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Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: A meta-analysis. Am J Hypertens. 2014;27(9):1129–37.

What We Know, Think We Know, or Are Starting to Know

26-31% of female and male adults, respectively, are hypertensive in the UK and US. Public health recommendations to reduce sodium developed in earnest in the United Kingdom and other countries in the early 2000s, based off the relationship between sodium intake, hypertension, and cardiovascular disease.

The relationship between blood pressure and cardiovascular disease is hard to dispute [1,2]. The link between hypertension and cardiovascular disease like stroke, and coronary heart disease, satisfies every element of the Bradford-HIll criteria. The association is strong, consistent, specific, temporal [i.e., hypertension precedes disease[, graded [i.e., shows a clear - in this case linear - dose-response], has biological plausibility from experimental evidence [sodium reductions lowering blood pressure], and is coherent with the overall body of evidence.

In nutrition research, however, RCTs with death as an outcome are rare. RCTs tend to examine the effects of an intervention on intermediate risk factors, like blood pressure. In relation to the intervention of sodium reduction on blood pressure, over 100 RCTs provide a coherent and consistent evidence from controlled interventions that reducing sodium leads to reductions in blood pressure [3]. This robust body of evidence dates back to the 1990' s, an example of which can be seen in the initial publication of the Dietary Approaches to Stop Hypertension [4].

However, there have been questions raised over the link between sodium and cardiovascular disease at a population level [5]. In particular, it has been suggested that the relationship is a 'J-shaped curve' , where high and low levels are associated with adverse health outcomes. The present study was a meta-analysis of prospective cohort studies and randomised controlled trials evaluating the association between sodium intake and mortality, with the goal of identifying ranges of intake where the risks of of low or high intakes are minimal.

*Geek Box: Bradford-Hill Criteria

In 1965, Sir Austin Bradford Hill described his criteria for inferring causation, a framework that encapsulates the concept of considering converging lines of evidence to form conclusions. At the time, the tobacco industry was throwing up smoke and mirrors against the relationship between smoking and cancer, and arguing there was no "proof" of causality. Bradford-Hill published his seminal paper on evaluating causal relationships from observational research. However, in the 1970's, the term "meta-analysis" was coined, and this approach to synthesising research quickly became a new dogma [more on this in the next Geek Box], superseding the scientific process of considering multiple lines of evidence, and thoroughly thinking through evidence from multiple angles. The Bradford-Hill criteria includes: strength of the association, consistency, specificity, temporality, dose-response, plausibility, coherence, reversibility [i.e., does reducing the exposure influence frequency of disease], and experimental evidence. It gives us a framework to consider evidence when we don't have The-Unicorn-RCT-That-Tells-Us-Everything-We-Want-To-Know. And when we consider evidence through this criteria, we are forced to engaged our 'Big Picture' thinking about be critical. Interestingly, because of the limitations of tools like meta-analysis for nutrition science, researchers appear to be turning back to using the Bradford-Hill criteria for assessing the evidence for different research questions. The criteria remains as relevant today as it was when Bradford-Hill published his seminal paper on the environment, disease, and causation.

The Study

The investigators included cohort studies with an individual measure of dietary sodium intake, and RCTs allocating participants to low, usual, or high sodium diets and having outcome data on all-cause mortality and/or cardiovascular events/mortality. Participants were grouped in sodium exposure groups:

i. low sodium (mean daily sodium intake <115mmol; 2,645mg sodium);

ii. usual sodium (mean daily sodium intake of 115–215mmol; 2,645-4945mg sodium), and;

iii. high sodium (mean daily sodium intake >215mmol; 4,945 mg sodium).

The included cohort studies determined sodium intake through a number of collection methods, including 24-hour urinary sodium, spot urine tests [a single sample], 24-hour dietary recalls, and food-frequency questionnaires.

The high and low sodium groups were the exposures of interest, and were compared to the usual sodium group. Outcome measures included all-cause mortality, cardiovascular mortality and events [CVD], stroke mortality and events, and heart disease mortality and events.

*Geek Box: Meta-Analysis

The term "meta-analysis" was coined in 1976 by a psychologist, Gene Glass, as "an analysis of analyses". The conceptual basis was a means to address the sheer volume of studies published in medical and social sciences, and distill such large quantities of research into a summary estimate of the effect of an intervention or drug. Conducting a meta-analysis involves: (a) selecting the primary studies to be included in the meta-analysis; (b) calculating the magnitude of the effect of the particular exposure/intervention for each study; (c) assigning a statistical weight to each study, which is determined by the size and quality of the study [the weight is always out of 100%], and; (d) calculating a summary average of the magnitude of effect from all studies. This latter purpose has become the primary outcome of meta-analyses conducted by investigators, but meta-analysis can also be used to compare and contrast different studies for differences, and to identify patterns amongst the included studies. Epidemiologists have long argued that these latter two functions would be a much more effective use of meta-analysis for observational research, however, many investigators continue to remain myopically focused on attempting to synthesise the results into a "conclusive" summary estimate. However, the summary estimate is only precise if the included studies are uniformly similar in methodological quality, and that is certainly not the case for nutrition science. As a result, summary estimates of nutrition studies are often untrustworthy. Meta-analysis in nutrition science can, consequently, be akin to throwing mud against a wall to see what sticks. Because they are considered the "platinum standard" of evidence, their results are often accepted unquestioningly, which is problematic when the results are misleading. Be cautious with meta-analysis; when it comes to nutrition science, their general status of "platinum standard" evidence is not warranted, and they take significant expertise in research methods, and in nutrition as a subject [which many investigators simply don't have the first clue if we're being honest], to do well.

Results: 25 studies were included in total, 23 of which were prospective cohort studies. The investigators stated that only 2 RCTs could be identified according to their inclusion criteria, and thus did not conduct a meta-analysis of RCTs. Most cohort studies adjusted for blood pressure and hypertension.

Comparing low sodium intake [<2,645mg] to usual sodium intake [2,645-4945mg], the risk of ACM and CVD was 9% lower [HR 0.91, 95% CI = 0.82-0.99]] in the usual sodium group, while there was no difference in stroke or HD. Comparing within the usual range sodium group from the lower intake of 2,645-3795mg to the higher intake of 3795-4945mg sodium, there was no significant difference in outcomes between groups. Finally, comparing the high sodium intake to usual sodium intake, the high intake group had a 16% increase in risk for ACM [HR = 1.16, 95% CI = 1.03–1.30], a 12% increase in risk for CVD [HR = 1.12, 95% CI = 1.02–1.24], an 18% increase in risk for stroke [HR = 1.18, 95% CI = 1.05–1.33], and a 17% increase in risk for heart disease [HR = 1.17, 95% CI = 1.08–1.27].

The Critical Breakdown

Pros: A significant number of total participants were included [n=274,683] across all cohort studies. This would have been more effective if the investigators had chosen a pooled analysis, where the primary data of the included studies is all compiled together, rather than meta-analysis, where a single summary result of the study is included. The analysis attempted to stratify sodium intake relative to recommended definitions.

Cons: The primary negative is the inclusion of studies which used a range of sodium assessment methods [more under Key Characteristic, below]. Only 11 studies had 24-hour sodium measures. This would have the effect of influencing all subsequent results. While combining the data together is intended to increase statistical power, when the comparison populations are divergent, it results in weakened power. Combining biased data does not erase the underlying issues of the included studies. In addition, the choice of comparison levels of intake, always a potential source of issues in nutritional epidemiology, and in this study the low levels were still around 1000mg higher than recommended adequate intake levels [1,500mg/d]. The comparison levels may have been inadequate to truly compare the effects of lowering sodium [more on this under Interesting Finding, below].

Key Characteristic

The primary limitation underpinning this entire meta-analysis is the methodological issues in a significant proportion of the included studies. The gold standard for assessing sodium intake at a population level is multiple non-consecutive 24-hour urinary sodium collections from the same participant, over a period of time. This is because the variance in sodium intake from day to day in humans is enormous, up to 5-fold differences in individual variations in sodium excretion [(6)]. Salt intake may vary within the same person as much as the variation from one person to the next, making associations with health outcomes difficult to detect unless more precise quantifications of sodium intake are taken. A single 24-hour urinary sodium collection fails to capture this within-person variance, and may underestimate sodium intake by up to 7.5g [(6)]. And dietary assessment records, whether 24-hour recalls or food-frequency questionnaires, do not correlate as with dietary sodium intake. Conversely, prospective cohort studies that use multiple 24-hour collections are prone to less variation, and provide more reliable information when factoring in population means of intake [(6)]. Using single measures or dietary records compromises the ability to detect true associations between individual sodium intake and CVD; the high degree of intra-individual variability in daily sodium means single samples increase the potential for error which is difficult to overcome in epidemiology even with large sample sizes or post-hoc adjustments [(7)]. Using the gold standard of assessing sodium levels in the population, the Trials of Hypertension Prevention, collected 3-7 non-consecutive 24-hour collections over 1.5-4-years; there was a linear 17% increase in CVD risk per 1000mg/d increase in sodium from levels starting at 1500mg/d [(8)].

Interesting Finding

They did not include a single RCT according to their criteria, and thus no meta-analysis of controlled trials was conducted. This appears to be due to the fact that the vast majority of RCTs do not investigate mortality as an outcome. However, interventions have addressed blood pressure and there is a significant body of literature investigating the effects of changes in sodium intake on blood pressure in participants with hypertension and normotensive participants. The Dietary Approaches to Stop Hypertension [DASH] interventions, together with other interventions, have specifically compared reductions in sodium to <2g/d vs. >2g/d, and found significant reductions of 3.47mmHg for systolic blood pressure and by 1.81mmHg for diastolic blood pressure when sodium intake was <2g/d [(9)]. There are over 100 trials with interventions to reduce sodium intake demonstrating that reductions in sodium lower blood pressure levels [(3)], and this is clinically relevant to reductions in CVD risk, and mortality.

Relevance

The goal of a meta-analysis is to achieve statistical precision in a result, but that is not possible if the results are invalid. Meta-analysis has become a tool for misuse in nutrition science, creating controversy with regard to dietary intake with important implications for population health. Meta-analyses like this, and their superficial interpretation, distract from the effectiveness of sodium reduction for improving population health. In the US population, estimated benefits of reductions in sodium intake to 2,300mg/d could prevent 11 million cases of hypertension and save $18 billion health care dollars [(10)]. In the UK, reformulation policy introduced in 2001 resulted in an average reduction of sodium intake in adults by 15%, contributing to a 40% reduction in ischemic heart disease incidence between 2003 and 2011 [(11)]. When we take both well-designed long-term prospective cohort studies and sodium-reduction intervention trials with a minimum of 6-months duration, there is strong evidence that lowering dietary sodium reduces risk of CVD events and mortality [(8,12)]. It is important that poor studies, such as the present under review, are not taken as countering a body of evidence weighted against its findings.

Application to Practice

The World Health Organisation, Public Health England, American Heart Association, and over 40 national health bodies across the world have advice to reduce sodium intake. There is no obvious need for an individual practitioner to decide against this, but to help achieve that reduction in the context of the individual' s diet. Reformulation has resulted in a dramatic reduction in added salt in processed foods, however, processed foods remain the primary source of added salt intake in the population. Established dietary patterns, such as the DASH diet, contain food-based recommendations to guide dietary changes towards a potassium-rich, lower sodium diet. The totality of evidence supports this dietary modification.

References

1. McMahon S, Peto R, Collins R. Blood pressure, stroke, and coronary heart disease *1Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. The Lancet. 1990;335(8692):765-774.
2. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. The Lancet. 1995;346(8991-8992):1647-1653.
3. Mozaffarian D, Fahimi S, Singh G. Global Sodium Consumption and Death From Cardiovascular Causes. Journal of Vascular Surgery. 2015;61(2):567.
4. Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA: The Journal of the American Medical Association. 1992;267(9):1213-1220.
5. Mente A, O' Donnell M, Rangarajan S. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. The Lancet. 2016;388(10043):465-475.
6. Cogswell M, Mugavero K, Bowman B, Frieden T. Dietary Sodium and Cardiovascular Disease Risk — Measurement Matters. New England Journal of Medicine. 2016;375(6):580-586.
7. Cogswell M, Maalouf J, Elliott P, Loria C, Patel S, Bowman B. Use of Urine Biomarkers to Assess Sodium Intake: Challenges and Opportunities. Annual Review of Nutrition. 2015;35(1):349-387.
8. Cook N, Appel L, Whelton P. Lower Levels of Sodium Intake and Reduced Cardiovascular Risk. Circulation. 2014;129(9):981-989.
9. Aburto N, Ziolkovska A, Hooper L, Elliott P, Cappuccio F, Meerpohl J. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ. 2013;346(apr03 3):f1326-f1326.
10. Polar K, Sturm R. Potential Societal Savings from Reduced Sodium Consumption in the U.S. Adult Population. American Journal of Health Promotion. 2009;24(1):49-57.
11. He F, Pombo-Rodrigues S, MacGregor G. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. BMJ Open. 2014;4(4):e004549.
12. He F, MacGregor G. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. The Lancet. 2011;378(9789):380-382.