Is Reducing Dietary Sodium Controversial? Is It the Conduct of Studies With Flawed Research Methods That Is Controversial? A Perspective From the World Hypertension League Executive Committee

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There were two recent publications from the *New England Journal of Medicine* (*NEJM*) relating to dietary sodium that are likely to generate controversy. One study reported that sodium intake <3000 mg/d was associated with an increase in mortality and cardiovascular disease while confirming the health risks of dietary sodium >6000 mg/d.[1] The other study largely confirmed the association between sodium intake and increased blood pressure (BP) but, unlike rigorous randomized controlled trials, found less of an impact of sodium intake <3000 mg/d on BP.[2] Both studies confirmed that lower dietary potassium is associated with both increased BP and adverse health outcomes. The studies were based on the Prospective Urban Rural Epidemiology (PURE) cohort of more than 100,000 people in 17 countries.

The PURE study, however, used weak research methodology in assessing dietary sodium. A single spot urine sample (first or second morning void) was used to estimate a person's sodium intake. Single spot urine samples simply are not a reliable method of sodium intake. In a systematic review comparing spot urine samples vs 24-hour urine samples, there was a very wide range of correlations found between spot and 24-hour urine sodium (from 0.17 to 0.92), with no known scientific basis for the variation.[3]

The PURE study did attempt to validate spot urine sodium to 24-hour urine sodium and found a moderate association; however, that validation study also had concerning methodological and quality control issues.[4,5] The study included 24-hour urine samples within 25% of predicted 24-hour excretion of creatinine as being complete even though the original method called for excluding urine that exceeded 15% of predicted creatinine excretion.[6] There was no rationale provided for revising the criteria for assessing complete urine collection but, even with the revised criteria, only 50% of 24-hour urine samples were "complete." Because the revised standards likely included many incomplete 24-hour urine samples, it would have overestimated the association between spot urine samples and 24-hour urine sodium samples and also resulted in the assessment of bias being unreliable. Further, single 24-hour urine samples are not a reliable estimate of usual salt intake as salt intake generally varies day to day in many settings.

Based on a currently unpublished meta-analysis and review of the literature, a World Health Organization expert group concluded that although more research was required, 300 to 400 spot urine sodium samples from individuals selected to be representative of the population could reflect the average sodium intake in a population (N. Campbell, personal communication, September 2, 2014). It has not been established how many spot urine samples are required to accurately reflect an individual's sodium intake.

The BP indicators from the PURE study also do not align well with several rigorous national BP surveys. For example, in Canada, the PURE study reported an age-adjusted hypertension prevalence of 30% and an uncontrolled BP (stage 1–3 hypertension) prevalence of 24.2%, while a carefully conducted population survey reported a prevalence of hypertension of 19% and uncontrolled hypertension of 6.5%.[7,8] The average population BP in PURE exceeded the population BPs of all age categories reported in the Canadian national survey.[7,8] The Canadian data were confirmed in two other recent population surveys and there was no demographic group identified in a large series of analyses that had a BP indicator profile similar to that of the PURE sample.[9] Similar concerns have been raised about BP data in other countries.[10]

The American Heart Association has also critiqued the PURE publication in *NEJM* indicating other methodological weaknesses such as reverse causality whereby sick people eat less salt rather than lower salt consumption causing illness (American Heart Association, http://newsroom.heart.org/news/excessive-sodium-consumption-has-dire-impact-on-global-health-new-study-finds). While the PURE study excluded individuals with a history of cardiovascular disease, diabetes, and cancer in an effort to address reverse causality, individuals with potentially high risk for an event such as patients with prehypertension, family history, and health screenings of high risk were included in the study. Thus, the correlation from the PURE results should be interpreted cautiously because it might be a result of reverse causation. Specifically, patients who have high risk but not an event tend to reduce their salt intake based on health and clinical recommendations.[11]

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The conclusions of the *NEJM* articles challenge global recommendations to reduce dietary salt,[12–17] including those of the World Hypertension League (WHL) and the International Society of Hypertension.[18] The WHL, with multiple partner organizations, has issued a call for setting standards for clinical research on dietary sodium because it was perceived that low-quality research was threatening the global effort to reduce dietary sodium to improve health.[19] The health threat related to dietary salt is reiterated in an accompanying *NEJM* article from the Global Burden of Disease study, which estimated that 1.65 million people a year die of conditions related to sodium consumption >2000 mg/d.[20]

The WHL, in association with multiple organizations, hosts a free publically accessible weekly systematic Medline analysis of clinical sodium research (Canadian Institute for Health Research and Heart and Stroke Foundation Chair in Hypertension Prevention and Control, http://www.hypertensiontalk.com/science-of-salt-weekly/). Many studies in the systematic review confirm and expand the associations between excess dietary sodium and important human diseases. Many but not all of these studies utilize more rigorous scientific methods than the PURE study but are published in journals with less scientific impact than *NEJM* and generate little publicity. The WHL is committed to regular reviews of the literature, the setting of minimum standards for research methods, and regular updates to dietary recommendations. While the basis for the findings of the PURE study on sodium are unclear, studies based on flawed methodologies are likely to continue to generate controversy and the scientific area will only be advanced by carefully conducted rigorous research.

Given the best estimates that the addition of sodium to food is causing hundreds of millions of people to have hypertension and millions of people to die and become disabled, the WHL urges scientists to use high-quality research methods and to be conservative in promoting controversial findings, especially those based on weak research methods.[21,22]

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