Standards Needed for Salt Studies As 'Big Food' Takes Sides
Shelley Wood | August 18, 2014

BOSTON, MA — The New England Journal of Medicine published three papers last week addressing the topic of dietary sodium and cardiovascular events. Two, as reported by heartwire, used data from the PURE study that relied—controversially—on fasting morning urine samples.

The PURE paper by Dr Martin O'Donnell (Population Health Research Institute [PHRI], Hamilton, ON) et al concluded that "moderate" sodium consumption (at levels higher than those recommended in most guidelines) was associated with the lowest risk of CVD, but that this risk increased at lower levels and at very high levels, >7 g per day[1]. That finding sparked headlines around the globe suggesting that sharply curbing sodium consumption could be harmful. A second PURE paper, led Dr Andrew Mente (PHRI), addressed the link between sodium excretion and blood pressure[2].

A third study, however, also looking at global sodium consumption, reached very different conclusions from the O'Donnell paper—namely, that risk of sodium consumption accrues in a linear dose-response fashion above 2 g per day[3]. Dr Dariush Mozaffarian and colleagues for the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NUTRICODE) used complex modeling that estimated sodium consumption with the use of 24-hour urine collections adjusted where possible using dietary-intake data. They then conducted meta-analyses of the effects of sodium on blood pressure and integrated this with an analysis of the effects of blood pressure on cardiovascular mortality. Finally, using comparative risk assessment, they estimated cardiovascular mortality related to sodium intake using a reference intake of 2 g of sodium per day—the amount recommended by the World Health Organization (WHO).

Following all of this data integration, Mozaffarian et al estimate the global mean level of sodium consumption, in 2010, was 3.95 g per day—almost double the WHO recommendations. Based on their meta-analyses, 1.65 million deaths annually and one in 10 deaths from cardiovascular causes can be attributed to sodium consumption above the reference level (2 g per day), with roughly two-thirds of those occurring in men. Of note, four out of five deaths occurred in low- and middle-income countries and two of five deaths occurred prematurely, before age 70.

Media Run with PURE

As media coverage of the papers makes clear, these disparate findings are once again fueling discussion about appropriate sodium targets, particularly since most of the initial news coverage focused on the PURE papers (including heartwire's). "Low-salt diets may pose health risks, study finds," reported the Wall Street Journal; "No benefit seen in sharp limits on salt in diet," reported the New York Times.

Yet, as Dr Norman Campbell (Libin Cardiovascular Institute of Alberta, Calgary), who reviewed the papers for heartwire, points out, Mozaffarian et al used what is universally accepted as the "state-of-the-art" methodology for estimating the true risks of sodium. By contrast, the PURE group has been repeatedly criticized for using morning urine tests to measure population-level sodium consumption.

Indeed, the American Heart Association (AHA), which recommends sodium intake of less than 1500 mg per day, released a press release in response to the papers stressing that PURE "used inaccurate measures of sodium intake and inclusion of sick people," which make it "challenging" to interpret the results.

That's a point also made in an accompanying editorial by Dr Suzanne Oparil, who points out that 24-hour urinary excretion on multiple occasions is the "accepted model for estimating sodium intake," a position also taken by the AHA [4].

Campbell put this another way, noting an expert group put together by the WHO has estimated that it would take 300 to 400 spot urine tests to get an accurate estimate of sodium intake, so using a single morning test is "absurd."

Moreover, Campbell notes, NUTRICODE counts among its members investigators from Harvard, Cambridge, Imperial
College London, and the US Centers for Disease Control, among others, and was developed under the auspices of the World Health Organization with funding from the Bill and Melinda Gates Foundation.

Also international in scope, the PURE studies have as their senior investigator the Public Health Research Institute’s Dr Salim Yusuf (McMaster University, Hamilton, ON) but include collaborators from North and South America, Eurasia, Africa, and the Middle East.

Yusuf, also speaking with heartwire, insisted that PURE did not use “spot” urine, calling this a “false” and “misleading statement promulgated by those who do not like our findings” or by those who “may not have read the paper carefully to clearly understand the results.”

Instead, PURE used first or second morning fasting urine, similar to what is used in glucose or cholesterol testing; these were then validated against 24-hour urine collections in 1100 people—the largest validation study ever conducted, in 11 countries. Third, PURE investigators conducted an analysis of the relationship between fasting morning urine and blood pressure and 24-hour urine and blood pressure and “found a nearly identical association.”

These validation analyses were published in the Journal of Hypertension earlier this year and also as appendices in the Mente paper, Yusuf added, so at least 15 independent reviewers have reviewed this methodology and accepted it, "otherwise the NEJM wouldn't have accepted our papers."

He also points out that it is simply not feasible to use 24-hour urine collection in large studies. When that's been done, he says, it results in high rates of incomplete collection, with one-third to one-half of subjects failing to do complete urine collections. What's more, many people will refuse to participate in studies if very large burdens are placed upon them [such as collecting all urine samples over a 24-hour period]. So studies that rely on this method may actually face a different type of confounding and be inferior to studies that use simpler methods, such as the fasting morning urine tests in PURE, he argued.

"I think the comments critical of the methodology of PURE are completely invalid and inaccurate. . . . There is a group of people who have dug in their heels that sodium reduction to extreme levels must be driven through at all costs. These people need to admit there is at least a sizable body of reputable investigators who have produced evidence to the contrary."

As for the NUTRICODE paper, it has its own limitations, Yusuf pointed out, calling it a "modeling exercise based on previously published data that preceded PURE." For one, he notes, they do not have enough data points to reliably distinguish whether the association between sodium and blood pressure is linear or nonlinear. Second, they are assuming that any approach to or degree of blood-pressure reduction and starting at any level of blood pressure will translate into a reduction in CVD, "and that's not true," Yusuf said, pointing to the ACCORD results.

Calls for Standardization

Campbell is leading the World Hypertension League’s (WHL) call for the standardization of sodium research methods that would include an agreed-upon method for estimating sodium intake. The WHL’s call for standards has the support of the AHA, the British Hypertension Society, the Canadian Stroke Network, the International Society of Nephrology, the World Stroke Organization, and the WHO, among others.

Campbell explained that universally agreed-upon standards for how sodium studies should be conducted would reduce the number of "low-quality" studies conducted and published in the past. He blames these studies—and the journals that have opted to publish them—for creating controversy where little or none should exist.

These include studies that were not long enough to capture any impact of sodium-reduction interventions; meta-analyses that combined both successful and failed sodium-reduction strategies and then declared no impact of reducing sodium; studies that controlled for blood pressure (even though sodium’s effects are largely mediated through blood pressure); and studies that used imprecise means of measuring sodium intake, as Campbell alleges was done in the PURE trial.

Yusuf, for his part, says would eagerly accept an end to the debate, something he believes could happen through a
large, rigorously designed randomized trial comparing moderate and low sodium intake conducted by unbiased parties.

Others have suggested that such a trial would be extremely difficult to do, given the amount of sodium in most foods, particularly processed foods. Yusuf says he himself doesn't have the time or resources to mount such a trial but says, if such a trial were well done and could be independently verified and showed that aggressive sodium restriction reduced CV events, "I'd change my position."

As for who should conduct such a study, he said: "The AHA has generally been a force for good, and they are in the position [and have the funds] to do the kind of study that's needed."

And to Campbell's call for research standards, Yusuf says he's supportive of this approach as well but insists it must be conducted by experts who don't already have a "stated position" on the topic.

"Debate" Continues

While many headlines around the globe used the term "debate" to characterize the three papers, Campbell insisted, as he has in the past, that most of the disagreement over the link between sodium and CVD is manufactured by the food industry. In fact, he said, all of the major national and international health organizations have agreed that the bulk of high-quality research supports a link between sodium consumption and cardiovascular death and disability.

"We will always have dissident scientists, regardless of the strength of the evidence, it doesn't matter what field—you will never have 100% of people agreeing. But in this case, we have the consensus of every national and international organization that has reviewed the topic."

On the other side, he said, "we have the world's largest industry, the food industry, a $3-trillion/year industry that takes those dissident scientists and creates public controversy."

In fact, speaking with heartwire last week, O'Donnell's advice was largely in keeping with that of the Mozaffarian paper, stressing that the "overall message" from the PURE papers "is the importance of a healthy diet pattern . . . and within that, avoiding high salt intake." Also, that higher sodium intake is particularly problematic in people with hypertension, a finding also reflected in the NUTRICODE paper.

Meanwhile, the Grocery Manufacturers Association (GMA), the trade group that represents many of the world's largest food and beverage companies, issued a press release last Thursday calling for more scientific and federal research on the effects of sodium intake, citing evidence from the O'Donnell paper. The paper "adds to the scientific evidence that low sodium consumption at levels recommended by public-health organizations may actually increase cardiovascular risk," the GMA states. No mention, however, is made in the GMA press release of the NUTRICODE paper published alongside the PURE research.

The GMA, along with Kraft Foods, Campbell's Soup, PepsiCo, and others, were sponsors of the 2014 Consensus Conference on Nutrition hosted earlier this year at the PHRI. Mente and Yusuf were both on the organizing committee for the meeting, which they declare in their disclosure statements. They specify, however, that no funds were received by any member of the conference planning committee or by their home institutions.

Asked about this, Yusuf said: "The issue is not where you get the money from, it's can you manage these in a transparent way? There were four or five people on the planning committee and the conditions were that we would not accept any suggestions from industry regarding topics or speakers, and industry did not try to do so because that was the condition on which we decided to hold such a meeting. A large number of highly reputable organizations accept this kind of funding." All conflicts of interest and sponsors have been publicly disclosed on a website, he added. Three reports from the conference, including one on nutrients and CVD and another on sodium and CVD, will be published in the near future, he added. "We don't think [hosting this meeting was] a conflict, but we declared it to the NEJM," Yusuf said.

What's more, he added, "[conflict-of-interest type]: one is financial and another one is professional, and some people have made their entire careers pushing a certain position. And it's hard to stop and pull
back and say oops, we may not have been right.” Yusuf himself might be considered to fit this description, but he says
he is willing to pull back and say “oops” if forthcoming evidence is persuasive, adding that he has had to do this in his
career at least twice.

Mozaffarian had no conflicts of interest. O’Donnell reports receiving lecture fees from Boehringer Ingelheim, Bayer,
Bristol-Myers Squibb, and Pfizer. Disclosures for all coauthors are listed in the articles. Campbell recently disclosed
being a short-term consultant or speaker for many regional, national governmental, and nongovernmental
organizations and meetings relating to dietary salt, many of which have provided travel support. Oparil reports
research support from AstraZeneca, Duke University, Merck, the National Heart, Lung, and Blood Institute,
Novartis, Takeda, and Medtronic. She receives other research support from Daiichi-Sankyo, Medtronic, and Vivus and
serves as a consultant/advisor to Backbeat, Bayer, Daiichi-Sankyo, Medtronic, Novartis, and Pfizer. Global Burden of
Diseases is supported by a grant from the Bill and Melinda Gates Foundation. The main PURE study and its
components are supported by the Heart and Stroke Foundation of Ontario, the Population Health Research
Institute, the Canadian Institutes of Health Research, unrestricted grants from several pharmaceutical companies
(with major contributions from AstraZeneca [Canada], Sanofi [France and Canada], Boehringer Ingelheim [Germany
and Canada], Servier, and GlaxoSmithKline and additional contributions from Novartis and King Pharma), and various
national or local organizations in participating countries. Yusuf disclosed grant support from Boehringer Ingelheim,
Sanofi, Bristol-Myers Squibb, AstraZeneca, Cadila Pharmaceuticals, and Bayer; personal fees from Boehringer and
Bayer; and serving on the planning committee the 2014 Consensus Conference on Nutrition, held at the Population
Health Research Institute (PHRI), that was sponsored in part by companies involved with food and nutrition, although
no funds were received by any member of the planning committee or their home institutions.

References


Editorial

Heartwire © 2014 Medscape, LLC

Cite this article: Standards Needed for Salt Studies As ‘Big Food’ Takes Sides. Medscape. Aug 18, 2014.