Sodium and Cardiovascular Disease: What the Data Show

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Considerable attention has been devoted to interpretation of cohort analyses used to study the relationship between sodium (Na) intake and cardiovascular disease (CVD). Reports have included analyses from individual studies, systematic reviews of the literature, and meta-analyses. Recently, Graudal *et al.* published a meta-analysis and concluded, "Both low sodium intakes and high sodium intakes are associated with increased mortality, consistent with a U-shaped association between sodium intake and health outcomes."[1] Before accepting this statement, one should consider the quality of the underlying studies, the appropriateness of pooling the data, study-specific methodological issues, results of cohort studies not included in Graudal *et al.*'s meta-analysis, evidence from randomized controlled trials (RCTs), and the consistency of Graudal *et al.*'s conclusion with those of other investigators.

Quality of the underlying studies

Every cohort analysis that has explored the relationship between Na and CVD (Na–CVD) was based on secondary examination of data from studies not originally designed to investigate the association. All were subject to methodological challenges,[2] including the potential for systematic bias in measurement of Na, reverse causality, and imprecision of urinary Na estimates. A recent systematic review of 31 independent Na–CVD analyses, based on experience in 26 cohorts, identified a direct association in 13 analyses (42%), a J-shaped curve in 2 (6%), a null relationship in 8 (26%), and an inverse relationship in the remaining 8 (26%).[3] On average, there were 3–4 methodological issues per study. Issues with greater and lesser potential to alter the direction of the association were noted in 96% and 69% of the studies, respectively, whereas issues with the potential to yield false-negative results were noted in 88%. Na intake was estimated by means of 24-hour recall or food frequency instruments in 15 (58%) of the studies, with only a single observation used in 13 (87%) of the 15 studies. Use of gold-standard 24-hour urine estimates was restricted to 9 (35%) of the studies, and all but 2[4,5] were based on use of a single 24-hour urine collection. A recent Na balance study identified an astounding degree of day-to-day variation in urinary Na excretion,[6] underscoring the importance of estimation based on an average derived from multiple 24-hour urine collections.

These issues have led several review panels to express serious concerns about the quality of the cohort data that have been used to assess the relationship between Na intake and CVD. The authors of the previously mentioned systematic review[3] judged the quality of the data as substandard and felt methodological issues might account for the inconsistent findings from these studies. Others have reached a similar conclusion. A 2013 Institute of Medicine (IOM) Committee report found the studies "were highly variable in methodological quality, particularly in assessing sodium intake."[7] A 2012 World Health Organization (WHO) report noted a significant direct relationship between Na and stroke but using GRADE methodology identified the quality of the evidence as "very low."[8]

Appropriateness of data pooling

Concerns regarding quality and heterogeneity of the methods used to assess the relationship between Na and CVD in cohort studies have led some to confine their exploration of Na–CVD cohort analyses to a systematic review without attempting to pool the data from individual studies.[3,7] Pooling of biased data, rather than eliminating the underlying error, is likely to provide a false sense of security and convey the impression of a more robust finding. The 2013 IOM Committee report[7] indicates, "It was the consensus of the committee that the lack of consistency among studies in the methods used for defining sodium intakes at both high and low ends of the range of typical intakes among various population groups precluded deriving a numerical definition for high and low intakes in its findings and conclusions." Dr. Gruadal was a participant in this consensus decision, and Dr. Alderman would have been aware of it because he served as a reviewer for the report.

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Study-specific concerns

Over and above the previously mentioned general concerns, the meta-analysis by Graudal *et al.*[1] raises a variety of additional study-specific methodological issues. Choice of cut points for quantitative estimation of exposures can dramatically influence findings in observational epidemiology.[9] Readers can only access the categorizations reported. The post hoc choice of nontraditional cut points by Gruadal *et al.* should lead to caution in the interpretation of their findings. They imply use of IOM recommendations to derive low and high Na cut points based on adequate intake (AI) and tolerable upper intake level. However, their Na AI of 115 mmol/day (2,645 mg/day) bears no resemblance to the IOM AI of 65 mmol/day (1,500 mg/day).[10] Likewise, their high Na cut point of >215 mmol/day (4,945 mg/day) is well above the IOM upper intake level of 2,300 mg/day.[10] Gruadal *et al.* conducted multiple testing for comparisons based on 4 clinical outcomes (all-cause mortality, CVD, stroke, and heart disease) and 5 levels of Na intake (low, usual, low usual, high usual, and high), raising the specter of chance findings due to type I errors. Their article and supplementary appendix provide insufficient results to determine the consistency of their findings. In their primary analysis, Graudal *et al.* choose to include studies based on first analysis of Na–CVD relationship in the NHANES I and NHANES III cohorts. Alternative analyses of these cohorts yielded very different results, highlighting the impact of inclusion/exclusion decisions and choice of analytic techniques on the findings. When the alternative analyses were used the usual vs. low Na hazard ratio for all-cause mortality changed from 0.91 (95% confidence interval (CI) = 0.82–0.99) to 0.99 (95% CI = 0.88–1.11).[1]

Other cohort studies

Two recent higher-quality cohort analyses have identified a direct relationship between Na and CVD.[4,11] Cook *et al.* used extended follow-up of Trials of Hypertension Prevention (TOHP) participants who were not part of the Na reduction intervention to examine the Na–CVD relationship.[4] Strengths of this study included enrollment of 2,275 participants who were healthy and not receiving blood pressure (BP) medication at baseline (making reverse causality unlikely), use of 3–7 carefully collected 24-hour urine collections to estimate average Na (reducing the possibility of systematic and random error in Na assessment), a distribution of Na intake similar to the US general population, follow-up for >10–15 years, blinded assessment of outcomes, Na categories based on recommendations in the public domain,[2,12] and use of spline curves for a continuous assessment of the Na–CVD relationship. There was a 17% increase in risk of CVD per 1,000 mg/day increase in Na ($P = 0.05$) and an apparent linear trend in the association from Na of 3,600 to 2,300 and 1,500 mg/day.

Other study designs

Randomized controlled trials (RCTs) should provide the most valid assessment of intervention effect. In the 1 RCT specifically designed to study efficacy of Na reduction in preventing CVD,[13] the CVD mortality hazard ratio for lower Na compared with usual Na was reported to be 0.59 (95% CI = 0.37–0.95). This analysis did not take into account the trial's cluster design, and the lower Na was achieved by a replacement salt that was higher in potassium as well as lower in Na. None of the BP-lowering Na reduction trials were powered to recognize an effect on CVD. However, Na reduction in the Trial of Nonpharmacologic Intervention in the Elderly resulted in a nonsignificant 23% decrease in CVD events.[2] Extended 10–15-year post-trial follow-up of TOHP participants identified a significant 30% decrement in CVD events and a nonsignificant 20% decrease in CVD mortality for those originally assigned to Na reduction compared with usual care.[2] RCTs are well suited to evaluation of intervention effect on clinical outcomes in high-risk settings but not in the lower-risk settings where prevention interventions such as Na reduction are assessed. A traditional 2-arm clinical events outcome Na reduction trial conducted in a Western country such as the United States would probably require randomization and 5-year follow-up of close to 30,000 participants.[2] The challenges of conducting and funding such a trial make it highly unlikely that it will be realized in the foreseeable future. Use of a cluster design in a high-risk setting would reduce the sample size, but funding and successful conduct of such a trial would still be a formidable challenge. A large-scale, cluster-designed community education and salt substitution RCT is being conducted in 120 communities in Northern China,[14] but it is only powered to recognize effects on 24-hour Na excretion (primary outcome) and on BP and hypertension (secondary outcomes), and its results will not be available for several years. The largest body of RCT evidence on the results of Na reduction relates to effects on BP, and overviews have consistently identified a reduction in BP that tends to be greater in participants with a higher baseline BP, older individuals, blacks, and those with greater intervention success.[2] BP is one of the best surrogate measures for CVD,[15] especially stroke, and the most important risk factor for worldwide mortality and disability-adjusted life years.[15]

Consistency of the interpretation

The interpretation by Graudal *et al.* differs from conclusions by authors of previous meta-analyses,[16,17] the 2013 IOM Committee,[7] 2 American Heart Association Committees,[2,3] the WHO,[8] and at least 40 national agencies around the world.[18]

Current Na intake

Based on 24-hour recall experience, Cogswell *et al.* estimated a median Na intake of 4,008 mg/day in US men, with an interquartile range of 3,326 to 4,787 mg/day, and a median Na intake of 2,826 mg/day in US women, with an interquartile range of 2,357 to 3,382 mg/day.[19] Dietary recalls underestimate Na intake by approximately 25%,[2] so the true medians are probably closer to 5,000 and 3,500 mg/day in men and women, respectively. In Cogswell *et al.*'s analysis, almost everyone was consuming Na at a level above that recommended by the American Heart Association and the 2010

federal Dietary Guidelines for Americans.[15] The same is true for other countries and world regions.[20] The vast majority of Na in the United States and other Western countries comes from addition during food processing.[2] This "unplanned experiment" is deeply rooted in food processing practices, but experience indicates voluntary and mandated changes in manufacturing can lead to a progressive gradual reduction in Na.[21,22] Even a modest reduction in Na should result in a substantial improvement in the health of the public.[23]

Summary

Data relating Na to BP are convincing, and evidence from the best-quality cohort analyses and RCTs are consistent with a direct relationship between Na and CVD. Information from cohort studies less well suited to answering the question should be interpreted with great caution. These reports should not be used to undermine existing policies that call for a progressive reduction in Na from our current high levels of intake. Population-wide reduction in Na should remain an important component of efforts to promote cardiovascular health and prevent CVD in the United States.

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