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Dietary Sodium and Cardiovascular Disease Risk

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THE AUTHORS REPLY

O'Donnell and colleagues cite studies purporting to show increased mortality with low sodium intake, but many studies of sodium and health outcomes are deeply flawed by measurement error, confounding, and reverse causality.[1] For studies of cardiovascular disease outcomes, long-term diet, rather than intake on a single day or a small number of days, is the relevant measure of sodium intake.[2] Urinary sodium excretion varies enormously throughout the day, from day to day, and according to diet, medications, chronic diseases, and hormonal fluctuations; only multiple, complete, 24-hour urine samples accurately reflect the usual sodium intake in an individual person.[1,2] Estimates of 24-hour sodium excretion that are based on spot urine samples, and therefore the apparent association between cardiovascular disease outcomes and spot urine samples, can be substantially biased.[3] Analysis without multiple 24-hour urine samples inaccurately categorizes sodium intake for many persons and contributes to an ostensible but invalid J-shaped association with cardiovascular disease in individual studies or in meta-analyses such as that cited by Alderman. In contrast, the use of multiple 24-hour urine collections indicates a positive and linear, not J-shaped, association with total mortality across a broad range of sodium intake, including among participants whose usual sodium intake was less than 2300 mg per day.[4]

In response to O'Donnell et al. and Graudal: the combination of trials with widely varying levels and durations of intended or achieved reduction in sodium intake may bias results. Clinical trials typically analyze sodium exposure on the basis of the intention-to-treat principle; if participants do not meet target reductions (e.g., because the food environment makes low sodium consumption extremely difficult), results are biased toward the null. Also, extreme, rapid reductions (e.g., down to levels below physiologic need, <500 mg) do not reflect the effects of long-term, moderate population-wide reductions in sodium intake such as those proposed by the Food and Drug Administration. According to a Cochrane review of 34 randomized trials involving normotensive participants and hypertensive participants, moderate and longer-term (>4 weeks) reduction in sodium intake, down to less than 1500 mg daily, significantly lowers blood pressure in a linear dose–response relationship; the effects on the renin–angiotensin–aldosterone system are small and within the expected physiologic range.[5] In a meta-analysis of long-term randomized trials, the effects of average reductions of 400 to 1200 mg in daily sodium intake significantly reduce the risk of cardiovascular events by 20% among normotensive participants and hypertensive

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participants combined, with a reduction of similar magnitude, albeit with inadequate sample size to show statistical significance, among the subgroup of normotensive participants.[6]

In response to O'Donnell et al., Alderman, and Johns: Hill's causal criteria focused on occupational hazards and preventive medicine and included examples that were related to cigarette smoking and diet. Hill stated that requiring strong evidence "does not imply crossing every 't' and swords with every critic, before we act." He concluded that "all scientific work is incomplete — whether it be observational or experimental" and emphasized not ignoring the knowledge we have. A general population trial to determine cardiovascular outcomes is impractical, because it would require tens of thousands of persons to maintain intended dietary sodium levels for many years.[6]

The 2013 IOM committee concluded, "Although the reviewed evidence on associations between sodium intake and direct health outcomes has methodological flaws and limitations … when considered collectively, it indicates a positive relationship between higher levels of sodium intake and CVD risk. This evidence is consistent with existing evidence on blood pressure as a surrogate indicator of CVD risk." To correct misinterpretation, the IOM committee chair wrote, "Rather than focusing on disagreements about specific targets that currently affect less than 10% of the U.S. population (i.e., sodium intake of <2,300 mg/d vs. <1,500 mg/d), the IOM, AHA, WHO, and DGA [*Dietary Guidelines for Americans*] are congruent in suggesting that excess sodium intake should be reduced." The 2015 Dietary Guidelines Advisory Committee, noting general population goals of less than 2300 mg of sodium per day, concluded that the totality of evidence of a cardiovascular benefit from limiting dietary sodium is strong and encouraged the food industry to reduce the amount of sodium added to foods in order to support healthy dietary choices.

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