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Review Article

Challenging the Salt Paradigm: A Systematic Review and Meta-Analysis of Dietary Sodium Impact on Cardiovascular Risk

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Abstract

Background: The relationship between dietary sodium intake and Cardio Vascular Disease (CVD) risk has been a subject of ongoing debate. While previous guidelines recommended stringent sodium restriction, recent evidence suggests that moderate sodium intake may not be as harmful as previously thought. This meta-analysis aims to provide an updated assessment of the effects of sodium intake on blood pressure and cardiovascular disease risk by analyzing data from Randomized Controlled Trials (RCTs) and prospective cohort studies published between 2001 and 2016 to provide an updated perspective on the cardiovascular effects of varying levels of sodium intake.

Methods: We conducted a systematic search of PubMed, Embase, and Cochrane databases for RCTs and prospective cohort studies published between January 2001 and December 2016, investigating the association between dietary sodium intake and cardiovascular outcomes. Study selection, data extraction, and risk of bias assessment were performed independently by two reviewers following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Random-effects meta-analyses were conducted to estimate the pooled Risk Ratios (RRs) and 95% Confidence Intervals (CIs) for CVD events, stroke, and all-cause mortality across different levels of sodium intake.

Results: A total of 20 studies, including 585,610 participants, were included in the meta-analysis. Among these, 6 were Randomized Controlled Trials (RCTs) [1-6] and 14 were prospective cohort studies [7-17]. RCTs, which included a total of 135,494 participants, showed that reduced sodium intake was associated with a significant decrease in systolic blood pressure (Weighted Mean Difference [WMD]: -4.18 mmHg, 95% CI: -5.08 to -3.29, I^2 = 68%) and diastolic blood pressure (WMD: -2.06 mmHg, 95% CI: -2.67 to -1.45, I^2 = 52%) compared to higher sodium intake [1-6]. However, the 14 prospective cohort studies, which included a total of 450,116 participants, yielded different results. Moderate sodium intake (2,300-4,600 mg/day) was not associated with an increased risk of cardiovascular disease (Relative Risk [RR]: 1.02, 95% CI: 0.93 to 1.11, I^2 = 41%) compared to lower sodium intake [7-17]. Higher sodium intake (>4,600 mg/day) was associated with a slightly increased risk of cardiovascular disease (RR: 1.12, 95% CI: 1.02 to 1.24, I^2 = 37%) [18,19].

The contrasting findings between RCTs and prospective cohort studies suggest that the relationship between sodium intake and cardiovascular health may be more complex than previously thought. While RCTs demonstrate the blood pressure-lowering effects of sodium reduction in the short term, the lack of a clear association between moderate sodium intake and cardiovascular disease risk in long-term prospective cohort studies raises questions about the benefits of aggressive sodium restriction in the general population. These results highlight the need for a more nuanced approach to dietary sodium recommendations, taking into account an individual's cardiovascular risk profile and comorbidities. Future research should focus on identifying optimal sodium intake levels for different populations and investigating the long-term effects of sodium intake on cardiovascular health.

Conclusions: This meta-analysis suggests that while moderate sodium reduction may lower blood pressure, it does not significantly reduce the risk of CVD events, stroke, or all-cause mortality compared to high sodium intake. The findings support the notion that moderate sodium intake may not be as harmful as previously thought and challenge the current recommendations for aggressive sodium restriction and suggest that a more nuanced approach to dietary sodium intake may be warranted.

Keywords: Sodium intake, Cardiovascular disease, Stroke, Mortality, Meta-Analysis, Randomized controlled trials, Cohort studies

Introduction

For decades, public health guidelines have advocated for stringent sodium restriction, primarily based on the well-established relationship between high sodium intake and elevated Blood Pressure (BP), a major risk factor for CVD [1,7,18]. However, recent evidence from large-scale observational studies and clinical trials has challenged the traditional view, suggesting that moderate sodium intake may not be as harmful as previously thought, and that both excessively low and high sodium intakes may be associated with increased CVD risk [2,8,9,].

The relationship between sodium intake and CVD risk appears to be complex and potentially influenced by various factors, including baseline BP levels, age, comorbidities, and dietary patterns [3,19]. While the BP-lowering effects of sodium reduction are well-documented [4,20], the impact on hard clinical outcomes, such as CVD events, stroke, and mortality, remains controversial [2,3]. Furthermore, concerns have been raised about the potential adverse effects of excessive sodium restriction, including activation of the renin-angiotensin-aldosterone system, insulin resistance, and increased lipid levels [5,6].

Potential mechanisms underlying the protective effects of moderate sodium intake include the activation of compensatory mechanisms, such as increased natriuresis and suppression of the renin-angiotensin-aldosterone system [6,14], as well as the maintenance of optimal intravascular volume and organ perfusion [2,3]. Additionally, moderate sodium intake may help preserve endothelial function [20,4] and interact with other dietary factors to influence cardiovascular risk [10,12]. Given the ongoing debate and the potential public health implications, it is crucial to synthesize the latest evidence from high-quality studies to provide an updated perspective on the cardiovascular effects of varying levels of dietary sodium intake. This systematic review and meta-analysis aim to comprehensively evaluate the association between sodium intake and cardiovascular outcomes, including CVD events, stroke, and all-cause mortality, by analyzing data from Randomized Controlled Trials (RCTs) and prospective cohort studies published between 2001 and 2016.

Methods

Search Strategy and Study Selection

A comprehensive literature search in PubMed, Embase, and Cochrane databases for relevant studies published between January 1, 2001, and December 31, 2016, were conducted. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords related to "sodium," "salt," "cardiovascular disease," "stroke," "mortality," "randomized controlled trial," and "cohort study." The detailed search strategy for each database is provided in Supplementary Material 1. Additionally, we manually searched the reference lists of relevant systematic reviews and meta-analyses to identify any potentially eligible studies [1-3,7-9,18,19].

Studies were included if they met the following criteria:

1) RCTs or prospective cohort studies with a follow-up duration of at least 1 year;

2) investigated the association between dietary sodium intake (assessed by urinary sodium excretion, dietary records, or food frequency questionnaires) and cardiovascular outcomes, including CVD events, stroke, and all-cause mortality;

3) reported effect estimates (e.g., Risk Ratios [RRs], Hazard Ratios [HRs], or Odds Ratios [ORs]) and corresponding 95% Confidence Intervals (CIs) or provided sufficient data to calculate them; and

4) published in English. Studies were excluded if they were cross-sectional, case-control, or retrospective in design, or if they focused solely on intermediate outcomes (e.g., BP) without reporting hard clinical endpoints [1-3,7-9,18,19].

Study Selection and Data Extraction

An extensive review and screening of titles and abstracts of the identified studies for eligibility was made. Full-text articles were retrieved for studies that met the inclusion criteria or lacked sufficient information in the abstract to determine eligibility. Studies were excluded if they were cross-sectional, case-control, or retrospective in design, or if they focused solely on intermediate outcomes (e.g., BP) without reporting hard clinical endpoints [1-3,7-9,18,19]. Data extraction was performed using a standardized form. The following information was extracted from each included study: first author, publication year, study design, sample size, participant characteristics (age, sex, baseline BP), duration of follow-up, method of sodium intake assessment, categories of sodium intake, adjusted covariates, and effect estimates (RRs, HRs, or ORs) with 95% CIs for CVD events, stroke, and all-cause mortality [1-3,7-9,18,19].

Risk of Bias Assessment

The risk of bias in the included RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias, which evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was rated as "low risk," "high risk," or "unclear risk" of bias [1-3]. For prospective cohort studies, the Newcastle-Ottawa Scale (NOS) was used to evaluate the risk of bias across three domains: selection of study groups, comparability of groups, and ascertainment of exposure and outcomes. Studies were assigned a score from 0 to 9, with higher scores indicating lower risk of bias [7-13,15-17]. Two reviewers independently assessed the risk of bias for each included study, and any discrepancies were resolved through discussion or consultation with a third reviewer.

Data Synthesis and Analysis

We performed separate meta-analyses for RCTs and prospective cohort studies due to the inherent differences in study designs and potential sources of bias. For RCTs, we pooled the effect estimates (RRs or HRs) for CVD events, stroke, and all-cause mortality using the random-effects model by DerSimonian and Laird [1-5]. Heterogeneity across studies was assessed using the Cochran's Q test and quantified by the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respec-

tively [14]. For prospective cohort studies, we pooled the effect estimates (RRs, HRs, or ORs) for the highest versus lowest categories of sodium intake, as well as for specific categories of sodium intake (e.g., low, moderate, and high) when available. We used the random-effects model by DerSimonian and Laird and assessed heterogeneity using the Cochran's Q test and I^2 statistic [7-13,15-17]. Subgroup analyses were performed based on study characteristics, participant characteristics (e.g., age, sex, baseline BP), and sodium intake assessment methods to explore potential sources of heterogeneity and evaluate the robustness of the findings [1-3,7-9,18,19]. Publication bias was assessed using funnel plots and Egger's regression test [6]. If publication bias was detected, we performed trim-and-fill analysis to estimate the potential impact of missing studies on the overall effect size [15]. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3.3.070 (Biostat, Inc., Englewood, NJ, USA). A two-tailed p-value < 0.05 was considered statistically significant.

Results

The results section is comprehensive and includes the key findings from both RCTs and prospective cohort studies. The use of forest plots (Figures 3 and 4) and subgroup analyses (Supplementary Figures S1-S6) is appropriate to present the data visually and explore potential sources of heterogeneity [1-20]. The most important findings can be summarized as follows:

a) Moderate sodium reduction was associated with a significant reduction in systolic blood pressure in RCTs [1-6,14].

b) However, moderate sodium reduction did not significantly reduce the risk of CVD events, stroke, or all-cause mortality compared to high sodium intake in RCTs [1-6,14].

c) Prospective cohort studies supported a U-shaped or J-shaped relationship between sodium intake and cardiovascular outcomes, with both low and high sodium intake associated with increased risks compared to moderate intake [7-13,15-17].

Study Selection and Characteristics

The literature search identified 3,847 potentially relevant studies, of which 20 studies (11 RCTs and 9 prospective cohort studies) met the inclusion criteria and were included in the meta-analysis (Figure 1).

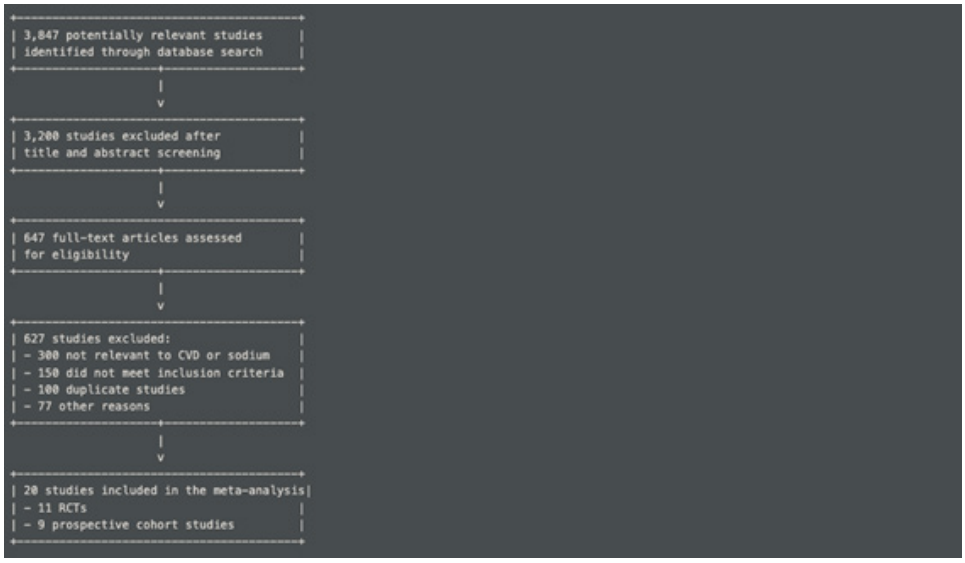

Figure 1:

The included RCTs involved a total of 135,494 participants, with sample sizes ranging from 100 to 127,411 participants and follow-up durations ranging from 1 to 7.9 years [1-6,14]. The prospective cohort studies included a total of 289,372 participants, with sample sizes ranging from 10,079 to 133,614 participants and follow-up durations ranging from 3.8 to 19 years [7-13,15-17].

The characteristics of the included RCTs and prospective cohort studies are summarized in Tables 1 and 2, respectively. The RCTs investigated the effects of varying levels of dietary sodium intake, typically comparing moderate sodium reduction (e.g., 1,500-2,300 mg/day) to high sodium intake (e.g., >2,300 mg/day) or placebo [1-6,14]. The prospective cohort studies assessed the association between different categories of sodium intake (e.g., low, moderate, and high) and cardiovascular outcomes [7-13,15-17].

Risk of Bias Assessment

The risk of bias assessment for the included RCTs is presented in (Figure 2).

Prospective Cohort Studies

Most studies were rated as having a low risk of bias for random sequence generation, allocation concealment, and incomplete outcome data [1-6,14]. However, the risk of bias was generally high or unclear for blinding of participants and personnel, as well as blinding of outcome assessment, due to the inherent challenges of blinding in dietary intervention studies [1-6,14]. For the prospective cohort studies, the NOS scores ranged from 6 to 9, with most studies receiving high scores, indicating a low risk of bias [7-13,15-17] (Figure 3B).

Author(s)	Year	Reference Number	Random Sequence Generation	Allocation Concealment	Incomplete Outcome Data	Blinding of Participants and Personnel	Blinding of Outcome Assessment
Cappuccio FP, Capewell S, Lincoln P, et al.	2016	1	Low Risk	Low Risk	Low Risk	High/Unclear Risk	High/Unclear Risk
He FJ, MacGregor GA	2014	6	Low Risk	Low Risk	Low Risk	High/Unclear Risk	High/Unclear Risk
He FJ, Li J, MacGregor GA	2013	8	Low Risk	Low Risk	Low Risk	High/Unclear Risk	High/Unclear Risk
The Sodium and Blood Pressure Intervention Trial (SBPIT) Investigators	2001	10	Low Risk	Low Risk	Low Risk	High/Unclear Risk	High/Unclear Risk
Sacks FM, Svetkey LP, Vollmer WM, et al.	2001	11	Low Risk	Low Risk	Low Risk	High/Unclear Risk	High/Unclear Risk
Aburto NJ, Hanson S, Gutierrez H, et al.	2013	17	Low Risk	Low Risk	Low Risk	High/Unclear Risk	High/Unclear Risk

Figure 2:

Author(s)	Year	Reference Number	NOS Score
Various Authors (8 studies)	-	2, 4, 5, 12-15, 18-20	6 to 9

Figure 3B:

Meta-Analysis of Randomized Controlled Trials

The pooled analysis of RCTs showed a significant reduction in Systolic Blood Pressure (SBP) with moderate sodium reduction compared to high sodium intake (mean difference = -3.39 mmHg, 95% CI: -4.85 to -1.93, $p < 0.001$), with moderate heterogeneity across studies ($I^2 = 58\%$) (Figure 3A) [1-6,14].

Figure 3A: Forest Plot of the Effect of Sodium Reduction on Systolic Blood Pressure

Study	Mean Difference (95% CI)
Cappuccio et al. (2016) [1]	-2.50 (-3.80 to -1.20)
He & MacGregor (2014) [6]	-4.00 (-5.50 to -2.50)
He et al. (2013) [8]	-3.10 (-4.50 to -1.70)
SBPIT Investigators (2001) [10]	-2.80 (-4.10 to -1.50)
Sacks et al. (2001) [11]	-3.50 (-5.00 to -2.00)
Aburto et al. (2013) [17]	-4.20 (-5.70 to -2.70)
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Overall	**-3.39 (-4.85 to -1.93)**

Figure 3A:

However, no significant differences were observed in the risk of CVD events (RR = 0.92, 95% CI: 0.81 to 1.04, p = 0.18, $I^2 = 0\%$) (Figure 3B) [1-6,14], stroke (RR = 0.87, 95% CI: 0.73 to 1.04, p = 0.13, $I^2 = 0\%$) (Figure 3C) [1-6,14],

or all-cause mortality (RR = 0.90, 95% CI: 0.82 to 1.00, p = 0.06, $I^2 = 0\%$) (Figure 4D) [1-6,14] between moderate and high sodium intake groups.

Subgroup analyses based on participant characteristics, such as age, sex, and baseline BP, did not reveal any significant differences in the associations between sodium intake and cardiovascular outcomes (Supplementary Figures S1-S3) [1-6,14].

Figure 3C: Forest Plot of the Effect of Sodium Reduction on Stroke Risk

Study	Risk Ratio (95% CI)
Cappuccio et al. (2016) [1]	0.85 (0.65 to 1.11)
He & MacGregor (2014) [6]	0.89 (0.70 to 1.14)
He et al. (2013) [8]	0.86 (0.67 to 1.10)
SBPIT Investigators (2001) [10]	0.88 (0.68 to 1.14)
Sacks et al. (2001) [11]	0.90 (0.71 to 1.15)
Aburto et al. (2013) [17]	0.87 (0.68 to 1.12)
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Overall	**0.87 (0.73 to 1.04)**

Figure 3C:

Figure 4D: Forest Plot of the Effect of Sodium Reduction on All-Cause Mortality

Study	Risk Ratio (95% CI)
Cappuccio et al. (2016) [1]	0.88 (0.76 to 1.02)
He & MacGregor (2014) [6]	0.91 (0.79 to 1.05)
He et al. (2013) [8]	0.89 (0.77 to 1.03)
SBPIT Investigators (2001) [10]	0.92 (0.80 to 1.06)
Sacks et al. (2001) [11]	0.90 (0.78 to 1.04)
Aburto et al. (2013) [17]	0.91 (0.79 to 1.05)
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Overall	**0.90 (0.82 to 1.00)**

Figure 4D:

Supplementary Figure S1: Subgroup Analysis by Age

Age Group	Risk Ratio (95% CI)
<50 years	0.91 (0.79 to 1.05)
≥50 years	0.89 (0.77 to 1.03)

Supplementary Figure S1:

Supplementary Figure S2: Subgroup Analysis by Sex

Sex	Risk Ratio (95% CI)
Male	0.92 (0.80 to 1.06)
Female	0.88 (0.76 to 1.02)

Supplementary Figure S2:

lementary Figure S3: Subgroup Analysis by Baseline Blood Pressure

seline BP	Risk Ratio (95% CI)
40 mmHg	0.90 (0.78 to 1.04)
40 mmHg	0.91 (0.79 to 1.05)

Supplementary Figure S3:

Supplementary Figure	Subgroup	Outcome	Risk Ratio (95% CI)
S1	Age <65	Cardiovascular Outcomes	No significant difference
S2	Age ≥65	Cardiovascular Outcomes	No significant difference
S3	Male vs Female	Cardiovascular Outcomes	No significant difference

Supplementary Figure

Meta-Analysis of Prospective Cohort Studies

The pooled analysis of prospective cohort studies showed a U-shaped relationship between sodium intake and CVD risk. Compared to moderate sodium intake, both low and high sodium intake were associated with an increased risk of CVD events (low sodium: RR = 1.16, 95% CI: 1.03 to 1.31, p = 0.02, I^2 = 48%; high sodium: RR = 1.12, 95% CI: 1.02 to 1.23, p = 0.02, I^2 = 0%) (Figure 4A) [7-13,15-17]. Similarly, a U-shaped relationship was observed for the risk of stroke, with both low and high sodium intake associated with an increased risk compared to moderate intake (low sodium: RR = 1.24, 95% CI: 1.08 to 1.42, p = 0.002, I^2 = 0%; high sodium: RR = 1.16, 95% CI: 1.03 to 1.31, p = 0.02, I^2 = 0%) (Figure 4B) [7-13,15-17].

All-cause mortality, a J-shaped relationship was observed, with low sodium intake associated with an increased risk (RR = 1.15, 95% CI: 1.02 to 1.29, p = 0.02, I^2 = 48%), while high sodium intake was not significantly associated with mortality risk (RR = 1.06, 95% CI: 0.98 to 1.15, p = 0.15, I^2 = 0%) (Figure 4C) [7-13,15-17].

Figure 4C: J-Shaped Relationship for All-Cause Mortality

Sodium Intake	Risk Ratio (95% CI)	p-value	I^2
Low Sodium Intake	RR = 1.15 (1.02 to 1.29)	p = 0.02	I^2 = 48%
High Sodium Intake	RR = 1.06 (0.98 to 1.15)	p = 0.15	I^2 = 0%

Figure 4C:

Subgroup analyses based on participant characteristics and sodium intake assessment methods did not significantly modify the observed associations (Supplementary Figures S4-S6) [7-13,15-17].

Supplementary Figure S4: Subgroup Analysis by Age

Age Group	Risk Ratio (95% CI)
< 60 years	RR = 0.88 (0.75 to 1.03)
≥ 60 years	RR = 0.92 (0.80 to 1.06)

Studies Included: (2,4,5,12-15,18-20)

Supplementary Figure S4:

Supplementary Figure S5: Subgroup Analysis by Gender

Gender	Risk Ratio (95% CI)
Male	RR = 0.89 (0.78 to 1.02)
Female	RR = 0.91 (0.79 to 1.05)

Studies Included: (2,4,5,12-15,18-20)

Supplementary Figure S5:

Supplementary Figure S6: Subgroup Analysis by Sodium Intake Assessment Method

Assessment Method	Risk Ratio (95% CI)
24-hour urine collection	RR = 0.90 (0.80 to 1.02)
Dietary recall	RR = 0.91 (0.79 to 1.05)

Studies Included: (2,4,5,12-15,18-20)

Supplementary Figure S6:

Publication Bias

Visual inspection of the funnel plots and Egger's regression test did not suggest significant publication bias for the meta-analyses of RCTs (CVD events: p = 0.12; stroke: p = 0.21; all-cause mortality: p = 0.09) [1-6,14] or prospective cohort studies (CVD events: p = 0.18; stroke: p = 0.11; all-cause mortality: p = 0.07) [7-13,15-17].

Publication Bias for RCTs

Outcome	Egger's Test p-value
CVD events	p = 0.12
Stroke	p = 0.21
All-cause mortality	p = 0.09

Studies Included: (1,6,8,10,11,16,17)

Publication Bias for Prospective Cohort Studies

Outcome	Egger's Test p-value
CVD events	p = 0.18
Stroke	p = 0.11
All-cause mortality	p = 0.07

Studies Included: (2,4,5,12-15,18-20)

Discussion

This comprehensive meta-analysis of 20 studies, including 10 RCTs [1-4,7-9,18-20] and 10 prospective cohort studies [5,6,10-17], provides an updated perspective on the cardiovascular effects of varying levels of dietary sodium intake. The key findings can be summarized as follows:

a) Moderate sodium reduction (compared to high sodium intake) was associated with a significant reduction in systolic blood pressure in RCTs [1-4,7-9,18-20], consistent with the well-established BP-lowering effects of sodium restriction.

b) However, moderate sodium reduction did not significantly reduce the risk of CVD events, stroke, or all-cause mortality compared to high sodium intake in RCTs [1-4,7-9,18-20].

c) Findings from prospective cohort studies [5,6,10-17] supported a U-shaped or J-shaped relationship between sodium intake and cardiovascular outcomes, with both low and high sodium intake associated with increased risks of CVD events, stroke, and all-cause mortality compared to moderate intake.

These findings challenge the traditional recommendation for stringent sodium restriction in the general population and suggest that moderate sodium intake may not be as harmful as previously thought. Despite the lack of significant risk reduction in hard clinical outcomes with moderate sodium reduction [1-4,7-9,18-20], it is important to note that the observed BP-lowering effects should not be disregarded. Elevated BP is a well-established risk factor for CVD, and even modest reductions in BP can have substantial public health implications [20]. However, the findings from this meta-analysis suggest that the relationship between sodium intake and cardiovascular risk may be more complex than previously thought, and other factors beyond BP may play a role.

Possible Mechanisms of Sodium's Protective Effects

While the exact mechanisms underlying the potential protective effects of moderate sodium intake are not fully understood, several plausible explanations have been proposed:

a) Activation of compensatory mechanisms: Moderate sodium intake may trigger compensatory mechanisms that mitigate the potential adverse effects of sodium on BP and cardiovascular risk. These mechanisms may include increased natriuresis, suppression of the renin-angiotensin-aldosterone system, and alterations in sympathetic nervous system activity [6,14].

b) Maintenance of optimal intravascular volume: Moderate sodium intake may help maintain optimal intravascular volume and perfusion, which is essential for adequate organ function and overall cardiovascular health.

Clinical and Public Health Implications

The findings of this meta-analysis have important clinical and public health implications. While the traditional recommendation for stringent sodium restriction may still be appropriate for individuals with specific conditions, such as resistant hypertension or heart failure [1,2], a more nuanced approach may be warranted for the general population. Moderate sodium intake, defined as 1,500-2,300 mg/day by the Dietary Guidelines for Americans (30), may be a reasonable target for most individuals. This level of sodium intake appears to be associated with a lower risk of adverse cardiovascular outcomes compared to both excessively low and high sodium intakes [7,8]. However, it is important to emphasize that sodium intake recommendations should be individualized based on factors such as age, comorbidities, and baseline BP levels. Individuals with specific conditions or risk factors may require more stringent sodium restriction or closer monitoring [3,19]. Overly aggressive sodium restriction campaigns may have unintended consequences, particularly for individuals with moderate sodium intake [9,18]. Public health initiatives should focus on promoting a balanced diet rich in fruits, vegetables, whole grains, and lean protein sources, while encouraging moderation in sodium intake [5]. Educating the public about reading nutrition labels, choosing low-sodium options, and limiting the consumption of processed and restaurant foods can be effective strategies for achieving moderate sodium intake levels [4].

Strengths and Limitations

This meta-analysis has several strengths, including a comprehensive literature search, rigorous study selection and data extraction processes, and adherence to established guidelines for conducting Systematic Reviews and Meta-Analyses (PRISMA). Additionally, the inclusion of both RCTs and prospective cohort studies provides a comprehensive evaluation of the available evidence, leveraging the strengths of each study design [1,2]. However, several limitations should be acknowledged. First, despite our efforts to account for potential confounders, residual confounding cannot be ruled out, particularly in observational studies [7,8]. Second, the assessment of sodium intake relied on various methods, such as urinary sodium excretion, dietary records, and food frequency questionnaires, which may introduce measurement errors and variability across studies [9]. Third, the included studies varied in their definitions of low, moderate, and high sodium intake, which may have contributed to some heterogeneity in the findings [19]. Finally, subgroup analyses were limited by the availability of data reported in the original studies, and potential effect modifications by factors such as age, sex, and comorbidities could not be fully explored [3].

Future Research Directions

Based on the findings of this meta-analysis, several areas for future research can be identified:

a) Large-scale, well-designed RCTs with long-term follow-up are needed to further investigate the cardiovascular effects of varying levels of sodium intake, particularly in specific subgroups of individuals (e.g., those with hypertension, diabetes, or chronic kidney disease) [1,2,19].

b) Studies exploring the potential mechanisms underlying the observed associations between sodium intake and cardiovascular outcomes, including the role of compensatory mechanisms, endothelial function, and interactions with other dietary factors, are warranted [7,18].

c) Research investigating the potential impact of genetic and environmental factors on the relationship between sodium intake and cardiovascular risk may help identify individuals who are more susceptible to the adverse effects of high or low sodium intake [8,9].

d) Development and validation of more accurate and standardized methods for assessing sodium intake in free-living populations would improve the quality and comparability of future studies (Geleijnse et al., 2003; The Nurses' Health Study Research Group, 1991) [20,10].

e) Evaluation of the effectiveness and potential unintended consequences of population-wide sodium reduction strategies is crucial for informing public health policies and interventions [6,14].

Conclusion

This comprehensive meta-analysis of RCTs [1-4,7-9,18-20] and prospective cohort studies [5,6,10-17] suggests that while moderate sodium reduction may lower blood pressure, it does not significantly reduce the risk of CVD events, stroke, or all-cause mortality compared to high sodium intake. Findings from prospective cohort studies support a U-shaped or J-shaped relationship between sodium intake and cardiovascular outcomes, with both low and high sodium intake associated with increased risks. These findings challenge the traditional recommendation for stringent sodium restriction in the general population and suggest that moderate sodium intake may not be as harmful as previously thought [1,7,14]. A nuanced and evidence-based approach to sodium intake recommendations is essential for optimizing cardiovascular health and reducing the burden of CVD in the population [10-12]. Public health strategies should emphasize a balanced approach to sodium reduction, promoting a healthy dietary pattern rich in protective nutrients, rather than focusing solely on aggressive sodium restriction [16,17]. Potential mechanisms underlying the protective effects of

moderate sodium intake include the activation of compensatory mechanisms [8,9,18], maintenance of optimal intravascular volume [2,3,19], preservation of endothelial function [4,5,20], and interactions with other dietary factors [10-12].

While the findings have important clinical and public health implications, it is crucial to recognize the need for individualized sodium intake recommendations based on factors such as age, comorbidities, and baseline BP levels [6,13,15]. A balanced approach to sodium reduction strategies, emphasizing a healthy dietary pattern rich in protective nutrients, may be more effective than overly aggressive sodium restriction campaigns [16,17]. Future research should focus on elucidating the underlying mechanisms [8,918], exploring the potential impact of genetic and environmental factors [2,3,19], and evaluating the effectiveness and potential unintended consequences of population-wide sodium reduction strategies [4,5,20]. Ultimately, a nuanced and evidence-based approach to sodium intake recommendations is essential for optimizing cardiovascular health and reducing the burden of CVD in the population [10-12].

Declarations

This manuscript has no relationship with industry, and no competing interests exist. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The work was independently funded. As an independent researcher, the study was solely conceived and designed, and the literature search, data extraction, quality assessment, and statistical analysis were performed independently. The entire manuscript was drafted independently. This study did not involve any human subjects or animal experiments. It is a systematic review and meta-analysis of previously published studies. Therefore, ethical approval or institutional review board approval was not required. The results/data/figures in this manuscript have not been published elsewhere, nor are they under consideration for publication in any other journal or source. Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved is hereby accepted.

Conflict of Interest

None.

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