Why You Should Take the Latest Sodium Study With a Huge Grain of Salt

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That's at least what the Harvard University School of Public Nutrition Source states in commenting on the confusing findings of a recent study of sodium intake and cardiovascular disease. The study, recently reported in *JAMA*,[1] created a great controversy, including making the front page of *The New York Times*.

The objective of this prospective population study was to assess whether 24-hour urinary sodium excretion predicted blood pressure and health outcomes. It involved 3,681 participants without apparent cardiovascular disease (CVD) who were randomly enrolled in the Flemish Study on Genes, Environment, and Health Outcomes (1985-2004) or in the European Project on Genes and Hypertension (1999-2001). Of 3,681 participants without CVD who had measurement of BP and sodium excretion at baseline, 2,096 were normotensive. 1,499 had blood pressure and sodium excretion measured at both baseline and last follow-up (2005-2008).

The main outcome measured was the incidence of mortality and morbidity in association with changes in blood pressure and sodium excretion. Multivariable-adjusted hazard ratios (HRs) expressed the risk in tertiles of sodium excretion relative to average risk in the whole study population. The results among 3,681 participants followed for a median of 7.9 years indicated that CVD deaths decreased across increasing tertiles of 24-hour sodium excretion. In the tertile with low excretion (mean, 107 mmol) there were 50 deaths or 4.1% (95% confidence interval [CI], 3.5%-4.7%); in the medium excretion tertile (mean, 168 mmol) there were 24 deaths or 1.9% (95% CI, 1.5%-2.3%), and in the high excretion group (mean, 260 mmol) there were 10 deaths or 0.8% (95% CI 0.5%-1.1%); $p < 0.001$).

In multivariable-adjusted analyses, this inverse association retains significance ($P = 0.02$): the Hazard Ratio (HR) in the low excretion tertile was 1.56 (95% CI, 1.02-2.36;P=0.04). Baseline sodium excretion predicted neither total mortality ($P = 0.10$) nor fatal combined with non-fatal CVD events ($P = 0.55$). Among 2,096 participants followed for 6.5 years, the risk of hypertension did not increase across increasing tertiles ($P = 0.93$). Incident hypertension was 187 (27.0%;HR,1.00;95%CI, 0.87-1.16) in the low, 190 (26.6%;HR,1.02;95%CI,0.89-1.16) in the medium, and 175 (25.4%;HR,0.98;95%CI,0.86-1.12) in the high sodium excretion group. In the 1,499 participants followed for 6.1 years, systolic blood pressure increased by 0.37 mm Hg per year ($P < 0.001$), whereas sodium excretion did not change (-0.45 mmol/year, $P = 0.15$). However, in multivariable-adjusted analyses, a 100-mmol increase in sodium excretion was associated with 1.71 mm Hg increase in systolic blood pressure ($P < 0.001$) but no change in diastolic blood pressure.

Their conclusions were that in this population-based cohort, systolic blood pressure, but not diastolic blood pressure, changed over time aligned with change in sodium excretion, but this association did not translate into a higher risk of CVD complications associated with hypertension. To the contrary, lower sodium excretion was associated with higher CVD mortality. They stated that their findings refute the estimates based on computer models of lives saved and healthcare costs reduced with lower salt intake. They also claim their results do not support the current recommendations of a generalized and indiscriminate reduction of salt intake at the population level. Their results did not, however, negate the blood pressure-lowering effects of a dietary salt reduction in hypertensive patients.

This study with its statements in the newspapers and other media flies in the face of decades of studies—mostly epidemiological but also clinical trials—showing that populations eating a lot of salt or segments of a population that eat large amounts of salt tended to have higher blood pressures. Populations with high salt intake in those previous studies seem to have had more CVD events, notably stroke, although rates of coronary disease were higher

as well. These data were so compelling that 32 countries in the world at this time have started programs to reduce the amount of salt in food. They have concentrated on processed foods because approximately 75% of the sodium that we eat is added to food during processing.

The data from previous studies which support the relationship between salt, blood pressure, and outcomes, were challenged by Dr. Michael Alderman in 1995[2] after his study that measured a one-time 24-hour urinary sodium excretion. Of almost 2,700 people, those with the lowest sodium intake (as low as 65 mmol of sodium per day), had the worst blood pressure and more unfavorable outcomes. They proposed that when sodium intake falls, plasma renin activity increases and the renin-angiotensin system is activated, which could be harmful.

Alderman's study was criticized because those in the study were instructed to reduce their salt intake for four or five days before 24 hour urine sodium was measured, so it may not have been an accurate reflection. Also, that same laboratory had shown earlier that you had to reduce your sodium much lower than 65 mmol in order to really activate the renin-angiotensin system.

WHAT ARE THE LATEST STUDY'S IMPLICATIONS?

Significant attention has been focused on developing public policies to reduce salt intake, due to consistent results from multiple studies, including a recent meta-analysis of multiple trials.[3] Of course the *JAMA* study discussed above was a population-based epidemiological study and not a trial. Rather than examining changes in the rate of events after a change in policy, the study examined the risk in people who consumed a specific amount of sodium. It represents a summary of several prospective observational cohorts of people without prior clinical cardiovascular disease and correlates urine sodium excretion with the risk for future cardiovascular events during the subsequent period of observation.

What are some of the potential weaknesses in this study? Many have pointed to its modest size with less than 4,000 participants—and only 84 deaths due to cardiovascular disease. They claim the study was too small to support the author's sweeping conclusions. Others say that its subjects were relatively young, with an average age of 40 years at the start. Another criticism is that it was done in Europe where population characteristics may be different from those in the United States. For example, there are many fewer African Americans in Europe, yet they are the ones whose blood pressure rises the most after a high salt load. There are also some data to show that we have more obese people in the United States than among the Europeans in the study group.

Another complaint was that they did a large number of statistical manipulations, which one might call data dredging, to find an association. Their findings weren't consistent with their initial hypothesis. Then after dredging they only found an association that fit their top tertile, but even within these data there are a lot of inconsistencies.

The Harvard Nutrition Source also faulted the study for basing their main findings on a single measurement of sodium excretion collected at the start of the study. They said, "It's weak science to use 1-day sodium excretion to predict heart disease or mortality decades later."[4] Harvard also stated that people who are taller or more active tend to have a lower risk of heart disease. They also tend to have higher sodium intakes, simply because they eat more food. They complain that in this study the authors don't account for differences in height, physical activity, and total calories. This could make it appear as though high sodium intakes protect against heart disease deaths, when in fact physical activity or height is responsible for lowered risk. Other problems, they claim, include missing or incomplete data from large numbers of participants, and that the researchers were asking questions their data were incapable of answering. The study's main methodological problems make its results unreliable.

Dr. Graham MacGregor of London, who has spearheaded a successful UK campaign to reduce sodium content in foods, agrees with the concern about "severe methodological problems," most notably with urine collection in the group that had the lowest salt intake. He states that "at a high-level meeting of The World Health Organization, salt reduction has been recommended as the next thing after tobacco reduction because it's so cost-effective to implement and so easy to do. " He also states that the problem in urine collection in the low-sodium group is evident after examining their creatinine excretion and the volume of urine. "If a group of people don't collect the proper 24-hour urine, they will have a lower sodium excretion, and these may be people who are less compliant with treatment and more likely to get events."

The CDC response is that there is a long-standing collective body of evidence demonstrating that lower sodium intake is associated with better cardiovascular health, and higher sodium intake is associated with high blood pressure and its complications.[5,6,7,8] Dr. Peter Briss of the CDC stated that "the people for whom salt reduction is most important are people who are older than 50 years of age; are African American; or who already have high blood pressure, diabetes, or chronic kidney disease. These groups taken together make up the majority of American adults." He went on to state that there would be very few cases in which salt reduction below the currently recommended levels might be problematic: for example, people who participate in heavy physical activity in hot environments or people with certain diseases, such as cystic fibrosis. People with salt-losing nephropathy, who are unusual, might also have to be careful about sodium restriction.

The American Heart Association is now proposing to lower sodium intake for the general population to less than 1500 mg per day by 2020. I see little harm to the general population by implementing this and, indeed, in our aging population with its multiple sodium sensitive diseases, I find that lowering salt intake is still in our best interest. Dr. MacGregor said it best, I believe, when he stated "there are seven different types of evidence about salt reduction, ranging from epidemiologic to migration studies, from genetic data to population studies and treatment trials. The treatment trials clearly show that lowering salt intake lowers blood pressure, and in this study they show this as well."

This obviously is not the end of the story, the authors of this article are continuing this study and promise further articles to explain their findings. We will await the next chapter of this ongoing controversy.

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