

Dietary sodium and cardiovascular disease in China: concerns about the methods, conclusions, and evidence review

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We are concerned about the scientific methodology and evidence review in the publication by Liu *et al.* [1]. Their study estimates 24-h urine sodium (based on an overnight fasting spot urine sample and the Kawasaki equation) and reports a positive association between the estimated sodium intake and blood pressure (BP) and a J-shaped association with cardiovascular disease (CVD) and mortality. They conclude that only sodium intake above 5000 mg/day should be lowered to reduce mortality and CVD and imply intake below 3000 mg/day could be increased. Their introduction and discussion provide highly selected studies that used flawed methods to support their results and conclusions.

Numerous independent governmental and nongovernmental evidence-based scientific reviews are highly consistent in recommending, at a minimum, sodium intake be less than 2400 mg/day [2]. Meta-analyses of randomized controlled trials demonstrate a linear relationship between sodium intake and SBP down to 1000 mg sodium/day [3–5]. Meta-analyses of outcome trials also show that relatively small reductions in sodium intake from an average of 3646, to 2690 mg/day reduced CVD by 26% and mortality by 15% [3]. Long-term follow-up of the Trials of Hypertension Prevention (TOHP), which assessed sodium intake with multiple 24-h urines, found reductions in CVD risk under 2300 mg sodium/day [6]. The Global Burden of Disease study estimates over 1.8 million deaths, and over 44 million disability-adjusted life years lost, were attributable to excess sodium consumption in 2019 [7]. Furthermore, the WHO recommends reducing dietary sodium as one of the most cost-effective interventions a country can do to improve population health.

The use of equations to estimate 24-h urinary sodium, such as the Kawasaki equation used by Liu *et al.*, has been shown to create a false J-curve with mortality, likely because of confounding variables in the equations (e.g. age, sex, body weight, urinary creatinine) [8]. The equations have a complex association with mortality independent of sodium (i.e. when constant sodium values are entered into the equation). Many studies cited by Liu *et al.* [1] to support their findings, which refute the benefits of lowering dietary sodium, also used spot urine sodium-estimating equations, and hence incorporated the same in-built bias towards J curves. Additionally, the use of single vs. multiple 24-h urine samples to assess long-term sodium intake markedly

attenuates the association with CVD outcomes and can result in a spurious J-curve [9]. A further study cited by Liu *et al.*, to refute lowering dietary sodium, used a food frequency questionnaire to assess sodium intake, another inadequate method [10]. The National Academies of Sciences states ‘the paradoxical J-shaped and U-shaped relationships of sodium intake and CVD disease and mortality are likely observed because of methodological limitations of the individual observational studies’ and calls the studies cited by Liu *et al.* ‘highly biased’ [3].

Major international health and scientific organizations have expressed concern that apparent controversies about reducing dietary sodium are related to low-quality research [2,11–14]. The use of spot urine samples (including overnight fasting samples) with estimating equations has been widely recommended not to be used [15,16]. On a practical level, the spot and short-term timed urine samples have been repeatedly demonstrated to be inaccurate with marked random error and systematically biased in assessing individual’s sodium consumption [15].

The PURE validation study, in particular, was problematic with a wide variety of methodological issues and lack of rigor. There was a high proportion of incomplete 24-h urine samples, altered criteria for assessing incomplete 24-h urine samples, and the inclusion of many incomplete collections in the validation, a comparison of a sample against itself resulting in a spuriously high correlation and a false low mean bias relative to other validation studies [17,18]. The PURE validation study had no valid standard of comparison. Nevertheless, as in other validation studies, there were large differences between measure of sodium consumption using the two methods with gross overestimations at low levels of sodium and underestimations at high levels, introducing a bias [13]. Lack of rigor was also found with numerous errata in the Kawasaki equation published in the validation study. Only repeated, complete 24-h urine collections obtained on nonsequential days is recommended to represent usual sodium intake for an individual [15].

Our letter is to ensure readers are aware that the methodology used in Liu *et al.*’s study should not be used as it is known to create spurious results leading to erroneous conclusions and interpretations. Furthermore, the evidence review in the manuscript is highly selected and not representative of the extensive evidence-base, all in the public domain, which supports major government and nongovernmental health and scientific organizations in recommending population salt reduction.

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Conflicts of interest

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Reply

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Campbell *et al.* make several incorrect assertions in their letter [1]. In our study, we used the *fasting morning* urine samples, not a *spot random* urine. The differences are important (just like the difference between fasting glucose and random glucose). The fasting morning urine samples, reflect overnight basal excretion, and is likely a better indicator of long-term sodium stored in tissues in the body [2], than spot urines. Sodium intake estimated from overnight fasting urine shows a similar association with BP as sodium estimated from 24-h urine collections [3,4].

Campbell *et al.* [1] claim that reductions in sodium intake will translate into reductions in cardiovascular disease (CVD) and mortality, regardless of initial levels of sodium intake but this has not been proven. They ignore a number of facts. First, to date, there are no interventions that can be