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Association of salt added to food with risk of cardiovascular diseases

A 2-sample Mendelian randomization study

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Abstract

Salt added to food is believed to potentially influence the risk of cardiovascular diseases (CVD), however, more evidence needs further verification. Here, we conducted a 2-sample Mendelian randomization (MR) study to systematically investigate the associations of salt added to food with 11 types of cardiovascular diseases in the general population. The primary MR analysis adopts the inverse-variance weighting (IVW) method, complemented by ancillary analyses utilizing IVW (fixed effects), weighted medium, maximum likelihood, and penalized weighted median methodologies. The main pleiotropy of genetic variation and sensitivity analysis were correspondingly applied to test the reliability of the results, and the MR-Egger test are the core evaluation methods. Notably, genetically predicted salt added to food demonstrates causal associations with vein thromboembolism (IVW odds ratio [OR]: 1.0084, 95% confidence interval [CI]: 1.0024–1.0143, $P = .0056$), atrial fibrillation and flutter (IVW OR: 1.3176, 95% CI: 1.0154–1.7098, $P = .0380$), ischemic stroke (IVW OR: 1.1852, 95% CI: 1.0092–1.3918, $P = .0383$) and peripheral artery disease (IVW OR: 1.0040, 95% CI: 1.0015–1.0065, $P = .0016$). These findings provide valuable insights that may guide the development of targeted prevention strategies and interventions focused on dietary habits in the context of cardiovascular diseases.

Abbreviations: AF = atrial fibrillation, GWAS = genome-wide association studies, IVW = inverse-variance weighting, MR = Mendelian randomization, SNPs = single-nucleotide polymorphisms.

Keywords: cardiovascular diseases, dietary habits, Mendelian randomization, salt added to food, salt intake

1. Introduction

Cardiovascular disease encompasses a spectrum of cardiac and vascular disorders, including coronary artery disease, heart failure, atrial fibrillation (AF), ischemic stroke, cerebrovascular disease, thrombotic disorders, and so on. Currently, CVD remains a foremost contributor to worldwide morbidity and mortality, constituting a substantial challenge to global public health. According to statistics, CVD accounted for approximately 19 million deaths in 2020, marking an increase of 18.7% over the past decade.[1,2]

Lifestyle determinants, such as dietary habits, smoking, physical activity, and body weight, exert a substantial influence on cardiovascular health.[3] Given the multifaceted etiology of CVD, a thorough exploration of its risk factors is imperative, with particular emphasis on the significant influence exerted by dietary elements. High sodium intake, often in the form of dietary salt supplementation, constitutes a primary risk factor for CVD.[4] It is reported that every additional 1 g increase in estimated sodium excretion is associated with an increment of 2.11 mm Hg in systolic blood pressure and 0.78 mm Hg in diastolic blood pressure.[5] According to recent research, there is a significant correlation between a high-sodium diet and an increased risk of stroke, AF, and hypertension.[6–8] Several health organizations advocate for the adoption of a low-sodium dietary plan (<2.3 g/day, approximately equivalent to 1 teaspoon of salt) for the general population.[9,10] The recommendation of such low-sodium intake regimen is rooted in the belief that reducing sodium consumption, regardless of its initial levels, will lead to the reduction of blood pressure,

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The datasets generated during and/or analyzed during the current study are publicly available.

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subsequently contributing to a decrease in the occurrence of cardiovascular events and death. However, given the indispensable role of sodium in human physiology, the relationship between salt intake and health risk is postulated to exhibit a "sweet spot" phenomenon, characterized by a J-shaped relationship. This suggests that both inadequate and excessive salt intake are anticipated to yield adverse health consequences.[5,11,12] In addition, there is mounting evidence to suggest that sodium restriction has the capacity to stimulate the renin-angiotensin-aldosterone system, which is linked to heightened cardiovascular risk.[13–15]

While numerous observational investigations have consistently established an association between high salt intake and hypertension, subsequently raising the risk of CVD, the causality of this relationship remains a subject of ongoing debate.[12–15] A significant obstacle is the absence of a validated and reliable method for the objective quantification of sodium intake among the general populace. While the utilization of multiple 24-hour urine collections is occasionally designated as the gold standard, this method exhibits inconsistencies, as approximately 30% of individuals encountered challenges in providing even a single complete urine collection.[16,17] Therefore, more testimony is imperative to prove the exact association between salt consumption and CVD.

Mendelian randomization (MR) is an established epidemiological approach used to investigate the causal relationship between a certain exposure (e.g., salt intake) and an outcome (e.g., CVD). Single-nucleotide polymorphisms (SNPs) with genetic variants are employed as instrumental variables.[18,19] Since the genes were determined by genetic variation during conception, MR mitigates the influence of confounding variables in conventional observational studies and counters inverse correlation bias. This establishes a sturdy framework for estimating causal effects.[20] To the best of our knowledge, we conducted a 2-sample MR study for the first time to investigate whether genetic indicators of salt intake is significantly associated with CVD risks in the current study.

2. Methods

We employed data derived from openly accessible published research studies or summaries of genome-wide association studies (GWAS). Ethical permission was obtained for the original investigations as well as for the utilization of data from several consortia. The studies incorporated into our analysis had received endorsement from the respective institutional review boards and ethical committees (Fig. 1).

2.1. Exposure and outcome measures

The exposure data were obtained from MRC Integrative Epidemiology Unit with 462,630 individuals of European descent. In order to mitigate the impact of linkage disequilibrium, a total of 106 SNPs were selected as instrumental variables. These SNPs met the established genome-wide significance threshold ($P < 5 \times 10^{-8}$, $R^2 > 0.001$ within a 10,000 kb window) for the respective exposures. By utilizing the PhenoScanner database V2,[21,22] potential pleiotropic effects were excluded.

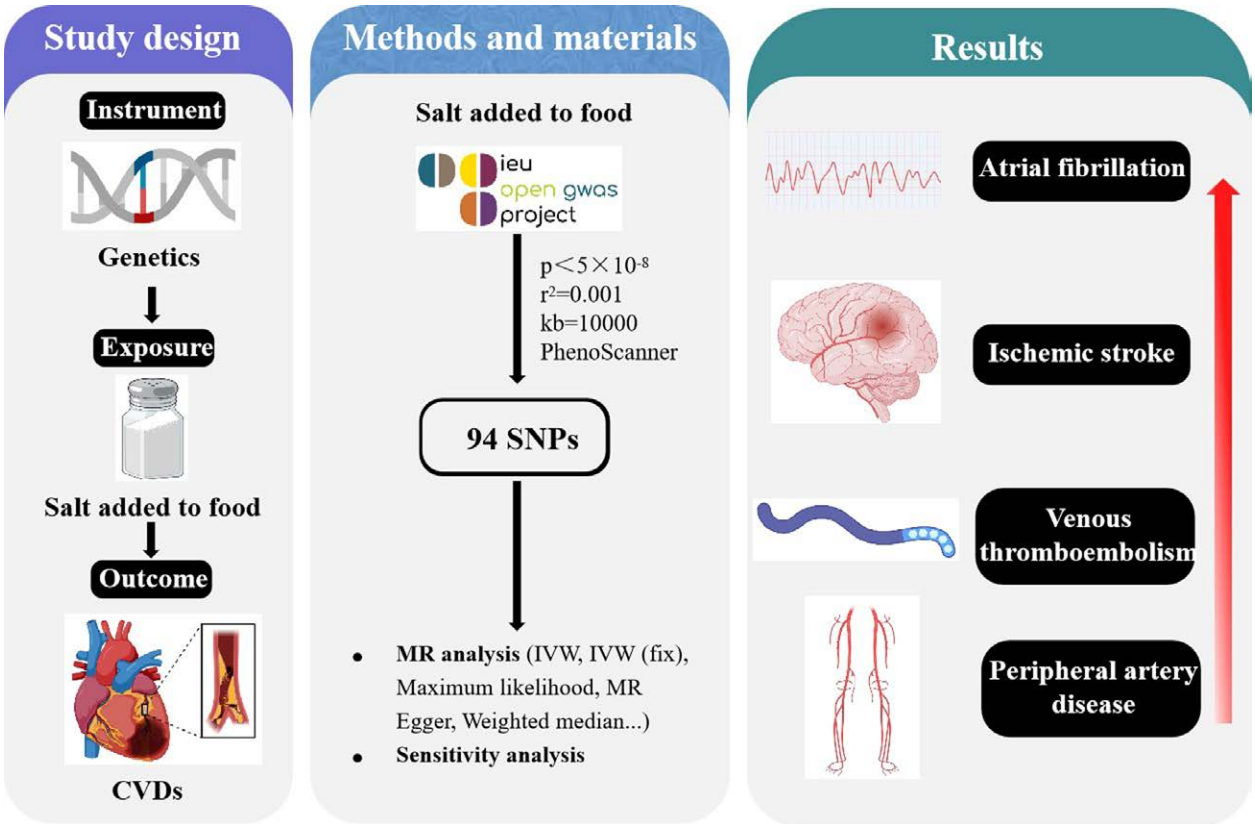

Figure 1. The graphical illustration of the MR study. Three fundamental hypotheses must be met by instrument variables: the genetic variant is independent of all confounders, the genetic variants are closely correlated with exposure, and it exclusively affect the outcome through the risk factor. The MR analysis test the 94 genetic variants of salt added to food against 11 types of cardiovascular diseases in genome-wide association study (GWAS) cohorts. Eventually, our MR analysis revealed a positive association between salt consumption and the occurrence of venous thromboembolism, atrial fibrillation, ischemic stroke, and peripheral artery disease. CVDs = cardiovascular diseases, GWAS = genome-wide association study, IVW = inverse-variance weighting, MR = Mendelian randomization, SNPs = single-nucleotide polymorphisms.

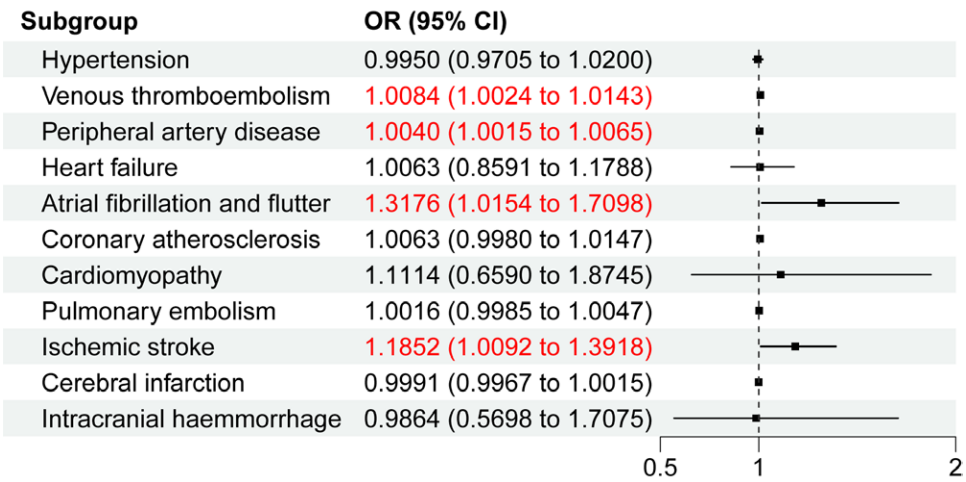

Figure 2. MR results show the causal effect of salt added to food exposure in CVDs susceptibility. CI = confidence interval, CVDs = cardiovascular diseases, MR = Mendelian randomization, OR = odds ratio.

A comprehensive overview of the demographics and the description of the GWAS included in this study were presented in Table S1, Supplemental Digital Content, http://links.lww.com/MD/O490. The IEU Open GWAS project (https://gwas.mrcieu.ac.uk/) provided all exposure and outcome data.

2.2. Mendelian randomization

All of our studies were conducted within a 2-sample MR framework, wherein SNP-exposure associations (salt added to food) and SNP-outcome associations (encompassing venous thromboembolism, pulmonary embolism, heart failure, atrial fibrillation and flutter, cerebral infarction, nontraumatic intracranial hemorrhage, hypertension, ischemic stroke, coronary atherosclerosis, cardiomyopathy, peripheral artery disease) were obtained from various cohorts. The MR analysis was carried out using the 2-Sample MR package (version 0.4.13, accessible at https://github.com/MRCIEU/TwoSampleMR). We employed multiple MR methods, including inverse variance weighting (IVW), MR-Egger, IVW (fixed effects), maximum likelihood, weighted median, penalized weighted median, weighted mode, and simple mode in the 2-sample MR analysis. This approach enabled us to assess the causal effects of exposure on the outcome.

Several sensitivity analyses were conducted in this study. To assess variability among estimates of individual genetic variations, Cochran's Q test was utilized. If the P value was found to be <.05, the final results of the Mendelian randomization analysis were calculated utilizing the random-effects model of IVW. Conversely, if the P value exceeded .05, the fixed-effects model was employed. Subsequently, the MR-Egger intercept approach was employed to investigate the presence of horizontal pleiotropy in instrumental variables. Furthermore, a leave-one-out sensitivity analysis was performed to assess the potential impact of individual SNPs on the results. Finally, the generation of funnel plots and forest plots was conducted in order to directly evaluate the presence of pleiotropy.

3. Results

3.1. Characteristics of the selected SNPs and the CVD outcomes

In our investigation, we conducted SNPs selection with a focus on salt added to food-associated genetic variants in relation to CVD risk, as identified through GWAS with a significance threshold of $P < 5 \times 10^{-8}$. To minimize the influence of linkage disequilibrium, SNPs with an LD threshold ($R^2 < 0.001$) within a 10,000-kb window were excluded. Subsequently, SNPs associated with CVD were retrieved from the PhenoScanner database. To enhance the specificity of our analysis, we excluded 12 SNPs (rs11126666, rs11130206, rs13400612, rs17805497, rs2263636, rs2521501, rs2547040, rs429358, rs6416794, rs7591518, rs8097544, rs9667150, rs597808, rs6679677, and rs389884) that were found to be associated with potential confounders (hypertension and coronary artery disease). Additionally, palindromic SNPs exhibiting a moderate allele frequency were excluded from the dataset. There was no evidence of bias towards weak tools revealed in the strength test of the independent variables (F statistic > 10, Supplementary File 1, Supplemental Digital Content, http://links.lww.com/MD/O491).

3.2. Causal effect of salt added to food on cardiovascular diseases

In our investigation, a diverse set of instrumental variables methods, including IVW, IVW (fixed effects), maximum likelihood, MR-Egger, weighted median, penalized weighted median, simple mode, and weighted mode were employed to estimate the causal associations between salt added to food and the risk of 11 distinct cardiovascular diseases. Within this study, the IVW method was considered as the primary assessment criterion, with the other MR methodologies serving as supplementary references. Meanwhile, the MR-Egger regression intercept test ($P > .05$) indicated that there was no evidence of horizontal pleiotropy in the instrumental variables of salt added to food in any type of CVD (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O492).

3.3. Relationship between salt added to food and cardiovascular diseases

Figure 2 illustrates the relationship between salt added to food and the risk of various cardiovascular diseases (details showed in Table S3, Supplemental Digital Content, http://links.lww.com/MD/O494). Specifically, for venous thromboembolism, our primary analysis employing the IVW method yielded an OR of 1.0084 (95% CI: 1.0024–1.0143), with a significant P value of .0056. Apart from the IVW assessment standards, IVW (fixed effects; OR: 1.0084, 95% CI: 1.0031–1.0137, $P = .0018$), maximum likelihood (OR: 1.0085, 95% CI: 1.0032–1.0139, $P = .0017$) MR-Egger (OR: 1.0141, 95% CI: 0.9950–1.0335,

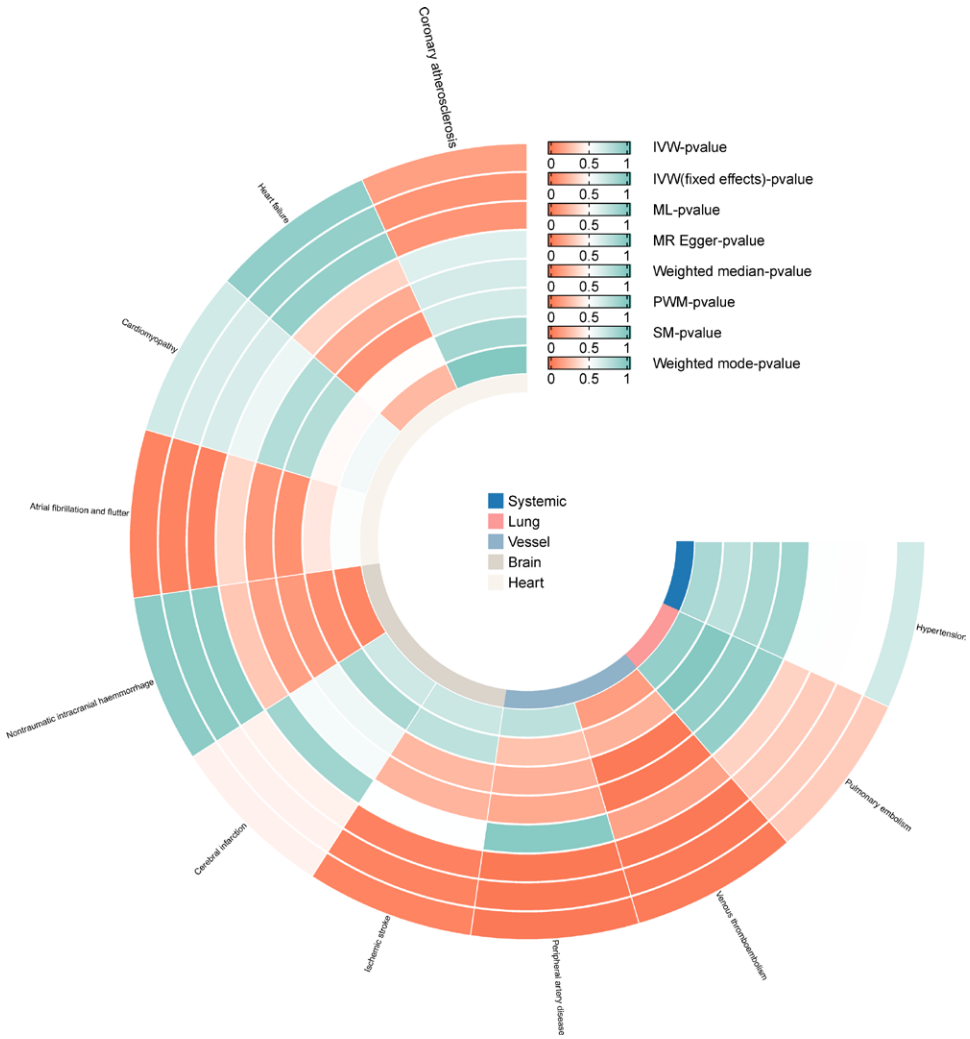

Figure 3. IVW, IVW (fixed effects), maximum likelihood, MR-Egger, weighted median, penalized weighted median, simple mode, and weighted mode were used in the 2-sample MR analysis. The color of each block represents the *P* value for each MR analysis. IVW = inverse-variance weighting, MR = Mendelian randomization.

P = .1534), weighted median (OR: 1.0121, 95% CI: 1.0038–1.0204, *P* = .0041), and penalized weighted median (OR: 1.0121, 95% CI: 1.0040–1.0203, *P* = .0032) consistently supported this association.

Furthermore, our analysis indicated that salt intake was associated with an increased risk of atrial fibrillation (IVW OR: 1.3176, 95% CI: 1.0154–1.7098, *P* = .0380). The remaining results of MR were validated as follows: IVW (fixed effects; OR: 1.3176, 95% CI: 1.0188–1.7039, *P* = .0355), maximum likelihood (OR: 1.3264, 95% CI: 1.0228–1.7202, *P* = .0332), MR-Egger (OR: 1.5056, 95% CI: 0.6400–3.5419, *P* = .3512), weighted median (OR: 1.3955, 95% CI: 0.9304–2.0932, *P* = .1072), penalized weighted median (OR: 1.4380, 95% CI: 0.9567–2.1616, *P* = .0807).

In the context of ischemic stroke, the IVW analysis revealed an OR of 1.1852 (95% CI: 1.0092–1.3918, *P* = .0383). The following validations were validated for the remaining MR results: IVW (fixed effects; OR: 1.1852, 95% CI: 1.0130–1.3867, *P* = .0339), maximum likelihood (OR: 1.1889, 95% CI: 1.0142–1.3937, *P* = .0329), MR-Egger (OR: 0.8306, 95% CI: 0.4833–1.4273, *P* = .5033), weighted median (OR: 1.1568, 95% CI: 0.9182–1.4573, *P* = .2166), penalized weighted median (OR: 1.1564, 95% CI: 0.9124–1.4658, *P* = .2295).

Similarly, for peripheral artery disease, the IVW analysis yielded an OR of 1.0040 (95% CI: 1.0015–1.0065, *P* = .0016). The remaining results of MR were validated as follows: the fixed effects IVW (OR: 1.0040, 95% CI: 1.0018–1.0063, *P* = .0005), maximum likelihood (OR: 1.0041, 95% CI: 1.0018–1.0064, *P* = .0004), MR-Egger (OR: 1.0001, 95% CI: 0.9922–1.0081, *P* = .9773), weighted median (OR: 1.0025, 95% CI: 0.9989–1.0060, *P* = .1759), penalized weighted median (OR: 1.0023, 95% CI: 0.9988–1.0058, *P* = .2018).

The occurrence of salt added to food, however, exhibited no significant association with the risk of 7 other types of cardiovascular diseases, including pulmonary embolism (OR: 1.0016, 95% CI: 0.9985–1.0047, *P* = .3082), heart failure (OR: 1.0063, 95% CI: 0.8591–1.1788, *P* = .9380), cerebral infarction (OR: 0.9991, 95% CI: 0.9967–1.0015, *P* = .4511), nontraumatic intracranial haemmorrhage (OR: 0.9864, 95% CI: 0.56981–1.7075, *P* = .9609), hypertension (OR: 0.9950, 95% CI: 0.9705–1.0200, *P* = .6916), coronary atherosclerosis (OR: 1.0063, 95% CI: 0.9980–1.0147, *P* = .1397), and cardiomyopathy (OR: 1.1114, 95% CI: 0.6590–1.8745, *P* = .6921).

Eight MR analyses were used in the estimation of the association between salt added to food and 11 types of CVDs, and *P* value for each MR analysis was shown in Figure 3. More details were represented in Table S3, Supplemental Digital Content, http://links.lww.com/MD/O494.

4. Discussion

In this study, we conducted a rigorous 2-sample MR analysis employing genetic data and instrumental variables derived from large-scale GWAS. The main objective of this study was to elucidate the possible causal association between salt added to food and cardiovascular diseases. Our MR analysis revealed a positive association between salt added to food and the occurrence of venous thromboembolism, atrial fibrillation, ischemic stroke, and peripheral artery disease. However, no compelling evidence emerged to support an association between salt added to food and the risk of 7 specific cardiovascular conditions, including pulmonary embolism, heart failure, cerebral infarction, nontraumatic intracranial hemorrhage, hypertension, coronary atherosclerosis, and cardiomyopathy. In the context of current World Health Organization recommendations for daily intake (<2.0 g sodium) in adults, O'Donnell's research recommend that moderate sodium consumption (3–5 g/day) is linked to the lowest risk of cardiovascular events and mortality. And low sodium intake also increased the risk of CVD event (OR: 1.27, 95% CI: 1.12–1.44).[23,24] A recent study that combined individual data from 6 cohorts measured multiple 24-h urine analyses to assess salt intake and found that a higher sodium intake (2000~6000 mg/d sodium, 5~15 g/d salt) and a lower potassium intake were each associated with an increased risk of cardiovascular events.[25]

The most prevalent cardiac arrhythmia that can cause stroke or sudden cardiac death is atrial fibrillation.[26] A recent prospective study investigated the connection between daily salt intake and the risk of AF, revealing a U-shaped relationship in males and a J-shaped pattern in females.[27] Nonetheless, recent meta-analyses have failed to establish a substantial increase in AF risk attributed to high salt intake.[28] Our results suggested that high dietary salt intake beyond a certain physiological level was correlate to the increased risk of atrial fibrillation. Elevated sodium consumption triggers elevated blood pressure, primarily through heightened intracellular osmolality and the release of antidiuretic hormone from the posterior pituitary. Hypertension stands as a pivotal risk factor for AF, with excessive sodium intake closely associated with elevated blood pressure. The precise mechanisms through which hypertension contributes to AF remain incompletely elucidated, likely involving structural and functional alterations in the atrium cordis followed by electrophysiological disturbances.[26,29,30] Apart from effects through hypertension, the correlation between salt intake and the risk of AF may be influenced by sodium-induced prolongation of the cardiac QT-interval.[31,32] Hypertension is associated with high salt intake in past researches.[5,33,34] However, in our MR analysis, salt added to food did not exhibit a significant association with hypertension (OR: 0.9950, 95% CI: 0.9705–1.0200, $P = .6916$). This inconsistency may be explained by 2 factors. Firstly, individuals exhibit a spectrum of sodium sensitivity, with certain individuals manifesting a notable increase in blood pressure in response to elevated sodium consumption, while others display minimal alterations. These variations are, to some extent, attributable to genetic variation in pathways associated with sodium handling and excretion. It is acknowledged that the epithelial sodium channel (ENaC) constitutes one of the principal transporters responsible for the re-absorption of sodium in the distal nephron, which might contribute to the variability in sodium-sensitivity among diverse populations.[35] Secondly, salt added to food, as a modifiable factor, is generally influenced by non-genetic variables, introducing potential confounding effects.

Venous thromboembolism is a pathological condition characterized by the development of blood clots within the deep veins, commonly occurring in the lower extremities, and the potential for these clots to dislodge and travel to the lungs, causing pulmonary embolism. According to our research findings, there exists a positive correlation between elevated salt consumption and an augmented susceptibility to venous thromboembolism (IVW OR: 1.0084, 95% CI: 1.0024–1.0143, $P = .0056$). Endothelial injury plays a crucial role in the pathogenesis of venous thrombosis through multiple mechanisms, including activation of the coagulation cascade, increased adhesion molecule expression, release of procoagulant factors, and impaired fibrinolysis. The luminal surface of endothelial cells is ensheathed by a complex meshwork composed of glycoproteins, proteoglycans, and hyaluronic acid/hyaluronan, collectively forming a gelatinous layer known as the endothelial glycocalyx. Excessive salt intake has been shown to induce damage to the endothelial glycocalyx, which subsequently compromises the integrity of vascular endothelial cells and augments the risk of thrombus formation and other cardiovascular pathologies.[36] In addition, high dietary salt intake is linked to a reduction in nitric oxide mediated vasodilation in pregnant women, which is attributed to heightened oxidative stress.[37] It was reported that a reduction of catalase activity concomitant with an elevation of NOX4 expression in the aortas during periods of high salt consumption. This alteration leads to an elevation in reactive oxygen species levels, which ultimately inflict damage upon endothelial cells.[38] Stasis of blood stream and dysfunction of endothelial cell are the key mechanism of venous thromboembolism, and high salt intake may deteriorate this effect. Currently, the link between salt intake and VTE is not a commonly discussed or well-documented relationship in medical literature. Our study may supply a view between venous thromboembolism and salt intake.

Each year, there are more than 795,000 incidents of stroke in the United States, with ischemic stroke accounting for 87% of all stroke cases.[39] It is also the fifth leading cause of death in the United States. A meta-analysis of high salt intake and stroke, which involved 12 studies, with 225,693 participants and 8135 stroke events, showed that high salt intake was associated with the risk of stroke event (OR: 1.11), ischemic stroke-related mortality (OR: 2.15), while it showed no significant association with the risk of onset of ischemic stroke (OR: 1.07).[40] Moreover, another observational and prospective study exploring the association between daily salt consumption and the risk of ischemic stroke risk revealed that patients who consumed a high-sodium diet exhibited a more than twofold greater likelihood of experiencing an ischemic stroke.[41] Similarly, our results are supported by an MR study indicating an association between elevated salt added to food and an increased risk of ischemic stroke (IVW OR: 1.1852, 95% CI: 1.0092–1.3918).

According to the findings of the Salt Substitute and Stroke Study (SSaSS), in comparison to the control group utilizing conventional table salt with a sodium chloride content ranging from 90% to 99%, the intervention group employing low-sodium salt containing 25% potassium chloride, exhibited a 14% reduction in both fatal and non-fatal strokes, a 13% decline in major adverse cardiovascular events, accompanied by a 12% reduction in all-cause mortality.[42] Nevertheless, even though low-sodium salt is considered safe and efficacious, current data suggest that its impact on reducing the incidence and prognosis of cardiovascular diseases appears to be less favorable than that of most established pharmaceutical interventions.[43] However, the potential public health implications of a low-sodium dietary regimen may transcend that of medications. First, low-sodium salt production costs are notably cost-effective. Second, pharmaceutical interventions, regardless of their demonstrated efficacy, are confined to the use within diagnosed patient cohorts. However, there exists a substantial portion of individuals who remain undiagnosed yet belong to the high-risk category for cardiovascular diseases. Above all, our MR analysis provided compelling evidence indicating a positive association between elevated salt intake and an increased risk of several cardiovascular diseases, including AF, ischemic stroke, venous thromboembolism and peripheral artery disease. It is imperative to highlight the significance of low-sodium diet and to emphasize the necessity for further research to investigate the intricate relationship between salt and CVDs.

Our study also has some limitations. First, it is unavoidable to eliminate the recall bias and measurement error inherent in self-reported dietary salt intake.[12] Secondly, the predominant representation of participants from Europe in this MR analysis complicates the generalization of the causal relationship between salt added to food and CVD to other populations. Thirdly, the relatively low odds ratio (OR) warrants careful interpretation. Even though the association between salts intake and CVD is still debatable and lower antihypertensive effect of decreasing salt intake than most existing drugs, its potential public health significance should be emphasized. We look forward to more in-depth exploration of the potential correlation between the exposure (salt added to food) and outcome (cardiovascular diseases) in the forthcoming research endeavors.

5. Conclusion

In conclusion, our investigation provides evidence supporting a potential causal relationship between salt intake and CVDs. The integration of these findings with evidence derived from observational studies emphasizes the significance of early cardiovascular risk evaluation and prevention in individuals with elevated salt intake. This underscores the need for the prompt implementation of individual-specific treatments. Meanwhile, it is essential to exercise caution in generalizing the results, given the relatively low OR.

Author contributions

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Funding acquisition: Yixin Wang, Xuren Wang.
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Methodology: Shaokang Wang, Huan Wang, Jie Sun, Xiaoying Lu, Xuren Wang.
Writing – original draft: Shaokang Wang.
Writing – review & editing: Yixin Wang, Xiaoying Lu, Xuren Wang.

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