

Dietary Sodium: Where Science and Policy Diverge

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In 2013, an Institute of Medicine (IOM) Committee, after reviewing available evidence, reached conclusions that differed importantly from conventional belief.¹ They reported that while harm exists with “excessive” sodium intakes, the term was specifically left undefined. In addition, they concluded, “evidence was insufficient to support (or refute) previous recommendations for population-based efforts to achieve sodium intake levels of less than 2.3 g/day in the general population or most population subgroups.” While recognizing that blood pressure was a strong surrogate for cardiovascular events, IOM nevertheless concluded that the health effect of dietary sodium should be determined through assessment of evidence directly linking sodium intake to actual health outcomes—and not through intermediate variables such as blood pressure.

Since the IOM report, several additional publications linking dietary sodium to health outcomes have confirmed, clarified, and extended its conclusions.^{2–6} While observational studies can determine associations, they do not establish causality, and can not generally be a basis for therapeutic intervention. The purpose of this review is to critically assess these recent reports in the context of already available evidence, as well as the IOM report, and to suggest policy options consistent with the evidence.

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POST IOM STUDIES

Gradual meta-analysis

This meta-analysis of 27 observational studies with 275,000 participants associated dietary sodium with all cause (ACM) and cardiovascular (CVD) mortality.² Those with intakes of <2.65 and >4.95 g/day each had significantly greater all cause and CVD mortality than those with intakes between 2.65 and 4.95. In addition, there was no outcome difference between lower or higher intake subgroups within the mid-, or usual sodium range. This analysis extended the IOM report by specifically identifying the optimal range of dietary sodium. Moreover, ACM or CVDM at intakes <2.65 g/day significantly exceeded that within the middle range in the primary and multiple supplementary analyses. This mid-range is coterminous with usual dietary intakes around the world. Finally, these findings indicate that dietary sodium intakes best fit a “J” or “U” shaped relation with health outcomes—consistent with all other nutrients and adherent to standard recommendations for assessing the health effects of nutrients.^{7,8}

PURE

PURE, a prospective observational study of more than 100,000 participants detected a nonlinear relation of sodium intake to systolic blood pressure (SBP).³ Each 1 g increment in sodium intake was associated with a 2.11 mm Hg higher SBP, but the slope was steeper with intakes >5 g/day (2.58 mm Hg) than <3.0 g/day (0.74 mm Hg). The effect size was greater in hypertensive and older than normotensive and younger subjects.

A second PURE paper found that sodium intake had a “J or U” shaped relation to all cause and CVD mortality.⁴ As compared with sodium excretion of

4.00 to 5.99 g per day (the reference category), estimated excretion of 7.00 g/day or more was associated with increased ACM (odds ratio, 1.15; 95% confidence interval [CI], 1.02–1.30), death from cardiovascular causes (odds ratio, 1.54; 95% CI, 1.21–1.95), and stroke resulting in death or hospitalization (odds ratio, 1.29; 95% CI, 1.02–1.63).

Moreover, when compared to the reference category, excretion of less than 3.00 g/day was also associated with increased ACM (odds ratio, 1.27; 95% CI, 1.12–1.44; death from cardiovascular causes (odds ratio, 1.77; 95% CI, 1.36–2.31), and stroke resulting in death or hospitalization (odds ratio, 1.37; 95% CI, 1.07–1.76). These associations remained significant after adjustment for blood pressure or prior diagnosis of hypertension.

Increased CVD mortality at intakes >7.0 g/day was limited to persons with hypertension, while blood pressure (BP) was not associated with CVD mortality at sodium intakes <3.0 g/day.

Notably, the highest relative risk (1.62, 1.29–2.05) of CVD mortality among those consuming <3.0 g/day was found among persons at low CVD risk (without CVD history or medications, smoking, or diabetes). Exclusion of participants with prior CVD, cancer, diabetes, or current smokers, as well as those with events in the first 2 follow-up years, did not materially alter these findings—mitigating the possibility that reverse causality (the possibility that the low sodium intake is due to a condition that causes both reduced sodium intake as well as increased mortality) could explain the findings. These results are consistent with three other individual studies,^{9–11} as well as the Graudal meta-analysis.²

NUTRICODE

NUTRICODE⁵ is conceptually and methodologically similar to previous models, and yielded similar results:

The 1991 United Kingdom analysis predicted annual prevention of 75,000 deaths,¹² and in 2010, up to 92,000 US deaths.¹³ The more ambitious Mozaffarian model was constructed by merging analyses of separate data sets. Usual population sodium intake was based on 3 sets of cross-sectional studies spanning the globe. Mean sodium was 3.6 g/day. Sodium to BP was based upon reanalysis of randomized trials included in 2 Cochrane reports. Finally, 2 meta-analysis of studies from 66 countries determined the association of BP to mortality. The individual components of the model were then sequentially merged to conclude that universal reduction of sodium intake to <2.0 g/day would save 1.65 million CVD deaths/year.⁵ There is no clinical evidence that mortality or morbidity would be lower if sodium intakes were reduced to <2.0 g/day.²

The validity of this analysis assumes the relations of sodium to BP, and BP to CVD, and sodium to CVD all to be linear. Recent evidence has invalidated these assumptions.²⁻⁴ the relation of sodium to BP is greater at intakes >5.0 than at <3.0 g/day (2.58 vs. 0.74 mm Hg);³ BP is associated with CVD risk at levels of BP >130/80, but not at lower levels³; and the sodium to CVD association is “J” shaped.^{2,4} Moreover, there are adverse physiologic effects associated with sodium intakes <2.5 g/day.¹⁴ Finally, in a number of observational studies, the effects of sodium intake on CVD and BP have been disassociated. In reality, multiple intermediate effects as well as interactions with other (i.e., Potassium) nutrients determine the health consequences of sodium intake. The 2013 IOM Committee did not consider this kind of analysis useful in assessing the relation of sodium intake to health.

Trials of hypertension prevention follow-up

Trials of hypertension prevention (TOHP) was a randomized clinical trial comparing usual and reduced sodium in obese and prehypertensive persons. To assess the association of usual sodium intake to outcomes, this latest observational follow-up of the original TOHP trial participants included only those originally randomized to the control

group.⁶ Morbidity and mortality outcomes were analyzed for 2000–2005 (10–15 years after study completion). In the fully adjusted model, compared with those with sodium 3.6 to <4.8 g/day, risk for those with sodium <2.3 g/day was 32% lower after multivariable adjustment (P for trend = 0.13). When sodium was considered as a continuous term, risk increased linearly, with a 17% increase in risk per 1,000 mg/day increase in sodium ($P = 0.054$). Disappointingly, while the authors published outcomes for a subgroup of the “control group,” they failed to disclose the results of an intention-to-treat analysis with mortality as endpoint for the whole “control group.” This unbiased information would have placed these subgroup analyses in its appropriate context.⁶

In a previous follow-up analysis of TOHP, an intention to treat analysis found a 20% lower mortality among those in the sodium reduction intervention (0.80, 0.51–1.26, $P = 0.34$) compared to controls. Twenty-five deaths were due to CVD; 10 in the intervention groups and 15 in the comparison groups (0.62, 0.28–1.40, $P = 0.25$).¹⁵

Post hoc analysis of subgroups constructed after study completion, even if they produced significant findings, are weak evidence and best limited to hypothesis generation.

Dietary sodium intakes in TOHP (3.63 g/day) and in PURE (4.93 g/day) are both well within the usual range (2.5–6.0 g/day). Thus, regardless of whether a single 24-hour urine, spot urine, or dietary recall was the method of estimating sodium intake, sodium intakes vary around a universal mean.^{2,3} The finding in TOHP that 90% of subjects consumed >2.3 g/day of sodium, and only 1.4% <1.5 g/day, is consistent with most other studies of general populations.

Where the evidence now stands

Scientific conclusions about a medical hypothesis must take into account all the valid evidence. Ideally, a hypothesis can be tested experimentally. However, this may not be possible in the case of sodium. Instead, there is an abundance of observational evidence drawn from different times, places, genetic groups, including where unique dietary cultural patterns exist.^{1,2}

Observational studies, inherently weaker than experimental investigations, are rightly viewed with caution. Coherence, methodological rigor, and a biological rationale, are the essential elements of a scientifically credible hypothesis. This is an evolutionary process involving repeated reassessment of hypotheses as evidence accumulates.

Observational studies, even as robust as in this case, still have limitations. Residual confounding can never be entirely eliminated.⁸ However, concerns of greatest importance can be addressed. These include reliability of estimates of exposures and outcomes, and the possibility of “reverse causality.”

While it is challenging to determine the usual sodium intake of individuals, estimations of population sodium intake are remarkably consistent over time and space. Hundreds of studies, world wide, over the past 50 years, in different circumstances, using different methods, have found sodium intake to average about 3.6 g/day. Moreover, 90% of the world’s population consumes between 2.5 and 6.0 g/day.¹⁶ This may reflect neuro-regulation of sodium appetite.¹⁷ Mortality, all cause or CVD, has been gold standard for outcome in many observational studies. Moreover, the issue of reverse causality has been addressed through multiple analyses that minimized the possibility in PURE, TOHP, and many of the previous studies.

Finally, no study has detected a benefit accruing to persons consuming <2.3 g/day compared to those in consuming 2.5–6.0 g/day.⁴ This middle range, outside of which, risk of CVD and ACM increase, is also where physiological aberrations begin. At sodium intakes <2.5 g/day, plasma renin activity (PRA) increases and mortality increases, while at >6.0 g/day, blood pressure rises along with other physiological effects, PRA is suppressed, and mortality rises.^{18,19} This confluence of clinical and physiological aberrations provides strong support for the “U” shaped hypothesis.⁸

The belief that there was a direct linear relation of sodium to health outcomes grew from the assumption that blood pressure to sodium and to CVD was direct and linear, and the only health effect of sodium reduction.²⁰ Observational studies, mostly of persons with very high sodium intakes, seemed to confirm that increased sodium led

to increased CVD.^{21,22} But subsequent studies, with different distributions of sodium intake, found an inverse association at lower levels of intake. The most recent studies further support the more complex hypothesis that sodium, like all other nutrients, has a “U” shaped relation to health outcomes.²³

Policy implications

Studies published since the IOM report confirm its general conclusions. Now, additional evidence has made it possible to more precisely define “excessive.” In addition, concerns about the possibility of harm at sodium intake <2.3 g/day have defined the optimal sodium range (2.5–6.0 g/day). No doubt, future research will further parse the “U” shape and identify modifications appropriate for population subgroups, and in different circumstances.

With the possible exception of TOHP,⁶ the American Heart Association and Centers for Disease Control and Prevention dismiss observational studies as having fatal methodological flaws.^{24,25} At this writing, these respected agencies support goals <2.3 g/day, or, for half the population, to <1.5 g/day.²⁶ Presumably, they are unfazed by its implications—to change the sodium diet of nearly 300 million Americans absent direct evidence of its safety or benefit.²⁷

It is, however, necessary to recognize that while observational studies can establish risk, they do not provide reliable guidance for intervention. Recommendations to reduce dietary fat, or for postmenopausal hormone replacement therapy, are only examples of the hazards of such inferences.²⁸

FACTS SUPPORTED BY THE EVIDENCE

- (1) Average sodium intake, worldwide, is 3.6 g/day, with a range of 2.5–6.0 g/day.
- (2) Sodium reduction lowers mean population BP, the effect attenuates as intake declines.
- (3) The reduction of sodium needed to reduce blood pressure also has adverse physiological consequences.
- (4) There is a “J” or “U” shaped association of sodium to health outcomes, with optimal range of roughly 2.5–6.0 g/day.

POLICY OPTIONS CONSISTENT WITH THE FACTS

- (1) No recommendation for dietary sodium intake, while rejecting results of observational studies.
- (2) No recommendation to alter sodium intake for the general population, while noting possible risk above and below usual intakes of 2.5–6.0 g/day.
- (3) Recommend clinical trials to determine safety and benefit of altering sodium intake above and below usual range.
- (4) Recommend that physicians of patients at CVD risk determine sodium intake and provide appropriate care.

The practical consequences of these policy options differ only slightly. Those whose sodium intakes lie outside the usual range will need individual medical attention to determine sodium intake, and obtain appropriate care. This should be an issue for persons at known risk for CVD. The vast majority of Americans can take comfort in knowing their chosen dietary sodium intake is not a health hazard.

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