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Comments by the Center for Science in the Public Interest

AHRQ Draft Systematic Review: Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors

The Center for Science in the Public Interest (CSPI) is a non-profit consumer education and advocacy organization that since 1971 has been working to improve the public's health through better nutrition and food safety policies. CSPI is an independent organization that does not accept any government or corporate funding. We appreciate the opportunity to submit comments on the draft sodium report.

Overall, several aspects of the draft report bring much-needed clarity to the broad body of evidence on sodium and potassium. For example, the draft makes it clear that observational studies have a high risk of bias if they assess sodium intake with a spot urine, a timed urine, a single 24-hour urine, or a 24-hour urine collection without quality control measures, instead of multiple 24-hour urine collections with quality control measures (Appendix E-7). AHRQ's recognition that measurement error can create bias may resolve some of the confusion and inconsistency in this body of evidence.

However, the draft report could further resolve confusion and inconsistency in the sodium literature by basing its conclusions on only the highest-quality randomized trials and observational studies, even if these are few in number. For example, the draft report might have found high-strength, rather than moderate, evidence that reducing sodium lowers blood pressure (BP) if it had relied only on randomized controlled trials (RCTs) that documented a sufficient difference (e.g., 40 mmol/day) between people consuming a higher vs. a lower sodium intake. Including less well-conducted studies adds imprecision and creates a perception of less certainty than may be justified.

Similarly, the draft report would have reached stronger conclusions if it had excluded studies at high risk of bias. The draft states, "Although we hoped to exclude prospective cohort studies that used methods other than multiple nonconsecutive measures of 24-hour urinary sodium excretion to assess status, doing so would have excluded most large cohort studies. Therefore, we included these studies but their risk of bias is higher" (ES-14). Instead of including those studies, AHRQ could have limited its review to studies at low risk of bias, even if the remaining, higher-quality studies were few. At a minimum, AHRQ could have looked separately at the evidence from studies with a high vs. low risk of bias and based its conclusions on studies at low risk of bias.

Below, we comment in more detail on the draft's strengths and limitations.

KQ 1. Effect of interventions to reduce dietary sodium intake on blood pressure.

The AHRQ review concludes that reducing sodium intake lowers blood pressure in adults, but rates the evidence as moderate-strength, rather than high-strength, because of "some inconsistency across study outcomes and high heterogeneity" (p. 27). AHRQ should conduct additional analyses to determine how much of the inconsistency and heterogeneity is due to inadequate reduction or measurement of sodium intake. For example, only 27 of the 48 RCTs included in AHRQ's analysis reported that the mean difference in sodium intake between groups was at least 40 mmol/day, the minimum difference required for inclusion in a 2013 WHO systematic review and meta-analysis.[1] The remaining studies achieved a mean difference in sodium intake as low as 2 mmol/day. (The low differences likely reflect the failure of study subjects to comply with the intake recommendations for the study arm to which they were assigned.) AHRQ could further clarify the impact of lowering sodium intake on blood pressure by looking separately at RCTs that achieved sufficient differences in sodium intake (e.g., 40 mmol/day or more) based on at least one 24-hour urinary sodium level. AHRQ should give the greatest weight to trials such as DASH-Sodium, which had the most tightly controlled sodium intake because all foods were provided by the investigators. Including poorly controlled studies obscures the impact of lowering sodium intake on blood pressure.

KQ 2. Among adults and children, what is the association between dietary sodium intake and blood pressure?

The AHRQ review concludes that "a low strength of evidence supports a lack of association of sodium exposure with systolic or diastolic BP in adults based on observational studies. All studies had high risk of bias based on the methods used to assess sodium intake (typically single 24-hour urine excretion with or without validation)" (p. 49). We question AHRQ's conclusion that the observational evidence supports a lack of association between sodium and BP in adults.

AHRQ's summary of studies using 24-hour urinary excretion—which is a better measure than estimated 24-hour urinary excretion—relies on only two studies. One has a high risk of bias.[2] The second is TOHP-1, which has a low risk of bias.[3] TOHP-1 reported that both systolic and diastolic blood pressure were significantly lower in the sodium-reduction group. Given that

[1] Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ. 2013 Apr 3;346:f1326. doi: 10.1136/bmj.f1326**.**

[2] Singer P, Cohen H, Alderman M. Assessing the associations of sodium intake with long-term all-cause and cardiovascular mortality in a hypertensive cohort. American Journal of Hypertension. 2015 1;28(3):335-42.

[3] The 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. 1992 Mar 4;267(9):1213-20. AHRQ incorrectly identified TOHP as having a high overall ROB and a high ROB for sodium ascertainment (p. 52, Appendix E-41, E-42). In fact, the TOHP studies used multiple 24-hour urine analyses with validation (Appendix C-84) and were rated as having a low risk of bias (Appendix E-20, E-34).

TOHP, the only study reviewed in this section with a low risk of bias, found a significant association between 24-sodium excretion and systolic BP, it is inappropriate to conclude that sodium exposure is not associated with BP. (Furthermore, stronger evidence from randomized trials makes it clear that lowering sodium intake reduces blood pressure.)

KQ 3. Among adults, what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on CVD and kidney disease morbidity and mortality and on total mortality?

Total mortality

AHRQ appropriately concludes that sodium reduction decreases the risk of all-cause mortality (low strength of evidence). This conclusion is bolstered by the TOHP Follow-up studies, which reported a nonsignificant 15 percent lower risk of mortality in the sodium reduction group (HR 0.85; 0.66 to 1.09).[4] A meta-analysis combining TOHP with other studies found a borderline significant benefit (RR 0.92, CI 0.84, 1.00).

CVD mortality

We question AHRQ's conclusion that sodium reduction does not affect the risk of CVD mortality (low strength of evidence). As AHRQ notes, the TOHP Follow-up studies—which contributed two of the three studies used to reach this conclusion—reported 10 CVD deaths in the reduced sodium groups and 15 CVD deaths in the comparison groups. While that difference was not quite statistically significant, it suggests that a larger sample size might have yielded significant results. It is inappropriate for AHRQ to conclude that sodium reduction does not affect the risk of CVD mortality when the available studies may be underpowered to detect an effect.

Stroke

We question AHRQ's conclusion that sodium reduction does not affect the risk of stroke (low strength of evidence). AHRQ based this conclusion on only 3 RCTs. One reported a mean difference of only 15 mmol/day in sodium consumption in an 8-week study on only 80 people.[5] (One person in the reduced-sodium group and none in the control group suffered a stroke.) Another reported a difference of only 7 mmol/day in sodium consumption in a 9-month study on only 40 people.[6] Clearly, these studies are too small, too short, and achieved too small a reduction in sodium intake to constitute a reasonable test of whether lowering sodium intake reduces the risk of stroke. Only one RCT (TONE) reported a mean difference of 24-hour sodium excretion of at least 40 mmol/day in a trial that involved 681 people and lasted an average of

[4] Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. J Am Coll Cardiol. 2016 Oct 11;68(15):1609-1617.

[5] Charlton KE, Steyn K, Levitt NS, et al. A food-based dietary strategy lowers blood pressure in a low socioeconomic setting: a randomized study in South Africa. Public Health Nutr. 2008 Dec;11(12):1397-406.

[6] Gilleran G, O'Leary M, Bartlett WA, et al. Effects of dietary sodium substitution with potassium and magnesium in hypertensive type II diabetics: a randomised blind controlled parallel study. J Hum Hypertens. 1996 Aug;10(8):517-21.

nearly 28 months.[7] (One person in the reduced-sodium group and two in the control group had a stroke.) It is inappropriate for AHRQ to conclude that sodium reduction does not affect the risk of stroke when the available studies may be underpowered to detect an effect.

Any CVD Event

We question AHRQ's conclusion that sodium reduction does not affect the risk of any CVD event (low strength of evidence). As AHRQ notes, the TOHP I and II Follow-up studies found a statistically significant 25 percent reduction in the adjusted relative risk of CVD outcomes.[8] Furthermore, AHRQ found a non-statistically significant beneficial effect of sodium reduction when it pooled the (unadjusted) TOHP results with the only three other trials, two of which did not report a difference in achieved sodium (RR 0.85, CI 0.69, 1.05). Based on the highest-quality available studies, AHRQ should conclude that sodium reduction decreases the risk of a CVD event.

KQ 4. Among adults, what is the association between dietary sodium intake and CVD, CHD, stroke and kidney disease morbidity and mortality and between dietary sodium intake and total mortality?

All-cause mortality

AHRQ concludes that "a low level of evidence supports the association between higher sodium levels and higher risks for all-cause mortality (data are insufficient to determine the linearity)" (ES-8). We question whether the data are insufficient to determine whether the association is linear. In the TOHP Follow-up studies, there was a direct linear relationship between intake and later mortality, with no evidence of a J-shaped or nonlinear relationship.[4] These studies are the only observational studies with a low risk of bias considered in this section.[9] Therefore, AHRQ should conclude that the available studies at low risk of bias support a linear association between sodium levels and all-cause mortality.

CVD morbidity and mortality

We question whether it is appropriate for AHRQ to conclude that "a low level of evidence supports a lack of association of sodium intake levels and risk for combined CVD morbidity and mortality" (ES-8). As noted above, the TOHP I and II Follow-up studies, two of the few observational studies with a low risk of bias, found a statistically significant 25 percent reduction in the adjusted relative risk of CVD outcomes and a non-significant 15 percent reduction in the risk of total mortality.[4,8] Given that all the other observational evidence in this section was at high risk of bias—

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[7] Appel LJ, Espeland MA, Easter L, et al. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). Arch Intern Med. 2001 Mar 12;161(5):685-93.

[8] Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ. 2007 Apr 28;334(7599):885-8.

[9] The risk of bias for the TOHP Follow-up studies appears to be incorrectly identified as high in the Appendix, pp. E-41, 42.

and given the well-established relationship between blood pressure and stroke and CVD—it is inappropriate to conclude that an association is lacking.