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Association Between Sodium Intake and Risk of Hypertension, Heart Failure, Stroke, and Myocardial Infarction: A Systematic Literature Review and Meta-analysis

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Introduction

- Sleep disorders, such as narcolepsy and idiopathic hypersomnia, are associated with high cardiovascular comorbidity burden[1,2]
- Substantial evidence supports a strong relationship between excess sodium consumption and increased risk of cardiovascular morbidity and mortality[3-7]
- Accordingly, US and international health and nutritional guidelines, including the US Department of Agriculture, American Heart Association, American College of Cardiology, and World Health Organization, recommend limiting dietary sodium intake to reduce the risk of cardiovascular disease[4,5,8-14]
- Certain medications can contribute to sodium consumption in excess of recommended limits (<2300 mg/day for most adults);[4,5] for example, some narcolepsy medications contain up to 1640 mg of sodium per nightly 9 g dosage[15,16]

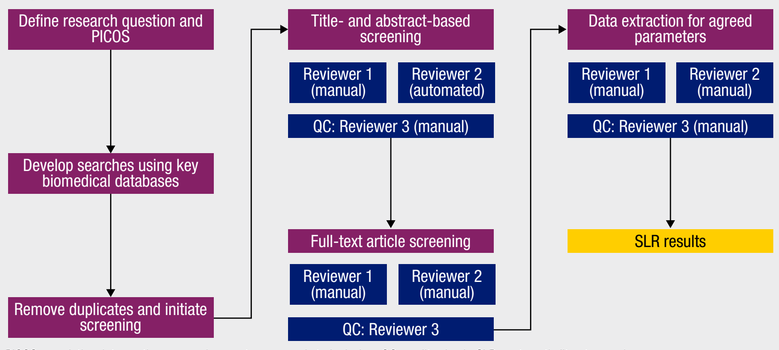
Objective

- This up-to-date systematic literature review (SLR) and meta-analysis qualitatively and quantitatively evaluated the relationship between sodium intake and the risk of hypertension (HTN), stroke, heart failure (HF), and myocardial infarction (MI)

Methods

- A comprehensive, gold-standard SLR was conducted using Embase®, MEDLINE®, CENTRAL®, conference proceedings, and clinical trial registries to identify studies published up to 7 December 2023
- Study selection, data extraction, and risk of bias assessments (Cochrane RoB2.0[17] and Newcastle-Ottawa Scale[18]) were conducted manually by 2 independent human reviewers
  - For title and abstract screening, 1 human reviewer was replaced with an artificial intelligence-based tool (GPT-4)
  - Discrepancies were resolved by a third human reviewer
- Meta-analyses were conducted for studies meeting prespecified *Population, Intervention, Comparison, Outcomes, and Study design* (PICOS) criteria, including observational or interventional designs assessing associations between higher vs lower sodium levels (variably defined across studies) and the risk of HTN, stroke, HF, or MI in adults
  - Meta-analysis results are reported as odds ratios or hazard ratios

Figure 1. SLR Process Overview



PICOS, population, intervention, comparison, outcomes, and study design; QC, quality check; SLR, systematic literature review.

Table 1. PICOS Criteria

Inclusion Criteria	Exclusion Criteria
Population	
• Adults (≥18 years) with any condition or presentation, including individuals with and without pre-existing medical conditions, irrespective of gender, race, ethnicity, and region	• Individuals <18 years old • Studies for which outcomes for adults are not presented separately
Intervention/Exposure	
• No restriction on the type of intervention/exposure (eg, dietary or drugs), dose, or dosage form	• Sodium reduction beyond recommended limits (eg, 500 mg daily is the minimum body requirement according to AHA)
Comparator/Control	
• No restriction on the type of comparator/control; including studies that compare higher to lower/non-exposed sodium intake groups	• Sodium reduction beyond recommended limits (eg, 500 mg daily is the minimum body requirement according to AHA)
Outcomes	
• Hypertension, myocardial infarction, stroke, and heart failure outcomes	• Studies that do not report a health outcome of interest
Study design	
• Observational or interventional designs assessing associations between higher vs lower sodium levels and the risk of hypertension, stroke, heart failure, or myocardial infarction	

AHA, American Heart Association; CV, cardiovascular; PICOS, population, intervention, comparison, outcomes, and study design.

- Both fixed-effects and random-effects models were applied to the primary analysis (all eligible studies) and subgroup (studies where sodium levels were assessed via 24-hour urine collection to minimise bias and heterogeneity in sodium measurement) meta-analyses
  - Pooled effect estimates were derived using STATA v18.5 SE
- Statistical heterogeneity of effect estimates was assessed using the I^2 statistic
- Publication bias was evaluated using funnel plots, where asymmetry may indicate potential bias, such as selective reporting

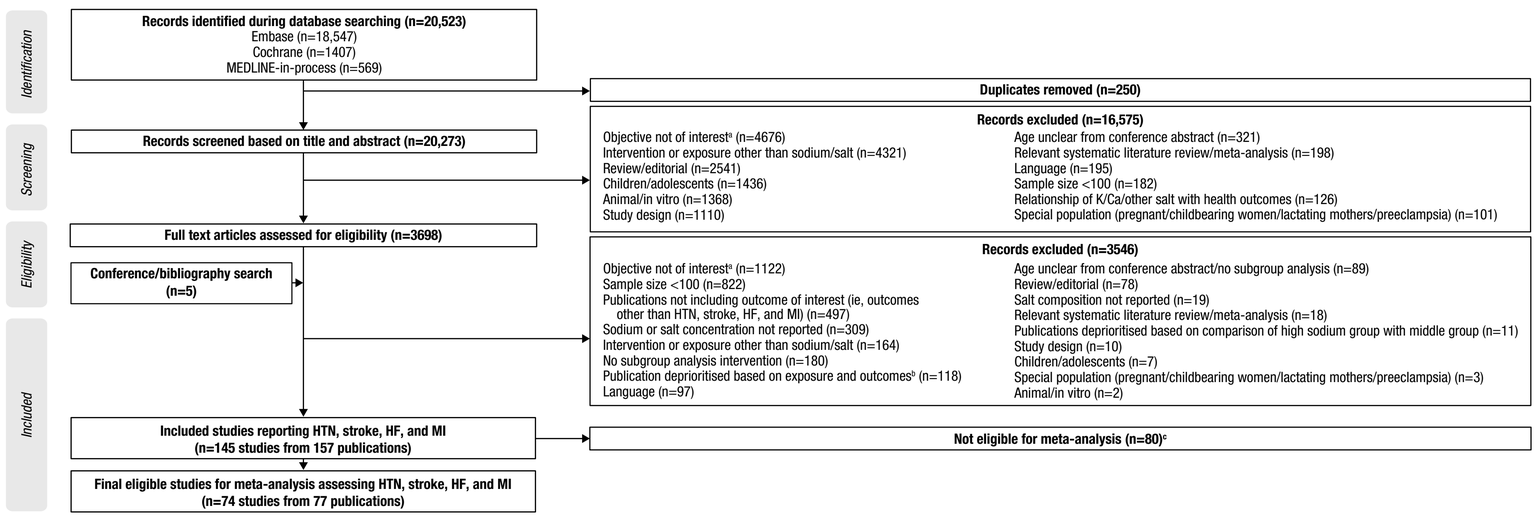
References: 1. Ben-Joseph RH, et al. *Sleep.* 2023;46(10):zsad161. **2.** Saad R, et al. *Sleep Med.* 2025;133:106587. **3.** Wang X, et al. *Mayo Clin Proc.* 2023;98:1641-52. **4.** Whelton PK, et al. *Circulation.* 2018;138:e426-e83. **5.** National Academies of Sciences, Engineering, and Medicine. Dietary reference intakes for sodium and potassium. Washington, DC: The National Academies Press. 2019. https://doi.org/10.17226/25353. **6.** US Food and Drug Administration. Voluntary sodium reduction goals: target mean and upper bound concentrations for sodium in commercially processed, packaged, and prepared foods (edition 2): guidance for industry. 2024. https://www.fda.gov/media/180784/download. **7.** Strazzullo P, et al. *BMJ.* 2009;339:b4567. **8.** US Department of Agriculture, US Department of Health and Human Services. Dietary guidelines for Americans, 2020-2025. 2020. https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials. **9.** World Health Organization. Guideline: sodium intake for adults and children. Geneva, Switzerland: World Health Organization. 2012. **10.** American Heart Association. How much sodium should I eat per day? 2024. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/how-much-sodium-should-i-eat-per-day. **11.** US Food and Drug Administration. Sodium reduction. 2021. https://www.fda.gov/food/food-additives-petitions/sodium-reduction. **12.** Arnett DK, et al. *J Am Coll Cardiol.* 2019;74:e177-e232. **13.** World Health Organization. WHO global report on sodium intake reduction. Geneva, Switzerland: World Health Organization. 2023. **14.** Jones DW, et al. *Hypertension.* 2025; 14 Aug [Online ahead of print]. **15.** Xyrem® (sodium oxybate) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **16.** Lumryz™ (sodium oxybate) for extended-release oral solution, CIII [prescribing information]. Chesterfield, MO: Avadel CNS Pharmaceuticals. **17.** Sterne JAC, et al. *BMJ.* 2019;366:l4898. **18.** Wells G, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2011. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Support and Acknowledgements: This study was supported by Jazz Pharmaceuticals. Under the direction of the authors, Aeja Jackson, PhD, MS, and Eleanor Bush, MA, of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support for this poster, which was funded by Jazz Pharmaceuticals.

Disclosures: C Drachenberg, S Mettam, JK Alexander, M Whalen, and **L Pinto** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **B Singh, S Attri,** and **R Dubey** are full-time employees of Pharmacoevidence Pvt. Ltd. Pharmacoevidence provides consultancy services to pharmaceutical companies and consultancies. Jazz Pharmaceuticals contracted Pharmacoevidence to conduct this study. **LA Surkin** is a consultant to Alkermes, Jazz Pharmaceuticals, and Takeda.

Results

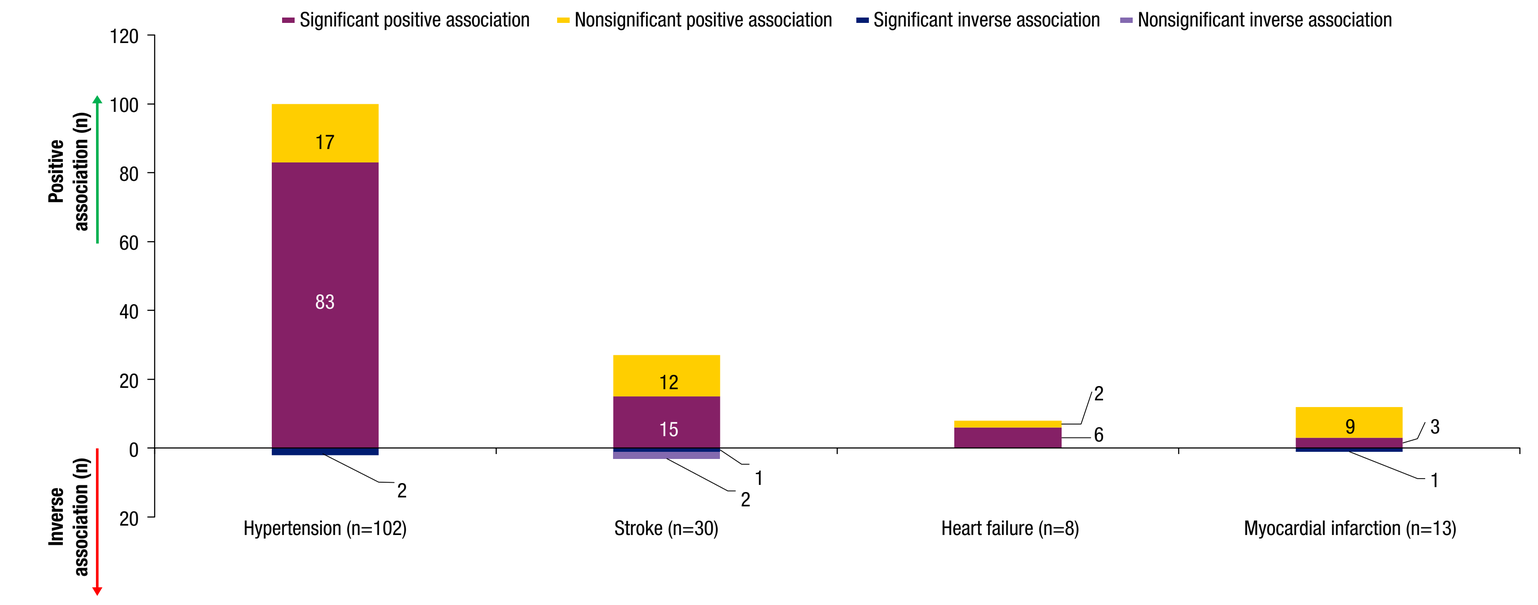
Figure 2. PRISMA Diagram



[a]Publications reporting associations of genetic variations with outcome response to salt; associations of outcomes with parameters other than salt intake; influence of sodium exposure on effectiveness of pharmacological interventions; 0.9% sodium chloride as comparator; relationship of sodium/salt with minerals and hormones; adherence/preference data; or results from statistical modelling. [b]Publications reporting associations between sodium/potassium ratio, sodium/creatine ratio, sodium density, and outcome of interest; or outcomes such as DALY or annual percentage change in prevalence rate across different years. [c]Fewer than 2 studies per outcome and analysis set; sample size not reported; sodium concentration <500 mg or <20 mmol; results reported per gram increase; or data for subgroup of interest not reported.
Ca, calcium; DALY, disability-adjusted life year; HF, heart failure; HTN, hypertension; K, potassium; MI, myocardial infarction; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

- The SLR included 145 studies reporting HTN, stroke, HF, and MI; low risk of bias was observed in most studies (n=142, 97.9%)

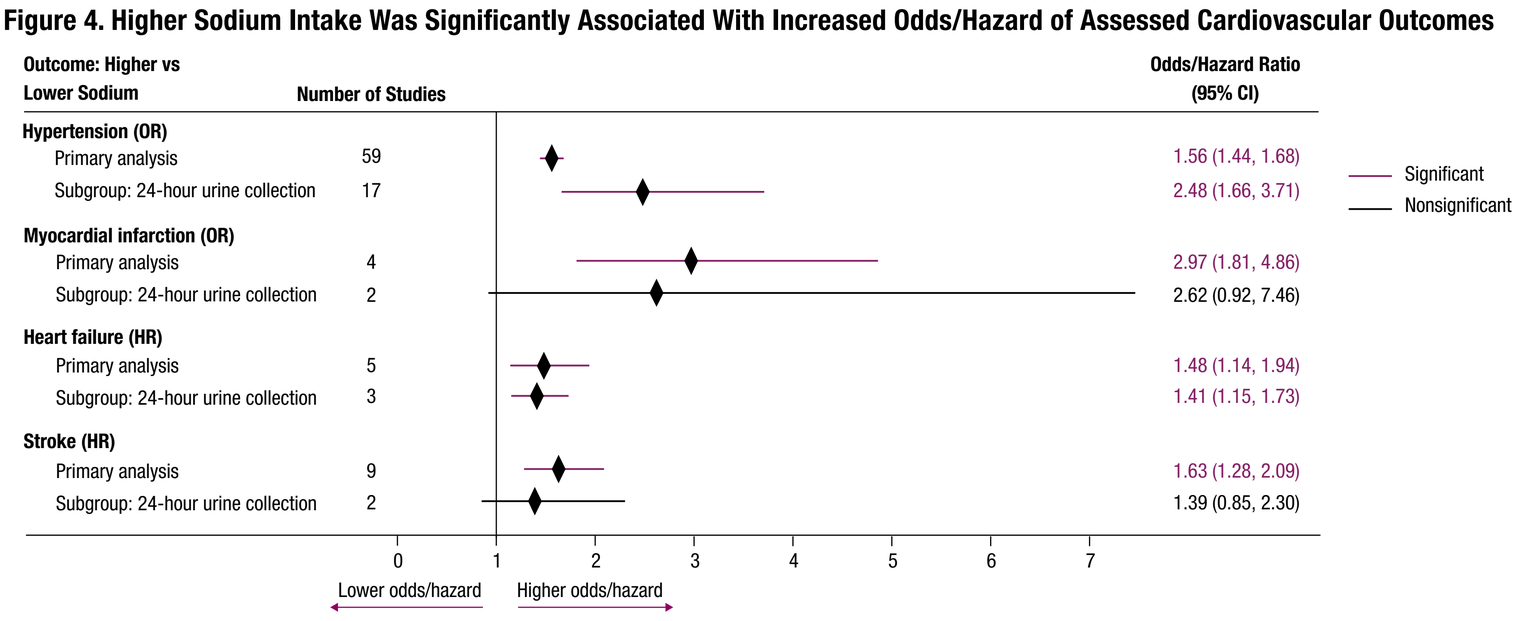
Figure 3. Most Studies Reported That Higher Sodium/Salt Intake Was Significantly Associated With Increased Risk of HTN, Stroke, and HF



HF, heart failure; HTN, hypertension; MI, myocardial infarction.

- Higher sodium/salt intake was significantly associated with increased risk of HTN (83/102 studies), stroke (15/30), HF (6/8), and MI (3/13)

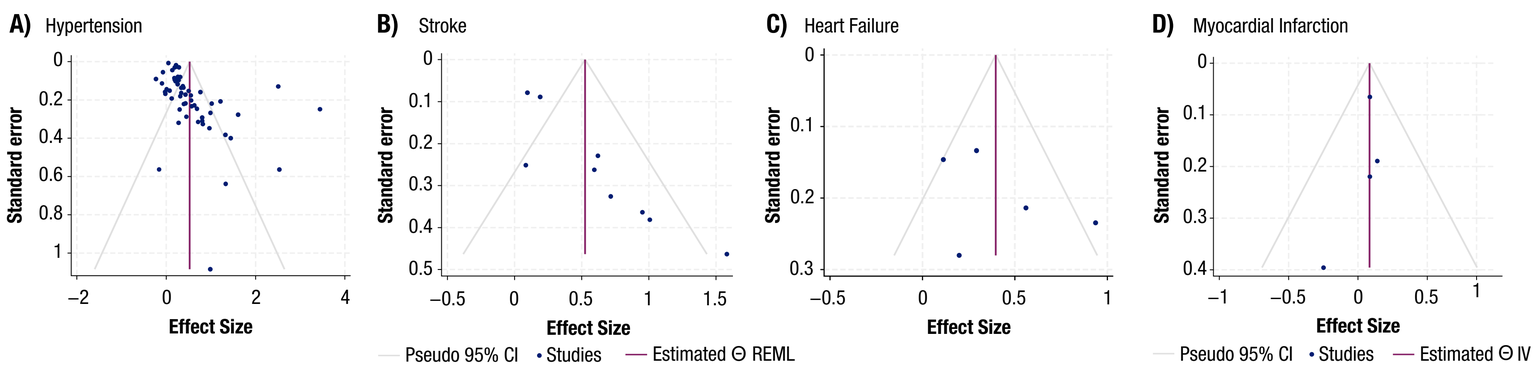
Figure 4. Higher Sodium Intake Was Significantly Associated With Increased Odds/Hazard of Assessed Cardiovascular Outcomes



CI, confidence interval; HR, hazard ratio; OR, odds ratio.

- Meta-analysis of 74 studies (HTN=59; stroke=9; HF=5; MI=4) found that higher sodium intake was significantly associated with increased odds/hazard of HTN (odds ratio [OR]: 1.56, 95% confidence interval [CI]: 1.44–1.68), stroke (hazard ratio [HR]: 1.63, 95% CI: 1.28–2.09), HF (HR: 1.48, 95% CI: 1.14–1.94), and MI (OR: 2.97, 95% CI: 1.81–4.86)
- Subgroup analyses of studies using 24-hour urine collection to measure sodium were comparable to those observed in the primary analysis for HTN (OR: 2.48, 95% CI: 1.66–3.71) and HF (HR: 1.41, 95% CI: 1.15–1.73)
  - A directionally similar trend to the primary analysis was observed for stroke (HR: 1.39, 95% CI: 0.85–2.30) and MI (OR: 2.62, 95% CI: 0.92–7.46)
- Statistical heterogeneity was low in MI (I^2 0%), moderate in stroke (I^2 70.4%) and HF (I^2 61.1%), and high in HTN (I^2 94.0%) studies

Figure 5. Funnel Plots for Studies Evaluating Associations Between Higher vs Lower Sodium and A) Hypertension B) Stroke C) Heart Failure D) Myocardial Infarction



CI, confidence interval; IV, inverse variance; REML, restricted maximum likelihood.

- Funnel plots showed no evidence of asymmetry for MI, some evidence of asymmetry for stroke and HF, and substantial asymmetry for HTN studies

Conclusions

- This up-to-date and expansive SLR and meta-analysis are consistent with and expand upon the robust evidence base demonstrating that higher sodium intake is significantly associated with increased risk of HTN, stroke, HF, and MI
  - Subgroup analyses measuring sodium using 24-hour urine collection were consistent with the primary analysis that included broader study designs
- As with all SLRs and meta-analyses, these analyses relied on published literature, where studies with positive or significant findings may be overrepresented
- Findings reinforce clinical and health authority recommendations to reduce sodium intake to protect cardiovascular health, particularly in populations at elevated risk of cardiovascular morbidity and mortality

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Presented at World Sleep Congress; 5–10 September 2025; Singapore