Dietary Sodium and Cardiovascular Disease Risk — Measurement Matters

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Hypertension is a common and major risk factor for the leading U.S. killer, cardiovascular disease.[1–5] Reducing excess dietary sodium can lower blood pressure, with a greater response among persons with hypertension.[6–9] Nine of 10 Americans consume excess dietary sodium, defined as more than 2300 mg per day.[10,11] Many leading medical and public health organizations recommend reducing dietary sodium to a maximum of 2300 mg per day on the basis of evidence indicating a public health benefit.[11–17] Yet this benefit has been questioned, mainly on the basis of studies suggesting that low sodium intake is also associated with an increased risk of cardiovascular disease.[18–22]

In science, conflicting evidence from studies with methods of different strengths is not uncommon. Studies that measure sodium intake vary widely in their methods and should be judged accordingly. Accurate measurement matters.[23–26] Paradoxical findings based on inaccurate sodium measurements should not stall efforts to improve the food environment in ways that enable consumers to reduce excess sodium intake. Gradual, stepwise sodium reduction, as recommended by the Institute of Medicine,[27] remains an achievable, effective, and important public health strategy to prevent tens of thousands of heart attacks and strokes and save billions of dollars in health care costs annually.[28]

LOW SODIUM INTAKE AND INCREASED CARDIOVASCULAR RISK — ASSOCIATION OR CAUSATION?

In prospective cohort studies, baseline exposure (e.g., sodium intake) is assessed and then examined in relation to subsequent health outcomes (e.g., cardiovascular events). In some analyses of these studies,[29–32] both low and high intakes of sodium, as compared with "usual" intake (defined most recently as 3000 to 5000 mg per day),[32] were associated with an increased risk of cardiovascular disease. Prospective cohort studies can have significant methodologic problems that alter the direction of the results.[26] To address the question "Does low sodium intake cause cardiovascular disease?" we applied Hill's classic criteria for determining whether an observed association is causal: strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment, and analogy.[33]

(Questions that help explain each criterion are listed in the box.) Here we evaluate the strength of the evidence relating low sodium intake to increased risk of cardiovascular disease.

STRENGTH

In one analysis of prospective studies, both low and high intakes of sodium were weakly associated with an increased risk of cardiovascular disease and death from any cause (a 10 to 20% increase).[29] Weak associations, Hill suggests, may be more subject to alternative explanations than strong ones are.[33] Reverse causality is a particular concern in studies that recruit ill participants, but it may also be a concern in general population cohort studies.[26] In studies reporting an apparent J- or U-shaped relationship between sodium intake and one or more cardiovascular outcomes, a higher proportion of participants in the low-sodium groups than in groups with other intake levels had diabetes, hypertension, preexisting cardiovascular disease, or more severe chronic illness at baseline.[26,30–32] Patients who are ill may have lower sodium intake because they eat less or are trying to eat lower-sodium foods, which may lead to a noncausal association between low sodium intake and increased cardiovascular events.[26,34,35]

Because participants in prospective cohort studies are not randomly assigned to low and high levels of sodium intake, other factors that are associated with sodium intake and cardiovascular disease could confound the association.[26] When one analysis was limited to general population studies adjusted for multiple confounders, high intake, but not low intake, of sodium was significantly associated with an increased risk of cardiovascular disease, but the association of low intake, but not high intake, of sodium with all-cause mortality remained significant.[29] Residual confounding may explain the association of low sodium intake with increased mortality. For example, in some studies, the investigators did not take into account the presence or absence of chronic kidney disease as a factor in this association.[29–32] Patients with chronic kidney disease, on average, have lower sodium intake and an increased risk of death.[35,36] In many studies, other factors, such as calorie intake and physical activity, are poorly measured, and adjustment does not eliminate confounding in such cases.

Measurement matters, and accurate, reliable measurement of usual individual sodium intake requires great care.[24–26] Analyses showing a J- or U-shaped relationship between sodium intake and one or more cardiovascular outcomes in general population samples used convenient but potentially biased methods to estimate individual intake.[29–32] Multiple, nonconsecutive, 24-hour urine collections are the gold standard for assessing sodium intake.[24,26] Some sodium measures, such as spot urine tests, unacceptably overestimate individual intake at low levels and underestimate intake at high levels, by plus or minus 3000 mg, even while being unbiased at the average level.[24,37] In association studies, individual-level accuracy matters. Having large numbers of participants does not trump concerns about ascertainment bias and misclassification.

CONSISTENCY

In keeping with the linear dose–response effect of sodium intake on blood pressure and of blood pressure on the risk of cardiovascular disease or death,[3–9] analyses of general population cohort studies[6,38–40] or of specific groups, such as patients with chronic kidney disease,[41] support a positive linear association from low to high levels of sodium intake and an increased risk of cardiovascular disease. One analysis indicated that the rate of death from cardiovascular disease increased linearly by 1% with every 230-mg increase in daily sodium intake (4% for every 1000 mg).[38] This association, however, is probably attenuated by reporting and coding errors in dietary measures of sodium intake and, for urinary biomarkers, the use of one or two consecutive 24-hour urine collections.[24,25,29,38,42] Because the foods we eat vary from day to day, a person's variability in sodium intake can be as great or greater than interpersonal variability.[24,25] Even on a fixed sodium intake, the day-to-day variance in 24-hour urine sodium excretion may be up to 40% of a person's average long-term sodium excretion.[24,43,44] Multiple, preferably nonconsecutive, days are required to mitigate the attenuation of the effect-size estimate from day-to-day variability.[24–26]

Using the gold-standard measure of individual sodium intake — multiple (three to seven) nonconsecutive 24-hour urine collections over 1.5 to 4 years — the Trials of Hypertension Prevention (TOHP) showed a "linear 17% increase in [cardiovascular disease] risk per 1000 mg [per day] increase in sodium" from levels starting at 1500 mg per day among 2275 participants, approximately 10% of whom had a sodium intake of less than 2300 mg (P=0.05).[40] The association reported in the TOPH analysis[40] is much stronger than that reported in studies based on less accurate measurement methods.[29–32,38,42] Furthermore, potential participants with diabetes, preexisting cardiovascular disease, and hypertension at baseline were excluded from this study[40] to equalize these cardiovascular risk factors across sodium-intake groups. Similarly, a study involving patients with chronic kidney disease that used the average of three nonconsecutive 24-hour urine collections over about 2 years of follow-up revealed a strong linear association between higher urinary sodium excretion and an increased risk of cardiovascular disease.[41] Studies that use better measures and methods are more likely to show actual health effects.

SPECIFICITY

An association of low or high sodium intake with all-cause mortality is unlikely. The fact that two thirds of deaths in the United States are from causes other than cardiovascular disease ought to mean that sodium consumption should correlate more tightly with cardiovascular death than with death from any cause.[1,2,33] In a 20-year follow-up of participants in one study, the previously reported association of low sodium intake with increased cardiovascular mortality was no longer significant.[45,46] The association between estimated low sodium intake and all-cause mortality resulted from an increased risk of death from causes other than cardiovascular disease.[45] In this study, sodium measurement was a single 24-hour urine collection, and participants were advised to avoid "excessively salty food" for 4 to 5 days preceding collection. The authors concluded, "The inconsistent results

cast doubt on whether a single measurement can reliably predict mortality over a prolonged follow-up period."[45]

TEMPORALITY

In the United States, a low-sodium diet is uncommon and hard to follow, given the nature of dietary patterns, the ubiquity of salt in the food supply, and the high correlation between sodium and calorie intake.[47] Even among people who are trying to lower their intake because of cardiovascular risk, it is possible that sodium intake was not reduced soon enough, or for long enough, to prevent subsequent adverse health outcomes. These possibilities are of particular concern in studies with short follow-up.

Conversely, in countries such as the United Kingdom, Finland, and Japan, which have implemented population-level strategies that include setting sodium-content targets for processed foods, there has been a decrease in the risk of cardiovascular disease.[48–50] In 2003, the United Kingdom set voluntary sodium target levels for food manufacturers. From 2001 through 2011 in the United Kingdom, the average daily sodium intake among adults between the ages of 19 and 64 years decreased by about 15% (or by 560 mg), the average systolic blood pressure decreased by 3.0 mm Hg, and the rate of death from stroke or ischemic heart disease decreased by approximately 40%.[48] Declines in other cardiovascular risk factors explained only a portion of the downward trend. Although mortality had decreased for three decades before 2001, the rate of decline slowed in 2002 to 2004, particularly among younger adults.[51] The intervention is at the food-supply level, rather than requiring individual behavior change. This temporality suggests a causal connection between reduced sodium levels in the food supply and decreased cardiovascular events and deaths.

BIOLOGIC GRADIENT — DOSE–RESPONSE

The purported J- or U-shaped association between sodium intake and the risk of cardiovascular disease could mean that blood pressure does not decrease below a certain threshold of sodium intake (e.g., 2300 mg per day) or that an additional biologic risk factor is the cause. An analysis of more than 100 trials lasting at least 7 days (including some in which participants consumed <1500 mg of sodium daily) suggests that each incremental daily sodium reduction of 1000 mg is associated with an average decrease in systolic blood pressure of 1.7 mm Hg.[8] Consistently, a significant dose–response decrease in blood pressure is observed in rigorously controlled trials with three or more confirmed levels of dietary sodium, down to about 1200 to 1500 mg per day, consumed for at least 4 weeks.[52,53] Thus, a threshold effect at 2300 mg seems unlikely. Hence, if a lower sodium intake is associated with higher cardiovascular risk, it must be adversely affecting some major risk factor for cardiovascular disease. However, the evidence does not support such a conclusion, as discussed below.

PLAUSIBILITY

Some authors suggest that low sodium intake increases levels of cholesterol, triglycerides, renin, aldosterone, and catecholamine, a hypothesis that purports to explain the association

between low sodium intake and increased cardiovascular risk.[9] The physiologic response to a marked acute sodium restriction is increased aldosterone and angiotensin levels, which increases the reabsorption of sodium and water and maintains the electrolyte balance.[54] However, this readjustment is temporary and unlikely to have population effects. When analyses are limited to interventions lasting at least 4 weeks, reduced sodium intake does not adversely affect blood lipids, catecholamine levels, or renal function, and renin and aldosterone effects are as expected as a physiologic response to blood-pressure lowering.[6,7]

Some investigators suggest that low sodium intake may increase insulin resistance. According to systematic reviews and meta-analyses, sodium reduction does not affect fasting glucose levels or consistently affect insulin resistance,[55] nor does it affect glycated hemoglobin levels in patients with diabetes.[56] Conversely, sodium reduction has health benefits beyond blood-pressure lowering, such as improved creatinine clearance in patients with diabetes and a lower risk of proteinuria in those with chronic kidney disease.[56,57]

COHERENCE

The association between low sodium intake and increased cardiovascular risk conflicts with the evidence of the effects of sodium reduction on blood pressure and of blood-pressure reduction on the risk of cardiovascular disease.[4,6–9] The effects of excess sodium intake on blood pressure can be both short-term and cumulative and long-lasting, in keeping with the higher prevalence of hypertension among older people, as shown in meta-analyses and global observational studies such as INTERSALT.[3,58,59] In addition, physiological studies in animals and humans indicate that sodium reduction could reduce cardiovascular risk through mechanisms independent of blood pressure, such as improved endothelial functioning, decreased arterial stiffness, and decreased left ventricular mass.[60]

EXPERIMENT

Although few randomized, controlled trials have examined the effects of sodium reduction on cardiovascular events, available evidence suggests that sodium reduction lowers the risk of cardiovascular disease. Diet, like other complex behaviors, is difficult to fit into the guidelines of pharmaceutical trials, since sustaining high compliance can be challenging, blinding is infeasible, and interactions between dietary components are probable.[23] When data from six trials involving 5912 participants with both normal levels of blood pressure and hypertension were pooled, sodium reduction was shown to result in a significant (23%) decrease in cardiovascular events at the longest follow-up.[61] The direction of the effect in the four larger trials was toward the prevention of cardiovascular disease. These trials included TOHP I and II,[62] TONE (Trial of Nonpharmacologic Interventions in the Elderly),[63] and a trial involving Taiwanese veterans.[64] Among four of these trials assessing compliance, the average daily sodium reduction was 529 to 1010 mg.[61] In the trials that included blood-pressure measurements, the average decrease in systolic blood pressure was 1.3 to 4.2 mm Hg.[61] The results are consistent with a previous meta-analysis of individual-level interventions, which excluded salt-substitution trials and indicated a significant (20%) reduction in cardiovascular events with a reduction of 800 to 920 mg in sodium intake over 6 to 36 months.[65] The authors of both analyses noted insufficient adherence to sodium

restriction with individual behavior change as the main limitations, which highlights the need for population-level interventions such as broad reductions of sodium in the food supply. As noted above, comprehensive national interventions in other countries, such as setting target sodium levels for foods, have been accompanied by large reductions in the rate of cardiovascular disease.[48–50]

ANALOGY

If low sodium intake increased cardiovascular risk, we would expect that other interventions with analogous mechanisms for blood-pressure–lowering effects (such as diuretics) might also increase the risk. However, analogously to sodium reduction, the use of antihypertensive medications, including diuretics, is associated with a 20% reduction in cardiovascular events and a 13% reduction in all-cause mortality for each decrease of 10 mm Hg in systolic blood pressure, according to analyses of 123 randomized trials involving 613,815 participants.[4]

FUTURE DIRECTIONS?

The application of Hill's criteria to the putative association between low sodium intake and an increased risk of cardiovascular disease indicates that the association is not causal. As Hill asked, "Is there any other answer equally, or more, likely than cause and effect?"[33]

Measurement matters. Because of measurement challenges and day-to-day variability in sodium intake, estimating population averages is far less subject to error than estimating individual intake. That fact may explain why countries with successful public health interventions that reduce sodium intake in the population show reductions in blood pressure and cardiovascular disease, whereas prospective cohort studies using short-term individual measures sometimes do not.

There is strong evidence of a linear, dose–response effect of sodium reduction on blood pressure. In addition, the evidence shows that sodium reduction prevents cardiovascular disease. This evidence is based on findings from prospective cohort studies with accurate measurement of usual sodium intake, analyses of long-term intervention trials, human and animal physiological studies, and public health interventions at the population level. Undue emphasis on observational studies with large numbers of participants but invalid measurement of sodium intake and other methodologic limitations can lead to erroneous conclusions and delay effective public health action to reduce blood pressure and save lives. Accurate measurement of sodium intake is critical to identifying its true contribution to cardiovascular risk.

Nearly half of Americans are already trying to reduce their dietary sodium, and most want low-sodium foods.[34,66] Yet sodium levels are high before food reaches the kitchen or table, and the sodium density of the U.S. diet has changed little despite consumer education encouraging individual behavior change.[10,27] Most of the sodium consumed is already in the foods we purchase and cannot be removed by consumers.[27] By reducing the amount of sodium in foods, manufacturers and food-service operators can give consumers more control over their sodium intake.[27] Reducing the average sodium intake by just 400 mg per day

could potentially avert as many as 28,000 deaths and save $7 billion in health care costs annually in the United States.[28] Reducing population sodium intake, through reducing excess sodium in manufactured and restaurant food in the United States, represents an important opportunity to prevent heart disease and stroke and reduce health care costs.[28,67]

Acknowledgments

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Hill's Criteria for Evaluating Whether an Association Is Causal.*

Strength

What is the degree to which the exposure (low sodium intake) is associated with the outcome (cardiovascular disease)?

Consistency

Has the association "been repeatedly observed by different persons, in different places, circumstances, and times"?

Specificity

Is the observed association limited to the exposure and outcome?

Temporality

"Does a particular diet lead to disease or do early stages of disease lead to those with peculiar dietetic habits?"

Biologic gradient

Is there a dose–response relationship between the exposure and outcome?

Plausibility

Is there a physiological basis for the observed association?

Coherence

Does the "cause-and-effect interpretation" of the association "seriously conflict" with "generally known facts about the natural history and biology of the disease"?

Experiment

"Is the frequency of associated events [outcomes]" affected by actions to prevent the exposure?

Analogy

Does an exposure with a similar action (physiologically) cause the outcome?

*Adapted from Hill.[33]