementation of strategy	Model A┼			Model B╫			Model C╪		
	$\beta^{\#}$	95%CI	p	$\beta^{\#}$	95%CI	p	β#	95%CI	p
eUNaE (g/day)	−0.11	(−0.14, −0.08)	< 0.01	−0.11	(−0.14, −0.08)	< 0.01	−0.11	(−0.14, −0.08)	< 0.01
eUKE (g/day)	0.33	(0.30, 0.36)	< 0.01	0.34	(0.31, 0.37)	< 0.01	0.34	(0.31, 0.37)	< 0.01
Na/K ratio	−0.33	(−0.36, −0.30)	< 0.01	−0.33	(−0.36, −0.30)	< 0.01	−0.33	(−0.36, −0.30)	< 0.01
Change in eUNaE (g/day)*	−0.12	(−0.15, −0.09)	< 0.01	−0.12	(−0.15, −0.09)	< 0.01	−0.12	(−0.15, −0.09)	< 0.01
Change in eUKE (g/day)*	0.35	(0.32, 0.37)	< 0.01	0.34	(0.31, 0.37)	< 0.01	0.34	(0.31, 0.37)	< 0.01
Change in Na/K ratio (g/day)*	−0.34	(−0.37, −0.31)	< 0.01	−0.34	(−0.37, −0.31)	< 0.01	−0.34	(−0.37, −0.31)	< 0.01
DBP (mmHg)	0.001	(−0.03, 0.03)	0.95	0.01	(−0.02, 0.04)	0.66	0.01	(−0.02, 0.03)	0.68
SBP (mmHg)	0.01	(−0.02, 0.05)	0.43	0.02	(−0.01, 0.05)	0.25	0.02	(−0.01, 0.04)	0.24
Change in SBP (mmHg)*	−0.01	(−0.05, 0.02)	0.38	−0.02	(−0.05, 0.02)	0.37	−0.02	(−0.05, 0.02)	0.31
Change in DBP (mmHg)*	−0.003	(−0.04, 0.03)	0.86	−0.004	(−0.04, 0.03)	0.81	−0.01	(−0.04, 0.03)	0.74
BMI (kg/m^2)	0.003	(−0.03, 0.04)	0.86	0.01	(−0.01, 0.03)	0.26	0.01	(−0.01, 0.03)	0.26
Change in BMI*(kg/m^2)*	−0.02	(−0.06, 0.01)	0.16	−0.02	(−0.05, 0.01)	0.18	−0.02	(−0.05, 0.01)	0.18
	OR$^{\$}$	95%CI	p	OR$^{\$}$	95%CI	p	OR$^{\$}$	95%CI	p
Salt intake ≤ 6g/d	1.97	(1.45, 2.68)	< 0.01	1.96	(1.44, 2.66)	< 0.01	1.96	(1.44, 2.67)	< 0.01
Normal BP	1.01	(0.93, 1.28)	0.29	1.01	(0.93, 1.28)	0.29	1.01	(0.92, 1.29)	0.32

#Estimated based on linear regression; $Estimated based on logistic regression; *Calculated by subtracting baseline levels from 1 year after; ┼ Model A: crude model; ╫ Model B: adjusted for age, sex, alcohol usage and smoking, BMI; ╪Model C: adjusted for variables in Model B plus hypertension, diabetes, chronic gastritis, hyperglycemia and dyslipidemia.
SR, salt restriction; SS, salt substitute; eUNaE, estimated urinary sodium excretions; eUKE, estimated urinary potassium excretions; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; BMI, body mass index.

Supplementary Tables S5, S6). Stratification analysis showed that the effects of SS on BP, BMI, sodium, and potassium did not differ significantly between hypertensive and non-hypertensive subgroups (Supplementary Table S7).

Safety outcomes

In the present study, we did not observe any AEs. Neither the SS nor SR groups showed severe arrhythmias (high apex of T waves, prolonged PR interval, multiple premature ventricular tachycardias, ventricular tachycardias, etc.) or hyperkalemia.

Discussion

To the best of our knowledge, this study is the first to evaluate the impact of salt substitute on sodium and potassium intake, as well as blood pressure, among the general population in the real world. These findings indicate that salt restriction, including the consumption of salt-restricted spoons, has a very limited effect on improving sodium and potassium intake and that choosing salt substitute under the recommendation of physicians can significantly reduce sodium intake and increase potassium intake in the general population. However, the benefits of salt substitute in controlling blood pressure in the general population have not been shown, especially in the 13% KCl salt substitute group.

The expected impact of reducing sodium and increasing potassium intake can be calculated by replacing regular salt with a salt substitute. However, previous studies, including our own, have shown significant differences between theoretical predictions and actual measurements. In the SSaSS study, which was conducted among elderly participants in rural northern China, it was estimated that only 40–60% of dietary salt was replaced with salt substitute (19). In our own study, the SS group had a decrease of only − 0.68 g in sodium and an increase of 0.01 g in potassium. This may be due to an increase in sodium intake from processed foods worldwide as well as in China (20). Furthermore, our study was conducted among urban participants who consume more prepared food than rural residents. Additionally, the majority of salt substitutes available on the market contain only 13% KCl. Therefore, over 75% of participants in our study consumed salt substitute with 13% KCl. In contrast, the salt substitute used in the SSaSS and Yuan's study contained 25% KCl provided by the researchers (5, 6). Therefore, our study may offer insight into the true effect of salt substitute on sodium and potassium intake among the general population in the real world.

Before the popularization of salt substitute, the primary strategy for minimizing salt consumption involved educating the public on salt restriction, particularly by promoting the use of salt-restricted

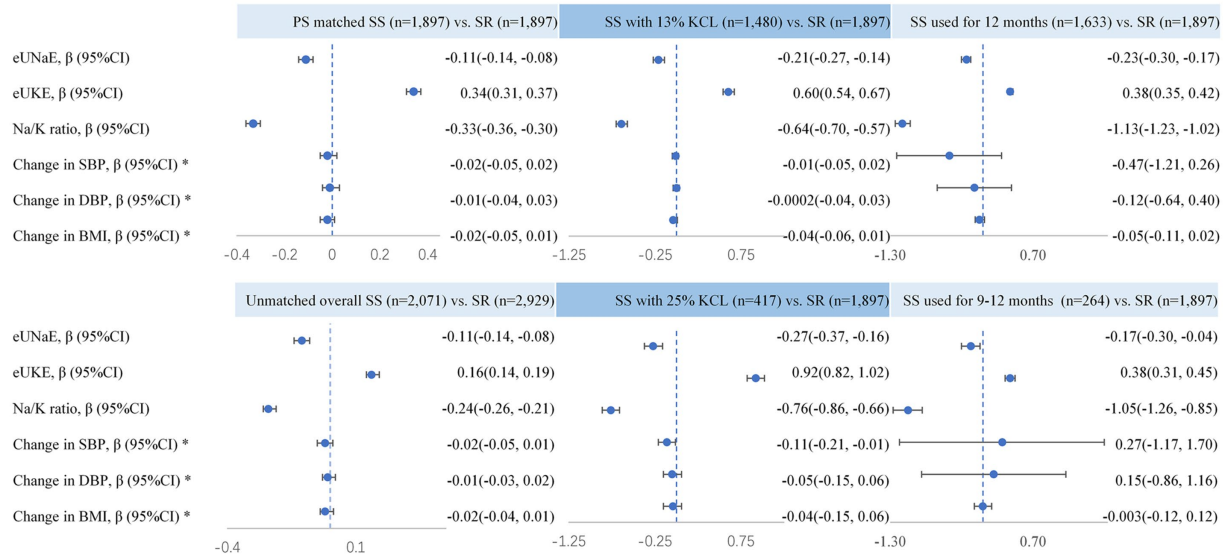

FIGURE 2
Effects of salt substitute usage compared with a regular salt restriction strategy among different exposure population. Changes in those indices were calculated by subtracting baseline levels from 1 year after and the effects of SS on those indices were adjusted for age, sex, alcohol usage and smoking, hypertension, diabetes, chronic gastritis, hyperglycemia, and dyslipidemia.

spoons. Compared to salt restriction, exposure to salt substitute with either 13% or 25% KCl may result in lower levels of eUNaE, consistent with other study (21). The results indicate that salt substitute has a better effect in reducing eUNaE level than salt restriction for the public. The Chinese diet is well known as a high-sodium and low-potassium diet (4, 5, 22–24). Therefore, increasing potassium intake is equally important. Surprisingly, the level of eUKE decreased significantly in the salt restriction group after 1 year. Given that potassium intake primarily originates from fresh vegetables, we hypothesize that the intervention group's consumption of high-potassium foods may decline. Regrettably, this study did not collect data on dietary intake and is thus unable to offer a definitive explanation for this observation. Furthermore, it leads to an increase in the Na/K ratio, which is associated with high blood pressure and cardiovascular disease (1, 2, 7). Therefore, in addition to sodium restriction, potassium addition should be generalized to the Chinese diet. Of course, based on the results in the current study, salt substitute may be an alternative strategy for elevating potassium intake and reducing the Na/K ratio.

Reducing sodium and/or increasing potassium intake has well-established blood pressure-lowering effects. There is empirical evidence that replacement of sodium substitute lowers systolic and diastolic blood pressure (average net changes [95% CI] were − 5.58[−7.08 to − 4.09] mmHg and − 2.88[−3.93 to − 1.83] mmHg, respectively) (25). Thus, salt substitute is a potential BP-lowering strategy under consideration by several countries, including China (26, 27). In our previous study, less sodium intake and higher potassium intake resulted in a decrease in blood pressure in hypertensive, normal blood pressure and hypotensive populations (28). Bruce et al. (5) observed a significant decrease in systolic blood pressure after implementation of the salt restriction strategy, and the change in blood pressure in the salt substitute group was greater than that in the routine salt restriction group. Yuan's study suggested that the use of a salt substitute may lower blood pressure in elderly care facilities in China6. However, in our study, we did not observe significant changes in blood pressure. Nonetheless, we did find a difference in the change in SBP between the 25% KCl SS and SR groups, as well as between the 25% KCl SS and 13% KCl SS groups. Therefore, we believe that a low-level KCl salt substitute may not be as effective as a high-level salt substitute in reducing eUNaE and blood pressure. It's noteworthy that the previous studies all utilized 25% KCl SS, which has beneficial effects on blood pressure reduction. However, in the area where this study was conducted, 13% KCl SS is currently more prevalent on the market. Based on our findings, we recommend promoting the production and distribution of 25% KCl SS alternatives. This approach could maximize the health benefits of sodium reduction while potentially enhancing potassium intake.

Moreover, we also found that even using 25% KCl as a salt substitute resulted in a lower reduction in systolic blood pressure compared to previous studies. The discrepancy may be because the SSaSS study enrolled individuals with high CVD risk factors4, whereas our group enrolled the general population with lower hypertension morbidity rates. A meta-analysis of 5 trials indicated that the beneficial effects of salt substitute on blood pressure was greater in participants with hypertension and smaller, nonsignificant in participants without hypertension 21. We conducted further analysis on the effect of salt substitute on blood pressure in the hypertensive population but found no significant changes. It is worth conducting further studies on the general population, especially those without hypertension or risk of cardiovascular disease.

The potential for an increased risk of hyperkalemia and related arrhythmia among participants using salt substitute was carefully evaluated in previous studies (4, 29–32). Overall, there is insufficient evidence regarding the effects of potassium-enriched salt substitute on the occurrence of hyperkalemia. Numerous cases of life-threatening hyperkalemia have been reported in chronic kidney disease or the use

of medications that impair potassium excretion (33, 34). In the current study, all participants were asked by physicians to exclude contraindications; moreover, most of the participants used 13% KCl salt substitute in the current study. Thus, we did not find an adverse effect of salt substitute.

In summary, the current study first assessed the changes in urinary sodium and potassium levels, as well as blood pressure, by utilizing a salt substitute or implementing a salt restriction strategy at the population level in real-world settings in China. Our study has several limitations. First, this study did not use the gold standard 24-h urine test to evaluate sodium and potassium intake. Although the formula we employed is the least biased among the INTERSALT and Tanaka methods (35–37), potential bias might exist in our study, which may attenuate the observed association. Second, although the study adjusted for major sociodemographic characteristics and cardiometabolic factors, residual confounding in our study results may still exist. Third, an important limitation to consider is that the use of salt substitute was tracked only for home cooking, and we were unable to account for salt intake from meals consumed away from home. Fourth, we did not collect dietary questionnaires and distinguish between sodium and potassium intake from natural foods and those from additive sources. Finally, owing to the nature of a real-world propensity-matched retrospective cohort study, the current study was not equivalent to an RCT study, and the effect of salt substitute is worth further study.

Conclusion

Compared with salt restriction, salt substitute over a year results in more sodium reduction and greater potassium increase, with no apparent adverse effects. The effect of salt substitute on lowering blood pressure in the general population requires further study in the real world.

Data availability statement

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

Ethics statement

The studies involving humans were approved by all participants signed informed consent forms, and the study was approved by the Ethics Committee of the Third Xiangya Hospital (2020-S498). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HW: Conceptualization, Writing – original draft, Data curation, Methodology, Writing – review & editing. WO: Data curation, Methodology, Writing – original draft. JD: Funding acquisition, Investigation, Writing – original draft. YH: Data curation, Investigation, Writing – original draft. LY: Methodology, Supervision, Writing – review & editing. XC: Investigation, Project administration, Supervision, Writing – review & editing. ZC: Funding acquisition, Investigation, Writing – review & editing. PY: Investigation, Methodology, Writing – review & editing. YW: Formal analysis, Supervision, Writing – original draft. YL: Conceptualization, Funding acquisition, Methodology, Writing – review & editing. XH: Funding acquisition, Validation, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1504152/full#supplementary-material.

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Effect of plasma homocysteine on cardiometabolic multimorbidity among Chinese adults: a population-based and real-world evidence study

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Aims: To explore the effect of plasma homocysteine (Hcy) on cardiometabolic multimorbidity (CMM) among Chinses adults.

Methods: This study combined a community-based cross-sectional study with a 1:1 matched case–control study using propensity score method among adults aged over 30 years in six districts randomly selected from Hunan Province, China. We recruited 5,258 people, of whom 4,012 met the study criteria were enrolled. CMM was defined as the coexistence of two or more cardiometabolic diseases, including diabetes, hypertension, coronary heart disease and stroke. The plasma Hcy and other laboratory data was measured by chemical automatic detector. Lifestyles and personal characteristics were collected by a questionnaire. Multivariate models were used to explore the associations. We calculated the attributable risk proportion (ARP) for the association of Hcy with CMM. The dose–response relationship was evaluated using restricted cubic splines method.

Results: Of the 4,012 adults, 436 had CMM, with a population prevalence of 10.9%. In the propensity-score-matched case–control study, 828 (414 cases and 414 controls) were included, and those with high plasma Hcy level (>16.2 μmol/L) had a higher risk of CMM than those with lowest level (<10.4 μmol/L) (adjusted OR = 2.83, 95% CI: 1.84–4.36, $p < 0.001$), with a multivariate ARP of high level of exposure was 64.66% (95% CI: 46.24–77.06%). The largest effect combination of CMM was the coexisting of diabetes, hypertension and coronary heart disease (adjusted OR = 2.26, 95%CI: 1.43–3.57, $p < 0.001$). An inverse association and dose–response relationship were observed between CMM and plasma Hcy levels. Notably, we recognized a significant mediation effect by C-reactive protein, total cholesterol, triglyceride and waist circumference, and they mediated approximately 8 ~ 23% of the effect of Hcy on risk of CMM.

Conclusion: Our findings add new evidence to this field that of high level of plasma Hcy was consistently associated with higher risk of CMM among Chinses adults, with the largest effect combination of being coexisting diabetes, hypertension and coronary heart disease. These findings have implications for cardiologists that CMM can be attributable to high level of plasma Hcy, and for

decision makers that Hcy has become a public threat that persistently affects cardiovascular health in humans.

KEYWORDS

homocysteine, cardiometabolic multimorbidity (CMM), Chinese adults, population-based study, real-world evidence

Introduction

Globally, cardiometabolic multimorbidity (CMM) referring to the coexistence of two or more cardiometabolic diseases (CMDs), including diabetes, hypertension, coronary heart disease (CHD) and stroke, is closely related to decreased quality of life and increased economic burden of disease (1–3).

Currently, scientists became interested in new risk factors for CMDs. Here, plasma homocysteine (Hcy), a sulfur-containing amino acid, an intermediate product of methionine metabolism, has been identified as a newly discovered potential risk factor for a variety of diseases including diabetes, hypertension, neurodegenerative diseases, osteoporosis, and cancer (4). Its mechanisms refer to inflammatory response and oxidative stress, vascular endothelial cells damage, prothrombotic, pro-smooth muscle cell proliferation, methylation, and lipid metabolism disorder *in vivo* (5). Numerous epidemiological studies have established the associations between an increase in plasma Hcy levels and CMDs. For instance, an 11-year follow-up study from NHANES found that Hcy was a promising biomarker in risk stratification among diabetic patients (4). Additionally, it has been shown that 75% of hypertension cases also have hyper-Hcy (HHcy), called H-type hypertension, which was first introduced by Chinese researcher in 2008 (6, 7). The risk of CVDs in hypertension patients with HHcy was approximately 5 and 12 times that of single-hypertension and healthy people, respectively (8), and HHcy was independently associated with atherosclerotic plaques and stroke (9). Although the associations between Hcy and single CMDs are well-established, a limited number of studies examined the associations between Hcy and CMM. So far, only one study has reported an association between Hcy and CMM, while no positive result has been found (10).

Studies have confirmed that the generation of Hcy is completely dependent on the methionine cycle metabolism pathway, and human methionine is completely obtained from food, so the influence of diet on HCY cannot be ignored (11). The association between Hcy and CMM will be differed by confounders level (such as diet and lifestyles, etc.) in different directions and magnitudes. Thereby, a case–control study based on propensity-score-matched method was conducted in this study, using a semiparametric approach to increase the likelihood of a reasonable match between the case and the control group, and dealing with multiple confounders or stratification, greatly improving the reliability of the results (12). Additionally, the prevalence of HHcy is much higher among adults in China than in other countries (13–15). And most of epidemiological studies only focused on hospital-based populations, with few based on general community populations, which may limit interpretation of these data. Those were mainly concentrated in North China and rare in South China (14). Thus, we conducted a community-based, propensity-score-matched, and case–control study to obtain the real-word evidence of the association between Hcy and CMM by investigating the multi-aspects influencing factors of CMM, to determine the common biomarkers of CMM, and to provide a scientific basis for the preventive and therapeutic strategies of CMM in Chinese adults.

Methods

Study design and sample

In this study, firstly, we conducted a population-based cross-sectional study to explore the association of Hcy with CMM, then, a 1:1 matched case–control study was conducted using propensity-score-matched method to validate this association. A representative sample was obtained by multistage cluster random sampling design from July 2013 to March 2014 in Hunan Province (including 14 districts and a population of more than 66 million), China. Detailed information on study design of this population has been described in our previous study (16). Those met the inclusion and exclusion criteria signed written informed consent. After obtaining informed consent, eligible participants were asked to complete a questionnaire. Accordingly, 4,012 participants were included in the population-based cross-sectional study to explore the relationship between Hcy and CMM. Furtherly, a 1:1 matched case–control study based on the propensity-score-matched method (414 No-CMM and 414 CMM) was conducted to verify this effect (Figure 1). The matched factors include age, sex, educational attainment, family income, occupation status, marital status, current smoking, heavy alcohol consumption, unhealthy diet, inactive exercise, sedentary behavior, BMI, WC, TC, TG, LDL-C and HDL-C because each factor individually contributes to increased risk of cardiometabolic diseases according to previous researches (16, 17).

The sample size estimation formula for cross-sectional studies was as follow: $n = \frac{u_\alpha{}^2 p(1-p)}{\delta^2}$, here, δ and p represents the estimated allowable error and population rate π, respectively. According to the previous study, the prevalence of HHcy in the population is 35.4% (18), with an error requirement of no more than 3%, if We assume $\alpha = 0.05$, then, the sample size obtained is 977. A total of 4,012 subjects were included in this study, which meet sample size needs. The test power was 1.000 based on the prevalence of HHcy (58.3and 32.2%, respectively) in the CMM group (436 participants) and non-CMM group (3,576 participants). In addition, the sample size estimation formula for 1:1 case–control study was as follows: $m = \frac{\left[Z_{1-a/2}/2 + Z_\beta\sqrt{P(1-P)}\right]^2}{(P-0.5)^2}$, here, m refers to the number of pairs with inconsistent exposure status between the case and control, and $P = OR/(1+OR)$. Next, calculate the total number of required pairs (M): $M = \frac{m}{P_0(1-P_1)+P_1(1-P_0)}$, here, P_0 and P_1 are estimated exposure rates for the control group and the case group, respectively.

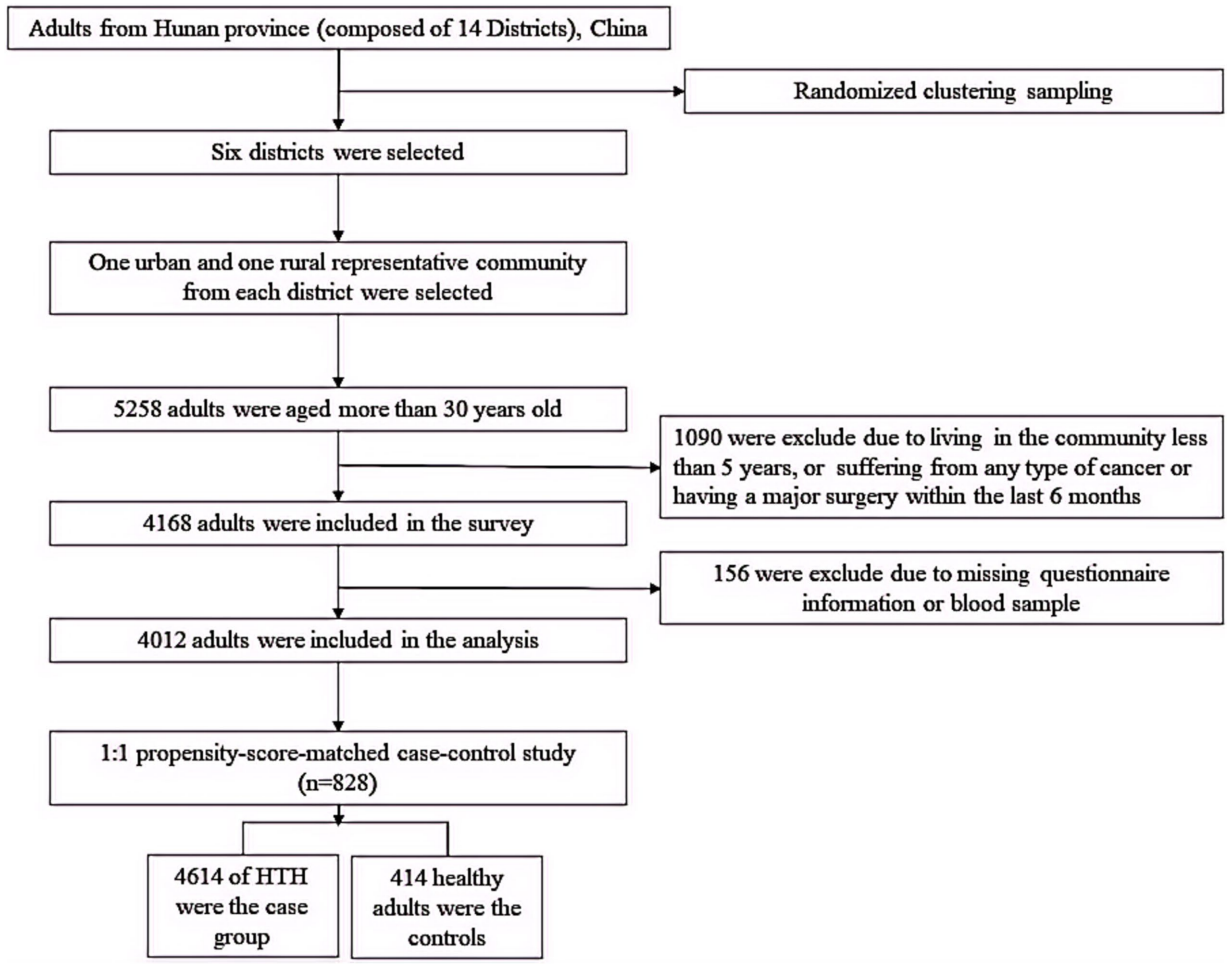

FIGURE 1
Flowchart of the study.

Based on previous literature reports, the HHcy exposure rate in the control group was 66.4%, OR = 2.08 (19), and the setting $\alpha = 0.05$ (bilateral), $\beta = 0.20$, and the final estimated sample size was 127 pairs. The case and control groups in this study included 414, respectively, which meet the sample size needs. The test power was 1.000 based on the prevalence of HHcy in the case and control groups (57.2 and 36.7%, respectively).

Data collection

Well-trained investigators collected data on socioeconomic characteristics through face-to-face and one-to-one questionnaires, which was referred the questionnaire of the China Health and Retirement Longitudinal Study (CHARLS) (20), including demographic characteristics (including age, sex, education, family income, occupation status and marital status) and lifestyles factor (including smoking, alcohol drinking, exercise and diet). Here, a test–retest reliability test was performed on the questionnaire, with a Cronbach's α coefficient in this sample being 0.778. Education level: below of high school, ordinary/vocational high school and undergraduate/college degree. Family income per year was asked for every participant, and further divided into three groups: low, medium and high. Marital status groups: unmarried, married/cohabitation and divorce/widow. Occupation types: wage-laborer, white-collar worker, farmer and retiree. Smoking was defined in the questionnaire as smoking more than 100 cigarettes in life. The drink frequency (days) and amounts (drinks) in the past week were reported according to a set of simple and easy-to-understand photos to measure the drinks of different kinds of drinks (see in Supplementary Figure S1). The average daily alcohol drinks were estimated as follows: average daily alcohol drinks = (frequency [days] × (amounts [drinks] in each of those days))/7 (18). Heavy alcohol consumption level was defined as average daily alcohol drinks ≥2. We evaluated dietary status using food frequency questionnaire according to a more recent dietary recommendation for blood pressure and combining with traditional Chinese eating habits, which considered adequate consumption of fresh fruit, fresh vegetables, unprocessed meats (including red meat, fish or shellfish), reduced consumption of high-fat, high-salt and sugar-sweetened food. We defined an unhealthy diet as meeting less than four items of the recommendations (see Supplementary methods for details). For physical activity, the number of days per week that the participants did physical activities (such as weightlifting, stair climbing, fast cycling, aerobics, running, etc.) and the time of each exercise were obtained through the questionnaires. Inactive exercise was defined as having lasting for less than 10 continuous minutes

per week (21). Sedentary behavior was defined as sitting still for more than 3 hours per day.

Anthropometric measurement

Systolic and diastolic blood pressure was measured by professionally trained staff using the calibrated electronic automatic tester. Each participant had their blood pressure measured three times with at least 5 min of rest each time. The average of the 3 values was calculated and documented as the final blood pressure value. Weight, height, and waist circumference (WC) were measured by trained staff using well-calibrated instruments. Body-mass index (BMI) was calculated as bodyweight in kg divided by the square of height in meters, and a value more than or equal to 24 was defined as an abnormal BMI.

Biochemical measurement

Blood samples were collected at 07:30–10:00 after a fasting period of 12 h. The plasma Hcy was measured by trained laboratory technicians using the microplate enzyme immunoassay method, with homocysteine Detection Kit of MedicalSystem Biotechnology Co., Ningbo, China (Reagent batch number, 13082408). Other laboratory indicators included fasting blood-glucose (FPG), plasma total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP) were detected using a Hitachi 7,600 Automatic Biochemistry Analyzer (Hitachi).

Definition of cardiometabolic diseases

Among cardiometabolic diseases, we focus on the diabetes, hypertension, coronary heart disease, and stroke. Diabetes mellitus was defined as a fasting blood glucose level ≥ 7.0 μmol/L or clinically diagnosed with diabetes mellitus or taking hypoglycemic drugs. Hypertension was defined as a diastolic/systolic blood pressure ≥ 90/140 mm/Hg or clinically diagnosed with hypertension or taking antihypertensive drugs. Coronary heart disease and stroke could be defined as a self-reported disease diagnosed by a physician or hospitalization record. Cardiometabolic multimorbidity was defined as the coexistence of two or three cardiometabolic diseases, including hypertension, diabetes, coronary heart disease and stroke.

Statistical analysis

The mean and standard deviation were used to describe the normal distribution of quantitative variables, and the *t* test was used to compare the differences. The median and quartile intervals were used to represent the quantitative variables that did not follow the normal distribution, and the *Wilcoxon rank sum* test was used to compare the differences. Categorical variables were expressed as counts and percentages (%), and differences were compared using *Chi-square* test or *Fisher exact probability* method.

Participants were categorized into two groups based on the number of CMM: ≥2 and none. Quartile classifications of Hcy level was generated (first quartile [Q1]: < 10.4 μmol/L, second quartile[Q2]: 10.4 ~ 13.2 μmol/L, third quartile[Q3]:13.3 ~ 16.2 μmol/L, fourth quartile [Q4]: >16.2 μmol/L). Logistic regression models were employed to evaluate the associations between Hcy and CMM using odds ratios (ORs) and 95% confidence intervals (CIs). The potential non-linear relationships of Hcy with CMM was estimated by using a restricted cubic spline (RCS) model. "VennDiagram" and "openxlsx" R packages were used to implement multimorbidity pattern analysis.

Here, to validate the association of Hcy with CMM, a 1:1 matched case–control study was established using propensity score matching method. The data before and after matching were, respectively, compared to see whether the patients were balanced in important covariates. The difference of the covariates after matching was greater than 0.06, indicating that the covariates after matching were balanced among groups (see Supplementary Table S1 for details). In this case–control study, to examine the proportion of CMM in the exposed population that theoretically would not have occurred if all participants had adhered to the lowest level of Hcy (Q1), we calculated the attributable risk proportion (ARP) under the assumption of a causal relationship between the highest level of Hcy (Q4) and CMM risk. The formula for calculating ARP was as follows: ARP = (OR−1)/OR×100%.

To identify the potential mechanism for the association, we conducted a mediation effect model as Hcy (X) → biomarker (M) → CMM(Y). A biomarker was selected if it was significantly correlated with both Hcy and CMM. Detailly, a logistic model was used when CMM was the dependent variable, and a linear model was used when the biomarker was the dependent variable. Bias-corrected *bootstrap* method with 1,000 resamples was used to obtain 95% CIs of the direct and indirect effects (22). Age, sex, educational attainment, family income, occupation status, marital status, current smoking, heavy alcohol consumption, unhealthy diet, inactive exercise and sedentary behavior were adjusted in mediation models as covariates. Coefficients are presented in standardized form, using standardized coefficients as indices of effect. A statistically significant mediation effect is observed when the 95%CI does not include zero. The mediated proportion was used to evaluate the effect size of the mediation analysis.

To assess the robustness of the results, four models were constructed in the sensitivity analysis based on previous researches (16, 18). In model 1, no covariate was adjusted. In model 2, we adjusted for age, sex, education, family income, marital status and occupational status. In model 3, sedentary behavior should be added as an adjusted variable. In model 4, additionally adjusted for serum FPG, TC, TG, LDL-C and HDL-C and CRP based on Model 3. In addition, subgroup analyses were performed according to different combinations of CMMs.

All statistical analyses were conducted using STATA version 18.0 (Institute, Gary, NC, United States) and R version 4.4.1. A two-sided $p < 0.05$ was considered statistically significant.

Results

Population characteristics

A total of 4,012 participants were enrolled in this study for analysis (Table 1). The study population had a mean age of 54.6 years (SD 12.6). 1,644 (41.0%) were males and 2,368 (59.0%) were females. Among them, 2,179 (54.3%) of 4,012 individuals did not have a CMD,

TABLE 1 Baseline characteristics of participants by cardiometabolic disease status[a].

Characteristics	Total	No-CMM	CMM	*p*-value
N	4,012	3,576	436	
Age, mean (SD)	54.6 (12.6)	53.34 (12.3)	64.7 (10.4)	<0.001
Sex (%)				<0.001
Male	1,644 (40.1)	1,408 (39.4)	236 (54.1)	
Female	2,368 (59.0)	2,168 (60.6)	200 (45.9)	
Educational attainment (%)				<0.001
Below of High School	2033 (50.7)	1726 (48.3)	307 (70.4)	
Ordinary or vocational high school	1,154 (28.7)	1,058 (29.6)	96 (22.0)	
Undergraduate or college degree	825 (20.6)	792 (22.1)	33 (7.6)	
Family income[b] (%)				<0.001
Low	1,159 (38.8)	1,348 (37.7)	211 (48.4)	
Medium	1,439 (35.9)	1,286 (36.0)	153 (35.1)	
High	1,014 (25.3)	942 (26.3)	72 (16.5)	
Occupation (%)				<0.001
Wage laborer	595 (14.8)	555 (15.5)	40 (9.2)	
White-collar worker	1,102 (27.5)	1,064 (29.8)	38 (8.7)	
Farmer	714 (17.8)	624 (17.4)	90 (20.6)	
Retiree	1,601 (39.9)	1,333 (37.3)	268 (61.5)	
Marital status (%)				0.057
Unmarried	65 (1.6)	59 (1.6)	6 (1.4)	
Married/Cohabitation	3,808 (94.9)	3,384 (94.6)	424 (97.2)	
Divorce/Widow	139 (3.5)	133 (3.7)	6 (1.4)	
Current smoking (%)	1,079 (26.9)	904 (25.3)	175 (40.1)	<0.001
Heavy alcohol drinking (%)	962 (24.0)	837 (23.4)	125 (28.7)	0.017
Unhealthy diet (%)	1974 (49.2)	2,308 (64.5)	347 (79.6)	<0.001
Inactive exercise (%)	2,610 (65.1)	2,319 (64.8)	291 (66.7)	0.460
Sedentary behavior (%)	2,333 (58.2)	2060 (57.6)	273 (62.6)	0.045
BMI ≥24Kg/m^2 (%)	1,578 (39.3)	1,347 (37.7)	231 (53.0)	<0.001
WC, mean (SD)	84.4 (9.9)	83.8 (9.6)	88.9 (10.6)	<0.001
DBP, mean (SD)	127.4 (21.0)	78.7 (11.4)	87.5 (13.7)	<0.001
SBP, mean (SD)	79.6 (12.0)	124.2 (18.6)	153.7 (20.5)	<0.001
FPG, mean (SD)	5.7 (1.6)	5.4 (1.3)	7.5 (2.4)	<0.001
TC, mean (SD)	4.8 (0.9)	4.8 (0.9)	4.9 (1.0)	0.013
TG, mean (SD)	2.0 (16)	1.9 (1.6)	2.4 (2.0)	<0.001
LDL-C, mean (SD)	2.6 (0.8)	2.6 (0.8)	2.6 (0.8)	0.056
HDL-C, mean (SD)	1.3 (0.3)	1.3 (0.3)	1.3 (0.4)	0.970
CRP, mean (SD)	5.5 (1.6)	5.4 (1.4)	6.1 (2.3)	<0.001
HCY, mean (SD)	13.8 (7.7)	13.5 (7.9)	15.9 (4.5)	<0.001
Diabetes (%)	491 (12.2)	227 (6.3)	264 (60.6)	<0.001
Hypertension (%)	1,394 (34.8)	994 (27.8)	400 (91.7)	<0.001
Stroke (%)	114 (2.8)	42 (1.2)	72 (16.5)	<0.001
CHD (%)	310 (7.7)	134 (3.7)	176 (40.4)	<0.001
CMM (%)				<0.001
0	2,179 (54.3)	2,179 (60.9)	0 (0.0)	

(Continued)

TABLE 1 (Continued)

Characteristics	Total	No-CMM	CMM	*p*-value
1	1,397 (39.1)	1,397 (39.1)	0 (0.0)	
≥2	436 (10.9)	0 (0.0)	436 (100.0)	

CMM = cardiometabolic comorbidities, CHD = coronary heart disease, SD = standard deviation; BMI = body mass index; WC = waist circumference; FPG = fasting blood-glucose, TC = total cholesterol, TG = triglyceride, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, CRP = C-reactive protein, HCY = Homocysteine.
[a]Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as number (percentage). *p-values* were calculated using analysis of variance for continuous variables, and Pearson chi-squared test or Fisher's exact for categorical variables.
[b]Family income was divided into high, medium, and low level according to triquartile method.

whereas 1833 (45.7%) had at least one of these diseases. The prevalence rate of diabetes, hypertension, CHD and stroke were 12.2% (491/4012), 34.8% (1,394/4012), 7.7% (310/4012), and 2.8% (114/4012), respectively. The prevalence of CMM was 10.9% (436/4012). Compared with people who did not have CMM, those with CMM were more likely to be older, male, have low educational attainment and family income, be farmers or retirees, be currently smoking, heavy drinking, unhealthy in diet, sedentary and overweight/obesity, and have diabetes, hypertension, stroke and CHD (Table 1). The CMM group had elevated mean levels of WC, FPG, SBP, DBP, TG, TC and CRP (88.9 ± 10.6, 7.5 ± 2.4, 153.7 ± 20.5, 87.5 ± 13.7, 2.4 ± 2.0, 4.9 ± 1.0, and 6.1 ± 2.4 mmol/L, respectively) than the No-CMM group. The prevalence rate of diabetes, hypertension, CHD and stroke were 12.2% (491/4012), 34.8% (1,394/4012), 7.7% (310/4012), and 2.8% (114/4012), respectively. Notably, those with CMM were more likely to have high level of plasma Hcy than population with No-CMM.

Multimorbidity pattern analysis

Figure 2 provides details about the combinations of different cardiometabolic diseases and includes 15 combinations in total. Among the 4,102 participants enrolled in this study, 1833 had at least one of CMD (45.7%) and 436 (10.9%) met the diagnostic criteria for CMM, which includes metabolic disorders such as hypertension, diabetes mellitus, stroke and CHD. Of those with CMM, the most two frequent combinations were the "Diabetes + Hypertension" and "Hypertension + CHD," corresponding to 47.5% (207/436) and 26.8% (117/436), respectively. Additionally, among the total study participants 9.2% (40/436) had there or more component conditions of CMM (Figure 2). Here, the associations of plasma Hcy with the risk of specific combination of CMD were displayed in Supplementary Table S2. After adjusting for age, sex, educational attainment, family income, occupation status, marital status, current smoking, heavy alcohol consumption, unhealthy diet, inactive exercise, sedentary behavior, BMI, WC, TC, TG, LDL-C, HDL-C and CRP, we found those with diabetes, hypertension and CHD had corresponding ORs of 1.97 (95% CI: 1.15–3.56, $p = 0.013$), 11.35 (95% CI: 5.58–23.09, $p < 0.001$), and 1.98 (95% CI: 1.05–3.74, $p = 0.034$), respectively. No significant association was found between plasma Hcy and stroke (OR = 1.00, 95% CI: 0.92–1.05, $p = 0.691$).

Associations of homocysteine with cardiometabolic multimorbidity and its ARP

Multiple logistic regression models were carried out to examine the impact of plasma level of Hcy on the risk of CMM (Figure 3). In the cross-sectional study based on 4,012 participants, after adjusted for the covariables (including age, sex, educational attainment, family income, occupation status, marital status, current smoking, heavy alcohol consumption, unhealthy diet, inactive exercise, sedentary behavior, BMI, WC, TC, TG, LDL-C, HDL-C and CRP), compared with the lowest level of plasma Hcy [Q1], the third (OR = 1.51, 95%CI:1.06–2.16, $p = 0.023$) and fourth quartile levels [Q4] (OR = 2.82, 95%CI: 2.03–3.91, $p < 0.001$) of Hcy were significantly and positively associated with increased CMM risk. Moreover, RCS analysis showed that there was an inverse dose–response relationship between plasma Hcy concentration and CMM after adjusted for the covariables, suggesting that escalating levels of Hcy was associated with an increasing risk of developing CMM ($p < 0.001$) (Figure 4).

In the propensity-score-matched case–control study (414 non-CMM vs. 414 CMM), 828 participants were included. We validated the results of the above cross-sectional study that plasma Hcy had positive impact on risk of CMM (Table 2). For details, compared with those with lowest quartile level of Hcy, the risk of CMM was increased by 183% (OR = 2.83, 95% CI: 1.84–4.36, $p < 0.001$) among those with highest fourth quartile level of Hcy. Table 2 also summarized the ARP for plasma level of Hcy. In case–control study, the multivariate ARP of highest fourth quartile level of Hcy was 64.66% (95% CI: 46.24–77.06%).

Mediation analysis

Supplementary Tables S3, S4 illustrated the correlations of plasma Hcy with various potential mediated indicators and the association of potential mediated indicators with CMM. Since CRP, TC, TG and WC were significantly correlated with both Hcy and CMM, we hypothesis that these indicators may mediate the association we investigated. We performed a causal mediation analysis, and recognized a proportion of effect mediated by CRP, TC, TG and WC as 7.77% (95% CI: 2.87–16.00%, $p < 0.001$), 12.00% (95% CI: 5.10–21.00%, $p < 0.001$), 18.93% (95% CI: 8.96–40.00%, $p < 0.001$) and 22.58% (95% CI: 11.26–56.00%, $p < 0.001$), respectively (Supplementary Figure S2).

Sensitivity and subgroup analysis

In sensitivity analyses, we constructed several models, then, we found the results remained similar in all sensitivity analyses (Figure 3). Moreover, we conducted subgroup analysis. Supplementary Figure S3 showed the results stratified by different combinations of CMM. For details, the plasma level of Hcy was mostly correlated with the combination of diabetes, hypertension and CHD (OR = 2.26, 95%CI: 1.43–3.57, $p < 0.001$), followed by the combination

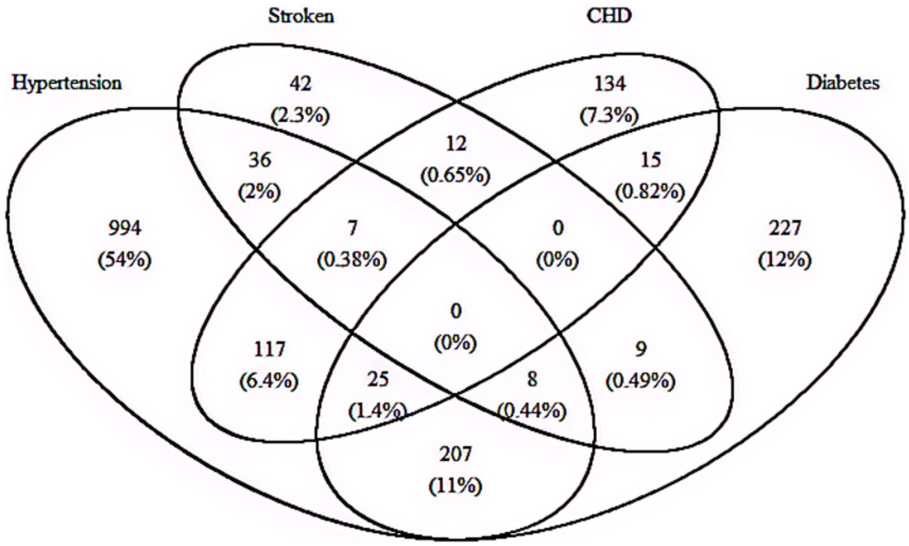

FIGURE 2
Multimorbidity pattern analysis. CHD, coronary heart disease.

of diabetes and hypertension (OR = 1.34, 95%CI: 1.23–1.44, $p < 0.001$), the combination of hypertension and CHD (OR = 1.32, 95%CI: 1.21–1.44, $p < 0.001$) and the combination of hypertension and stroke (OR = 1.19, 95%CI: 1.04–1.37, $p = 0.013$), respectively (Supplementary Figure S3).

Discussion

In this community-based study, we investigated the association of Hcy with CMM (two or more conditions in diabetes, hypertension, coronary heart disease, and stroke) in a group of adults over 30 years of age in China, with the largest effect combination of CMM being diabetes, hypertension and coronary heart disease. An inverse association and dose–response relationship were observed between CMM and plasma Hcy levels. Highest level of plasma Hcy (> 16.2 μmol/L) explained about 64.66% of the CMM risk. We also recognized a significant mediation effect by C-reactive protein, total cholesterol, triglyceride and waist circumference in associations of Hcy with CMM, with corresponding mediation proportion ranging from 8 to 23%. Our findings suggested a targeted approach to dynamically monitor and reduce plasma Hcy levels to reduce the risk of cardiometabolic multimorbidity.

Hcy was identified by Butz et al. (23), as an important intermediate product in the methionine cycle and cysteine metabolism. Subsequently, an 8-year-old intellectually disabled boy died strangely from a severe heart attack, and HHcy's description was first reported. Since that time, the number of clinical and basic studies of Hcy has increased exponentially. In certain situation, the risks associated with HHcy may be significantly elevated. There is evidence that HHcy is a high predictive value for diabetes patients (24), hypertension (25), and cardiovascular and cerebrovascular diseases (26). In our study, we found high level of plasma Hcy was positively related to elevated risk of diabetes, supporting the result from other study (24). In addition, Hcy was also associated with increased risk of the occurrence of complications of diabetes, such as diabetic nephropathy, diabetic retinopathy, etc. In the future, Hcy can potentially be used as an early screening indicator for diabetic microvascular complications (27). Additionally, homocysteine, as one of one-carbon metabolism components, is also closely entwined with gestational diabetes mellitus risk (28). Therefore, it is very important to understand the origin and metabolism of homocysteine and the pathway of its change in diabetes pathogenesis.

In 2007, a study on the efficacy and safety of enalapril folic acid tablets in lowering blood pressure and plasma Hcy was conducted in six major cities in China (6). Thus, Chinese researchers first proposed the concept of HTH, and found elevated Hcy levels were associated with 75% of the hypertension cases (7). Numerous human epidemiological studies have reported the relationship between plasma Hcy levels and hypertension different populations (25, 29). In our study, we found those with over 16.2 umol/L plasma Hcy level had a 11.35 times higher risk of hypertension than those in lowest levels (<10.2 umol/L), which was consistent with serval studies (25, 29, 30). Notably, HTH was significantly amplifying the damage of hypertension to blood vessels, increasing the risk of heart, brain, and kidney complications, and increasing the risk of cardiovascular events, especially stroke (9).

Since the observation, by McCully et al., of severe arteriosclerotic lesions in children with high level of plasma Hcy, a numerous series of observational studies have demonstrated elevation of plasma Hcy level was considered be related to cardiovascular disease (CVD), stroke, and venous thromboembolism (31, 32). Another study suggested that even slight increases in plasma Hcy levels can enhance the risk of CVD (33). In our study, we recognize the high level of plasma Hcy (> 16.2 μmol/L) plays a key role in prevalence to coronary heart disease (OR = 1.98, $p = 0.034$). A review reported that primary stroke can at least in part be prevented by lowering total homocysteine. Detailly, total Hcy values in adults of 10 μmol/L or below are probably

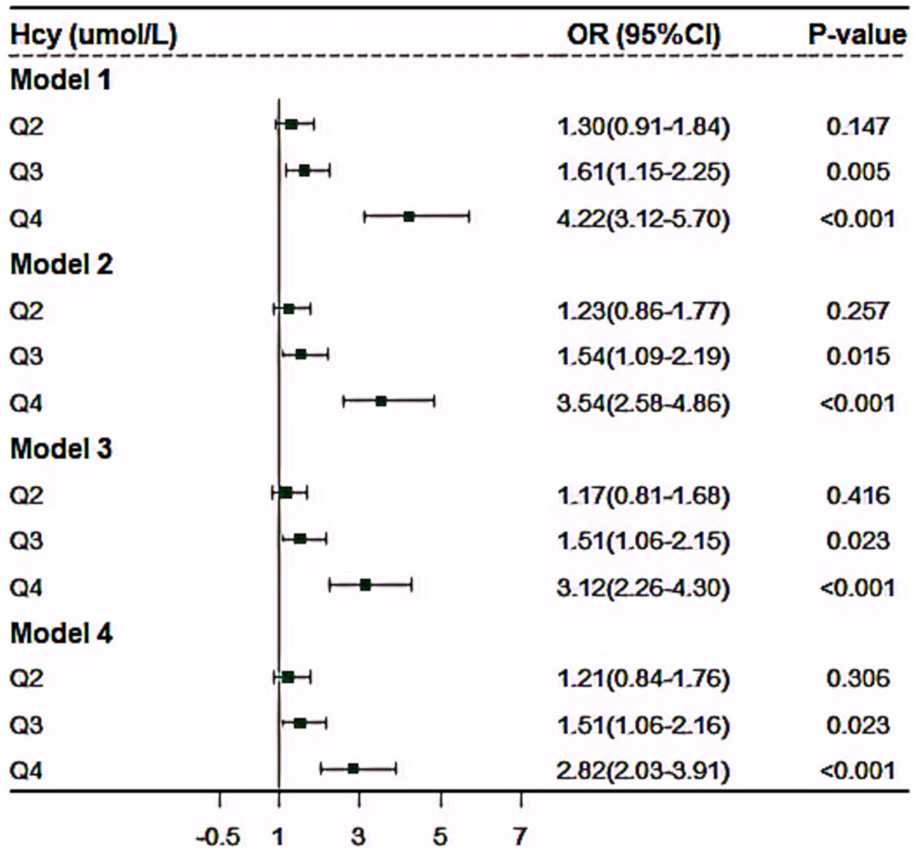

FIGURE 3
The effect of plasma homocysteine levels on cardiometabolic multimorbidity based on 4,012 community population. Model 1, no covariate was adjusted; Model 2, we adjusted for age, sex, education, family income, marital status and occupational status; Model 3, as further adjusted for current smoking, heavy drinking, unhealthy diet, inactive exercise and abnormal BMI based on Model 2; Model 4, additionally adjusted for serum FPG, TC, TG, LDL-C and HDL-C, and CRP based on Model 3.

safe, but that values of 11 μmol/L or above may justify intervention (34). The strongest evidence that Hcy plays a causal role in atherothrombosis reducing stroke has been provided by studies using animal models (35). These studies support the role of Hcy in the pathogenesis of atherosclerosis, suggesting that Hcy may be a disease biomarker (34). However, some studies have proposed different views on the relationship between Hcy and stroke. Recent meta-analysis did not show that reducing Hcy treatment was associated with incidence rate of all-cause death or coronary artery disease, except for prevention for stroke (36). Therefore, it is still uncertain that whether Hcy is a causative factor or a biomarker of vascular disease in human beings. Further research may be needed to elucidate its causal role and mechanism on vascular disease in different populations.

With the aging of the global population and the development of medical technology, the number of chronic diseases is constantly expanding, and more and more chronic diseases are being controlled at a certain level, resulting in delayed survival time for patients (37). This has led to an increasing number of people suffering from CMM (co-occurrence of at least two CMDs, including diabetes, hypertension, stroke and coronary heart disease), posing a huge challenge to the healthcare system (38). It has been confirmed that plasma Hcy is highly correlated with individual CMDs (such as diabetes, hypertension and coronary heart disease), as shown by our present findings, to the best of our knowledge, however, no research has further evaluated the impact of plasma HCY on CMM, except for one research that reported negative result (10). Our study provides important and innovative results to explore the strong correlation between plasma Hcy and CMM, and dose–response relationship analysis suggests that the higher the plasma Hcy level, the greater the risk of CMM. And, in our sensitivity analysis, the results were not materially changed with those of the main analyses. Notably, our subgroup analysis showed that high level of plasma Hcy was most associated with the combination of coexistence of diabetes, hypertension and CHD among the general population in China. Critically, we calculate the ARP for exposure on high level of plasma Hcy. In case–control study, the multivariate ARP of highest fourth quartile level of Hcy was 64.66% (95% CI: 46.24–77.06%). It means that the percentage of CMM attributable to Hcy in those exposed to the highest levels of plasma Hcy (> 16.2 umol/L) was 64.66%, indicating that 64.66% of those with high levels of Hcy would avoid CMM if they reduced their Hcy levels to the lowest one.

Cardiometabolic disease spectrum has gradually expanded to any metabolic disease that can affect the function and/or structure of the heart, including diabetes, CVD, hypertension, chronic renal insufficiency, etc., forming a chronic disease spectrum characterized by metabolic disorder of multiple organ systems (39). In terms of mechanism, with the continuous deepening of relevant clinical and basic research, the academic community has

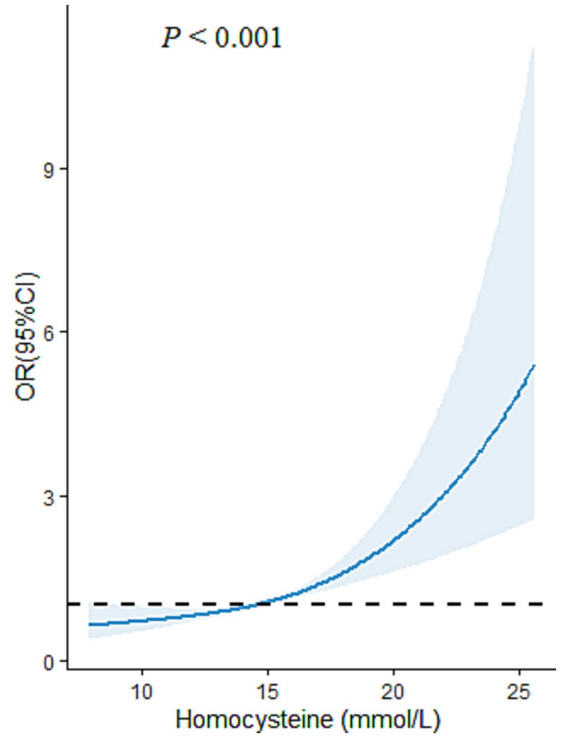

FIGURE 4
The restricted cubic spline (RCS) model for the relationship of plasma Hcy level with CMM in Chinses adults. The reference value for Hcy was set as a cut-off value for the first quartile. Three nodes were selected for all models. All models were adjusted for age, sex, educational attainment, family income, marital status, occupational status, smoking, heavy alcohol consumption, unhealthy diet, inactive exercise, sedentary behavior.

TABLE 2 The effect of plasma homocysteine levels on cardiometabolic multimorbidity and its attribution risk percentage based on 1:1 matching case–control study[a].

Homocysteine (mmol/L)	NO-CMM *vs.* CMM		
	OR	95%CI	*p*-value
Q1	1.00		
Q2	1.16	0.73–1.84	0.535
Q3	1.50	0.95–2.38	0.083
Q4	2.83	1.84–4.36	<0.001
Trend for per unit	1.12	1.08–1.16	<0.001
ARP (%, 95CI)	64.66	46.24–77.06	

[a]Adjusted for age, sex, educational attainment, family income, occupation status, marital status, current smoking, heavy alcohol consumption, unhealthy diet, inactive exercise, sedentary behavior, BMI, WC, TC, TG, LDL-C and HDL-C.

found that a series of pathological and physiological changes, such as inflammation, glucose and lipid metabolism disorders, oxidative stress, hormone regulation imbalance, and changes in intracellular and extracellular signaling pathways, are involved in the pathogenesis of CMM (40). Among them, inflammation damage caused by macrophages which typically exhibit classic M1 polarization, then secrete pro-inflammatory cytokines, participate in inflammatory responses (such as CRP, IL-6, etc.), and promote vascular damage, playing a core role in the development of CMD (41, 42). In other hand, lipid metabolism disorder caused by excessive oxidative stress participates in the pathogenesis of CMD (40). Similarly, data from UK Biobank found that evidence of serum TC and TG are causally related to the risks of cardiometabolic multimorbidity (43). In our study, cellular inflammatory factor (CRP) and abnormal indicators of lipid metabolism (TC, TG and WC) mediate a small proportion (approximately 8 ~ 23%) of the association of Hcy with CMM, suggesting that the unexplained variations might be attributable to other mechanisms of CMM. CRP and lipids indicators (TC, TG) may serve as early biomarkers of Hcy-related CMM. However, more investigations are warranted to target the clinical heterogeneity of CMM.

This study we conducted has some strengths. To the best of our knowledge, our study provides important and new evidence to this field that those with plasma Hcy levels exceeding 16.2 umol/L have a higher risk of CMM, and confirmed that Hcy was mostly associated with the combination of diabetes, hypertension and CHD, implicating for cardiologists and decision makers that CMM can be attributable to high level of plasma Hcy and it has become a public threat persistently affecting cardiovascular health in humans. Furthermore, we use a PSM case–control study to verify the positive association between Hcy and CMM found in cross-sectional study, which can enhance the objectivity of our results, using similar covariate distributions to construct case and control groups without affecting the results of the study (12). As a semi-parametric method, PSM was an important set of tools for estimating causes of disease or treatment effects in observational studies, enabling adjustment for measured confounders in an easy-to-understand and transparent way (12). However, there were still several potential limitations that should be considered when interpretating the results. Firstly, the plasma Hcy level was only assessed by at only one-time point, which could not successfully reflect the true dynamic levels of individual Hcy exposure. Future studies with repeated assessment are very important and indispensable. Besides, participants in current study are from Hunan province, China, and the sample of this special population is considered large, however, the generalizability of our results may be constrained in other regions in China and in other countries. Therefore, multiprovince or multinational monitoring studies will be necessary. Additionally, some variables, like lifestyle factors, were self-reported and only evaluated at a point in time, and it was not possible to completely avoid recall or evaluation biases. Moreover, due to the cross-sectional and case–control design of this study, causality cannot be inferred. Therefore, further larger prospective investigations are required to confirm our results. Finally, the associations between Hcy and single CMDs (hypertension, diabetes and CHD) are well-established, however, a limited number of studies examined the associations between Hcy and CMM. Our study provides important and new evidence to this fields, however, it still needs to be validated in other additional studies in the future.

In conclusion, our findings add new evidence to this field that of high level of plasma Hcy is consistently associated with higher risk of CMM among Chinses adults, with the largest effect combination of coexistence of diabetes, hypertension and coronary heart disease. These findings have implications for cardiologists that CMM can be attributable to high level of plasma Hcy, and for decision makers that Hcy has become a public threat that persistently affects cardiovascular health in humans. There is an urgent need for a

targeted approach to dynamically monitor and reduce plasma Hcy levels to reduce the risk of CMM.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Hunan Normal University (No. 034/2017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LL: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. JiaW: Formal analysis, Writing – review & editing. JL: Writing – review & editing. ML: Data curation, Writing – review & editing. JieW: Writing – review & editing. TL: Investigation, Writing – review & editing. YZ: Data curation, Writing – review & editing. XT: Writing – review & editing. YP: Writing – review & editing. XH: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1522212/full#supplementary-material

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Association between fat-soluble vitamin co-exposure patterns and blood pressure in people with hypertension: a cross-sectional study

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Background: Existing epidemiological studies investigated the association between a single vitamin and hypertension. However, the potential relationship between the level of circulating multivitamins and blood pressure has not been explored. We aimed to investigate the association between multiple fat-soluble vitamin levels and blood pressure.

Methods: A total of 2052 participants with essential hypertension were sampled nationwide. The plasma concentrations of fat-soluble vitamins (A, E, D, and K) were assessed using liquid chromatography coupled with the mass spectrometry method. Participants were categorized into different co-exposure patterns using the unsupervised K-means clustering method. The multiple linear regression model was used for subsequent analyses.

Results: Participants were classified into two co-exposure patterns of fat-soluble vitamins. The levels of vitamins were relatively low in pattern 1, compared to pattern 2. Participants in pattern 2 had no significantly different blood pressure levels compared to pattern 1. However, the plasma 25-hydroxyvitamin D_3 (VD_3) levels were negatively associated with SBP (logarithmic 10 transformed) (β = −0.002, 95% CI: −0.004, 0); participants in the fourth α-tocopherol quartile had mean SBP levels that were 1.02% (95% CI: 0.43, 1.61%) greater than those in the lowest quartile (p for trend <0.01). In addition, no significant relationships were found between plasma VA/VK concentrations and blood pressure.

Discussion: Although no significant association between fat-soluble vitamin co-exposure patterns and blood pressure was found, further analyses could imply that plasma α-tocopherol levels may offset the potential protective effect of plasma VD_3 on blood pressure among hypertensive adults. This provided a novel perspective for exploring the joint effects of fat-soluble vitamins on blood pressure. Further studies are warranted to better understand the implications.

KEYWORDS

fat-soluble vitamins, co-exposure patterns, blood pressure, essential hypertension, cross-sectional study

1 Introduction

Hypertension poses a great threat to public health worldwide. Globally, almost 1.3 billion adults suffered from hypertension in 2019 (1). Increased blood pressure is considered a major risk factor for premature death. An estimated 8.5 million deaths globally were attributable to high systolic blood pressure in 2015 (2). Owing to the striking prevalence and related significant mortality, the prevention and management of hypertension is imperative. Considering that medication therapy always has some adverse effects (3), modifying lifestyle factors was advocated to improve blood pressure. Apart from improving some traditional risk factors, such as smoking, alcohol consumption, and physical inactivity, the potentiality of nutrients in regulating blood pressure has been given considerable interest recently (4, 5).

Prior epidemiological studies have explored the association between vitamins and blood pressure (6–8). However, the results were equivocal. For instance, individuals with insufficient vitamin D (VD) possibly had a higher risk for hypertension (9), while some intervention trials designed to address the effects of VD supplementation on blood pressure showed inconsistent results (10); some observational studies reported no association between vitamin A (VA) intake and hypertension (11, 12), but an inverse association was observed between dietary VA intake and new-onset hypertension (13).

Most studies mentioned above focused on the relationship between single fat-soluble vitamin instead of multivitamin exposure and blood pressure. However, recent studies demonstrated that some vitamins may exert their blood pressure regulatory functions by interacting with other vitamins (14, 15). Moreover, the assessment of some vitamin exposure levels via estimating the vitamin contents of diets and supplements in numerous previous studies is far from accurate, because vitamin loss may occur during food storage, processing, or cooking and the absorption of vitamins varies among different populations (16–18). Using metabolomics methods such as liquid chromatography coupled with mass spectrometry (LC–MS) to detect circulating vitamins and/or their direct metabolites could be more reliable for vitamin status assessment (19, 20). Up to now, there has been no study exploring the relationship between circulating multivitamin status and blood pressure in hypertensive adults.

Clustering methods, as a powerful unsupervised machine algorithm, have been used in the nutrition field to determine dietary patterns and in the environmental health field to identify mixed pollutant exposure (21, 22). It is implied that the classification of individuals based on their vitamin exposure patterns through clustering methods could be effective in exploring the association between vitamin co-exposure and blood pressure.

Accordingly, the present study was conducted primarily to elucidate the associations between circulating concentrations of multivitamins (vitamins A, D, E, and K) and blood pressure among hypertensive adults.

2 Methods

2.1 Study design and participants

A multicenter epidemiological study, initiated in February 2017 with ongoing enrollment, was conducted to identify, register, and educate the hypertensive population in China. The inclusion criteria for study participants contained the following: (1) systolic/diastolic blood pressure $\geq$ 140/90 mmHg or taking antihypertensive drugs (23); and (2) voluntarily participating and signing the written informed consent. The exclusion criteria contained the following: (1) suffering from serious mental disorders or being unable to express themselves; and (2) having other obvious abnormal physical signs, laboratory detecting results, or clinical diseases, unable to participate. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Peking University First Hospital, Beijing, China (Ethics code: 20161231). During the enrollment, individuals were informed of the study protocol and then decided by themselves whether to participate in the study. It was entirely voluntary. The informed consent would be signed only if they wanted to participate.

Two subsamples from this ongoing study without duplication were the participants in the current study. Briefly, stratified by province, 800 individuals enrolled from June to August 2017 were firstly selected from 9 provinces (Beijing, Hebei, Liaoning, Gansu, Guangxi, Hunan, Jiangsu, Sichuan, and Jiangxi) at random. Then another 1,543 participants enrolled from February 2017 to May 2018 were randomly selected from 14 provinces (Anhui, Ningxia, Heilongjiang, Shandong, Yunnan, and the 9 provinces in the first sampling). Finally, after combining two subsamples and excluding outliers, a total of 2052 participants were included (Supplementary Figure S1).

2.2 Basic characteristics of participants

Participants' anthropometric, sociodemographic, lifestyle, and comorbid factors were collected. Calibrated instruments were used to measure height and weight to an accuracy of 0.1 cm and 0.1 kg,

respectively. Body mass index (BMI) was computed by dividing weight (kg) by height squared (m^2).

Participants' age, sex, ethnicity, northern or southern region, marital status, education level, smoking status, alcohol use, physical labor intensity, living standard, nervousness, and use of anti-hypertension medications were obtained by questionnaire. The marital status of participants was divided into five categories: married, widowed, divorced or separated, never married, and others. Level of education was reported on a 9-category scale and was further classified into three broad categories: lower levels (primary school or less), medium levels (general intermediate education or intermediate vocational education), and higher levels (general secondary education, higher vocational education, bachelor, master or higher).

Smoking and drinking status were categorized as never, former, and current tobacco or alcohol users. Participants reported the start time and the amount of smoking or alcohol consumed. Physical labor intensity was categorized as mild, moderate, and heavy levels. Nervousness was self-reported as mild, moderate, and severe degrees. The living standard was classified into three grades: poor, average, and good. In addition, the medical history of hypertension, diabetes, dyslipidemia, stroke, and coronary heart disease was asked of participants. The use of antihypertensive drugs and multivitamin supplements was investigated.

2.3 Measurement of blood pressure

Systolic and diastolic blood pressures were measured in the upper arm after 15 min of seated rest, using an electronic sphygmomanometer (Yuwell brand). The right brachial artery blood pressure should be measured at least three times, with an interval of 3–5 min between each measurement. The difference between each measurement should be less than 10 mmHg (23). We calculate the mean blood pressure by several measurements.

2.4 Measurement of vitamins

Blood samples were collected from all participants. Plasma was separated within 30 min after venous blood collection and stored at −80°C temperature until detection. Plasma concentrations of VA (retinol), VD (25-hydroxyvitamin D_3 [$25(OH)D_3$]), VE (α-tocopherol), and VK levels were measured using liquid chromatograph-mass spectrometer (LC–MS) method in Beijing DIAN Medical Diagnostics Laboratory (24, 25). The corresponding standard sample was used as a reference. For quality control, duplicate samples were randomly placed in the detected samples, and the coefficients of variation for them from the same batch and different batches were calculated. During the detection process, the personnel were unaware of the grouping status of the samples.

2.5 Statistical methods

The basic characteristics of participants were described as median and interquartile range for skewed continuous variables and proportions for categorical variables. The Wilcoxon rank-sum test and chi-square test were used to compare the differences of basic characteristics between the two subsamples.

Participants' multivitamin co-exposure patterns were determined through the K-means clustering method. Average silhouette width, Gap Statistic, "NbClust" package in R, and biological interpretability were considered to help determine the appropriate number of clusters (26). Afterward, we included the co-exposure pattern in the multiple linear regression model to explore its association with blood pressure. We further used stratified analyses and interaction tests to explore the possible modifiers of the association between co-exposure patterns and blood pressure.

Additionally, we also used simple and multiple linear regression analyses to investigate the association between each vitamin and blood pressure. As for multiple linear regression models, model 1 was adjusted for age, sex, and BMI. Model 2 was further adjusted for region, physical labor intensity, living standard, nervousness, education levels, and smoking and drinking status. Model 3 was additionally adjusted for the family history of hypertension, stroke, coronary heart disease, comorbidity (dyslipidemia and diabetes), and the use of anti-hypertension drugs. Furthermore, restricted cubic spline regression analysis was used to explore the potential non-linear association between each vitamin and blood pressure.

All statistical analyses were performed using R software, version 4.1.2. The two-sided p-value of <0.05 was considered statistically significant in all analyses.

3 Results

3.1 Basic characteristics of study participants

The sociodemographic, anthropometric, lifestyle, and comorbid characteristics of participants are presented in Table 1. Among the 2052 included participants, the mean age was 63.8 (SD, 13.2) years, and 52.9% of participants were male. The median SBP and DBP of the participants were 144 (133, 154) mmHg and 88 (80, 95) mmHg, respectively. More than half of the participants (59.2%) had a higher BMI (≥24 kg/m^2), and 1,124 (54.8%) participants reported a family history of hypertension. According to the survey, 0.3% of the total participants claimed the supplementation of multivitamins. There were 1,505 (73.3%) individuals using anti-hypertension drugs. The mean concentrations of plasma retinol and 25(OH)D3 were 0.53 ± 0.17 g/mL and 19.51 ± 8.57 μg /L, respectively. The median concentrations of plasma α-tocopherol and vitamin K were 10.27 (8.33, 12.50) g/mL and 0.94 (0.53, 1.62) μg /L, respectively.

3.2 Multiple fat-soluble vitamin co-exposure patterns of participants

The heatmap elucidating the pairwise correlation among the four studied vitamins is shown in Supplementary Figure S2. Correlation coefficients between any two studied vitamins ranged from 0.08 to 0.45. The significantly positive correlation was displayed between every two vitamins.

The values of circulating vitamin levels were standardized to eliminate the dimensional difference. The distributions of standardized values are shown in Supplementary Table S1. Based on standardized values, the 2052 participants were classified into

TABLE 1 Basic characteristics of all participants in this study.

Characteristics	Sample 1 (*n* = 715)	Sample 2 (*n* = 1,337)	Total (*n* = 2052)	*p*-value*
n (%)				
Male	418 (58.5%)	667 (49.9%)	1,085 (52.9%)	<0.001*
Age (years)				
20–39	25 (3.50%)	40 (2.99%)	65 (3.17%)	0.783
40–59	244 (34.1%)	468 (35.0%)	712 (34.7%)	
≥60	446 (62.4%)	829 (62.0%)	1,275 (62.1%)	
Ethnicity				
Han	589 (93.5%)	1,127 (94.1%)	1716 (93.9%)	0.697
Other ethnic minorities	41 (6.51%)	71 (5.93%)	112 (6.13%)	
Region				
North	399 (55.8%)	803 (60.1%)	1,202 (58.6%)	0.069
South	316 (44.2%)	534 (39.9%)	850 (41.4%)	
Education				
Primary school or less	302 (42.2%)	560 (41.9%)	862 (42.0%)	0.052
General intermediate education	232 (32.4%)	379 (28.3%)	611 (29.8%)	
General secondary education or higher	181 (25.3%)	398 (29.8%)	579 (28.2%)	
Marital status				
Married	600 (83.9%)	1,086 (81.2%)	1,686 (82.2%)	0.643
Widowed	105 (14.7%)	226 (16.9%)	331 (16.1%)	
Divorced or separated	4 (0.56%)	12 (0.90%)	16 (0.78%)	
Never married	5 (0.70%)	10 (0.75%)	15 (0.73%)	
Others	1 (0.14%)	3 (0.22%)	4 (0.19%)	
BMI				
<18.5 kg/m^2	21 (2.94%)	35 (2.62%)	56 (2.73%)	0.704
18.5–23.9 kg/m^2	283 (39.6%)	498 (37.2%)	781 (38.1%)	
24.0–27.9 kg/m^2	328 (45.9%)	644 (48.2%)	972 (47.4%)	
≥28.0 kg/m^2	83 (11.6%)	160 (12.0%)	243 (11.8%)	
Smoking				
Never	480 (67.1%)	964 (72.1%)	1,444 (70.4%)	0.003*
Former	69 (9.65%)	146 (10.9%)	215 (10.5%)	
Current	166 (23.2%)	227 (17.0%)	393 (19.2%)	
Alcohol drinking				
Never	530 (74.1%)	1,007 (75.3%)	1,537 (74.9%)	0.096
Former	44 (6.15%)	107 (8.00%)	151 (7.36%)	
Current	141 (19.7%)	223 (16.7%)	364 (17.7%)	
Physical labor intensity				
Mild	498 (69.7%)	937 (70.1%)	1,435 (69.9%)	0.484
Moderate	188 (26.3%)	332 (24.8%)	520 (25.3%)	
Heavy	29 (4.06%)	68 (5.09%)	97 (4.73%)	
Living standard				
Poor	23 (3.22%)	59 (4.41%)	82 (4.00%)	0.366
Average	486 (68.0%)	883 (66.0%)	1,369 (66.7%)	
Good	206 (28.8%)	395 (29.5%)	601 (29.3%)	

(Continued)

TABLE 1 (Continued)

Characteristics	Sample 1 (n = 715)	Sample 2 (n = 1,337)	Total (n = 2052)	p-value*
Nervousness				
Mild	515 (72.0%)	1,006 (75.2%)	1,521 (74.1%)	<0.001*
Moderate	176 (24.6%)	246 (18.4%)	422 (20.6%)	
Severe	24 (3.36%)	85 (6.36%)	109 (5.31%)	
Dyslipidemia				
No	581 (81.3%)	1,002 (74.9%)	1,583 (77.1%)	0.001*
Yes	134 (18.7%)	335 (25.1%)	469 (22.9%)	
Diabetes				
No	592 (82.8%)	1,113 (83.2%)	1705 (83.1%)	0.844
Yes	123 (17.2%)	224 (16.8%)	347 (16.9%)	
Family history of hypertension				
No	292 (40.8%)	560 (41.9%)	852 (41.5%)	0.899
Yes	396 (55.4%)	728 (54.5%)	1,124 (54.8%)	
Unknown	27 (3.78%)	49 (3.66%)	76 (3.70%)	
Family history of stroke				
No	556 (77.8%)	1,095 (81.9%)	1,651 (80.5%)	0.072
Yes	135 (18.9%)	209 (15.6%)	344 (16.8%)	
Unknown	24 (3.36%)	33 (2.47%)	57 (2.78%)	
Family history of CHD				
No	624 (87.3%)	1,146 (85.7%)	1770 (86.3%)	0.418
Yes	65 (9.09%)	146 (10.9%)	211 (10.3%)	
Unknown	26 (3.64%)	45 (3.37%)	71 (3.46%)	
Median (P_{25}, P_{75})				
SBP (mmHg)	145 (135, 155)	143 (133, 154)	144 (133, 154)	0.071
DBP (mmHg)	89.0 (81.0, 95.0)	88.0 (79.0, 95.0)	88.0 (80.0, 95.0)	0.049
VA (g/mL)	0.52 (0.43, 0.64)	0.50 (0.40, 0.61)	0.51 (0.41, 0.62)	<0.001*
VD (μg /L)	19.7 (14.2, 25.6)	18.1 (12.7, 24.6)	18.7 (13.2, 25.0)	0.002*
VE (g/mL)	9.94 (8.07, 12.1)	10.4 (8.50, 12.8)	10.3 (8.33, 12.5)	<0.001*
VK (μg/L)	0.84 (0.48, 1.45)	1.01 (0.56, 1.71)	0.94 (0.53, 1.62)	<0.001*

VA, vitamin A; VD, vitamin D; VE, vitamin E; VK, vitamin K ; BMI, body mass index; CHD, coronary heart disease; P_{25}, 25th percentile; P_{75}, 75th percentile.
p-values were calculated by chi-square test and Wilcoxon rank-sum test for categorical and continuous variables, respectively. The symbol * represents statistically significant results.

two clusters, determined by both statistical results and biological interpretability. The centers of the two clusters are shown in Supplementary Table S2. With respect to the two clusters, we designated the 'low-level exposure group' to cluster 1, considering the values of plasma vitamin concentrations close to their 25th percentiles, 'high-level exposure group' to cluster 2 for the reason that the values of plasma vitamin concentrations close to their 75th percentiles. The levels of all studied vitamins were relatively low in cluster 1, while the levels were relatively high in cluster 2. Participants in clusters 1 and 2 occupied approximately the same proportions of the total sample. The differences between the studied vitamin concentrations of the two clusters were visualized through a violin plot with a boxplot (Figure 1).

After clustering analysis, we further described the basic characteristics of study participants according to the two clusters, as shown in Supplementary Table S3. There existed significant differences in almost all basic characteristics between the two clusters. In brief, those with lower levels of studied vitamin co-exposure were more likely to be ≥60 years old (71.4%), northerners (68.5%), never drinking (79.4%), and have lower education levels, and less likely to be overweight and have dyslipidemia and family histories of chronic diseases.

3.3 Relationship of multiple fat-soluble vitamin co-exposure and blood pressure

Considering the values of blood pressure were skewed, we log-transformed the data. After adjusting for age, sex, and BMI, participants in the high-level exposure group had no significantly different SBP levels compared to the reference group (low-level exposure group). After further adjustment for potential confounders

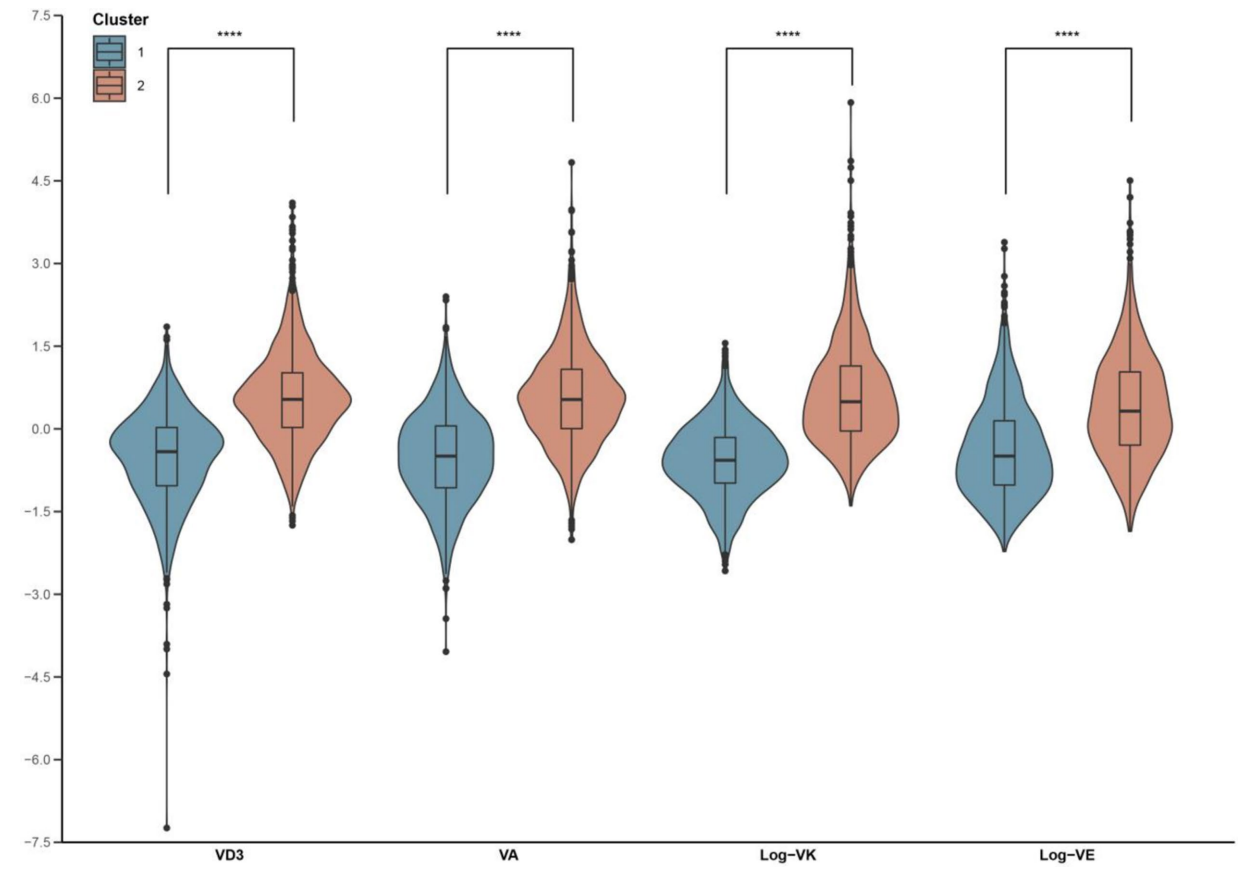

FIGURE 1
Violin plot of plasma vitamin concentrations grouped by the two clusters. The x-axis indicated the four vitamins and the different two colors represented the two clusters. The y-axis indicates plasma vitamin concentrations. VA, vitamin A; VD, vitamin D; VE, vitamin E; VK, vitamin K. Log indicated logarithmic 10 transformation. The symbol **** represents statistically significant results.

(models 2 and 3), the results remained unchanged. Similarly, no significant association was observed between studied vitamin co-exposure patterns and DBP (Table 2).

We performed stratified analyses according to potential factors to estimate potential modifying effects (Supplementary Table S4). The associations of multivitamin co-exposure patterns and DBP were stronger among participants <65 years old (p for interaction = 0.05), with general intermediate education (p for interaction = 0.004) and currently drinking (p for interaction = 0.031). There was no other significant interaction found between multivitamin co-exposure patterns and DBP/SBP (all p for interaction ≥0.05).

3.4 Association of each studied vitamin and blood pressure

The preliminary exploration for the association of each studied vitamin and blood pressure (logarithmic 10 transformed) was made through univariate linear regression. The results were shown by scatter plots and fitted lines with the 95% CIs (Supplementary Figure S3). All four vitamins were significantly associated with DBP, but not SBP. In the multiple linear regression model 3 (Table 3), the plasma VD levels were in a significantly negative association with SBP (β coefficient = −0.002, 95% CI: −0.004, 0). A similar association could be found between plasma VD levels and DBP, but was insignificant. In contrast, after adjusting for age, sex, and BMI, higher SBP levels were observed with per SD increment in plasma VE concentrations (β coefficient = 0.002, 95% CI: 0, 0.004). After further adjustment (models 2 and 3), the results remained significant (β coefficient = 0.003, 95% CI: 0.001, 0.005 in model 2; β coefficient = 0.004, 95% CI: 0.002, 0.006 in model 3). The concordant result was obtained for the association of plasma VE concentration and DBP in model 3. In addition, no significant relationships were found between plasma VA/VK concentrations and SBP/DBP.

In addition, similar results were obtained when we categorized vitamin variables into quartiles. In the full-adjusted model, participants in the fourth VE quartile had mean SBP levels that were 1.02% (95% CI: 0.43, 1.61%) greater than those in the lowest VE quartile (p for trend <0.01, Figure 2). As for DBP, higher plasma levels of VE were associated with elevated mean DBP levels, albeit this trend was not statistically significant (p for trend = 0.07, Supplementary Figure S4). On the contrary, individuals in the higher VD quartiles had lower mean SBP levels compared to those in the first VD quartile, although the significance was attenuated in the third VD quartile and the trend was insignificant (p for trend = 0.07, Figure 2).

Dose–response curves for the relationship between each studied vitamin and SBP/DBP are shown in Supplementary Figure S5, which presented similar trends to the results aforementioned. No significant

TABLE 2 Covariates adjusted β coefficient (95% CI) of multivitamin co-exposure patterns in association with blood pressure.

Variable	Model 1		Model 2		Model 3	
	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value
Systolic blood pressure (logarithm 10 transform)						
Cluster 1	Ref		Ref		Ref	
Cluster 2	0 (−0.004, 0.004)	0.988	0.001 (−0.003, 0.005)	0.689	0.001 (−0.003, 0.005)	0.61
Diastolic blood pressure (logarithm 10 transform)						
Cluster 1	Ref		Ref		Ref	
Cluster 2	0.001 (−0.004, 0.006)	0.725	0.001 (−0.004, 0.006)	0.588	0.002 (−0.003, 0.007)	0.36

Model 1 was adjusted for age, sex, and BMI.
Model 2 was adjusted for age, sex, BMI, region, physical labor intensity, living standard, nervousness, education level, smoking status, and alcohol-drinking status.
Model 3 was further adjusted for the family history of chronic diseases (hypertension, stroke, and coronary heart disease), the comorbidity (dyslipidemia and diabetes), and the use of anti-hypertension drugs.

TABLE 3 Multivariable associations of fat-soluble vitamin concentrations and blood pressure.

Variables		Log-SBP		Log-DBP	
		β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value
VA	Model 1	0 (−0.002, 0.003)	0.729	−0.001 (−0.003, 0.002)	0.511
	Model 2	0.001 (−0.001, 0.003)	0.414	−0.001 (−0.003, 0.002)	0.496
	Model 3	0.001 (−0.001, 0.004)	0.18	0 (−0.002, 0.002)	0.946
VD	Model 1	−0.001 (−0.003, 0.001)	0.248	0 (−0.003, 0.002)	0.796
	Model 2	−0.001 (−0.004, 0.001)	0.216	0 (−0.003, 0.002)	0.956
	Model 3	**−0.002 (−0.004, 0)**	**0.053**	−0.001 (−0.003, 0.002)	0.535
Log-VE	Model 1	**0.002 (0, 0.004)**	**0.04**	0.001 (−0.001, 0.003)	0.346
	Model 2	**0.003 (0.001, 0.005)**	**0.012**	0.001 (−0.001, 0.004)	0.238
	Model 3	**0.004 (0.002, 0.006)**	**0.001**	**0.003 (0, 0.005)**	**0.028**
Log-VK	Model 1	0 (−0.002, 0.002)	0.781	0.001 (−0.002, 0.003)	0.562
	Model 2	0 (−0.002, 0.003)	0.693	0.001 (−0.002, 0.003)	0.612
	Model 3	0.001 (−0.001, 0.003)	0.292	0.002 (−0.001, 0.004)	0.202

Log indicated logarithmic 10 transformation. Data were presented as β coefficient (95% CI) per SD of the vitamin.
Model 1 was adjusted for age, sex and BMI.
Model 2 was additionally adjusted for age, sex, BMI, region, physical labor intensity, living standard, nervousness, education level, smoking status, alcohol drinking status.
Model 3 was further adjusted for the family history of chronic diseases (hypertension, stroke and coronary heart disease), the comorbidity (dyslipidemia and diabetes) and the use of anti-hypertension drug.
Bold values indicated statistical significance ($p < 0.05$).

non-linear associations were between each studied vitamin and SBP/DBP (all *p* for non-linearity ≥0.05).

4 Discussion

In this current study, we evaluated joint effects on blood pressure of circulating multiple fat-soluble vitamins in nationally representative Chinese adults. There was no significant relationship between multiple fat-soluble vitamins and blood pressure. Further analyses on the separate associations of each vitamin and blood pressure showed that there was an inverse relationship between plasma VD level and SBP, but a positive association between plasma VE and SBP.

4.1 Multiple fat-soluble vitamin co-exposure patterns and blood pressure

People are usually exposed to multiple vitamins from diverse foods and natural environments in their daily lives. In our study, we defined two vitamin co-exposure patterns by distinct plasma vitamin concentration profiles. The k-means clustering method derived two co-exposure patterns that yielded simple structure and great interpretability, as follows: low-level fat-soluble vitamins exposure and high-level fat-soluble vitamins exposure. In line with the present study, this method was also used in previous studies to explore the relationship between multiple nutrients and various chronic diseases (27–29), which served as evidence for the practicability of our study method.

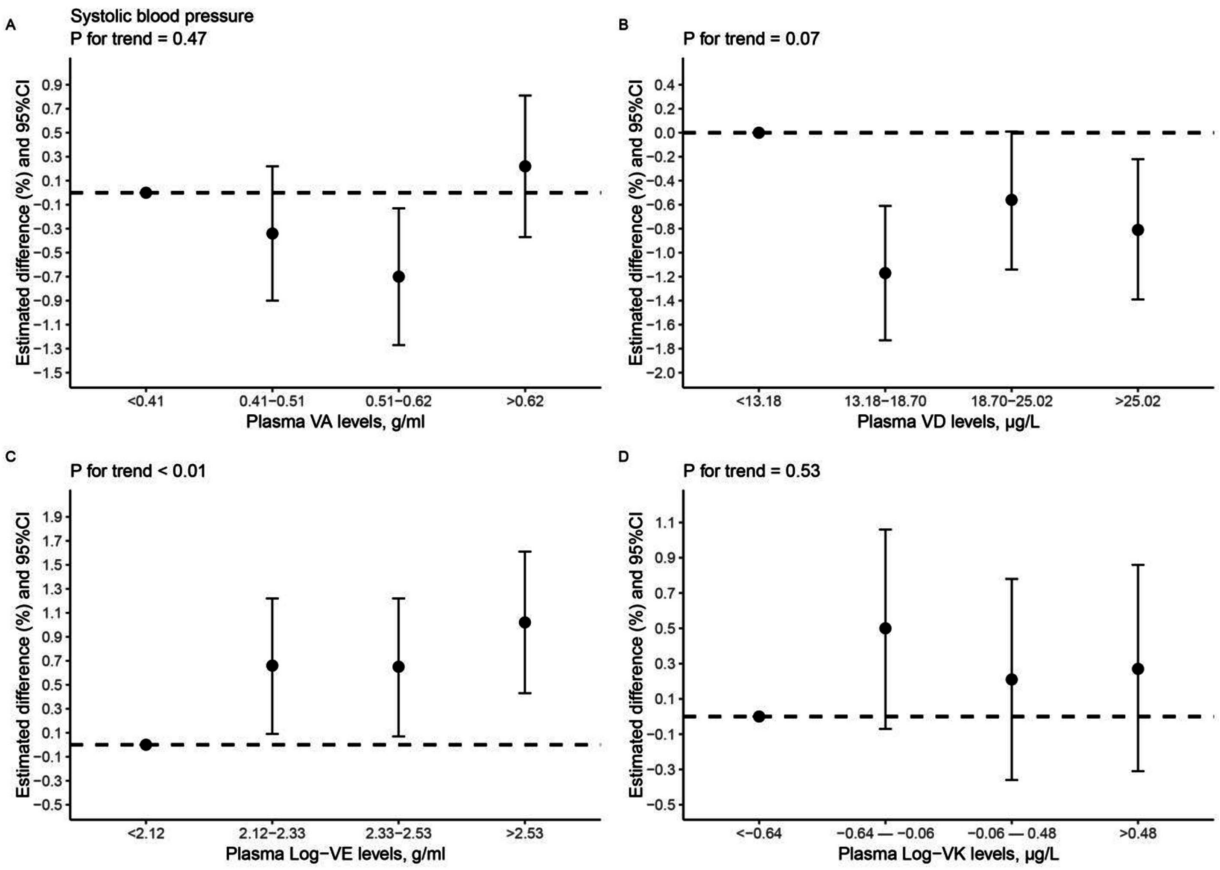

FIGURE 2
Estimated difference (%) and 95% CI in systolic blood pressure with *p* for trend for each interquartile in plasma vitamin concentrations. **(A)** VA and SBP; **(B)** VD and SBP; **(C)** VE and SBP; **(D)** VK and SBP. VA, vitamin A; VD, vitamin D; VE, vitamin E; VK, vitamin K; SBP, systolic blood pressure. Log indicated logarithmic 10 transformation.

Few studies have explored the association between multiple fat-soluble vitamins and hypertension. A recent cross-sectional study demonstrated that the factor analysis derived nutrient pattern of fats and fat-soluble vitamins was significant in relation to the prevalence of high blood pressure (29), which somewhat stood by our results of stratified analyses. Additionally, a few randomized controlled trials (RCTs) focused on the efficacy of multivitamin supplementation on blood pressure. One meta-analysis pooling the results of relevant RCTs showed that the lowering effect of multivitamin supplementation on SBP was significant in hypertensive patients, but not on DBP (30). However, the sample size for the hypertension subgroups was only 58. In addition, the above studies only explored the relationship between vitamin intake and blood pressure from the perspective of dietary evaluation or supplements. Previous studies have found that the circulating levels of fat-soluble vitamins can reflect the long-term exposure level of vitamins in the body (31, 32). To our knowledge, the simultaneous effects of circulating multiple vitamin concentrations on blood pressure have not been investigated among hypertensive adults yet. Our study included more hypertensive participants to investigate the association between multiple fat-soluble vitamins in circulation and blood pressure. Overall, there was no significant association between multiple fat-soluble vitamin exposure levels and blood pressure. This may be due to the different relationships between different fat-soluble vitamins and hypertension. Our further analysis also found that there was an inverse relationship between plasma VD levels and SBP, but a positive correlation between plasma VE levels and SBP.

4.2 The plasma 25(OH)D_3 levels and blood pressure

Among the four studied vitamins, we observed an inverse association with SBP for plasma 25(OH)D_3 concentrations. The result was in line with evidence from similar observational studies relating to VD status and blood pressure. The negative correlation between circulating 25(OH)D levels and SBP was also found in the Chinese rural population (33), albeit the study subjects from a certain province were less than those in this nationwide study. Consistent with our finding, another study among US hypertensive adults unraveled that lower circulating 25(OH)D levels were associated with higher SBP/DBP by 0.5/2.4 mmHg (34). Potential mechanisms underlying the relationship between VD and blood pressure have been investigated via experimental studies, including regulating the renin–angiotensin–aldosterone system (RAAS), activating the nuclear VD receptor highly expressed in the vascular smooth muscle endothelium and cardiomyocytes, and attenuating inflammation through direct action with nuclear factor kappa beta (35, 36).

However, data emerging from intervention trials to evaluate the impact of VD supplementation on hypertension were inconclusive. The recent umbrella review demonstrated that the association between VD concentration and hypertension was only statistically significant in meta-analyses of observational studies or Mendelian randomization studies. In contrast, meta-analyses of RCTs reported marginally significant or no effects of VD supplementation on the prevention or improvement of hypertension (37). This discrepancy was likely linked to the inducer of endogenous VD and population-specific study characteristics. Cutaneous VD_3 is the predominant source of systemic VD instead of dietary intake or VD supplements. The synthesis of VD_3 is driven by UV-B radiation from sunlight, which could be affected by many long-term natural factors including latitude, season, or atmosphere construction (38, 39). Accordingly, the limited duration of VD supplementation could not compensate for the long-term VD_3 insufficiency. In addition, numerous individual factors containing skin pigmentation, age, and obesity may also influence the solar VD_3 synthesis (38, 40, 41). As a result, specific populations appear to be prone to a more effective response to VD supplementation in terms of regulatory effects on blood pressure.

4.3 The plasma α-tocopherol levels and blood pressure

A recent meta-analysis of RCTs in general populations found no significant lowering effects of VE supplementation on both SBP and DBP yet (42). However, there existed inconsistent results which showed that 200 IU/day VE supplement for 27 weeks could significantly decrease SBP and DBP in mild hypertensive adults (43). This discrepancy could be partially owing to different forms of VE. Vitamin E, as a powerful antioxidant, has eight isomers and among them, α-tocopherol is the most biologically active one (44). Most trials did not investigate the α-tocopherol levels as did in this current study but explored the effects of VE supplements on blood pressure directly or combined with other antioxidants (45). In addition, the multiplicity of epidemiological studies explored the effects of tocotrienol supplementation or γ-tocopherol mainly from dietary VE on blood pressure (46).

In contrast, we investigated the effects of circulating α-tocopherol on blood pressure. There was a significant trend toward the positive relationship between achieved VE levels and blood pressure. Epidemiological evidence for the relationship between VE and blood pressure was limited and controversial (44). Concordant with our results, one cross-sectional study in the Korean general population also reported that blood pressure was positively associated with serum α-tocopherol levels (47). The above suggests that α-tocopherol may mask the protective effect of plasma 25-hydroxyvitamin D3 on blood pressure.

4.4 Strengths and limitations

Our study comes with several strengths. We for the first time assessed the association of multivitamin co-exposure levels and blood pressure among hypertensive adults. The co-exposure patterns of multiple vitamins were assessed via the unsupervised K-means clustering method. Due to a lack of clinical criteria, the machine learning method helps to classify the circulating vitamin levels of hypertensive adults. In addition, we assessed the vitamin status by measuring the distinct active products of vitamins, which have been validated to be reliable markers for vitamins. The majority of the prior studies evaluated vitamin intake by dietary questionnaires, which may have unavoidable limitations.

Nevertheless, our study has also some limitations that should be noted. First, the present cross-sectional study could not determine the causation between the plasma vitamin levels and blood pressure due to the observational design. Second, the confounding effects from unmeasured or unknown variables may not be excluded, albeit we have adjusted many confounders in our models. Finally, the current study only included Chinese hypertensive adults, it is unsure about the multivitamin co-exposure patterns among other population and their relationships to blood pressure.

5 Conclusion

Although we did not find a significant association between fat-soluble vitamin co-exposure and blood pressure, higher plasma VD levels were associated with reduced SBP among study participants. There was a significant increase in blood pressure with the rise of plasma VE levels. Our findings provided a novel perspective for exploring the joint effects of fat-soluble vitamins on blood pressure. Further studies are warranted to better understand the implications.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Peking University First Hospital, Beijing, China. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SD: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. PW: Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft. SW: Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft. HC: Formal analysis, Writing – review & editing. ZC: Formal analysis, Writing – review & editing. WL: Formal analysis, Writing – review & editing. ZZ: Methodology, Writing – review & editing. NZ: Methodology, Writing – review & editing. ZW: Investigation, Writing – review & editing. TL: Investigation, Writing – review & editing. YS: Investigation, Writing – review & editing. LL: Data curation, Investigation, Software, Validation, Writing – review & editing. XH: Resources, Writing – review & editing.

PC: Investigation, Writing – review & editing. GT: Resources, Writing – review & editing. YD: Resources, Writing – review & editing. HZ: Investigation, Writing – review & editing. BW: Investigation, Resources, Supervision, Writing – review & editing. YY: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. ZT: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1502139/full#supplementary-material

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Sex differences in the associations of water, coffee and tea consumption with cardiovascular diseases: a prospective cohort study

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Background: Water, coffee and tea are the primary sources of daily hydration. However, the sex-specific relationship between these beverages and cardiovascular disease (CVD) among remains unclear.

Methods: In total, 210,239 men and 251,383 women from the UK Biobank were included. The consumption of water, coffee and tea were self-reported. CVDs, including coronary heart disease (CHD), stroke and heart failure (HF) were followed till March 1st, 2023. Sex-specific Cox models were utilized to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations.

Results: During a median follow-up of 8.7 years, 11,098 (2.40%) participants developed new-onset HF, 33,426 (7.24%) participants developed new-onset CHD, and 9,706 (2.10%) participants developed new-onset stroke. After adjustments, higher water consumption was generally associated with reduced risk of CVDs among both men and women. In contrast, heavy coffee consumption (particularly ≥6 cups/day) was associated with a greater risk of HF [1.16 (1.03–1.31) in men vs. 1.25 (1.12–1.40) in women], a greater risk of CHD [1.27 (1.18–1.36) in men vs. 1.21 (1.14–1.29) in women] and a greater risk of stroke [1.13 (0.99–1.29) in men vs. 1.20 (1.03–1.31) in women]. Similarly, heavy tea consumption was associated with an increased risk of HF (men: HR 1.19 [1.08–1.31]; women: HR 1.12 [1.02–1.23]) and CHD (men: HR 1.12 [1.05–1.18]; women: HR 1.18 [1.12–1.24]).

Conclusion: Our study revealed that water consumption was associated with a lower risk of CVDs, with a lower risk of CVDs, while heavy coffee or tea consumption was linked to a higher risk. Notably, coffee and tea consumption partially attenuated the protective association of water intake with CVDs. Furthermore, significant sex differences were observed in the associations between coffee or tea consumption and CHD incidence.

KEYWORDS

water consumption, coffee consumption, tea consumption, cardiovascular disease, population-based cohort study

Background

Cardiovascular diseases (CVDs) are the leading cause of mortality posing substantial challenges to public health systems worldwide (1). In 2020, an estimated 19.05 million deaths were attributed to CVDs, reflecting a concerning 18.71% increase from the mortality figures recorded in 2010 (2). According to the NHANES 2017–2020 data, the prevalence of CVDs, which encompasses heart failure (HF), stroke, coronary heart disease (CHD), and hypertension, among adults was 48.6% (3). This prevalence escalates with increasing age in both sexes, thereby contributing to a significant risk of premature mortality and escalating healthcare costs.

Sexual dimorphism significantly influences the epidemiology, development, and management of CVDs in both men and women (4). Compared to men, women possess an additional X chromosome, which may result in variations in gene expression and functional outcomes within the cardiovascular system (5). Literature data suggest that women experience a two-fold incidence of CVD-related mortality compared to men (6), indicating that biological sex is a critical determinant in disease severity and resultant heterogeneity (7).

Sex hormones are known to influence behavior and lifestyle. Lifestyle behaviors, including dietary habits, have been recognized as a preventive factor in mitigating the risk of CVDs. Water, coffee and tea, being the most consumed beverages globally (8), could potentially exert significant biological effects that impact population heath. Previous studies have established a correlation between the consumption of water, coffee and tea and cardiovascular health. However, it remains uncertain whether sex could modify the aforementioned association. Therefore, this study aims to examine the potential sex differences in the association between the intake of water, coffee and tea, and the development of CVDs, utilizing data from the UK Biobank.

Method

Study population

The UK Biobank is a large-scale prospective cohort study that enrolled approximately 500,000 participants, aged 40 years and older, from 22 assessment centers across England, Scotland, and Wales from 2006 and 2010. All participants provided informed consent prior to their participation in this study. The study was approved by the North West Multicenter Research Ethics Committee (MREC) and the Human Tissue Authority (HTA). The study procedures were conducted in compliance with the ethical principles delineated in the World Medical Association's Helsinki Declaration for Medical Research (9).

The exclusion criteria were as follows: (1) had pre-existing conditions of heart failure, coronary heart disease, stroke, or dementia at baseline (n = 8,650); (2) had incomplete data on water, coffee or tea consumption (n = 6,254); (3) had missing or unknown information on the outcome of HF, CHD, stroke or dementia (n = 25,885); and (4) had missing information on baseline age (n = 2). Ultimately, 461,622 participants were included in our analyses (Figure 1).

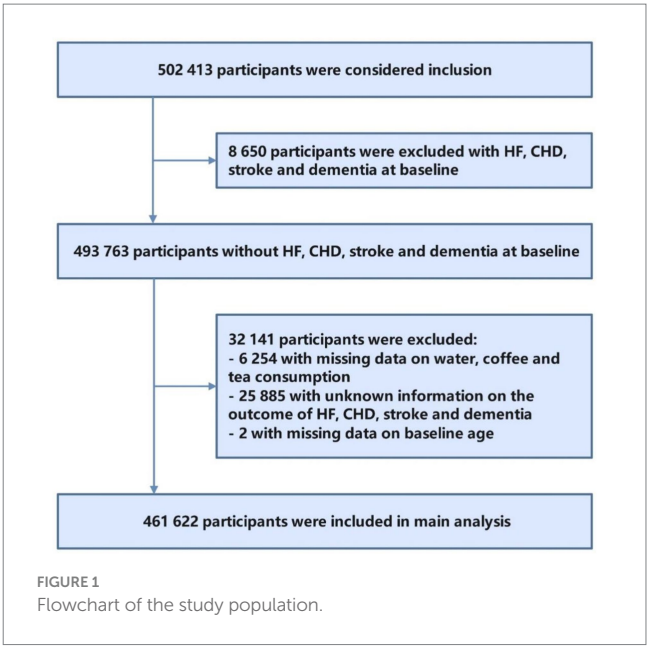

FIGURE 1
Flowchart of the study population.

Exposure assessment

Based on previous studies, we chose the ACE touchscreen questionnaire to complete the assessment of exposure factors. Participants were requested to provide a daily account of their intake of water, coffee, and tea via a touchscreen questionnaire with the assistance of research personnel. The ACE touchscreen questionnaire included the following prompt for coffee intake: "Please indicate the number of cups of coffee you consume on a daily basis, including decaffeinated varieties." Similarly, participants were asked about tea consumption: "How many cups of tea do you consume on a daily basis?" and water consumption: "How many cups of water do you drink on a daily basis?". The Participants were instructed to provide an estimate of their average daily consumption of these beverages over the previous year. In cases of uncertainty, participants were encouraged to provide an estimate or select the "Do not know" option. Any anomalous responses, such as "<0 cups/day" and ">99 cups/day," were excluded from the analysis. If a participant reported an intake of ">10 cups/day," they were prompted to verify this information. Additionally, a composite variable was created to aggregate the daily intake of coffee and tea for each participant.

The reported consumption varied from "0 cups/day" to "99 cups/day." Responses such as "Do not know" and "Prefer not to answer" were excluded from the analysis. Adhering to established protocols from previous studies, We categorized the daily consumption of water, coffee and tea into five distinct groups (none, 0.5-1 cup/day, 2–3 cups/day, 4–5 cups/day, and ≥6 cups/day). Similarly, the daily consumption of the composite variable was categorized into five groups (none, 0.5-2 cup/day, >2–4 cups/day, >4–8 cups/day, and >8 cups/day) (Figure 2).

Outcome assessment

New-onset CVDs, encompassing incident cases of HF, stroke and CHD, were identified from hospital admission, primary care and/or death registry data linked to the UK Biobank (9). Diagnoses were determined using the International Classification of Diseases-10th Revision (ICD-10) coding system. Specifically, HF was defined as ICD-10 codes: 150; CHD was defined as ICD-10 codes: I20-22, 24, 25; and stroke was defined as ICD-10 codes: I60-64. Follow-up ended on

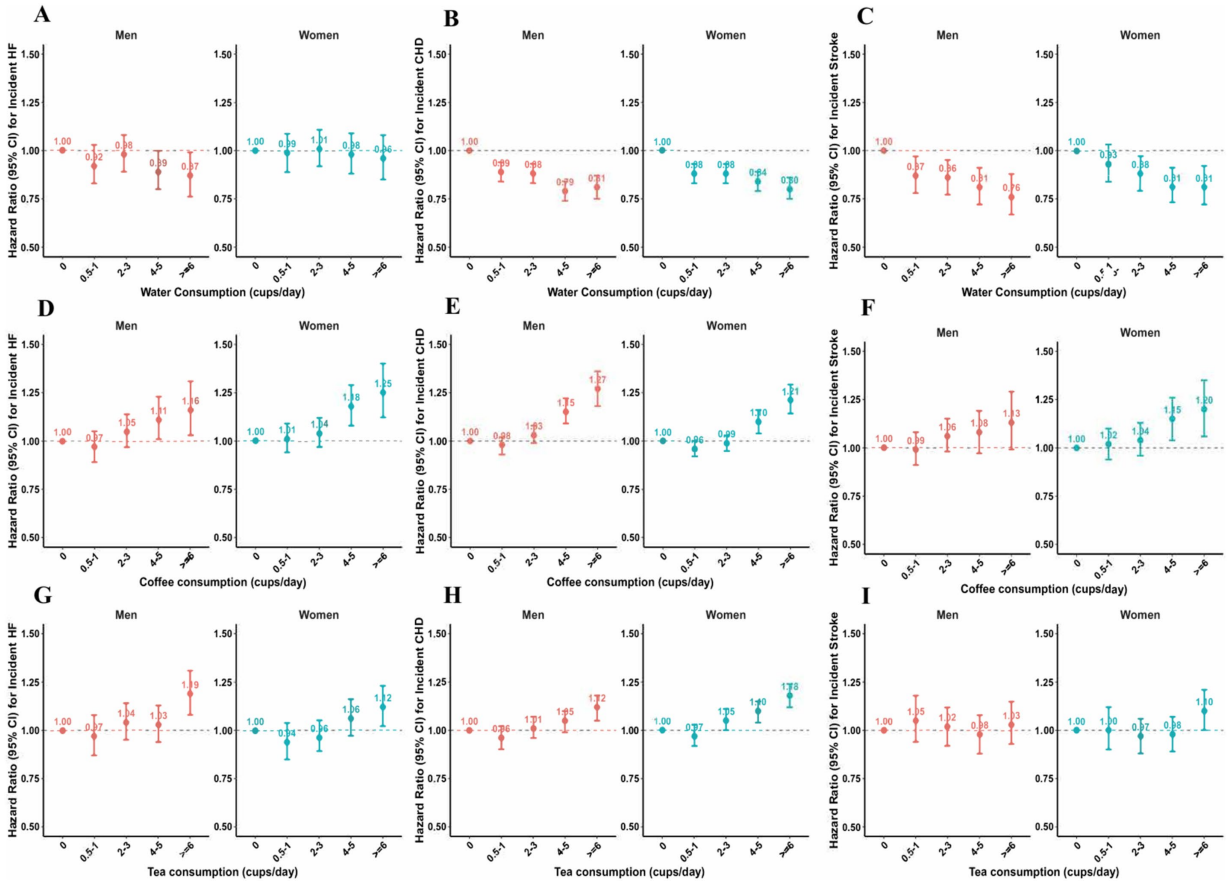

FIGURE 2
Association of water, coffee and tea intake with cardiovascular diseases among men and women. **(A–C)** Associations of water with HF, CHD and Stroke events in fully-adjusted model. **(D–F)** Associations of coffee with HF, CHD and Stroke events in fully-adjusted model. **(G–I)** Associations of tea with HF, CHD and Stroke events in fully-adjusted model. The multivariable model was adjusted for baseline age, ethnicity, education, income, smoking status, physical activity, diet pattern, body mass index, systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein, low-density lipoprotein, long-standing illness, disability or infirmity, Townsend Deprivation Index, alcohol consumption and milk consumption.

March 31, 2021. The participants were censored at the end of the follow-up period, the date of death, or loss to follow-up, whichever occurred first.

Assessment of covariates

Age, ethnic (White, Black or Black British, and other ethnic groups), education (university or college educational level, other), average pre-tax income (less than £18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 to £100,000, greater than £100,000), smoking status (never, previous, and current), physical activity, alcohol consumption, milk consumption (daily milk intake, including full cream, semi-skimmed, skimmed, soya or other types of milk; never/rarely drink milk) and dietary pattern [healthy or unhealthy, healthy diet was based on consumption of at least 4 out of 7 dietary components: (1) fruit: ≥3 portions per day; (2) vegetables: ≥3 portions per day; (3) fish: ≥2 portions/week; (4) processed meat: ≥1 portion/week; (5) unprocessed red meat: ≥1.5 servings/week; (6) whole grains: ≥3 servings/day; (7) refined grains: ≥1.5 servings/day (10, 11)] were self-reported during the interview process. Height, weight, and blood pressure were measured at the assessment center, with BMI calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured twice using an Omron 705 IT electronic monitor, and average levels were utilized. Serum cholesterol was measured in the central laboratory. Townsend Deprivation Index (TDI), reflecting socioeconomic status with scores inversely related to socioeconomic status, was defined according to participant's postcode, using a combination of unemployment, noncar ownership, nonhome ownership, and household overcrowding (12).

Statistical analysis

Baseline characteristics were stratified by sex. Continuous variables are presented as the mean and standard deviation (SD), while categorical variables are expressed as percentages (%). To assess the mediating role of sex differences to the association between water, coffee and tea consumption and CVDs, exposure factors were converted into numerical factors for analysis.

The reference group in our study consisted of individuals who did not consume water, coffee, or tea daily. We employed Cox proportional hazard regression models to assess the associations between water,

coffee and tea intake and the incidence of CVDs, including HF, stroke and CHD. The findings from these models were presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). The multivariable models underwent multiple rounds of adjustment. In the first model, adjustments were made for baseline age and ethnicity. In the fully adjusted model, additional potential confounders were incorporated. These included factors such as educational qualification, employment status, income, smoking habits, physical activity patterns, dietary patterns, body mass index (BMI), systolic and diastolic blood pressure, triglyceride levels, LDL-cholesterol, HDL-cholesterol, presence of long-term illness, and consumption patterns of alcohol, water, tea, coffee, and milk.

To enhance the robustness of our study results, we conducted several sensitivity analyses. First, we excluded individuals with long-standing illnesses, disabilities, or infirmities at baseline and re-analyzed the remaining participants. Second, we performed a stratified analysis by age (categorized at 60 years) to explore potential variations in the effects based on baseline age. Third, we repeated our main analysis in the 375,094 containing coffee consumed type (caffeinated coffee or decaffeinated coffee). In our analysis, we performed multiple imputation through chained equations with 5 iterations to manage missing values, which were less than 20%. Detailed information regarding missing data is provided in Supplementary Table S1. Two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using the R software package, version 4.3.2.

Results

Baseline characteristics

A total of 461,622 participants were included in our study. Among the 461,622 participants, 251,383 (54.42%) were women, and 210,239 (45.58%) were men. The average age at baseline for women was 56.34 years (SD ± 8.00) and 56.73 years (SD ± 8.20) for men. Compared to women, men were more likely to be older, of White ethnicity, have higher educational attainment, maintain more stable employment, demonstrate lower TDI (indicating a higher socioeconomic status), exhibit higher BMI and triglyceride levels, engage in current smoking, and report a higher frequency of alcohol consumption. Further details are provided in Table 1. During a median follow-up period of 8.71 years for new-onset CVDs (especially HF, CHD and stroke), 11,098 participants (2.40%) developed HF, 33,426 patients (7.24%) developed the CHD and 9,706 patients (2.10%) developed stroke.

Water consumption and cardiovascular disease risk

Our findings suggest that water consumption is associated with a decreased risk of CVDs incidence (Figure 2). After adjusting for ethnicity and baseline age, we found that individuals who consumed ≥6 cups/day of water were associated with a reduced risk of HF in both sexes [HR (95% CI): 0.73 (0.64–0.82) in men; 0.82 (0.73–0.92) in women]. However, after comprehensive adjustment, we found a negative association among men, not women. Compared to non-water drinkers, the HRs (95% CIs) for consuming ≥6 cups of water per day were 0.87 (95% CIs: 0.76–0.99) in men and 0.96 (95% CIs: 0.85–1.08) in women. The p value for the sex interaction was 0.14 in Model 1 and 0.22 in fully adjusted Model, highlighting a moderate sex difference.

Likewise, water consumption was associated with a lower incidence of CHD in both men and women, as observed in Model 1 and Model 2. As shown in Supplementary Table S2, the results from the multivariate Cox model (Model 2) showed that water consumption was associated with a reduced incidence of CHD. Those who consumed who drank ≥6 cups of water per day were associated with a 20% lower incidence of CHD compared with those who did not consume water [HR (95% CI): 0.81 (0.75–0.87) in men; HR (95% CI): 0.80 (0.75–0.86) in women], all p for trend < 0.001. A similar association was observed between water consumption and stroke incidence in both men and women. After adjusting for confounders in Model 2, compared to non-water drinkers, people who consumed ≥6 cups/day of water were associated with a lower risk of stroke [HRs (95CIs): 0.76 (0.67–0.88) in men; 0.81 (0.72–0.92) in women], all p for trend <0.001.

Coffee consumption and cardiovascular disease risk

Heavy coffee consumption was associated with a higher risk of CVDs incidents in both men and women (Figure 2). As shown in Supplementary Table S3, after full adjustment, we observed that men and women who consumed ≥6 cups/day of coffee were associated with a higher risk of HF [HR (95% CI): 1.16 (1.03–1.31) in men, p for trend = 0.001; 1.25 (1.12–1.40) in women, p for trend = 0.001]. After adjusting for ethnicity and baseline age, we found that moderate coffee consumption was associated with a lower risk of CHD, particularly among those who consumed 0.5–3 cups/day of coffee. Nevertheless, in the fully-adjusted model, we find the positive associations both in men and women. Compared with non-coffee drinkers, men who consumed ≥6 cups/day of coffee per day were associated with a 27% increase in CHD events [HR (95% CI): 1.27 (1.18–1.36), p for trend <0.001] and a 13% increase in stroke events [HR (95% CI): 1.13 (0.99–1.29), p for trend = 0.02]. In the women's group, compared with non-coffee consumers, We observed a 21 and 20% increase in the incidence of CHD and stroke, respectively, associated with those who consumed ≥6 cups of coffee per day. Additionally, we found a statistically significant gender difference between coffee consumption and incident CHD, with a p-value < 0.05.

Tea consumption and cardiovascular disease risk

Heavy tea consumption was associated with a higher risk of HF and CHD in both men and women (Figure 2). As shown in Supplementary Table S4, after adjusting for ethnicity and baseline age, compared to non-tea drinkers, men who consumed 0.5–1 cups of tea per day were associated with a 12% reduced risk of incident HF [HR (95% CI): 0.88 (0.79–0.98)], and women who consumed 0.5–1 cups of tea per day were associated with a 15% reduced risk of incident HF [HR (95% CI): 0.85 (0.77–0.94)]. In Model 2, we found a positive association between tea consumption and HF incidence among men and women. After full adjustment, we found that those who drank ≥6 cups of tea per day were associated with a higher risk of HF compared

TABLE 1 Baseline characteristics of the study population.

Characteristic	Women	Men	*p* values
Number (*n*, %)	251,383 (54.4)	210,239 (45.6)	–
Age (years)	56.34 (8.00)	56.73 (8.20)	<0.001
Ethnic (*n*, %)			<0.001
White	226,823 (90.2)	190,487 (90.6)	
Black or Black British	23,419 (9.3)	18,396 (8.8)	
Other	1,141 (0.5)	1,356 (0.6)	
Body mass index (kg/m^2)	27.0 (5.1)	27.8 (4.2)	<0.001
Systolic blood pressure (mmHg)	137.2 (20.2)	142.7 (18.5)	<0.001
Diastolic blood pressure (mmHg)	80.7 (10.5)	84.0 (10.5)	<0.001
LDL-cholesterol (mmol/L)	3.62 (0.87)	3.48 (0.86)	<0.001
HDL-cholesterol (mmol/L)	1.59 (0.37)	1.28 (0.32)	<0.001
Townsend deprivation index	−1.38 (3.04)	−1.35 (3.06)	<0.01
Education, university or college (*n*, %)	77,713 (30.9)	70,499 (33.5)	<0.001
Employment (*n*, %)			<0.001
Working	139,731 (55.6)	127,738 (60.8)	
Retired	87,732 (34.9)	65,435 (31.1)	
Unemployment	21,093 (8.4)	14,655 (7.0)	
None of the above	2,827 (1.1)	2,411 (1.1)	
Income (*n*, %)			0.67
Less than £18,000	54,807 (21.8)	45,719 (21.7)	
£18,000 to £30,999	63,668 (25.3)	53,318 (25.4)	
£31,000 to £51,999	66,753 (26.6)	55,532 (26.4)	
£52,000 to £100,000	52,141 (20.7)	43,831 (20.8)	
£100,000 and above	14,014 (5.6)	11,839 (5.6)	
Smoking status (*n*, %)			<0.001
Never	149,897 (59.6)	103,051 (49.0)	
Previous	78,899 (31.4)	80,773 (38.4)	
Current	22,587 (9.0)	26,415 (12.6)	
Healthy physical activity (*n*, %)	159,312 (63.4)	133,496 (63.5)	0.39
Healthy diet pattern (*n*, %)	51,217 (20.4)	42,355 (20.1)	0.06
Alcohol consumption (*n*, %)			<0.01
Never	19,467 (7.7)	15,891 (7.6)	
Special occasions only	56,950 (22.7)	47,083 (22.4)	
One to four times a week	123,736 (49.2)	104,058 (49.5)	
Daily or almost daily	51,230 (20.4)	43,207 (20.6)	
Water consumption (cups/d)	2.74 (2.25)	2.73 (2.27)	0.095
Coffee consumption (cups/d)	2.01 (2.06)	2.02 (2.08)	0.008
Tea consumption (cups/d)	3.40 (2.85)	3.41 (2.86)	0.260
Have milk consumption (*n*, %)	243,041 (96.70)	203,236 (96.70)	0.819

Values are shown as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Difference between women and men are compared using Student's *t* test or chi-square test accordingly. LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol.

to the reference [HR (95% CI): 1.19 (1.08–1.31) in men; HR (95% CI): 1.12 (1.02–1.23) in women, all p for trend <0.001].

In our study, we found that moderate tea consumption was associated with a lower risk of CHD incidence among men and women (Model 1). After adjusting for ethnicity and baseline age, compared to those who did not drink tea daily, the HRs (95% CIs) for drinking tea 0.5–1 cup/day and 2–3 cups/day were 0.90 (0.84–0.95) and 0.93 (0.89–0.98) among men, respectively; the

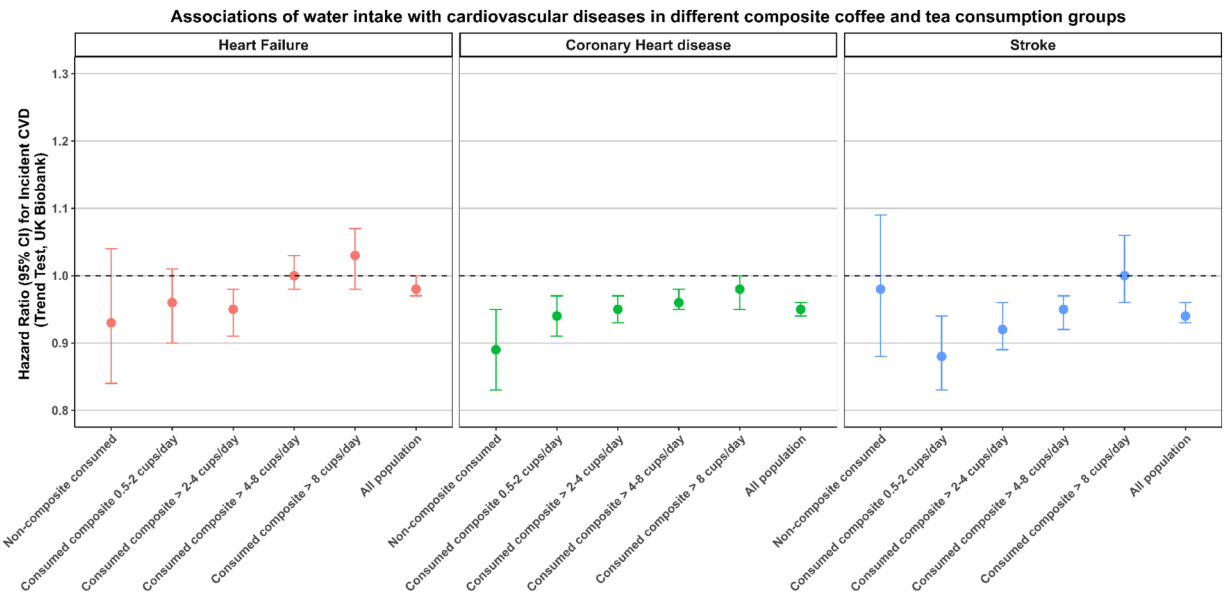

FIGURE 3
Associations of water intake with CVD incidence in different composite coffee and tea consumption groups. The multivariable model was adjusted for baseline age, ethnicity, education, income, smoking status, physical activity, diet pattern, body mass index, systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein, low-density lipoprotein, long-standing illness, disability or infirmity, Townsend Deprivation Index, alcohol consumption, milk consumption, coffee consumption and tea consumption.

HRs (95% CIs) for drinking tea 0.5–1 cup/day and 2–3 cups/day were 0.91 (0.86–0.97) and 0.98 (0.94–1.03) among women, respectively. According to Model 2, heavy tea consumption was associated with a higher risk of CHD in both men and women. Compared to non-tea drinkers, women who consumed ≥6 cups/day of coffee were associated with a 18% increased risk of CHD [HR (95% CI): 1.18 (1.12–1.24), p for trend < 0.001]; men who consumed ≥6 cups/day of coffee had a 12% increased risk of CHD [HR (95% CI): 1.12 (1.05–1.18), p for trend < 0.001]. Additionally, we found a statistically significant gender difference between tea consumption and incident CHD, with a p-value < 0.05.

Coffee and tea consumption and cardiovascular disease risk

Our results revealed that heavy coffee and tea consumption was associated with a higher risk of HF and CHD. As shown in Supplementary Table S5, the results from the multivariate Cox model (Model 3) showed that compared to non-coffee or non-tea drinkers, people who consumed more than eight cups per day were associated with a greater risk for incident HF [HRs (95% CI): 1.48 (1.20–1.84) in men; 1.48 (1.22–1.80) in women, with all p for trend < 0.001].

Similarly, results from the multivariate Cox model (Model 3) showed that compared to those who did not drink coffee or tea per day, those who consumed more than 8 cups of coffee and tea on a daily basis were associated with approximately 48% higher probability of experiencing a CHD event [HRs (95% CI): 1.48 (1.30–1.69) in men; 1.49 (1.33–1.68) in women, with all p for trend < 0.001].

Stratified analysis

The results of our study indicated a negative association between daily water consumption and the incidence of CVD, while a positive association was observed between daily coffee and tea consumption and the incidence of CVD. Consequently, we devised a composite beverage consumption, representing the sum of participants' daily coffee and tea consumption. The Spearman correlation coefficients between daily water consumption and composite consumption was calculated, yielding a value of −0.24. We used this composite consumption to ascertain whether the inverse correlation between daily water consumption and cardiovascular incidents diminished in different populations due to increase consumption of the composite variable. Additionally, we evaluated the impact of the positive correlation between daily coffee and tea consumption and cardiovascular incidents in the context of increased daily water consumption. As illustrated in Figures 3, 4, the results obtained for these two sets of associations do not diverge in opposite directions. The inverse association between water consumption and the incidence of CVD, as illustrated in Figure 3, exhibited a decreasing trend as the daily intake of coffee and tea increased.

Sensitivity analysis

The findings of the primary analyses were consistent in individuals aged 60 years and older, in a control group of individuals without long-term illness, and in the caffeine-only population. The daily consumption of water, coffee, and tea did not significantly differ between the sexes among individuals aged 60 years and above (Supplementary Table S6). Compared to non-water drinkers, individuals aged 60 years and above had a decreased risk of

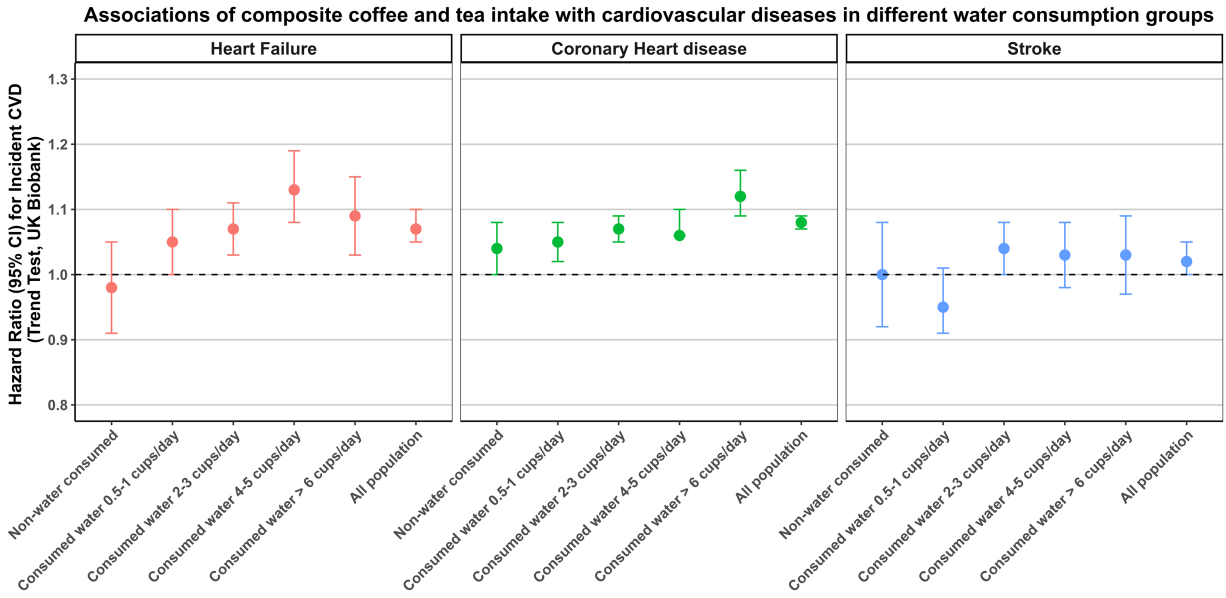

FIGURE 4
Associations of composite coffee and tea intake with cardiovascular diseases in different water consumption groups. The multivariable model was adjusted for baseline age, ethnicity, education, income, smoking status, physical activity, diet pattern, body mass index, systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein, low-density lipoprotein, long-standing illness, disability or infirmity, Townsend Deprivation Index, alcohol consumption and milk consumption.

cardiovascular events associated with increased daily water intake (Supplementary Table S7). Compared to non-coffee drinkers, there was an increased risk of stroke and CHD incidence associated with increased daily coffee intake among individuals aged 60 years and above (Supplementary Table S8). Compared to non-tea drinkers, there was an increased risk of HF and CHD incidence associated with increased daily tea intake among individuals aged 60 years and above (Supplementary Table S9). We found a statistically significant difference between sexes in coffee and tea consumption and in the incidence of CHD events among participants aged 60 years and above (Supplementary Tables S8, S9). Similarly, we replicated the findings of the main analysis in the population without long-term illness population and found no violations of the hypothesis (Supplementary Tables S12–S14). Additionally, we repeated our main analysis in the caffeine-only population, and we found that statistically significant associations between water and coffee consumption and incident CVD remained, consistent with the results of the main analysis. The statistical significance between tea consumption and CVD event incidence became weaker in this population (Supplementary Tables S16–S20).

Discussion

In this large prospective cohort study, we investigated the relationship between the consumption of water, coffee and tea, and the incidence of CVDs among both sexes. The main findings of the study are as follows: (1) enough daily water intake is associated with reduced risk of the incidence of HF, CHD and stroke; (2) high coffee consumption is associated with a greater risk of HF, CHD and stroke among both sexes; (3) heavy tea consumption is associated with a greater risk of HF and CHD in both sexes; and (4) stable positive association emerged between daily coffee and tea consumption and cardiovascular events, regardless of water consumption; and (5) statistically significant gender differences have been found with regard to coffee and tea consumption and the subsequent incidence of CHD.

Water consumption with CVDs

Several studies have investigated the link between water consumption and cardiovascular diseases, but the findings have been inconsistent. In the Adventist Health Study, a prospective examination involving 8,280 men and 12,017 women, higher water consumption was negatively associated with the risk of fatal CHD, with the negative association with water stronger in men (13). Additionally, during a large prospective study initiated in 1988–1990 involving 46,465 men and 64,327 women, they found that water intake from foods and beverages was associated with reduced risk of mortality from CHD and total CVD with higher reduced risk of mortality in women (14). These findings underscore the potential role of water consumption as a protective factor against cardiovascular diseases (13–18). However, some studies revealed a positive or no association between water consumption and cardiovascular disease (19–24). Two cross-sectional studies, one using NHANES 2005–2006 data (19) and the other using KNHANES 2012 data (21), found no statistically significant associations between water intake and cardiovascular diseases. However, it is important to note that both studies relied on observational data and utilized cross-sectional analysis. As a result, they may only provide minimal information for making causal inferences.

In the present study, we found a significant association between water consumption and a reduced risk of both CHD and

stroke among men and women. Notably, our research benefits from its reliance on prospective cross-sectional data sourced from a large population, which enhances the robustness of our conclusions. The findings of our present study may be explained by several potential biological mechanisms. Inadequate water intake is related to a reduced risk of inflammation (18) and increased blood viscosity (25), which are major determinants of atherosclerosis and stroke (26, 27). Additionally, chronic dehydration may lead to elevated levels of hemorrhagic factors, which, consequently, are associated with increased levels of coagulation factors, blood viscosity, fibrinogen, arterial stiffness and hematocrit (28, 29). These factors are correlated with arterial thrombosis, thus contributing to the development of both CHD and stroke (30, 31).

However, it is equally important to consider the risks associated with excessive water consumption. Overhydration may lead to hyponatraemia (low sodium levels), a potentially life-threatening condition characterized by symptoms such as nausea, confusion, and seizures (32). Hyponatremia has been associated with adverse cardiovascular outcomes, including arrhythmias and heart failure, due to the resulting electrolyte imbalance (33). Further research is needed to establish an optimal range of water consumption for cardiovascular health, balancing the risks of dehydration and overhydration.

Coffee consumption with CVDs

Our study revealed a positive association between high coffee intake and the risk of heart failure, CHD, and stroke among both sexes. This correlation was particularly significant for individuals who consumed four or more cups of coffee per day. Several case–control and prospective studies have revealed that the development of CVD may be associated with coffee intake (34–37). Zhou et al. reported that among 347,077 individuals from the UK Biobank, those who consumed >6 cups/day of coffee had a multivariable RR of 1.22 (95% CI: 1.07–1.40) for the incidence of CVD compared with those who consumed 1–2 cups/day (38). Chen et al. reported that compared with noncoffee drinkers, people who drank ≥6 cups of coffee per day had greater risks of CVD, CHD and stroke, with HRs and 95% CIs of 1.03 (0.98–1.09), 1.04 (0.98, 1.10) and 1.02 (0.92, 1.14), respectively (39). Our findings are consistent with the results of these prospective studies, all of which used data from the UK Biobank database.

The increased risk of cardiovascular disease associated with heavy coffee consumption can be explained by the following potential biological mechanisms. First, the most commonly consumed type of coffee in the UK is instant coffee, which contains dairy products and sugar. The high consumption of coffee may increase the burden on the cardiovascular circulatory system, potentially leading to cardiovascular events. Additionally, coffee contains a diverse array of bioactive compounds, including caffeine, CGA, diterpene alcohols, minerals such as potassium and magnesium, niacin and lignans (40). High short-term coffee intake may dramatically increase plasma renin activity, catecholamine concentrations and blood pressure, increase vascular tension, and induce cardiac arrhythmias (41).

Tea consumption with CVDs

In our study, we found that individuals who consumed ≥6 cups/day of tea were associated with a moderate increase in the risk of HF and coronary heart disease both in men and women. Few previous studies reported findings consistent with our current analysis. Previous studies have reported that tea, a popular lifestyle component, can promote cardiovascular health due to its antioxidant effects and anti-inflammatory mechanisms (42, 43). The results from a systematic review showed that moderate tea consumption was associated with a lower risk of coronary heart disease, but a large amount (>4–6 cups/day) of tea consumption has been shown to increase the risk of coronary heart disease (44).

In our study, we also found that the consumption of 0.5–1 cup/day tea was associated with a lower risk of CHD in both men and women, but fully adjusted models were not used. Interestingly, research has shown that tea consumption may be associated with a lower risk of coronary heart disease in Japanese (45), Saudi Arabian (46), and Chinese adults (47, 48), but similar results have rarely been found in the British population. The type of tea consumed and the tea-drinking habits of the British people may explain this difference. For example, the British population prefers to drink black tea with milk and sugar, but previous studies have reported that black and green tea may have inconsistent biological effects on coronary heart disease risk. Green tea catechins have been shown to inhibit oxidation, vascular inflammation, atherogenesis and thrombogenesis and favorably modulate the plasma lipid profile and vascular reactivity, suggesting a broad spectrum of beneficial effects on CHD (49). Similarly, excessive consumption of milk and sugar also increases the risk of coronary heart disease.

Sex interaction between fluid consumption and cardiovascular diseases

The focus on the sex-specific epidemiology, manifestation, pathophysiology, treatment and outcome of major chronic diseases has been increasing steadily, and the interaction of sex differences in disease development needs to be considered. In our study, the sex interaction effect was statistically significant only for the associations between coffee and tea consumption and the incidence of CHD. However, we did not find inconsistent results regarding fluid consumption or coronary heart disease among men and women. We also found that the hazard ratios for the same dose of fluid intake were greater in women than in men for the same exposure factors and study endpoints. However, it is important to note that these findings are statistically significant, and further research is necessary to validate this conclusion.

Strengths and limitations

The strengths of our study include its prospective design, large sample population, long follow-up time, and well-validated covariate information. However, several potential limitations still should be considered. First, information on water, coffee and tea consumption was derived from self-reported questionnaires at baseline, which may have recall bias and may not reflect consumption patterns over time, leading to potential misclassifications of the exposures. Second, although we adjusted for confounders such as coffee and tea intake in investigating the association between water consumption and major

chronic diseases, we did not account for other confounders (e.g., sugar intake, beverage additives, other sources of water intake) due to experimental design limitations, which may have affected the accuracy of our findings. Third, due to the lack of data on tea type (black tea, green tea), we were unable to investigate whether the type of tea consumed affects the association between tea consumption and cardiovascular disease incidence. Future studies are needed to investigate the association of tea consumed type in incident CVDs in the general population. Forth, participants in the UK Biobank cohort tended to be more health conscious than nonparticipants, and a large number of them were White people. Consequently, this may diminish the generalisability of the findings to more heterogeneous demographics or regions. It is therefore essential to exercise caution when generalizing these findings to other populations.

Conclusion

In our study, we found that high coffee and tea consumption was associated with an increased risk of cardiovascular diseases in both sexes (especially when they consume ≥6 cups/day); daily water consumption was associated with a lower risk of cardiovascular diseases in both men and women. Our research indicates the significance of moderate fluid consumption in daily life.

Data availability statement

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

Author contributions

DK: Conceptualization, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. YW: Writing – original draft, Writing – review & editing. YH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. WS: Software, Validation, Visualization, Writing – review & editing. JK: Data curation, Investigation, Validation, Visualization, Writing – review & editing. XZ: Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. HY: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Software, Writing – review & editing. ZH: Funding acquisition, Project administration, Supervision, Writing – review & editing. ZL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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

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Association of dietary patterns with hypertension among adults residing in Tibetan China: findings from a population-based study

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Objectives: This study aimed to investigate the dietary patterns of Tibetan residents and explore their association with the prevalence of hypertension.

Methods: A multi-stage, stratified, random sampling method was employed to include Tibetan residents from Luhuo County, Garze Tibetan Autonomous Prefecture, Sichuan Province, China. Dietary information was collected through face-to-face interviews using a Food Frequency Questionnaire (FFQ) consisting of 92 food items. Participants were asked to report the frequency and portion size of their consumption of each food item over the past year. The collected data were subsequently converted into average daily intake, with the 92 food items grouped into 23 distinct categories. Principal Component Analysis (PCA) was then used to identify dietary patterns. Binary logistic regression analysis was conducted to investigate the association between dietary patterns and the prevalence of hypertension, adjusting for potential confounders including age, gender, living area, education, physical activity, current smoking, current alcohol consumption, diabetes, dyslipidemia, and overweight/obesity. A *P* value <0.05 was considered statistically significant.

Results: A total of 1,262 Tibetan residents participated in the study, with an average age of 46 ± 15 years. Among them, 36.8% were male, and the prevalence of hypertension was 30.2%. Three distinct dietary patterns were identified among Tibetan residents and were subsequently named as the "Tsamba-red meat-tuber," "Rice-vegetable-fruit," and "Dairy products" patterns. After adjusting for confounding factors, individuals in the highest quartile following the "Tsamba-red meat-tuber" pattern were found to be associated with a higher prevalence of hypertension (OR = 3.04, 95% CI: 2.06–4.50; *P* for trend <0.001). In contrast, individuals in the highest quartile following the "Rice-vegetable-fruit" pattern were associated with a lower prevalence of hypertension (OR = 0.45, 95% CI: 0.30–0.67; *P* for trend <0.001). Additionally, those in the highest quartile of the "Dairy products" pattern also showed a lower prevalence of hypertension (OR = 0.58, 95% CI: 0.39–0.85; *P* for trend = 0.002).

Conclusion: The "Tsamba-red meat-tuber" pattern is associated with a higher risk of hypertension, whereas the "Rice-vegetable-fruit" and "Dairy products" patterns are associated with a lower risk of hypertension in this population.

KEYWORDS

Tibetan, dietary patterns, hypertension, food frequency questionnaire, principal component analysis

1 Introduction

Hypertension is a major risk factor for cardiovascular and cerebrovascular diseases (1). Among the primary ethnic groups in China, Tibetans, numbering over 6 million, have been shown to exhibit a high prevalence of hypertension, ranging from 23.4 to 55.9% (2–4), with this heterogeneity in prevalence potentially attributable to differences in altitude (5) and lifestyle factors (2, 6) among the studied populations. These rates are substantially higher than the national average of 23.5% (7). Hypertension is influenced by both genetic and environmental factors, with diet being one of the most significant environmental contributors (8). The high-altitude, low-oxygen environment of Tibetan regions has shaped unique dietary habits, including a preference for tsamba, beef and mutton, and dairy products. However, the detailed characteristics of the Tibetan diet and its relationship with hypertension remain inadequately understood.

To comprehensively evaluate the relationship between diet and disease, nutritionists have proposed the concept of dietary patterns (9). Dietary patterns take into account multiple foods and nutrients as a whole, emphasizing their interactions, and thus better reflect the impact of overall dietary exposure on disease (10, 11). Research evidence suggests that dietary patterns, such as the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet, are strongly associated with a lower risk of hypertension, while the Western diet is correlated with a higher risk (12). A longitudinal study from the China Health and Nutrition Survey (1991–2018) found that adherence to the modern dietary pattern, characterized by a high intake of fruits and dairy products, was negatively associated with systolic blood pressure (SBP), while the meat-based dietary pattern was positively associated with diastolic BP (DBP) and the risk of hypertension (13). However, few studies have investigated the link between Tibetan dietary patterns and hypertension. A cross-sectional study conducted in Diqing, Yunnan, which included a multi-ethnic population with 35% Tibetans, identified three major dietary patterns: 'Grassland healthy,' 'Tuber and meat,' and 'Fruit and vegetable.' The 'Grassland healthy' pattern was found to be associated with a lower risk of hypertension (14). Additionally, a cohort study of Tibetan adults in the Tibetan Plateau region identified three primary dietary patterns: modern, urban, and pastoral dietary patterns. The modern dietary pattern was positively associated with elevated BP, while the pastoral dietary pattern showed a negative association with elevated BP (15). Tibetans are mainly distributed across southwestern China, including Tibet, Sichuan, Qinghai, Yunnan, and other regions. Garze Tibetan Autonomous Prefecture in Sichuan is the second-largest Tibetan area in China. This region not only preserves traditional Tibetan dietary habits but also absorbs influences from the culinary culture of southwestern China. Furthermore, with improved transportation access, the diversity of available ingredients has significantly increased. As a result, Garze Tibetan Autonomous Prefecture has developed a unique dietary profile. However, no studies have yet explored the dietary patterns in this region or their association with hypertension.

Therefore, this study aims to investigate the dietary patterns of Tibetan residents in Ganzi Tibetan Autonomous Prefecture using a food frequency questionnaire (FFQ) and explore their potential correlation with hypertension risk.

2 Materials and methods

2.1 Subjects

Luhuo County is located in the central and northern parts of the Garze Tibetan Autonomous Prefecture in Sichuan Province and is a semi-agricultural, semi-pastoral area, with the majority of the population being Tibetan (94.8%). The locals have preserved traditional Tibetan food habits and ways of life. Therefore, we conducted a multi-stage, stratified, and randomly sampled survey in Luhuo County from January 2018 to October 2020. First, two towns were selected from each of the four administrative districts in Luhuo County. Then, 2–3 villages were selected from each town, and finally, 95 Tibetan residents were randomly selected in each village, all of whom were aged between 18 and 80 years. We excluded the following individuals from the study: those with self-reported mental illnesses, serious physical illnesses, or visual/hearing impairments; those with a recent history of angina, acute myocardial infarction, heart failure, or cerebrovascular disease within the past 6 months; those with severe liver/kidney damage (serum alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal, serum creatinine >260 μmol/L); those with severe digestive system diseases or known malignant tumors; and pregnant or breastfeeding women. A total of 1,262 subjects, with data on dietary surveys and medical history, were included in the study, out of 1,423 participants overall (Figure 1). This study was approved by the Ethics Committee of West China Hospital, Sichuan University. All participants provided informed consent after being informed of the objectives and potential benefits of the study.

2.2 Dietary assessment

According to our prior dietary survey of 86 Tibetan residents, we compiled a list of foods commonly consumed by this population. Using nutritional epidemiology methods as a reference (16), we developed a Food Frequency Questionnaire (FFQ) containing 92 food items for dietary assessment. Our trained investigators, with the assistance of local Tibetan translators, conducted face-to-face dietary surveys with the participants. Participants were asked to report the frequency and portion size of each food item consumed over the past year. Standard containers, such as bowls, cups, and spoons with marked scales, as well as concentric circles of different sizes and pictures of foods, were used to assist participants in recalling their food intake. The portion weights for each food item were determined in advance. The dietary information obtained from the FFQ was subsequently converted into average daily intake, calculated by multiplying the intake frequency by the portion size and its corresponding weight. To facilitate the identification and interpretation of dietary patterns in subsequent analyses, we utilized the classification of the China Food Composition Table (17) and considered the dietary habits of the Tibetan region. The 92 food items listed in the FFQ were consolidated into 23 distinct food groups, including rice and its products, wheat and its products, tsamba, whole grains, tubers, beans and their products, vegetables, mushrooms, pork, beef and mutton, poultry, animal organs, aquatic products, eggs, dairy and its products, fruits, nuts, pastries, butter tea/mike tea, sweet beverages, tea, salt, and oils. Among these, tsamba, a staple food crop

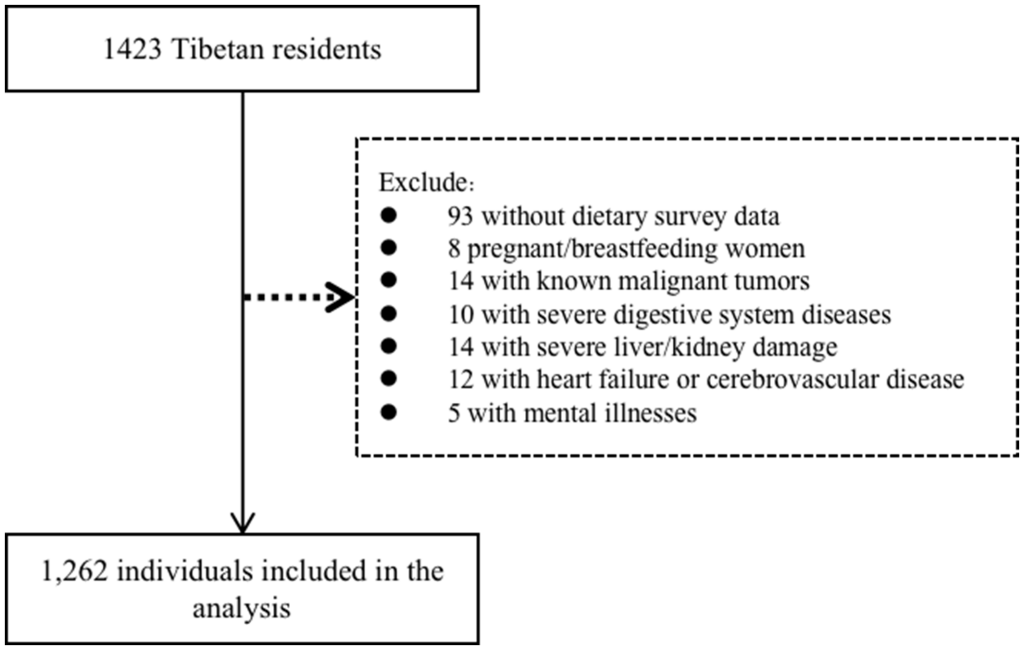

FIGURE 1
Flow diagram illustrating the study population inclusion process.

widely consumed by Tibetans, is made from roasted Tibetan barley (13, 18).

2.3 Covariates

2.3.1 Covariates measurement and collection

The interview involved the collection of demographic data (e.g., sex, education, living area), clinical data (e.g., current smoking status, medical history), and information related to lifestyle (e.g., physical activity).

Participants' height and weight were measured while they were wearing lightweight clothing and without shoes, with precision to 1 cm and 0.2 kg. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

BP was measured using a standardized automatic electronic sphygmomanometer (Omron HBP-1100), following a standardized protocol (19). Readings were taken three times at 2-min intervals after at least 5 min of rest in a warm and quiet indoor setting. The mean value of the three readings was used in subsequent statistical analyses.

Blood samples were drawn from the antecubital vein in the morning after an 8-h fast. The blood samples were then transported to the Department of Laboratory Medicine at West China Hospital of Sichuan University and analyzed for fasting blood glucose (FBG), fasting serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) using an automatic biochemistry analyzer (Roche Cobas8000).

2.3.2 Related definitions of covariates

Hypertension was defined as a SBP of at least 140 mmHg and/or a DBP of at least 90 mmHg, or self-reported current use of antihypertensive medications (20). Diabetes was defined as a fasting blood glucose level of at least 7.0 mmol/L, or self-reported current use of insulin or hypoglycemic agents (21). Dyslipidemia was defined as the self-reported current use of antilipidemic medications or meeting at least one of the following criteria: TC $\geq$ 5.2 mmol/L, LDL-C $\geq$ 3.4 mmol/L, HDL-C < 1.0 mmol/L, or TG $\geq$ 1.7 mmol/L (22). BMI was categorized as overweight (BMI 24–27.9 kg/m^2) and obesity (BMI $\geq$ 28 kg/m^2). Current smoking was defined as smoking at least one cigarette per day within the past year, while current drinking was defined as consuming alcohol at least once per week within the past year. Physical activity levels were classified into four categories based on daily activity duration: <30 min (level 1), 30 min to 1 h (level 2), 1 to 1.5 h (level 3), and > 1.5 h (level 4) (19).

2.4 Statistical analyses

Dietary patterns were identified using Principal Component Analysis (PCA). Prior to conducting the analysis, the Kaiser-Meyer-Olkin measure of sample and Bartlett test of sphericity were employed to evaluate the suitability of the data for factor analysis (23). A total of 23 factors were initially extracted. Based on eigenvalues (>1.0), the scree plot (indicating the point where the slope levels off), the proportion of variance explained by each factor (>5%), and the interpretability of the factors, three primary dietary patterns were retained. The scree plot is provided in Supplementary material. Subsequently, the Varimax orthogonal rotation method was applied to the factor matrix to produce uncorrelated factors, facilitating simpler data interpretation. Next, to identify the important food items for each pattern, food items with rotated factor loadings >0.3 or < −0.3 were retained (14, 18). The naming and interpretation of the patterns were determined based on these retained food items. Dietary pattern

scores were calculated for each participant and categorized into quartiles. The characteristics of the study population were summarized as frequencies and percentages for categorical variables and as means ± standard deviations (SD) for continuous variables. Differences in demographic and clinical characteristics between two groups were assessed based on an analysis of categorical variables using the Chi-square test, independent t-tests for normally distributed variables, and non-parametric Mann–Whitney or Wilcoxon tests for skewed variables. Binary logistic regression analysis was performed to explore the association between dietary pattern score quartiles and hypertension, using Quartile 1 (Q1) as the reference group. Demographic characteristics and comorbidities that might be associated with hypertension were included as covariates in the model. Model 1 adjusted for demographic factors such as age (per 1 year), gender (male or female), living area (urban, farming, or pastoral area), education (no schooling, primary school, middle school, or > middle school), physical activity (levels 1, 2, 3, or 4), current smoking status (smoker or non-smoker), and current drinking status (drinker or non-drinker), while Model 2 further adjusted for comorbidities, including diabetes (diabetic or non-diabetic), dyslipidemia (dyslipidemic or non-dyslipidemic), and overweight/obesity (overweight/obese or non-overweight/non-obese). The results were reported as odds ratios (OR) with 95% confidence intervals (95% CI) to quantify the strength of the association between dietary patterns and hypertension. We conducted tests for linear trend by entering the median value of each category of dietary pattern score as a continuous variable in the models. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics version 23.

3 Results

3.1 Participant characteristics

This study included a total of 1,262 Tibetan residents, with 38.7% from farming areas, 29.6% from pastoral areas, and 31.6% from urban areas. The study population had a mean age of 46 ± 15 years, with 36.8% being male. The prevalence rates of hypertension, diabetes, overweight/obesity, and dyslipidemia were 30.2, 5.5, 61.9, and 50.2%, respectively. Men were observed to be more likely than women to have higher BMI, SBP, and TG levels, and lower HDL-C levels. No significant differences were noted between the two genders for DBP and LDL-C. A greater proportion of men were current smokers, consumed alcohol, and were overweight or obese, while a higher proportion of women had diabetes. No significant differences were found in the prevalence of hypertension or dyslipidemia between genders (Table 1).

TABLE 1 Participant characteristics.

Variables	Total (*n* = 1,262)	Male (*n* = 487)	Female (*n* = 775)	*P*-value
Age, yrs	46.18 ± 14.57	43.58 ± 15.19	47.80 ± 13.72	<0.001#
BMI, kg/m^2	25.74 ± 4.26	26.26 ± 4.25	25.41 ± 4.23	0.001*
SBP, mmHg	123.93 ± 21.18	125.67 ± 20.51	122.84 ± 21.53	0.021*
DBP, mmHg	75.66 ± 13.05	76.35 ± 13.46	75.22 ± 12.77	0.137
FBG, umol/L	4.94 ± 1.34	4.62 ± 1.18	5.13 ± 1.40	<0.001#
TC, mmol/L	4.75 ± 1.14	4.61 ± 1.16	4.83 ± 1.12	0.001*
TG, mmol/L	1.18 ± 0.70	1.23 ± 0.78	1.14 ± 0.63	0.038*
LDL-C, mmol/L	2.79 ± 0.92	2.73 ± 0.96	2.82 ± 0.90	0.086
HDL-C, mmol/L	1.35 ± 0.51	1.22 ± 0.32	1.43 ± 0.58	<0.001#
Living area, *n* (%)				
Urban area	399 (31.6)	139 (28.5)	260 (33.5)	
Farming area	489 (38.7)	179 (36.8)	310 (40.0)	
Pastoral area	374 (29.6)	169 (34.7)	205 (26.5)	0.007*
Education, *n* (%)				
No school	747 (59.2)	290 (59.5)	457 (59.0)	
Primary school	271 (21.5)	98 (20.1)	173 (22.3)	
Middle school	130 (10.3)	44 (9.0)	86 (11.1)	
>Middle school	114 (9.0)	55 (11.3)	59 (7.6)	0.093
Physical activity, *n* (%)				
Level 1	288 (22.8)	124 (25.5)	164 (21.2)	
Level 2	302 (23.9)	119 (24.4)	183 (23.6)	
Level 3	303 (24.0)	91 (18.7)	212 (27.8)	
Level 4	369 (29.2)	153 (31.4)	216 (27.9)	0.004*
Current smoking, *n* (%)	29 (2.3)	28 (5.7)	1 (0.1)	<0.001#
Current drinking, *n* (%)	32 (2.5)	31 (6.4)	1 (0.1)	<0.001#
Hypertension, *n* (%)	381 (30.2)	330 (67.8)	551 (71.1)	0.209
Diabetes mellitus, *n* (%)	69 (5.5)	11 (2.3)	58 (7.5)	<0.001#
Overweight/ Obesity, *n* (%)	781 (61.9)	321 (65.9)	460 (59.4)	0.02*
Dyslipidemia, *n* (%)	634 (50.2)	250 (51.3)	384 (49.5)	0.537

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. A *P*-value < 0.05 was considered as statistically significant; *$P < 0.05$; #$P < 0.001$.

3.2 Identification of major dietary patterns

Table 2 presents the factor loadings for the three major dietary patterns. Three distinct dietary patterns were identified, namely "Tsamba-red meat-tuber," "Rice-vegetable-fruit," and "Dairy products," which together accounted for 25.4% of the variance in total food intake. The "Tsamba-red meat-tuber" pattern was characterized by frequent consumption of Tsamba, beef, mutton, tubers, wheat and

TABLE 2 Factor loading of three major dietary patterns among subjects.

Food items	"Tsamba-red meat-tuber" pattern	"Rice-vegetable-fruit" pattern	"Dairy products" pattern
Tsampa	**0.705**	-	-
Beef and mutton	**0.623**	-	-
Tubers	**0.642**	-	-
Butter tea/mike tea	**0.531**	-	-
Wheat and its products	**0.433**	-	-
Oils	**0.399**	-	-
Vegetables	-	**0.685**	-
Rice and its products	-	**0.607**	-
Pork	-	**0.581**	-
Fruits	-	**0.403**	-
Mushrooms	-	**0.399**	-
Eggs	-	**0.328**	-
Dairy and its products	-	-	**0.679**
Whole grains	-	-	-
Beans and their products	-	-	-
Poultry	-	-	-
Animal organs	-	-	-
Aquatic products	-	-	-
Nuts	-	-	-
Pastries	-	-	-
Sweet beverages	-	-	-
Tea	-	-	-
Salt	-	-	-
Total variance explained	**14.65**	**7.47**	**5.8**

Absolute values > 0.3 or < −0.3 are shown in bold.

its products, and oil. The "Rice-vegetable-fruit" pattern was characterized by frequent consumption of vegetables, rice and its products, pork, fresh fruits, mushrooms, and eggs. The "Dairy products" pattern was characterized by frequent consumption of dairy and its products.

3.3 Characteristics according to dietary patterns

Table 3 presents the characteristics of participants in the highest and lowest quartiles of each dietary pattern. Individuals in the highest quartile of the "Tsamba-red meat-tuber" pattern were more likely to reside in farming and pastoral areas and to have lower education levels compared to those in the lowest quartile. Individuals in the highest quartile of the "Rice-vegetable-fruit" pattern were more likely to reside in urban and farming areas, with a higher proportion having completed middle school or higher education compared to the lowest quartile. Individuals in the highest quartile of the "Dairy products" pattern were more likely to reside in urban and pastoral areas, engage in higher levels of physical activity, and demonstrate a lower prevalence of smoking and drinking compared to those in the lowest quartile.

3.4 Prevalence of hypertension according to dietary patterns

Significant differences were observed in the prevalence of hypertension across quartiles of the three major dietary pattern scores. As the scores for the "Tsamba-red meat-tuber" pattern increased, the prevalence of hypertension rose from 21.5 to 41.6%. In contrast, as the scores for the "Rice-vegetable-fruit" and "Dairy products" patterns increased, the prevalence of hypertension declined from 41.9 to 21.3% and from 39.4 to 24.1%, respectively. These findings are presented in Table 4.

3.5 Association between dietary patterns and hypertension

Logistic regression analysis was conducted to investigate the association between the three major dietary patterns and the prevalence of hypertension (Table 4). Univariate regression analysis indicated that, compared to the lowest quartile group, participants in the highest quartile of the 'Tsamba-red meat-tuber' pattern had a significantly higher prevalence of hypertension, with an OR of 2.60 (95% CI: 1.83–3.68; *P* for trend <0.001). Conversely, the highest quartiles of the 'Rice-vegetable-fruit' and 'Dairy products' patterns were associated with significantly lower prevalence of hypertension, with ORs of 0.38 (95% CI: 0.26–0.53; *P* for trend <0.001) and 0.49 (95% CI: 0.34–0.69; *P* for trend <0.001), respectively. After adjusting for confounding factors, including sex, age, living area, education level, physical activity, current smoking, current alcohol consumption, BMI, FBG, TC, TG, LDL-C, HDL-C, these associations remained statistically significant. The adjusted OR for the highest quartile of the 'Tsamba-red meat-tuber' pattern was 3.07 (95% CI: 2.07–4.55; *P* for trend <0.001), while the adjusted ORs for the highest quartiles of the 'Rice-vegetable-fruit' and 'Dairy products' patterns were 0.43 (95% CI: 0.29–0.65; *P* for trend <0.001) and 0.55 (95% CI: 0.37–0.82; *P* for trend =0.002), respectively.

4 Discussion

In this study, we conducted a dietary survey using a FFQ among 1,262 Tibetan residents in farming, pastoral, and urban areas of Luhuo County in Garze Tibetan Autonomous Prefecture in Sichuan Province. Three major dietary patterns were identified among Tibetan residents: the "Tsamba-red meat-tuber," "Rice-vegetable-fruit" and "Dairy

TABLE 3 Characteristics according to dietary patterns.

Variables	"Tsamba-red meat-tuber" pattern			"Rice-vegetable-fruit" pattern			"Dairy products" pattern		
	Q1 (*n* = 316)	Q4 (*n* = 315)	*P* value	Q1 (*n* = 315)	Q4 (*n* = 315)	*P* value	Q1 (*n* = 315)	Q4 (*n* = 315)	*P* value
Age, yrs	46.36 + 14.06	45.10 + 14.56	0.27	46.39 ± 14.76	45.75 ± 14.05	0.576	46.19 ± 15.18	46.95 ± 12.79	0.5
Male, *n* (%)	116 (36.7)	126 (40)	0.414	120 (38.1)	123 (39)	0.87	120 (38.1)	113 (35.9)	0.621
Living area, *n* (%)									
Urban area	132 (41.8)	72 (22.9)	0.001*	89 (28.3)	123 (39)	0.001*	86 (27.3)	116 (36.8)	0.001*
Farming area	106 (33.5)	139 (44.1)		107 (34)	116 (36.8)		144 (45.7)	88 (27.9)	
Pastoral area	78 (24.7)	104 (33.0)		119 (37.8)	76 (24.1)		85 (27)	111 (35.2)	
Education, *n* (%)									
No school	168 (53.2)	197 (62.5)	0.001*	174 (55.2)	179 (56.8)	0.001*	190 (60.3)	180 (57.1)	0.064
Primary school	67 (21.2)	75 (23.8)		73 (23.2)	72 (22.9)		67 (21.3)	60 (19)	
Middle school	31 (9.8)	27 (8.6)		47 (14.9)	21 (6.7)		40 (12.7)	38 (12.1)	
>middle school	50 (15.8)	16 (5.1)		21 (6.7)	43 (13.7)		18 (5.7)	37 (11.7)	
Physical activity, *n* (%)									
Level 1	63 (19.9)	78 (24.8)	0.453	81 (25.7)	69 (21.9)	0.6	85 (27)	54 (17.1)	0.011*
Level 2	84 (26.6)	72 (22.9)		80 (25.4)	78 (24.8)		74 (23.5)	68 (21.6)	
Level 3	77 (24.4)	73 (23.2)		67 (21.3)	78 (24.8)		68 (21.6)	84 (26.7)	
Level 4	92 (29.1)	92 (29.2)		87 (27.6)	90 (28.6)		88 (27.9)	109 (34.6)	
Current smoking, *n* (%)	12 (3.8)	5 (1.6)	0.138	9 (2.9)	10 (3.2)	1	14 (4.4)	4 (1.3)	0.029*
Current drinking, *n* (%)	12 (3.8)	7 (2.2)	0.352	11 (3.5)	13 (4.1)	0.836	20 (6.3)	3 (1)	0.001*

Q1, 1st quartile; Q4, 4th quartile; A *P*-value < 0.05 was considered as statistically significant; *$P < 0.05$; ‡$P < 0.001$.

products" patterns. The "Tsamba-red meat-tuber" pattern contributed the highest factor load (14.62%) and was considered the main dietary pattern among Tibetan residents, consistent with previous studies (18, 24). The "Rice-vegetable-fruit" pattern was similar to the main pattern of southern Chinese residents who mainly consume rice, vegetables, fruits and meat, more common in urban areas and among highly educated Tibetan residents (25). These changes may be related to urbanization in Tibetan areas, increased cultural exchange between Tibetan and Chinese cuisines, improved transportation and logistics, and greater food diversity (26, 27). Furthermore, as Tibetans originated from a nomadic ethnic group, dairy and its products remain important food sources. Our research found that Tibetans in pastoral areas, urban areas, with more physical activity and healthier lifestyles tended to prefer the "Dairy products" pattern.

This study found that the "Tsamba-red meat-tuber" pattern was a significant risk factor for hypertension among Tibetan residents. Beef and mutton, classified as red meat, are the primary food components of the "Tsamba-red meat-tuber" pattern. Both cross-sectional and longitudinal studies have demonstrated a positive association between red meat and hypertension (28). A recent umbrella review that included 43 meta-analyses found that higher consumption of red meat, particularly processed meat, was associated with an increased risk of hypertension. Further dose–response analysis revealed that an additional 100 g/day of red meat intake was positively associated with a 14% increased risk of hypertension, while consuming more than 50 g of processed meat per day was associated with a 12% increased risk of hypertension (29). Although this study did not examine the cooking methods or consumption levels of red meat, based on previous research, we suggest that red meat intake plays a significant role in the development of hypertension within the "Tsamba-red meat-tuber" pattern. Several mechanisms may explain the hypertension risk associated with red meat (28). Firstly, compared to unprocessed red meat, processed red meat—such as that which is cured, dried, fermented, or smoked—has a sodium content that is 400% higher (28). High sodium intake has been shown to be associated with elevated blood pressure and an increased risk of hypertension through mechanisms such as increasing extracellular volume, vascular resistance, and sympathetic activity, as well as worsening endothelial inflammation (30–32). Furthermore, red meat, particularly processed red meat, contains nitrite additives, with nitrite levels 50% higher than in unprocessed red meat (33). Studies have reported that each increase in the tertile of nitrate consumption is associated with a 3.1 mmHg increase in diastolic BP (34). Nitrite additives have been found to cause endothelial dysfunction, a key

TABLE 4 Prevalence of hypertension and logistic regression analysis between hypertension and dietary pattern.

Dietary pattern	Prevalence of Hypertension		*P*-value	Univariate analysis	*P* for trend	Model1	*P* for trend	Model2	*P* for trend
	n	%							
Tsampa-red meat-tuber									
Q1	68	21.5	<0.001#	1 (reference)	<0.001#	1 (reference)	<0.001#	1 (reference)	
Q2	80	25.4		1.24 (0.86–1.80)		1.25 (0.84–1.87)		1.27 (0.84–1.90)	
Q3	106	33.5		1.84 (1.29–2.63)		1.97 (1.34–2.91)		1.92 (1.29–2.85)	
Q4	131	41.6		2.60 (1.83–3.68)		3.09 (2.10–4.54)		3.07 (2.07–4.55)	<0.001#
Rice-vegetable-fruit									
Q1	132	41.9	<0.001#	1 (reference)	<0.001#	1 (reference)	<0.001#	1 (reference)	
Q2	95	30.1		0.60 (0.43–0.83)		0.71 (0.49–1.01)		0.69 (0.48–1.01)	
Q3	87	27.5		0.53 (0.38–0.74)		0.58 (0.40–0.83)		0.57 (0.39–0.84)	
Q4	67	21.3		0.38 (0.26–0.53)		0.47 (0.32–0.69)		0.43 (0.29–0.65)	<0.001#
Dairy products									
Q1	124	39.4	<0.001#	1 (reference)	<0.001#	1 (reference)	0.003*	1 (reference)	
Q2	99	31.3		0.70 (0.51–0.98)		0.75 (0.52–1.08)		0.74 (0.51–1.09)	
Q3	82	25.9		0.54 (0.39–0.76)		0.62 (0.43–0.91)		0.58 (0.39–0.86)	
Q4	76	24.1		0.49 (0.35–0.69)		0.58 (0.40–0.85)		0.55 (0.37–0.82)	0.002*

Q1: 1st quartile; Q2: 2nd quartile; Q3: 3rd quartile; Q4: 4th quartile; *n*, number. Model 1: Adjusted for age, gender, living area, education, physical activity, current smoking, and current drinking. Model 2: Adjusted for the factors in Model 1 as well as body mass index, fasting blood glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides. A *P*-value < 0.05 was considered as statistically significant; *$P < 0.05$; #$P < 0.001$.

pathophysiological factor in the development of hypertension (35). Moreover, red meat is rich in acylcarnitines, which are metabolized by intestinal microbiota and hepatic enzymes into trimethylamine-N-oxide (TMAO). TMAO has been associated with several adverse effects, including endothelial dysfunction, atherosclerosis, oxidative stress, and vascular aging, all of which could contribute to the development of hypertension (36, 37). Additionally, the "Tsamba-red meat-tuber" pattern is characterized by a higher intake of tubers, particularly potatoes. Some studies have found inconsistent results regarding the relationship between potato intake and hypertension, with the cooking method being a factor (38–40). However, a recent meta-analysis found no association between total potato intake and hypertension, though both fried and non-fried potato consumption may increase the risk of diabetes (41). Boiled white potatoes, with a glycemic load of 21 (42), can cause postprandial hyperglycemia, which is associated with endothelial dysfunction, oxidative stress, and inflammation—factors that may negatively impact BP regulation (8). Furthermore, tsamba, a staple food in this dietary pattern, is made from naked barley. Animal studies have shown that supplementation with partly milled highland barley in high-fat diet (HFD)-fed mice significantly reduces FBG, improves oral glucose tolerance, and prevents HFD-induced gut microbiota dysbiosis (43). However, Tibetans often mix tsamba with salt and butter, which may diminish its protective effects. Therefore, the "Tsamba-red meat-tuber" pattern, characterized by high consumption of beef, mutton, and tubers, may contribute to the elevated hypertension risk observed in this population. Nevertheless, few studies have explored the dietary habits of Tibetans and their relation to hypertension. For example, Peng et al. conducted a study on Tibetan adults in the Tibetan Plateau and identified a "Pastoral pattern" similar to the "Tsamba-red meat-tuber" pattern. This pattern, which includes high consumption of red meat, tsamba, Tibetan cheese, butter tea/milk tea, and whole-fat dairy, was not associated with elevated BP (18). These findings may stem from the higher intake of whole-fat dairy in the "Pastoral pattern," which has been found to act as a protective factor against hypertension (44), potentially offsetting the harmful effects of red meat on BP.

The Chinese traditional southern dietary pattern, characterized by a higher intake of vegetables, fruits, rice, pork, poultry, and aquatic products, has been shown to be associated with a reduced incidence of hypertension and a lower risk of future cardiovascular disease (25, 45). In our study, the "Rice-vegetable-fruit" pattern, which shares similarities with the traditional southern dietary pattern but contains relatively lower amounts of poultry and aquatic products, was observed to be associated with a lower incidence of hypertension among Tibetan residents. The observed antihypertensive effect may be attributed to the higher intake of vegetables and fruits. A recent meta-analysis of prospective studies found that a high intake of fruits and vegetables was associated with a reduced risk of hypertension, although the results for specific subtypes remain inconclusive and warrant further research (46). Several mechanisms may explain the association between vegetable and fruit consumption and lower BP. First, these foods are rich in dietary fiber, which helps regulate BP by improving vascular endothelial function, enhancing mineral absorption, reducing serum cholesterol levels, improving gastrointestinal function, and decreasing insulin resistance (47). Furthermore, fruits and vegetables are high in potassium, magnesium, vitamin C, folate, flavonoids, and carotenoids, which are thought to lower blood

pressure by enhancing endothelial function, modulating baroreceptor sensitivity, and increasing antioxidant activity (48, 49). Furthermore, the "Rice-vegetable-fruit" pattern features rice as the primary staple. While a prospective cohort study conducted in China reported an inverse association between rice intake and the risk of future cardiovascular events (45), a meta-analysis found no significant association between white rice consumption and specific chronic conditions (50). The association between rice intake, hypertension, and cardiovascular events requires further investigation. Moreover, while the role of red meat in hypertension has been emphasized, the "Rice-vegetable-fruit" pattern includes higher pork intake. Possible explanations for this contradiction include: (1) the BP-lowering effects of vegetables and fruits may counteract the impact of pork; (2) studies have shown a U-shaped relationship between red meat intake and new-onset hypertension, with the risk increasing beyond a certain threshold (51). The amount of pork intake may thus influence its effect on hypertension. Additionally, inconsistent findings have been reported. A community-based nationwide study conducted in Eastern China identified a "Rice-vegetable" dietary pattern, characterized by high consumption of vegetables, rice and rice products, and aquatic products, but did not find an association with hypertension. The study suggested that the potential antihypertensive benefits of vegetable consumption could be counterbalanced by the adverse effects of polished rice, oil, and salt commonly used in stir-frying vegetables in Chinese cuisine (52). These discrepancies may arise from differences in cooking methods or the ingredients themselves, suggesting the need for further research to clarify their impact.

Our study found that the 'Dairy products' pattern was associated with a lower risk of hypertension among Tibetan residents. The Tibetan ethnicity, which evolved from a nomadic heritage, continues the habitual consumption of dairy products. These dairy products commonly include yogurt, whole-fat milk, cheese, and butter residue, with yogurt being the most frequently consumed item. Recent meta-analyses have shown that total dairy consumption is associated with a lower risk of hypertension, especially low-fat dairy and milk, while yogurt is more strongly linked to a reduced risk of diabetes and overweight or obesity (44). The BP-lowering effects of dairy consumption have been attributed to several components, including calcium, vitamin D, magnesium, potassium, and whey protein, which may regulate BP by enhancing insulin sensitivity, promoting renal sodium excretion, lowering intracellular calcium concentrations, and increasing nitric oxide synthesis (53–55). Additionally, yogurt, which is rich in probiotics, has been shown to lower cholesterol levels and inhibit angiotensin-converting enzyme, thereby contributing to reduced BP (56). In line with our study results, Ruan and colleagues conducted a dietary survey in Diqing of Yunnan Province, southwest China, involving Han and multi-ethnic populations, and found that a "Grassland healthy" dietary pattern, characterized by a relatively high intake of yogurt, soy products, and eggs, was associated with a lower risk of hypertension (14).

There are some limitations to this study. First, the survey sample was restricted to Luhuo County in Ganzi Tibetan Autonomous Prefecture, Sichuan Province; therefore, the research results may not be generalizable of all Tibetan populations. Second, the cross-sectional design of the study limits the ability to establish a causal relationship between dietary patterns and hypertension. Third, the findings are based on self-reported dietary information, which may be subject to recall bias. Lastly, the study did not differentiate between processed and unprocessed red meat consumption, which limits the in-depth analysis of potential mechanisms by which red meat might affect hypertension.

5 Conclusion

In summary, our study identified three primary dietary patterns among the Tibetan population: the "Tsamba-red meat-tuber," the "Rice-vegetable-fruit," and the "Dairy products" pattern. The "Tsamba-red meat-tuber" pattern is associated with a higher risk of hypertension, whereas the "Rice-vegetable-fruit" and "Dairy products" patterns are associated with a lower risk of hypertension in this population. This study provides a theoretical foundation for developing dietary strategies aimed at preventing and managing hypertension among Tibetans, with a particular focus on the Garze Tibetan Autonomous Prefecture in Sichuan Province. Future prospective studies are still needed to establish the causality between these dietary patterns and hypertension.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics committee of West China Hospital, Sichuan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XL: Writing – original draft, Writing – review & editing. XZ: Writing – original draft, Writing – review & editing. QG: Data curation, Investigation, Writing – review & editing. QM: Investigation, Methodology, Writing – review & editing. XC: Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1534915/full#supplementary-material

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Interactive effect between Selenium and Vitamin C levels on risk of hypertension among adult women in the United States: evidence from NHANES 2011 to 2020

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Background: Hypertension poses an imperative global health risk, affecting over 1 billion people and contributing to cardiovascular disease, especially for women. While previous studies suggest micronutrients such as Vitamin C or Selenium can help reduce blood pressure, research on their interactive effects remains limited.

Methods: This cross-sectional study analyzed data from 9,343 women aged 20 years and older in NHANES (2011–2020). Logistic regression analysis was conducted to evaluate the effect of each micronutrient on hypertension. To account for potential interactions between micronutrients, we calculated the relative excess risk due to interaction, which assessed their combined effect on hypertension.

Results: We confirmed the individual associations of Vitamin C and Selenium with hypertension, showing significant negative correlations ($p < 0.05$). Participants were then divided into four groups, and those with high intakes of both Vitamin C and Selenium had a significantly lower risk of hypertension ($p < 0.05$), supporting the association between the combined intake of these nutrients and lower hypertension risk, though no synergistic effect was observed.

Conclusion: The findings support the combined intake of Vitamin C and Selenium in hypertension prevention, broadening thoughts on the level of nutrition for the treatment of hypertension. These results suggest a potential association between adequate supplementation of Vitamin C and Selenium and lower blood pressure. However, further rigorous clinical studies are essential to validate and strengthen these findings.

KEYWORDS

Selenium, Vitamin C, hypertension, women, NHANES

Introduction

Hypertension has been a significant global health challenge for human, affecting approximately 1.39 billion individuals worldwide, it is also the leading modifiable risk factor for cardiovascular disease and early mortality (1). Furthermore, hypertension is the primary factor of death among all cardiovascular disease risk factors. Meanwhile, it is a major contributor to the exacerbation of kidney failure (2, 3). Additionally, hypertension increases

the risk of heart disease and stroke, which ranked as the first and fifth leading causes of death in the United States for 2017 (4). Therefore, the adverse consequences of hypertension are notably multifaceted.

Previous research provides substantial evidence on the serious impacts of hypertension. As shown in Table 1, the prevalence of hypertension in the United States varies by age group and gender, with elderly women (aged 65 and above) having a higher prevalence of hypertension, highlighting the importance of early prevention (5). Furthermore, a cohort study found that hypertension and changes in blood pressure during early adulthood were linked to differences in brain volume and white matter in later life, which are associated with neurodegeneration and dementia (6). These results highlight the importance of preventing and managing hypertension in early adulthood.

Beyond the significant health implications, hypertension also imposes substantial economic burdens. Compared to normotensive individuals, those with hypertension had approximately 2.5 times the inpatient cost, nearly twice the outpatient cost, and almost triple the prescription medication expenditure (7). Additionally, women may face mounting disease and economic burdens due to hypertension, emphasizing the significance of research in the prevention of this disease.

Studies have shown that certain nutrients can promote the management of hypertension. A re-analysis of National Health and Nutrition Examination Survey (NHANES) data revealed that higher Vitamin E intake was significantly associated with a lower prevalence of hypertension, and another systematic review found that Vitamin D concentration was inversely associated with systolic blood pressure (8, 9). Also, some studies emphasize the importance of Selenium and Vitamin C in preventing hypertension individually. Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin, which can be obtained either through diet or dietary supplements (10). A meta-analysis has shown that Vitamin C supplementation has significantly reduced blood pressure in subjects with essential hypertension (11). As for Selenium, it is a nutrient, which is essential for the normal functioning of the immune system (12). Furthermore, as a component of glutathione peroxidase, Selenium is a key enzyme in the body's antioxidant defense system (13). For example, glutathione peroxidase helps maintain nitric oxide in its reduced form and protects against oxidative stress, which suggests that Selenium deficiency could increase the risk of cardiovascular disease (14). On the other hand, dietary Selenium intake has a linear negative correlation with hypertension prevalence in adults (15).

Despite studies exploring the individual effects of these micronutrients, there is a dearth of the interaction of diverse nutrients.

TABLE 1 Prevalence of hypertension in adults aged ≥20 years from NHANES 2011–2014.

Age group	Male	Female	Difference
20–34	10.7%	7.8%	−2.9%
35–44	23.1%	22.8%	−0.3%
45–54	36.1%	33.2%	−2.9%
55–64	57.6%	55.5%	−2.1%
65–74	63.6%	65.8%	2.2%
≥75	73.4%	81.2%	7.8%

This study aims to address the existing research gap by analyzing the interactive effects of Vitamin C and Selenium intake on hypertension and exploring the potential mechanisms among women aged 20 and above. The purpose of our study is twofold. We seek to validate the independent effects of these micronutrients and analyze their interactions, eventually providing new insights to guide nutritional strategies for hypertension prevention.

Methods

Study design

This research is a cross-sectional study utilizing data from NHANES, spanning from 2011 to 2020. NHANES, initiated in the early 1960s, is a long-standing research program aimed at evaluating the health and nutritional status of adults and children in the United States, enhancing the wider dissemination of perception of public health. The survey includes interviews that cover a range of topics, including demographic, socioeconomic, dietary factors, and health-related issues such as the history of hypertension and intake of trace elements (16). This extensive database indisputably provided imperative evidence to support our exploration of the interaction between Vitamin C and Selenium concerning hypertension in women.

Participants

As illustrated in Figure 1, we focused on women aged 20 years and older who had complete data for blood pressure measurements, dietary intake (including Vitamin C and Selenium), relevant demographic variables (age, race, education, and income), and behavioral factors (alcohol use, caffeine intake, sodium intake, and recreational activities). Exclusion criteria included missing or implausible dietary data and absence of valid blood pressure measurements, and 9,343 participants were retained for the final analysis.

Data collection

Blood pressure was measured using standardized procedures, and hypertension was determined if participants met at least one of the following criteria: (1) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, (2) told by a doctor or other health professional that have hypertension, and (3) current use of prescribed medicine for hypertension. Vitamin C, Selenium, caffeine, alcohol, and sodium were assessed by two days and determined by averaging the consumption of participants during this period.

Statistical analysis

We first conducted descriptive analyses to summarize participants' demographic and behavioral characteristics using proportions. To assess the individual associations of Vitamin C and Selenium intake with hypertension, we performed logistic regression with three

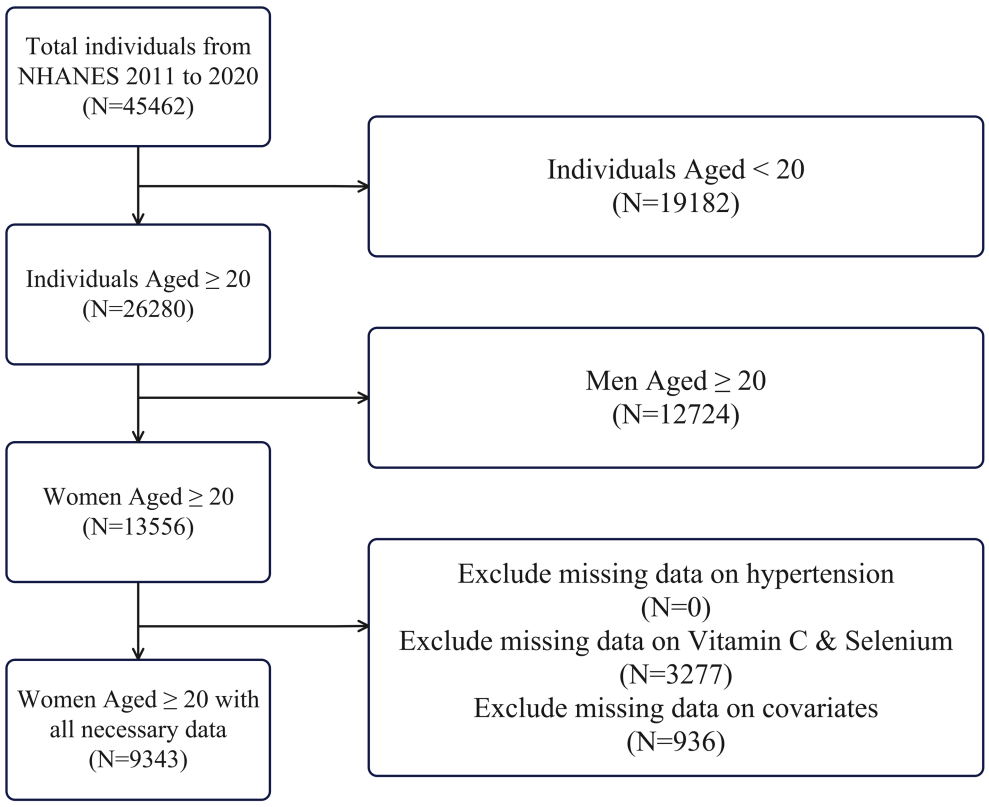

FIGURE 1
Flow process of participant selection.

models that incrementally adjusted for demographic variables (Model I), socioeconomic and behavioral variables (Model II), and dietary variables (Model III). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to quantify these associations. For the interaction analysis, participants were categorized into four groups based on whether their Vitamin C and Selenium intakes met the recommended dietary intake levels, and we calculated the relative excess risk due to interaction (RERI) to evaluate the combined effect of these micronutrients on hypertension. A *p*-value of less than 0.05 was considered statistically significant.

Results

Characteristics of participants

As indicated in Table 2, a total of 9,343 women aged 20 years and older were included in this study and divided into four groups based on whether their Vitamin C and Selenium intakes met the recommended: 75 mg/day of Vitamin C and 55 mg/day of Selenium for adult women, as outlined by the Dietary Reference Intakes from the Institute of Medicine, Food and Nutrition Board. Group 1 included women whose intakes of both Vitamin C and Selenium were below the recommended levels. Group 2 included those with Vitamin C intake above and Selenium intake below the recommended levels. Group 3 consisted of participants with Vitamin C intake below and Selenium intake above the recommended levels. Group 4 encompassed women whose intakes of both Vitamin C and Selenium were above the recommended levels.

After conducting a chi-square test, which is used to assess whether the distribution of a given categorical variable (e.g., age group, education level) differs significantly among the four groups (Group 1 to Group 4), we found that the demographic distribution was relatively balanced across different characteristics, as shown in Table 2, with the data rounded to two decimal places. For example, about 52.00% of participants were aged 50 years or younger. Regarding ethnicity, 39.24% of participants were Non-Hispanic White. In terms of education, 38.64% had up to a high school education.

Association of Vitamin C and Selenium individually with hypertension

The individual effects of Vitamin C and Selenium on hypertension serve as a critical foundation for our investigation of their interaction. First, we validated previous research on the independent relationships between hypertension and Vitamin C, as well as Selenium, using participants' data. The results were consistent with the prior findings that Vitamin C and Selenium have positive effects on preventing hypertension for the percentage of hypertension by quartiles of each nutrient exhibits a negative correlation, as shown in Figure 2.

Table 3 presents the results of the logistic regression analysis for these independent relationships. It shows that in all three models, both Vitamin C and Selenium had *p*-values below 0.05, indicating

TABLE 2 Weighted characteristics of the participants.

Variable	Total *N* = 9,343	Group 1 *N* = 854	Group 2 *N* = 4,732	Group 3 *N* = 364	Group 4 *N* = 3,393	*p*-value
Age group (%)						**0.000**
≤50 years	4,858 (52.00)	401 (46.96)	2,553 (53.95)	154 (42.31)	1,750 (51.58)	
>50 years	4,485 (48.00)	453 (53.04)	2,179 (46.05)	210 (57.69)	1,643 (48.42)	
Race (%)						**0.000**
Non-Hispanic White	3,666 (39.24)	365 (42.74)	2,013 (42.54)	121 (33.24)	1,167 (34.39)	
Others	5,677 (60.76)	489 (57.26)	2,719 (57.46)	243 (66.76)	2,226 (65.61)	
Education level						**0.000**
Less than high school	1,635 (17.50)	217 (25.41)	809 (17.10)	75 (20.60)	534 (15.74)	
High school	1,975 (21.14)	208 (24.36)	1,111 (23.48)	72 (19.78)	584 (17.21)	
More than high school	5,733 (61.36)	429 (50.23)	2,812 (59.43)	217 (59.62)	2,275 (67.05)	
Recreational activities (%)						**0.000**
Yes	3,918 (41.94)	308 (36.07)	1,823 (38.52)	156 (42.86)	1,631 (48.07)	
No	5,425 (58.06)	546 (63.93)	2,909 (61.48)	208 (57.14)	1,762 (51.93)	
Income (%)						**0.000**
<5	7,730 (82.74)	757 (88.64)	3,971 (83.92)	315 (86.54)	2,687 (79.19)	
≥5	1,613 (17.26)	97 (11.36)	761 (16.08)	49 (13.46)	706 (20.81)	
Alcohol (%)						**0.000**
<5	7,534 (80.64)	730 (85.48)	3,801 (80.33)	309 (84.89)	2,694 (79.40)	
≥5	1,809 (19.36)	124 (14.52)	931 (19.67)	55 (15.11)	699 (20.60)	
Caffeine (%)						**0.000**
<120	5,804 (62.12)	556 (65.11)	2,730 (57.69)	281 (77.20)	2,237 (65.93)	
≥120	3,539 (37.88)	298 (34.89)	2,002 (42.31)	83 (22.80)	1,156 (34.07)	
Sodium (%)						**0.000**
<3,000	5,417 (57.98)	835 (97.78)	2,601 (54.97)	353 (96.98)	1,628 (47.98)	
≥3,000	3,926 (42.02)	19 (2.22)	2,131 (45.03)	11 (3.02)	1,765 (52.02)	

Bold values indicate statistical significance.

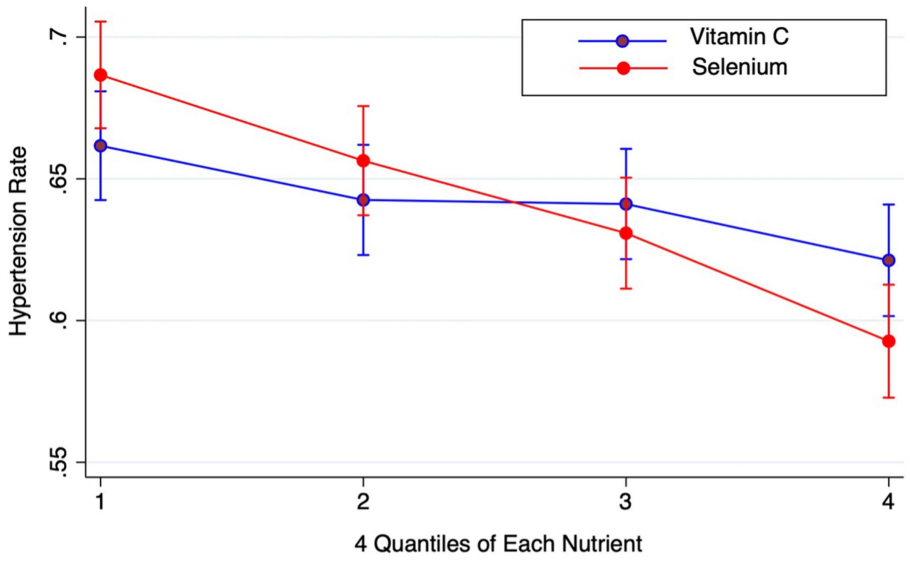

FIGURE 2
Hypertension rate by quartiles.

TABLE 3 Association of Vitamin C and Selenium individually with hypertension.

	Model I			Model II			Model III		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Vitamin C	0.999	0.998,0.999	**0.000**	0.999	0.998, 1.000	**0.001**	0.999	0.998, 0.999	**0.000**
Selenium	0.999	0.997,1.000	**0.006**	0.999	0.998, 1.000	**0.033**	0.998	0.997, 1.000	**0.025**

Model I: adjusted for age, race.
Model II: adjusted for recreational activities, education level, income on the base of Model I.
Model III: adjusted for alcohol, caffeine, sodium on the base of Model II.
Bold values indicate statistical significance.

statistically significant associations with hypertension. Additionally, the odds ratios suggest a slight negative correlation between these two nutrients and hypertension.

Association between the interaction of Vitamin C and Selenium with hypertension

To analyze the interactive effect of Vitamin C and Selenium with hypertension, we categorized participants into four groups based on the recommended intake levels of these two nutrients. The interaction between these groupings and hypertension was then analyzed using the RERI method, with the results shown in Table 4.

Notably, the *p*-value for Group 4 is well below 0.05, indicating that the result is statistically significant, which provides statistical support for the role of combined Vitamin C and Selenium intake in association with a lower risk of hypertension. However, from the perspective of excess relative risk (ERR), the value for Group 4 is close to −0.1, indicating that when both Vitamin C and Selenium intake exceed the recommended levels, the effect of their combined intake could be less beneficial or even worse than the individual intake of each nutrient concurrently.

TABLE 4 Interactive analysis.

	ERR	EIM Std.err.	95% CI	*p*-value
Group 2	0.080	0. 043	−0.000,0.167	0.051
Group 3	−0.043	0.025	−0.091,0.006	0.085
Group 4	−0.100	0.024	−0.147,-0.051	**0.000**

Group 2: Vitamin C intake is above the recommended value, Selenium intake is below the recommended value.
Group 3: Vitamin C intake is below the recommended value, Selenium intake is above the recommended value.
Group 4: Vitamin C intake is above the recommended value, Selenium intake is above the recommended value.

Discussion

While previous studies have examined the independent effects of Vitamin C and Selenium on cardiovascular health, there has been limited research on investigating their combined interaction effect on hypertension. This study aims to bridge this research gap by analyzing how the interaction of Vitamin C and Selenium intake affects hypertension among women in the United States using NHANES data from 2011 to 2020.

This research demonstrates that women with Vitamin C and Selenium intake individually showed significantly lower risk of developing hypertension compared to those with deficient intake of the nutrients. The result notably supports previous studies on the correlation between the intake of Vitamin C and Selenium on hypertension separately. Furthermore, it articulates that the interaction of Vitamin C and Selenium is associated with lower blood pressure among women in the United States, although no synergistic effect was observed and its causation cannot be definitively established.

Our findings both support and extend previous research on the role of Selenium in human health, which received less attention compared to Vitamin C. In the early 1990s, research showed that there is an association between serum Selenium levels and cardiovascular disease in populations that exhibit low Selenium concentrations (17). A study in 2007 found that consuming more foods rich in Selenium could have positive effects on human health, especially cancer prevention (18). In 2012, a study on Selenium and human health found that when Selenium is integrated into selenoproteins, it exerts a variety of pleiotropic effects, including antioxidant and anti-inflammatory actions, as well as the production of active thyroid hormones (19).

Nevertheless, most of the studies reviewed the relationship between Selenium consumption and human health. The interaction of other nutrients and their mechanisms still needs to be further explored. For example, a previous study concluded that the elevated blood pressure and higher prevalence of hypertension at high Selenium levels observed in the NHANES 2003–2004 study align with earlier research (20). It is important to note that high Selenium levels can have toxic effects, potentially leading to adverse health outcomes including selenosis, gastrointestinal disorders, and neurological complications which highlights the complexity of its role in human health (21). The interaction between diverse nutrients and Selenium on specific diseases still lacks enough attention from scholars, which remains an area that requires further accelerated expedition in the future.

Several limitations should be considered when interpreting these results. From the perspective of data transparency, this study obtained data from NHANES between 2011 and 2020, which consists of unilateral state samples, with certain demographic groups or geographic regions are underrepresented or excluded from the survey, potentially causing a dearth of validation and pervasiveness worldwide. In addition, the accuracy and reliability of some self-reported data like health behaviors, dietary intake, and blood pressure in NHANES may be affected by recall bias or social desirability bias,

which could lead to misclassification or underestimation of the true associations between nutrients and hypertension. Moreover, the use of cross-sectional data from NHANES restricts the ability to establish causal relationships between the intake of Vitamin C and Selenium and hypertension among the life course population in the United States, making infants, children, and adolescents neglected. Furthermore, while the large sample size provides statistical power, it may also detect very small effects that, although statistically significant, might not be clinically meaningful or could be due to chance rather than true associations.

Conclusion

In conclusion, our findings provide evidence that the combination of adequate Vitamin C and Selenium intake is associated with lower hypertension risk among U.S. women, suggesting that considering nutrient interactions, may be crucial for understanding and managing hypertension. This highlights the need for a more comprehensive approach to studying nutrient interactions in disease prevention, including their potential synergistic or antagonistic effects.

Future research should focus on longitudinal studies to validate these results and explore the underlying mechanisms of interacted effect between these nutrients and hypertension. Such studies would also benefit from including diverse populations to enhance the generalizability of the findings and provide clearer guidelines for hypertension prevention through nutrition.

Data availability statement

The original data presented in the study can be found at https://wwwn.cdc.gov/nchs/nhanes.

Ethics statement

Ethical review and approval were obtained from the Duke Kunshan University Institutional Review Board (No. FWA00021580) under protocol number 2024DW189. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

DW: Writing – original draft, Writing – review & editing. PF: Writing – original draft, Writing – review & editing. SC: Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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A retrospective cohort study of H-type hypertension and its influence on the prognostic effect in patients with non-dialysis CKD

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Background: The study aimed to investigate the impact of coexistence of hyperhomocysteinemia (HHcy) and hypertension (HTN), referred to as H-type hypertension on kidney outcomes and major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with non-dialysis chronic kidney disease (CKD).

Methods: This retrospective study enrolled 2,558 non-dialysis CKD patients admitted to two medical centers in China between 2010 and 2022. The participants were divided into four groups according to baseline blood pressure and homocysteine levels: (1) normotension with normohomocysteinemia; (2) normotension with HHcy; (3) hypertension with normohomocysteinemia; and (4) H-type hypertension. Cox regression model was applied to assess the relationship between these groups and renal outcomes/MACCEs. Mediation analysis was performed to assess the influence of HHcy on the link between hypertension and the outcomes.

Results: Three hundred and eighty renal endpoint events and 211 MACCEs were recorded. The H-type hypertension group demonstrated higher incidence of renal events (age-adjusted incidence: 83.71/1,000 person-years vs. 24.50/1,000 person-years) and MACCEs (age-adjusted incidence: 41.28/1,000 person-years vs. 17.21/1,000 person-years) compared to the normotension with normohomocysteinemia group. After adjusting for confounders, H-type hypertension independently elevated the risk of kidney outcomes by 312% (HR = 4.12, 95% CI: 2.66–6.37) and MACCEs by 127% (HR = 2.27, 95% CI: 1.28–4.02). No statistically significant mediated effect of HHcy on the relationship between hypertension and renal outcomes or MACCEs was observed.

Conclusion: H-type hypertension is associated with renal deterioration and cardiovascular events in non-dialysis CKD patients, early detections of H-type hypertension are essential to enhancing the prognosis for CKD patients.

KEYWORDS

CKD, hyperhomocysteinemia, H-type hypertension, prognosis, MACCEs

1 Introduction

Chronic kidney disease (CKD) is a prevalent chronic medical condition, and its burden on healthcare systems has intensified with the aging population. It is estimated that CKD affects 9.1% (8.5–9.8%) of the global adults (1), with over 100 million cases in China (2). Cardiovascular disease (CVD) remains the primary cause of poor prognosis among CKD patients (3). The elevated incidence of traditional and non-traditional cardiovascular risk factors contributes to the development of CVD in CKD patients. Previous studies have linked age, hypertension (HTN), diabetes, and dyslipidemia with renal deterioration (4). Furthermore, research into the pathogenesis of atherosclerotic cardiovascular events has highlighted hyperhomocysteinemia (HHcy) as a non-traditional risk factor for CVD (5), but the effect of HHcy in CKD patients was unclear. Identifying risk factors beyond hypertension is crucial to determining high-risk groups for adverse CKD outcomes.

As a sulfur-containing amino acid, plasma homocysteine (Hcy) levels exceeding 15 μmol/L are classified as HHcy. In China, a country without folate fortification policy and with differences in dietary patterns, the prevalence of HHcy in CKD patients reaches 52.78% (6), notably higher than in general population, and increases with advancing CKD stage. A prospective study by Ninomiya demonstrated that individuals with plasma Hcy levels in the highest tertile had a higher incidence of CKD compared to those in the lowest tertile (7). Previous researches have shown that HHcy linked to an elevated risk of cardiovascular atherosclerosis (8). In CKD patients, HHcy has been implicated in renal arteriosclerosis and declining glomerular filtration rates (GFR) (9). In addition to its role in renal outcomes, HHcy has been implicated in the pathogenesis of cerebrovascular events. For example, a recent retrospective cohort study demonstrated that elevated plasma Hcy levels were associated with an increased risk of ischemic stroke in hypertensive patients with obstructive sleep apnea (10). Furthermore, elevated serum homocysteine levels have been identified as a marker of CVD in individuals with end-stage renal disease (ESRD) or stable chronic kidney transplants (11, 12). However, the relationship between HHcy and CVD in CKD patients remains controversial, as studies by Suliman (13) and Kalantar-Zadeh (14) have reported conflicting findings, showing an inverse relationship between Hcy and cardiovascular mortality in ESRD patients.

The co-occurrence of hypertension and HHcy, known as H-type hypertension (HTH), has been observed in 44.14% of CKD patients (15). Compared to isolated HHcy or hypertension, patients with H-type hypertension were at a significantly greater risk of adverse cerebrovascular and cardiovascular events (16). Our previous study has demonstrated a link between H-type hypertension and carotid intima-media thickening, left ventricular hypertrophy, and elevated proteinuria levels in CKD patients (15). However, most of the evidence on the combined effect of homocysteine and hypertension comes from cross-sectional studies, primarily focusing on western populations, with limited prognostic data on CKD patients with H-type hypertension in China. Given the high incidence of CVD and the association between H-type hypertension and various organ damage in CKD patients, further investigation into the long-term prognosis is warranted. In this study, we enrolled non-dialysis CKD patients, measured baseline plasma Hcy levels, and evaluated the prognostic impact of H-type hypertension on renal outcomes and cardiovascular events in CKD patients.

2 Methods

2.1 Study design and participants

This retrospective study was conducted in the nephrology department of two large tertiary hospitals in Guangdong Province, China. The inclusion criteria comprised CKD patients diagnosed between August 2010 and December 2022 who met the following conditions: (i) diagnosis of non-dialysis CKD as per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and no history of kidney transplantation; and (ii) aged 18–75 years. Exclusion criteria included pregnancy, HIV infection, malignancy, acute kidney injury (defined as a ≥ 30% reduction in estimated glomerular filtration rate [eGFR] within 3 months), patients undergoing high-dose corticosteroid therapy (≥0.5 mg/kg/d), and those with a history of severe cardiovascular conditions (myocardial infarction, atrial fibrillation, heart failure, stroke). Patients with incomplete or invalid follow-up data (i.e., those who reached endpoints or were lost to follow-up within the first 6 months) were also excluded. All patients meeting the inclusion criteria were consecutively enrolled, without stratification or matching, to reflect the characteristics of a real-world clinical population. The study received approval from the local ethics committees. Informed consent was obtained from all participants in compliance with the Declaration of Helsinki.

2.2 Data collection

Clinical data were collected at the first admission within 48 h from medical records, including demographics (age, sex, smoking, alcohol consumption, body mass index [BMI]), primary glomerulonephritis, comorbidities (identified by prior International Classification of Diseases [ICD] code without time limit), medications (antihypertensive drugs and folate intake), clinic blood pressure, and laboratory parameters (homocysteine, hemoglobin, serum albumin, urea, creatinine, uric acid, calcium-phosphorus product, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], intact parathyroid hormone [iPTH], 24-h proteinuria). Diabetes mellitus was defined according to pre-existing diagnosis documented in electronic health records (EHRs) using ICD-10-CM codes: E10, E11, E12, E13, E14, G59.0, G63.2, H28.0, H36.0, M14.2, N08.3, O24, P70.2, T38.3, Y42.3, and Z88.825. Antihypertensive medications included pre-admission drugs or those prescribed during hospitalization as clinically indicated, which included calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α-blockers, and β-blockers. Folate was confirmed through either EHR documentation or self-reported medication histories prior to study enrollment or those prescribed during hospitalization as clinically indicated. Blood pressure measurement was conducted by trained nurses using validated oscillometric device with appropriately sized cuffs. Blood pressure was recorded on three separate occasions, spaced 1–2 min apart, and the average was calculated for analysis. Hyperhomocysteinemia was characterized by plasma Hcy concentration >15 μmol/L (15). Hypertension was characterized by blood pressure ≥140/90 mmHg. Based on blood pressure and plasma homocysteine levels, the cohort was divided into four groups: (1) normotension (NT) with normohomocysteinemia

(NHcy); (2) normotension with HHcy; (3) hypertension with normohomocysteinemia; and (4) H-type hypertension, characterized by both hypertension and hyperhomocysteinemia.

2.3 Outcome ascertainment

The primary clinical endpoint was renal outcomes, which included a ≥50% decline in baseline eGFR, a doubling of serum creatinine, or the commencement of renal replacement therapy (peritoneal dialysis, hemodialysis, or kidney transplantation). Major adverse cardiovascular and cerebrovascular events encompassed cardiovascular mortality, non-fatal acute coronary syndrome (unstable angina and myocardial infarction), non-fatal stroke (including hemorrhagic and ischemic), new-onset heart failure, vascular reconstruction, and peripheral vascular disease, as outlined in previous research (17). Deaths were verified through medical records and family reports. Follow-up occurred every 6 months via telephone interviews or regular clinic visits, and follow-up duration was determined from the initial admission date to the occurrence of any endpoint. For individuals not reaching an endpoint, follow-up was calculated until the most recent visit before May 2024.

2.4 Statistical analysis

The Shapiro–Wilk test was used to evaluate the normality of the data. Continuous variables followed a normal distribution were expressed as mean ± standard deviation (SD) and analyzed through the Student's t-test. For continuous variables that were not normally distributed, results were presented as median along with the 25th and 75th interquartile ranges (IQR), with the Mann–Whitney U test employed for between-group comparisons. Differences in categorical variables were assessed using the Chi-square test or Fisher's exact test. Multiple imputation (MI) was applied to address missing data when the proportion of missing values was below 20%; variables with a missing rate exceeding 20% were excluded. Little's test was used to assess whether the missing data were missing completely at random (MCAR). The comparison between pre- and post-interpolation was assessed using the Wilcoxon rank-sum test. Supplementary Table 1 showed the missingness report of our study, and we observed a consistent data distribution pattern both pre- and post-interpolation. Incidence rates, both crude and adjusted for age or sex, were calculated per 1,000 person-years. Kaplan–Meier survival curves and log-rank tests were used to analyze the cumulative risk differences among four groups, evaluating the impact of hypertension and hyperhomocysteinemia on prognosis. Directed acyclic graph (DAG) was employed to illustrate the relationship between outcomes and groups (Supplementary Figure 1). Multicollinearity was assessed using the variance inflation factor (VIF). Subsequently, univariate cox analysis was performed, and variables with p-values <0.05 and clinical relevance were selected for the multivariate cox regression model. Schoenfeld residuals were utilized to evaluate the proportional hazards assumption, and covariates that violated this assumption were subsequently modeled as time-dependent covariates. Hazard ratios (HR) and 95% confidence intervals (CI) were determined through cox regression models, using normal homocysteine level and blood pressure as reference group. Covariates in the model included sex, age, BMI, smoking, alcohol consumption, diabetes, 24-h proteinuria, hemoglobin, albumin, calcium-phosphate product, creatinine, uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and iPTH. Separate univariate and multivariate cox regression analyses were conducted for populations with hypertension and normotension using homocysteine levels (per 1 SD) as continuous predictor. Additionally, sensitivity analysis-multivariate cox regression analysis of end point events according to Hyperhomocysteinemia/Hypertension groups was conducted in the complete case dataset.

Subgroup analyses were performed based on sex, diabetes, smoking, alcohol consumption, BMI (categorized as <24 kg/m^2, 24–28 kg/m^2, or ≥28 kg/m^2), antihypertensive drugs or folate use, and eGFR (categorized as >60 mL/min/1.73 m^2 or ≤60 mL/min/1.73 m^2) to determine if demographic characteristics, lifestyle behaviors, and health conditions of CKD patients influenced the relationship between predictors and clinical outcomes. Interaction terms for the predictors and stratified variables were incorporated into the model, and the likelihood ratio test was utilized to evaluate the statistical significance of these interactions. The Benjamini–Hochberg procedure was applied to control the false discovery rate (FDR) in multiple hypothesis testing.

Mediation analysis was conducted to calculate the proportion of the effect of hypertension on outcomes mediated by hyperhomocysteinemia by comparing models with and without the proposed mediator (18). We performed 500 bootstrap resamples to compute bias-corrected 95% confidence intervals (CIs) for mediated proportion by the R package "mediation."

To address potential selection bias and strengthen the robustness of the retrospective study, propensity score matching (PSM) analysis was conducted using a caliper of 0.05. "Nearest neighbor" matching model was performed to compare H-type hypertension with non-H-type hypertension and HHcy/HTN with NHcy/HTN groups in 1:1 ratio. Covariates for matching included sex, age, BMI, diabetes, smoking status, alcohol consumption, 24-h proteinuria, hemoglobin, albumin, calcium-phosphorus product, uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and iPTH. Subsequently, cox regression models were utilized to evaluate the risks of adverse renal outcomes and MACCEs across the matched groups.

All statistical tests were two-tailed, with significance set at $p < 0.05$. All statistical analyses were conducted using RStudio software (version 1.1.423) and Prism 9 (GraphPad Software).

3 Results

3.1 Baseline characteristics of participants

Of the 3,841 registered patients, 701 were excluded based on baseline characteristics, and 582 were removed due to lack of follow-up data or events occurring within 6 months. Consequently, 2,558 patients were enrolled in the analysis (Figure 1). Table 1 showed the baseline characteristics of participants categorized by the presence of hyperhomocysteinemia and hypertension. The average age was 47.78 years, with 57.2% being male. A total of 580 patients (22.7%) had diabetes, 29.1% smoked, and 24% reported alcohol consumption.

The mean homocysteine level was 16.53 μmol/L (SD: 9.08). The prevalence of HHcy was 46.21% (1,182/2,558) among all participants and 54.32% (899/1,655) among those with

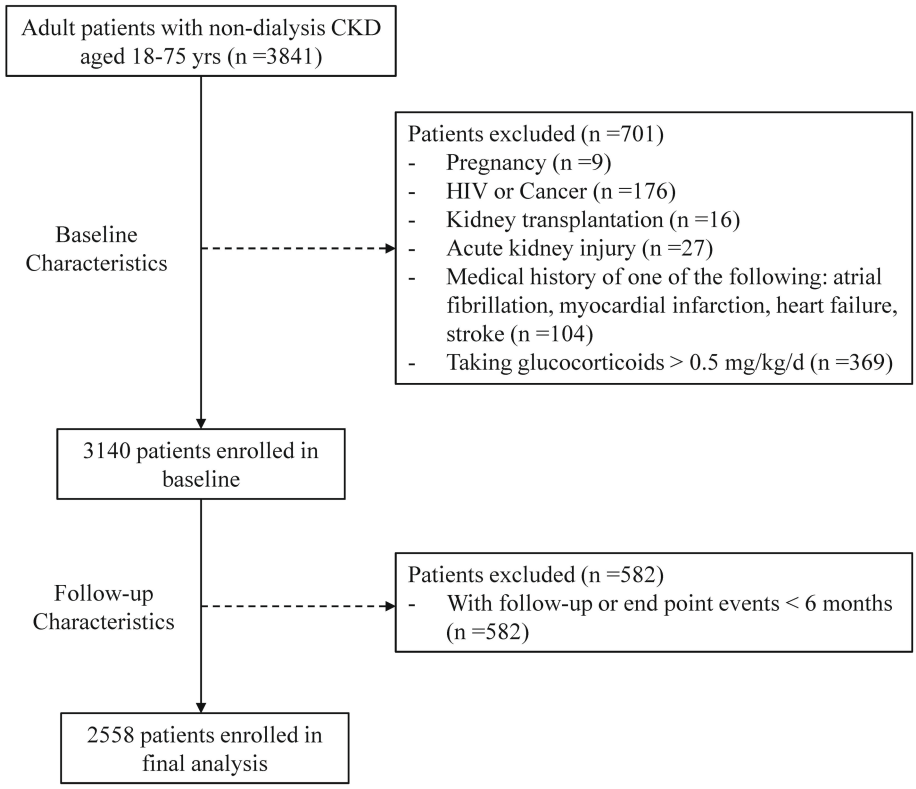

FIGURE 1
Enrollment of study population. CKD, chronic kidney disease; HIV, human immunodeficiency virus; AKI, acute kidney injury.

hypertension. Compared to the normotension with normohomocysteinemia group, individuals with H-type hypertension tended to be older, have a longer disease duration, a higher proportion of male, and were more likely to have diabetes, smoking, and consume alcohol. Additionally, the H-type hypertension group exhibited significantly higher levels of proteinuria, calcium-phosphate product, urea, serum creatinine, uric acid, triglycerides, and intact parathyroid hormone (iPTH), while showing lower levels of hemoglobin, total cholesterol, HDL-C, LDL-C, and eGFR.

3.2 H-type hypertension and prognosis

The median follow-up duration for renal outcomes and MACCEs was 42.17 months and 36.47 months, respectively. During follow-up, 380 renal outcomes and 211 MACCEs were recorded. Figure 2 illustrated the age- and sex-adjusted incidence rates per 1,000 person-years. Participants with H-type hypertension had markedly higher rates of renal events (83.71/1,000 person-years vs. 24.50/1,000 person-years) and MACCEs (41.28/1,000 person-years vs. 17.21/1,000 person-years) compared to those without hypertension or hyperhomocysteinemia. Kaplan–Meier survival analysis indicated that H-type hypertension was significantly associated with an elevated risk of both adverse renal outcomes (p value of log-rank test <0.001) and MACCEs (p value of log-rank test <0.001) (Figure 3). Subsequently, covariates for the multivariable cox regression analysis were selected based on significant associations identified in univariable cox regression analyses (Supplementary Table 2).

Table 2 detailed the unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for renal outcomes and MACCEs across groups. In the unadjusted model, the risks for renal outcomes and MACCEs in the H-type hypertension group were 7.60 (95% CI 5.10–11.33) and 4.81 (95% CI 2.83–8.17) times respectively, compared to the reference group. For kidney outcomes, the multivariable cox model included hemoglobin, serum creatinine, and intact parathyroid hormone as time-dependent covariates. After adjusting for covariates, H-type hypertension independently increased the risk of kidney outcomes by 312% (HR = 4.12, 95% CI: 2.66–6.37) and MACCEs by 127% (HR = 2.27, 95% CI: 1.28–4.02). The effect values were attenuated but remained significant after full adjustment. Notably, participants in the HHcy/NT group had a significantly elevated risk of renal outcomes (HR = 1.68, 95% CI: 1.00–2.91), whereas no significant difference was found for MACCEs (HR = 1.61, 95% CI: 0.80–3.22). The results of the sensitivity analysis indicate that the findings from the multivariate cox regression model before and after imputation are nearly consistent (Supplementary Table 3). In the adjusted model, every 1 SD rise in homocysteine levels corresponded to a 13% higher risk of renal outcomes (HR = 1.13, 95% CI: 1.03–1.25) among hypertensive CKD patients, while no significant association was found with MACCEs (HR = 1.10, 95% CI: 0.95–1.27). Among normotensive participants, no significant relationship between homocysteine levels and the outcomes was observed.

TABLE 1 Baseline characteristics of CKD patients with different blood pressure status and plasma homocysteine level.

	Total (*n* = 2,558)	Normotension and normohomocysteinemia (*n* = 620)	Normotension and hyperhomocysteinemia (*n* = 283)	Hypertension and normohomocysteinemia (*n* = 756)	H-type hypertension (*n* = 899)	*p* value
Sex: male (%)	1,463 (57.2)	264 (42.6)	207 (73.1)	390 (51.6)	602 (67.0)	<0.001
Age, yrs. (mean [SD])	47.78 (13.91)	40.84 (12.68)	46.33 (14.34)	49.03 (13.38)	51.96 (13.12)	<0.001
Course, mo (median [IQR])	8.00 [1.00, 36.00]	6.00 [1.00, 36.00]	7.00 [1.00, 36.00]	6.00 [1.00, 36.00]	12.00 [1.00, 36.00]	0.024
Composition of nephropathy						<0.001
Primary glomerulonephritis (%)	711 (27.8)	171 (27.6)	79 (27.9)	178 (23.5)	283 (31.5)	
IgA nephropathy (%)	512 (20.0)	161 (26.0)	63 (22.3)	143 (18.9)	145 (16.1)	
Membranous nephropathy (%)	188 (7.3)	53 (8.5)	14 (4.9)	96 (12.7)	25 (2.8)	
Minimal Change Disease (%)	84 (3.3)	39 (6.3)	9 (3.2)	28 (3.7)	8 (0.9)	
Focal Segmental Glomerulosclerosis (%)	59 (2.3)	19 (3.1)	4 (1.4)	18 (2.4)	18 (2.0)	
Diabetic nephropathy (%)	279 (10.9)	21 (3.4)	18 (6.4)	98 (13.0)	142 (15.8)	
Hypertensive nephropathy (%)	185 (7.2)	7 (1.1)	3 (1.1)	66 (8.7)	109 (12.1)	
Hyperuric acid nephropathy (%)	181 (7.1)	52 (8.4)	42 (14.8)	28 (3.7)	59 (6.6)	
Lupus nephritis (%)	57 (2.2)	18 (2.9)	7 (2.5)	17 (2.2)	15 (1.7)	
Polycystic Kidney Disease (%)	48 (1.9)	4 (0.6)	3 (1.1)	13 (1.7)	28 (3.1)	
Obstructive Nephropathy (%)	52 (2.0)	10 (1.6)	8 (2.8)	14 (1.9)	20 (2.2)	
Diabetes mellitus (%)	580 (22.7)	55 (8.9)	51 (18.0)	219 (29.0)	255 (28.4)	<0.001
Smoke (%)	745 (29.1)	115 (18.5)	102 (36.0)	194 (25.7)	334 (37.2)	<0.001
Alcohol (%)	613 (24.0)	114 (18.4)	65 (23.0)	186 (24.6)	248 (27.6)	0.001
Antihypertensive drugs						
Angiotensin-converting enzyme inhibitors (%)	113 (4.4)	5 (0.8)	1 (0.4)	71 (9.4)	36 (4.0)	<0.001
Angiotensin receptor blockers (%)	870 (34.0)	166 (26.8)	88 (31.1)	321 (42.5)	295 (32.8)	<0.001
Calcium channel blockers (%)	1,065 (41.6)	64 (10.3)	29 (10.2)	418 (55.3)	554 (61.6)	<0.001
β-blockers (%)	423 (16.5)	13 (2.1)	9 (3.2)	171 (22.6)	230 (25.6)	<0.001
α-blockers (%)	169 (6.6)	6 (1.0)	7 (2.5)	56 (7.4)	100 (11.1)	<0.001
Folate Tablets (%)	191 (7.5)	21 (3.4)	20 (7.1)	44 (5.8)	106 (11.8)	<0.001
BMI, kg/m^2 (median [IQR])	23.94 [21.53, 26.44]	22.56 [20.15, 25.61]	23.53 [21.12, 25.36]	24.34 [22.08, 26.83]	24.53 [22.23, 26.99]	<0.001
Clinic SBP, mm Hg (mean (SD))	137.04 (23.63)	119.76 (15.48)	124.88 (19.68)	142.31 (21.18)	148.36 (22.84)	<0.001
Clinic DBP, mm Hg (mean (SD))	86.11 (14.55)	78.57 (10.31)	79.76 (11.89)	88.76 (13.78)	91.08 (15.60)	<0.001
Proteinuria, g/24 h (median [IQR])	0.89 [0.22, 2.52]	0.55 [0.13, 1.74]	0.55 [0.15, 1.99]	0.82 [0.21, 2.72]	1.30 [0.42, 2.99]	<0.001

(Continued)

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TABLE 1 (Continued)

	Total (*n* = 2,558)	Normotension and normohomocysteinemia (*n* = 620)	Normotension and hyperhomocysteinemia (*n* = 283)	Hypertension and normohomocysteinemia (*n* = 756)	H-type hypertension (*n* = 899)	*p* value
Hemoglobin, g/L (mean (SD))	125.14 (25.18)	131.20 (21.66)	124.30 (25.41)	129.45 (24.06)	117.60 (26.34)	<0.001
Albumin, g/L (mean (SD))	37.63 (7.25)	37.69 (7.93)	38.80 (6.46)	37.00 (7.86)	37.75 (6.37)	0.004
Calcium*phosphate, mg^2/dL^2 (median [IQR])	2.41 [2.09, 2.90]	2.32 [2.02, 2.61]	2.49 [2.12, 3.10]	2.34 [2.06, 2.77]	2.59 [2.18, 3.13]	<0.001
Serum fasting glucose, mmol/L (mean (SD))	5.29 (1.91)	5.08 (2.20)	4.95 (1.54)	5.60 (2.08)	5.27 (1.58)	<0.001
Blood urea nitrogen, mmol/L (median [IQR])	6.40 [4.70, 10.46]	4.75 [3.90, 5.90]	7.40 [5.30, 12.04]	5.62 [4.45, 7.40]	10.10 [6.87, 15.54]	<0.001
Serum creatinine, μmol/L (median [IQR])	106.00 [75.00, 186.00]	74.00 [58.88, 95.93]	132.00 [95.00, 222.50]	88.25 [67.15, 120.10]	184.00 [120.00, 327.55]	<0.001
Uric acid, mmol/L (mean (SD))	437.71 (127.50)	382.40 (110.18)	474.07 (133.59)	414.60 (114.30)	483.84 (127.38)	<0.001
Total cholesterol, mmol/L (mean (SD))	5.17 (2.04)	5.36 (2.25)	4.78 (1.65)	5.54 (2.26)	4.86 (1.70)	<0.001
Triglyceride, mmol/L (median [IQR])	1.46 [1.01, 2.22]	1.22 [0.84, 1.88]	1.43 [1.02, 2.05]	1.58 [1.11, 2.40]	1.54 [1.10, 2.32]	<0.001
HDL-C, mmol/L (mean (SD))	1.18 (0.73)	1.34 (1.30)	1.09 (0.32)	1.20 (0.42)	1.07 (0.37)	<0.001
LDL-C, mmol/L (mean (SD))	3.08 (1.55)	3.26 (1.86)	2.83 (1.24)	3.29 (1.61)	2.85 (1.31)	<0.001
iPTH, pg/mL (median [IQR])	5.76 [3.72, 11.90]	4.46 [3.28, 6.41]	5.86 [3.66, 21.39]	5.20 [3.60, 9.39]	8.23 [4.81, 21.40]	<0.001
Homocysteine, μmol/L (mean (SD))	16.53 (9.08)	10.54 (2.54)	22.03 (9.89)	11.54 (3.14)	23.13 (9.61)	<0.001
eGFR, mL/min/1.73m^2 (mean (SD))	69.93 (86.78)	101.90 (38.39)	54.64 (36.23)	81.89 (39.41)	42.65 (130.64)	<0.001
Kidney outcomes (%)	380 (14.9)	27 (4.4)	29 (10.2)	96 (12.7)	228 (25.4)	<0.001
median follow-up, mo (SD)	42.17 (0.91)	45.97 (1.28)	36.50 (1.73)	48.00 (1.65)	36.50 (1.73)	–
MACCEs (%)	211 (8.2)	16 (2.6)	19 (6.7)	78 (10.3)	98 (10.9)	<0.001
median follow-up, mo (SD)	36.47 (0.77)	38.77 (1.34)	32.97 (1.58)	41.80 (1.68)	33.13 (0.98)	–

Data were presented by numbers (%) or mean or (SD) median (IQR).

SD, standard deviation; IQR, interquartile range; mo, month; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; iPTH, intact parathyroid hormone; eGFR, estimated glomerular filtration rate; MACCEs, major adverse cardiac and cerebrovascular events.

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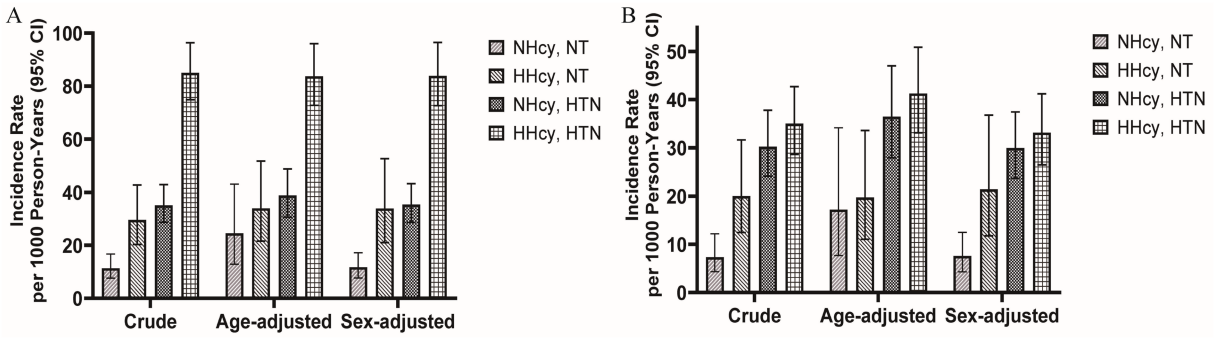

FIGURE 2
Age-adjusted and sex-adjusted incidence rates per 1,000 person-years with or without hyperhomocysteinemia/hypertension for **(A)** kidney outcomes and **(B)** MACCEs. MACCEs, major adverse cardiac and cerebrovascular events; NT, Normotension; NHcy, Normohomocysteinemia; HHcy, Hyperhomocysteinemia; HTN, Hypertension.

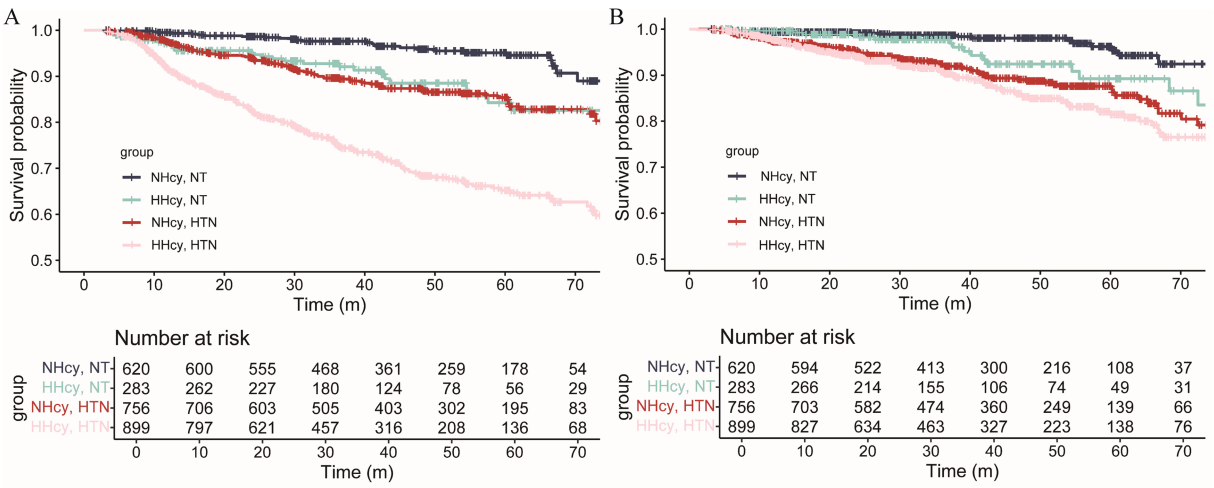

FIGURE 3
Survival curves of CKD patients with or without hyperhomocysteinemia/hypertension for **(A)** kidney outcomes and **(B)** MACCEs. The risk of kidney outcomes and MACCEs in the H-type hypertension group was significantly elevated (Log-rank test, $p < 0.001$). MACCEs, major adverse cardiac and cerebrovascular events; NT, Normotension; NHcy, Normohomocysteinemia; HHcy, Hyperhomocysteinemia; HTN, Hypertension.

3.3 Subgroup analysis

To examine the prognostic effects of H-type hypertension in different subgroups, Tables 3, 4 present the results of the subgroup analysis, stratified by demographic characteristics, health status, and medications. Significant interactions after adjusted by Benjamini–Hochberg procedure were found in alcohol consumption (yes vs. no). Regarding MACCEs, significant interactions were observed between diabetes (yes vs. no) with the association between H-type hypertension and MACCEs being stronger in the non-diabetic subgroups. These findings should be interpreted with caution due to imbalanced sample sizes and heterogeneous event rates across subgroups.

3.4 Mediation analysis

To calculate the mediated effect of HHcy, mediation analysis was performed. After adjusting for HHcy and other covariates, the hazard ratio for renal outcomes in the hypertensive group was 2.42 (95% CI: 1.80–3.26) compared to the normotensive group, and the HR for MACCEs was 1.82 (95% CI: 1.25–2.66). However, the mediation effect of HHcy on the outcomes was not statistically significant in either the hypertensive or normotensive groups.

3.5 PSM and clinical characteristics in CKD patients

Given the limited sample size and potential imbalance between groups, propensity score matching (PSM) was conducted. After PSM, 717 pairs of non-H-type hypertension and H-type hypertension patients, and 517 pairs of NHcy/HTN and HHcy/HTN patients, were included in the analysis (Supplementary Table 5). Histograms of matching pre- and post-propensity scores demonstrated the efficacy of PSM (Supplementary Figure 2). Covariates were balanced across groups following PSM, with standardized mean differences (SMDs)

TABLE 2 Incidence rates per 1,000 person-years and multivariate cox regression analysis of end point events according to hyperhomocysteinemia/hypertension groups.

	Cases/participants	Incidence rate per 1,000 person-years (95% CI)	HR (95% CI)	
			Univariate	Multivariate*
Kidney outcomes				
Groups:				
NHcy, NT	27/620	11.39 (7.67, 16.77)	Ref	Ref
HHcy, NT	29/283	29.64 (20.29, 42.84)	2.63 (1.55, 4.44)	1.68 (1.00, 2.91)
NHcy, HTN	96/756	35.32 (28.85, 43.15)	3.10 (2.02, 4.75)	2.43 (1.56, 3.79)
HHcy, HTN	228/899	85.55 (75.34, 96.97)	7.60 (5.1, 11.33)	4.12 (2.66, 6.37)
Hcy, per 1 SD:				
Total	380/2,558	43.31 (39.20, 47.84)	1.32 (1.26, 1.37)	1.13 (1.03, 1.25)
Hypertension	324/1,655	59.82 (53.73, 66.55)	1.28 (1.21, 1.35)	1.14 (1.03, 1.26)
Normotension	56/903	16.68 (12.74, 21.77)	1.58 (1.26, 1.97)	1.05 (0.72, 1.52)
MACCEs				
Groups:				
NHcy, NT	16/620	7.35 (4.35, 12.19)	Ref	Ref
HHcy, NT	19/283	20.00 (12.43, 31.66)	2.71 (1.39, 5.27)	1.61 (0.80, 3.22)
NHcy, HTN	78/756	30.26 (24.14, 37.81)	4.09 (2.39, 7.00)	2.38 (1.37, 4.14)
HHcy, HTN	98/899	35.02 (28.66, 42.69)	4.81 (2.83, 8.17)	2.27 (1.28, 4.02)
Hcy, per 1 SD:				
Total	211/2,558	24.81 (21.66, 28.40)	1.21 (1.09, 1.34)	1.10 (0.95, 1.27)
Hypertension	176/1,655	32.73 (28.22, 37.93)	1.15 (0.92, 1.29)	1.09 (0.93, 1.28)
Normotension	35/903	11.19 (7.93, 15.71)	1.42 (1.01, 2.01)	1.23 (0.86, 1.76)

Incidence rates per 1,000 person-years was calculated by the indirect method. *Multivariable model adjusted for sex, age, BMI, diabetes, smoking, alcohol consumption, proteinuria, hemoglobin, albumin, calcium-phosphorus product, serum creatinine, uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, intact parathyroid hormone. For kidney outcomes, the multivariable model included hemoglobin, serum creatinine, and intact parathyroid hormone as time-dependent covariates.
SD, standard deviation; Hcy, homocysteine; MACCEs, major adverse cardiac and cerebrovascular events; NT, Normotension; NHcy, Normohomocysteinemia; HHcy, Hyperhomocysteinemia; HTN, Hypertension.

below 0.10 (Supplementary Figure 3). Cox regression models showed that H-type hypertension remained an independent predictor for adverse renal outcomes (HR [95% CI]: H-type hypertension 1.94 [1.50, 2.52]; HHcy/HTN 1.47 [1.10, 1.96]) when compared to the reference. However, no significant difference in the risk of MACCEs was found between the H-type hypertension group and the control group (Supplementary Table 6).

4 Discussion

Our study was the first to demonstrate that participants with H-type hypertension experienced a significantly higher incidence of adverse renal outcomes and MACCEs compared to those without hypertension or hyperhomocysteinemia. Over a follow-up period of nearly 4 years, each standard deviation increased in homocysteine levels independently raised the risk of renal outcomes by 13% in CKD patients with hypertension. H-type hypertension was found to increase the risk of renal outcomes and MACCEs by 312 and 127%, respectively, in fully adjusted models. Mediation analysis revealed no significant intermediary effect of HHcy on renal outcomes or MACCEs. Overall, our findings suggested that H-type hypertension was a critical non-traditional risk factor contributing to poor prognosis in CKD patients.

Our research demonstrated a robust association between HHcy and a heightened risk of adverse renal outcomes in CKD patients. In the Chinese population, a high prevalence of methylenetetrahydrofolate reductase (MTHFR) polymorphisms (such as C677T and A1298C) and dietary deficiencies of folate and vitamin B are clinically important in the development of hyperhomocysteinemia and contribute to higher HHcy rates compared to western populations (19, 20). Various studies indicate that more than half of CKD patients exhibit HHcy (6). Among the general population (7), elderly individuals (21), and adults with diabetes (22) or hypertension (23), HHcy is a predictor of CKD onset and further deterioration of renal function. While previous prospective studies exploring the connection between HHcy and renal disease progression have yielded inconsistent results. For example, studies from Samuelsson (24) and Sarna (25) found no significant correlation between total Hcy levels and declining GFR in CKD patients. These discrepancies could be due to small sample sizes, ethnic differences, or varying national folate fortification policies. Nevertheless, HHcy remained a potentially modifiable risk factor, and appropriate folate supplementation should be considered for CKD patients with HHcy, but identifying HHcy in CKD patients remains a top priority.

Our research confirmed that H-type hypertension markedly raised the risk of kidney outcomes in CKD patients, with a higher risk

TABLE 3 Association between hyperhomocysteinemia/hypertension and risk of kidney outcomes by subgroups.[a]

	Cases/ participants	Normotension and normohomocysteinemia	Normotension and hyperhomocysteinemia	Hypertension and normohomocysteinemia	H-type hypertension	Adjusted *p* for interaction
Sex						0.280
Male	231/1,463	Ref	1.16 (0.57, 2.36)	1.42 (0.76, 2.63)	2.83 (1.58, 5.06)	
Female	149/1,095	Ref	2.25 (0.93, 5.41)	3.90 (2.06, 7.40)	4.56 (2.35, 8.87)	
Diabetes						0.265
No	250/1,978	Ref	2.64 (1.36, 5.10)	3.65 (2.12, 6.27)	5.80 (3.36, 9.99)	
Yes	130/580	Ref	0.39 (0.14, 1.10)	0.83 (0.37, 1.85)	1.40 (0.68, 2.90)	
Smoke						0.138
No	262/1,813	Ref	3.04 (1.60, 5.78)	3.63 (2.13, 6.17)	6.21 (3.70, 10.41)	
Yes	118/745	Ref	0.48 (0.18, 1.26)	0.80 (0.37, 1.77)	1.52 (0.76, 3.05)	
Alcohol						0.044
No	281/1,945	Ref	2.54 (1.38, 4.68)	3.16 (1.88, 5.31)	4.85 (2.88, 8.15)	
Yes	146/613	Ref	0.12 (0.02, 0.62)	0.74 (0.31, 1.78)	1.42 (0.64, 3.13)	
BMI						0.598
<24 kg/m^2	206/1,289	Ref	1.91 (0.93, 3.92)	2.83 (1.55, 5.17)	5.32 (2.97, 9.51)	
24–28 kg/m^2	117/901	Ref	1.66 (0.63, 4.37)	1.77 (0.79, 3.97)	2.57 (1.15, 5.76)	
≥28 kg/m^2	57/368	Ref	0.60 (0.06, 5.62)	1.68 (0.54, 5.25)	2.61 (0.84, 8.13)	
Antihypertensive drugs						0.054
No	57/790	Ref	1.19 (0.60, 2.38)	0.34 (0.07, 1.61)	0.99 (0.40, 2.45)	
Yes	323/1,768	Ref	1.50 (0.49, 4.56)	3.63 (1.57, 8.40)	6.32 (2.73, 14.65)	
Folate Tablets						0.598
No	297/2,367	Ref	1.59 (0.89, 2.85)	2.22 (1.39, 3.54)	3.86 (2.43, 6.11)	
Yes	83/191	Ref	4.27 (0.70, 26.01)	7.06 (1.40, 35.52)	6.00 (1.37, 26.25)	
eGFR						0.321
>60 mL/min/1.73 m^2	69/1,370	Ref	0.48 (0.10, 2.20)	2.46 (1.29, 4.68)	2.22 (0.94, 5.23)	
≤60 mL/min/1.73 m^2	311/1,188	Ref	0.87 (0.44, 1.71)	1.37 (0.74, 2.54)	1.73 (0.97, 3.08)	

[a]Cox proportional hazards models adjusted for sex, age, BMI, diabetes, smoking, alcohol consumption, proteinuria, hemoglobin, albumin, calcium-phosphorus product, serum creatinine, uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, intact parathyroid hormone. Each of the else groups were adjusted for all covariates expect itself. The *p*-value for the interaction was adjusted using the Benjamini–Hochberg procedure.
BMI, body mass index; eGFR, estimated glomerular filtration rate.

10.3389/fnut.2025.1554663

TABLE 4 Association between hyperhomocysteinemia/hypertension and risk of MACCEs by subgroups.[a]

	Cases/ participants	Normotension and normohomocysteinemia	Normotension and hyperhomocysteinemia	Hypertension and normohomocysteinemia	H-type hypertension	Adjusted *p* for interaction
Sex						0.774
Male	140/1,463	Ref	1.36 (0.55, 3.38)	2.48 (1.15, 5.31)	2.26 (1.05, 4.88)	
Female	71/1,095	Ref	2.68 (0.87, 8.20)	2.07 (0.91, 4.67)	2.44 (1.00, 6.00)	
Diabetes						0.010
No	121/1,978	Ref	2.73 (1.22, 6.12)	2.64 (1.30, 5.37)	2.67 (1.29, 5.51)	
Yes	90/580	Ref	0.17 (0.02, 1.47)	1.50 (0.62, 3.61)	1.19 (0.46, 3.04)	
Smoke						0.326
No	124/1,813	Ref	2.05 (0.87, 4.87)	2.47 (1.26, 4.84)	1.88 (0.91, 3.89)	
Yes	87/745	Ref	1.18 (0.36, 3.88)	1.94 (0.72, 5.22)	2.58 (0.97, 6.82)	
Alcohol						0.326
No	99/1,945	Ref	2.21 (1.01, 4.84)	2.42 (1.27, 4.61)	2.43 (1.24, 4.78)	
Yes	65/613	Ref	0.46 (0.08, 2.55)	2.07 (0.70, 6.12)	1.94 (0.66, 5.73)	
BMI						0.787
<24 kg/m^2	98/1,289	Ref	1.74 (0.67, 4.53)	2.71 (1.26, 5.81)	2.54 (1.14, 5.64)	
24–28 kg/m^2	77/901	Ref	0.70 (0.20, 2.42)	1.80 (0.73, 4.47)	1.36 (0.53, 3.44)	
≥28 kg/m^2	36/368	Ref	11.47 (1.14, 115.15)	5.87 (0.75, 46.18)	7.15 (0.87, 58.67)	
Antihypertensive drugs						0.326
No	37/790	Ref	2.36 (0.98, 5.68)	2.23 (0.72, 6.93)	0.96 (0.27, 3.42)	
Yes	174/1,768	Ref	1.36 (0.30, 6.22)	3.39 (1.06, 10.88)	3.28 (1.01, 10.65)	
Folate Tablets						0.461
No	187/2,367	Ref	1.70 (0.82, 3.51)	2.40 (1.35, 4.26)	2.53 (1.40, 4.58)	
Yes	24/191	Ref	0.84 (0.06, 11.38)	3.51 (0.32, 38.62)	0.90 (0.10, 8.03)	
eGFR						0.787
>60 mL/min/1.73 m^2	75/1,370	Ref	1.13 (0.35, 3.58)	2.15 (1.13, 4.10)	1.58 (0.67, 3.75)	
≤60 mL/min/1.73 m^2	136/1,188	Ref	1.91 (0.54, 6.81)	2.64 (0.79, 8.79)	2.49 (0.77, 8.09)	

[a]Cox proportional hazards models adjusted for sex, age, BMI, diabetes, smoking, alcohol consumption, proteinuria, hemoglobin, albumin, calcium-phosphorus product, serum creatinine, uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, intact parathyroid hormone. Each of the else groups were adjusted for all covariates expect itself. The *p*-value for the interaction was adjusted using the Benjamini–Hochberg procedure.

BMI, body mass index; eGFR, estimated glomerular filtration rate; MACCEs, major adverse cardiac and cerebrovascular events.

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ratio than either HHcy or hypertension alone. Early research has clarified the role of hypertension in advancing CKD. Substantial evidence suggested that HHcy induced atherosclerosis, leading to increased systemic vascular resistance and exacerbating hypertension (26). Xie et al. demonstrated that HHcy significantly elevated the risk of renal function decline in hypertensive patients, highlighting the additive effect of hypertension and HHcy on CKD progression (23). Data from the NHANES survey in the general population also revealed a synergistic interaction between hypertension and HHcy in increasing CKD incidence (27). However, to date, no studies have explicitly assessed whether H-type hypertension exacerbated renal prognosis in CKD patients, which was confirmed by our findings. The CSPPT sub-study showed that enalapril-folate treatment significantly slowed renal deterioration in mild to moderate CKD patients with hypertension compared to enalapril alone (28). A post-hoc analysis of CSPPT by Li et al. revealed that folate-enalapril therapy significantly reduced CKD progression risk in participants with higher baseline B12 levels (29). This finding contrast with results from two other RCTs involving B vitamin supplementation (the DIVINe (30) and HOST (31) studies), which suggested that high doses of B vitamins may accelerate renal function decline. The discrepancies across these studies may arise from differences in B vitamin dosages, baseline eGFR levels, or the fact that the CSPPT was conducted in China, where dietary folate fortification is uncommon, potentially influencing baseline folate and B vitamin levels. Additionally, our research revealed no significant intermediary effect of HHcy on renal outcomes or MACCEs. Potential explanations were as follows. While we adjusted for known confounders, residual confounding (e.g., genetic factors, dietary habits) may lead to violating these assumptions. Hcy levels were measured at baseline, whereas prognosis was assessed over follow-up. Time-dependent changes in Hcy or delayed biological effects may attenuate the observed mediation. The power to detect small-to-moderate mediation effects may have been limited by our cohort size. While HHcy is mechanistically linked to vascular outcomes, its role in hypertension-mediated prognosis may be secondary to other pathways (e.g., oxidative stress, endothelial dysfunction). Our study further emphasized the importance of H-type hypertension as a critical risk factor for CKD patients. Future research should investigate the clinical benefits of simultaneously managing hypertension and HHcy in CKD patients, as well as explore randomized trials to better understand the effects of folate supplementation on CKD progression.

Our study found that H-type hypertension significantly increased the risk of MACCEs in CKD patients, in line with previous research (16). Previous researches have consistently demonstrated that hyperhomocysteinemia was linked to an elevated risk of cardiovascular events, particularly stroke. Early research indicates that the combination of HHcy and hypertension leads to microvascular endothelial dysfunction, early carotid atherosclerosis (32), and increased risk of stroke and cardiovascular events (16, 33). A study on elderly populations revealed that individuals with H-type hypertension had significantly higher odds ratios for stroke incidence and mortality compared to those with either elevated Hcy levels (≥10 μmol/L) or hypertension alone (16). Furthermore, the role of HHcy in cerebrovascular damage was supported by studies showing a dose–response relationship between plasma homocysteine levels and white matter lesions, a marker of cerebrovascular injury, in hypertensive patients (34). This suggested that HHcy may contribute to MACCEs through direct vascular damage. Hcy accumulation in plasma due to impaired metabolic clearance in CKD patients further exacerbates dyslipidemia, insulin resistance (16) and blood pressure fluctuations (35), all of which exacerbate cardiovascular damage in CKD patients. However, the effect of HHcy on MACCEs was not statistically significant, suggesting that hypertension may play a more dominant role. This discrepancy between our results and previous studies could be due to variations in study populations, disease states, and confounding factors. In fact, epidemiological research presents conflicting views on the role of HHcy in the risk of cardiovascular events, particularly in CKD and ESRD patients (13, 14). The heterogeneity within CKD, often reflecting differing inflammation or nutritional status (36), complicates the quantification of cardiovascular risk factors. For example, CKD patients frequently present with hypoalbuminemia, a known predictor of adverse cardiovascular outcomes, and since serum albumin is the primary carrier of circulating Hcy, adjusting for albumin levels may obscure the true impact of Hcy on cardiovascular outcomes. Based on our findings, future research should explore the impact of cardiovascular disease burden in CKD patients with H-type hypertension.

Our data revealed heightened susceptibility to adverse renal and cardiovascular prognostic risk in CKD patients with H-type hypertension. Building on these findings, we propose targeted management strategies. First, folate supplementation should be prioritized in the management of H-type hypertension. Given the central role of HHcy in driving adverse outcomes, daily oral administration of 0.8–1.2 mg folate—a dose supported by the CSPPT trial (29)—is recommended to mitigate HHcy-mediated vascular and renal injury. This intervention may synergize with angiotensin receptor-neprilysin inhibitors (ARNIs). Second, tailored antihypertensive regimens are warranted. For HTH patients with comorbid diabetes or nephropathy, sodium-glucose cotransporter-2 inhibitors (SGLT2i) should be considered first-line (37). Third, individualized risk stratification is critical. Patients presenting with advanced age, reduced eGFR, or dyslipidemia may benefit from intensified monitoring (e.g., quarterly renal function assessments, annual cardiac imaging) and early dual-pathway therapy combining folate and statins to address concurrent vascular calcification risks.

Our study has several limitations. First, as a retrospective study with limited sample size, inherent biases are unavoidable. The stringent exclusion criteria may introduce selection bias, potentially limiting the generalizability of our findings to broader non-dialysis CKD populations. Some variables such as smoking, alcohol consumption, and folate intake were identified by self-report, which may lead to information bias. Second, the lack of intervention in this study prevents the determination of cause–effect relationship. Third, several unadjusted confounding factors, such as MTHFR genetic polymorphisms, nutritional deficiencies, and lifestyle, may have affected the results. Fourth, due to the limited number of participants in the CVD subgroups, we were unable to perform a detailed analysis of specific CVD types. Fifth, the follow-up period may have been too short to capture sufficient outcomes. Lastly, we did not track dynamic changes in Hcy levels during follow-up, and factors such as age, physical activity, smoking, and alcohol consumption could have influenced Hcy levels (38), which could attenuate the observed associations between HTH and adverse outcomes.

In conclusion, our study demonstrates that H-type hypertension is an independent risk factor for both renal progression and MACCEs in CKD patients, even after adjusting for traditional risk factors. These findings highlight the potential clinical value of dual targeting of hypertension and hyperhomocysteinemia in CKD population.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the institutional review board and ethical committee of the Fifth Affiliated Hospital of Sun Yat-sen University (Zhuhai, China). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XC: Writing – original draft, Writing – review & editing, Data curation, Investigation, Methodology, Software, Validation, Visualization. MJ: Writing – review & editing. XJ: Data curation, Writing – review & editing. SG: Supervision, Writing – review & editing. YH: Investigation, Writing – review & editing. SL: Resources, Writing – review & editing. HP: Resources, Writing – review & editing. ML: Conceptualization, Methodology, Supervision, Writing – review & editing. CW: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2025.1554663/full#supplementary-material

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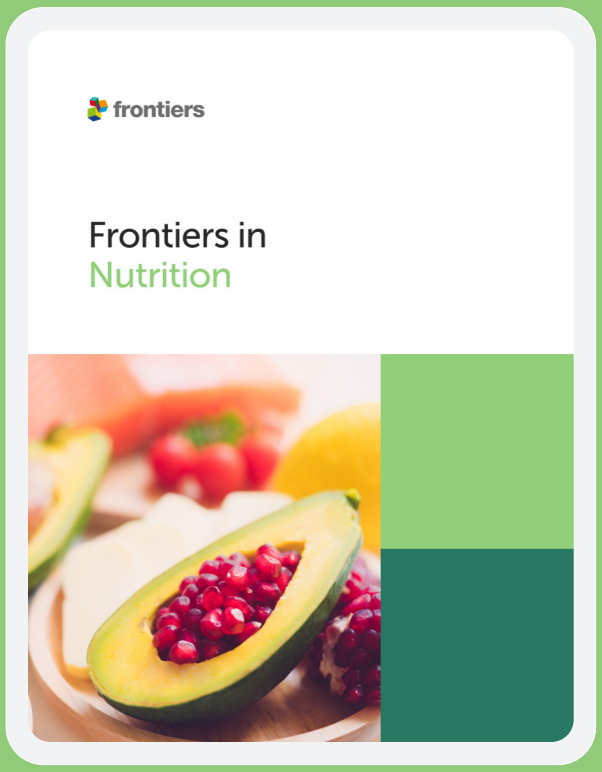

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