Dietary sodium and cardiovascular disease in China: addressing the authors' response, statements and claims

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The *Journal of Hypertension* has published a letter by Liu *et al.* in response to our critique of these authors' article [1–3]. We write with serious concerns about the letter by *Liu et al.,* specifically that it: miscategorized the nature of the disagreement, makes several inaccurate statements, and makes claims based on inappropriate research methods, and that are not supported by the best quality evidence. These statements and claims on dietary sodium counter main stream scientific consensus on a serious public health issue that is estimated to result in the death of almost two million people each year [3].

Mis-categorization of the nature of the disagreement

Liu *et al.* [3] frames the matter at hand as a dispute between one group of researchers and another group. This is a fundamentally flawed categorization. Co-authors in Liu *et al.* have repeatedly published inaccurate reports on the effect of sodium consumption and health outcomes that are inconsistent with the overwhelming consensus based on evidence comprehensively reviewed by international and national health and scientific organizations [4–17]. Liu *et al.* claim a better understanding of the relationship of sodium intake and blood pressure (BP) based, in part, on the use of the unreliable spot urine test. The methodology and interpretation of the literature by Liu *et al.* have been demonstrated to be incorrect and detailed critiques of the group's work have been published multiple times since 2011 [4–16]. In the past decade, Liu *et al.'s* [17] research and claims have been carefully reviewed and rejected by the multiple independent governmental and nongovernmental expert committees that develop national and international evidence-based nutrition recommendations. Yet several of the coauthors from Liu *et al.* persist in publishing research that is unreliable and have not accounted for sound criticism, and revised their methods and conclusions.

Inaccurate statements

Inaccurate statement 1 (paragraph 1) regarding the equivalent value of overnight fasting and 24-hour urine collections

Liu *et al.* state, 'Sodium intake estimated from overnight fasting urine shows a similar association with BP as sodium estimated from 24-hr. urine collections [3]'. This statement is inaccurate. In fact, the two methods yield different results. Liu *et al.* [3] arrive at the notion that the methods yield equivalent results using the inappropriate Kawasaki equation in their PURE study. However, the Kawasaki estimating equation markedly alters the association of estimated 24-h sodium to BP relative to measured 24-h urine sodium and has an association with BP independent of sodium values [18]. Further, the PURE study, which used a fasting first morning void sample and not an overnight fasting void, has been variably reported results by several of the Liu *et al.* coauthors as showing that there is no significant association of dietary sodium with BP below 3000 mg sodium/day [19], and that the association is curvilinear with less impact at lower levels of dietary sodium [20]. Yet, meta-analyses of randomized controlled trials (RCTs) utilizing 24-h urine sodium samples are more to the point of scientific validity and they show a linear graded association between dietary sodium greater than 800 mg/day and BP [10,21–23].

Inaccurate statement 2 (paragraph 1) regarding spot urine tests

At the outset, Liu *et al.* incorrectly imply that we misstated the urine collection method used by Liu *et al.* [3] as a 'random' urine sample. Yet, we never referred to the urine collection as 'random' [2].

Moreover, our letter used the term 'spot' in a manner consistent with the consensus opinion of scientists. The term 'spot' is commonly used to describe an 'untimed spontaneously voided urine sample (https://medical-dic-tionary.thefreedictionary.com/collection%2C+spot+urine#:-:text=The%20sampling%20of%20a%20single,%2C%20crea-tinine%2C%20or%20electrolyte%20content)'. It is defined as 'a single-voided urine collection that is not specifically timed, including untimed first morning voids' in an official position statement of the International Health Research Community [24]. In other words, it is generally agreed that a fasting morning first void sample is a sub-type of spot urine sample.

Inaccurate statement 3 (paragraph 2) regarding the existence of evidence that low sodium intake is associated with higher mortality

Lui *et al.* [3] state, 'no evidence exists demonstrating that reducing sodium intake to less than 2400 mg/day will reduce CVD or mortality (compared with intake between 3000 and 5000 mg/day)'. This statement is inaccurate. As our letter stated, a meta-analysis of RCTs showed that reducing dietary sodium has a linear association with cardiovascular disease (CVD) events in the range of 2300–4100 mg/day, and the one cohort study (TOHP) identified by the National Academy of Science, Engineering and Medicine reportas being at low risk of bias, shows the linearity continues below 2300 mg/day [10]. These studies did not show a lower limit of sodium intake where the association with CVD was not linear. Paradoxically, after

claiming there is no evidence at levels less than 2400 mg/day, Liu *et al.* effectively concede that there is such evidence, which it then critiques: the relatively strong evidence from the TOHP trial that associates linear reductions in cardiovascular events with sodium intakes below 2300 mg/day. The National Academy of Science, Engineering and Medicine report indicated the TOHP weaknesses favored the null hypothesis [10]. Liu *et al.* [10] reiterate selected evidence from studies that have been assessed as being of high risk of bias to support their claim of increased cardiovascular disease at lower sodium intake. Liu *et al.* ignore the fact that evidence-based dietary recommendations from around the world have not been substantively impacted by the data they present and the conclusions they make. Indeed, the National Academy of Science, Engineering and Medicine report indicates that the J-curves are likely the result of biased methodological issues [10].

It is surprising, therefore, to read the abovementioned statement by Liu *et al.*

Inaccurate claim 1 (paragraph 2) regarding our citation of a meta-analysis

Liu *et al.* imply we miscited a meta-analysis that examined sodium intake with CVD and mortality. This claim is inaccurate, given that we cited the 'National Academy of Science, Engineering and Medicine report' that conducted a series of meta-analyses to assess the association of sodium intake with CVD and death, and not the reference that Liu *et al.* [10] imply we cited.

Inaccurate claim 2 (paragraph 3) regarding the impact of sodium recommendations on other foods

Liu *et al.* [3] claim that the recommendations we cite were developed without consideration of other dietary foods. This statement is inaccurate. Some have claimed a potential adverse impact on other dietary nutrients using an assumption that diets with reduced sodium are based on eating the currently available low sodium processed foods. This claim has never been demonstrated. The original National Academy of Medicine report directly addressed the impact of reducing dietary sodium on other dietary nutrients in developing its dietary sodium recommendations [10,25]. Specifically, the original recommendations were based on ensuring the adequacy of nutrients other than sodium ('*... a diet that provided an average of approximately 1.5 g (65 mmol)/day of sodium can meet recommended intakes for other nutrients'* [25]). Several of the recommendation processes, have used the careful analyses of the original and updated National Academy of Science, Engineering and Medicine report on overall dietary impact. Further, the main recommended intervention to lower dietary sodium is to reduce the amount of sodium added to most foods and not by individuals selecting processed 'low sodium' alternative foods. When the food industry gradually reduces the large and unnecessary amount of sodium added to most foods, members of the public do not need to change their dietary behaviour. Indeed, they can continue to buy the foods they usually buy and do not even notice the changes in sodium content in the foods. Reducing sodium added to foods in processing has resulted in reductions in sodium intake, as has been demonstrated in several countries (e.g. the UK). Reducing sodium added to foods will also have, at most, a modest impact on other dietary factors. Reduced dietary sodium could reduce urinary losses of potassium and calcium, which may have a positive dietary impact on these minerals, which are generally deficient in the diet. Reduced dietary sodium might impact iodine intake from iodized salt; however, increasing the iodization of salt addresses this issue. Integrating iodine and sodium programs has been advocated to optimize the intake of both minerals [26].

Inaccurate claim 3 (paragraph 3) regarding offtarget adverse effects

Liu *et al.* [3] claim off-target adverse effects are not considered in dietary recommendations. This claim is inaccurate. Several of the dietary recommendations carefully assessed likelypotential adverse surrogate parameters (including the observation that studies of 4 weeks or longer do not find a significant activation of the renin-angiotensin-aldosterone system) [10,27].

Inaccurate claim 4 (paragraph 5) regarding the Kawasaki equation

Liu *et al.* [3] claim that we wrongly assert that the Kawasaki equation produces inaccurate results. We are correct to state that the Kawasaki equation produces inaccurate results. The fact that the Kawasaki equation and spot urine sampling are inaccurate has been convincingly demonstrated repeatedly, including in the original PURE validation study publication [24,28–30]. An official position statement supported by the *British and Irish Hypertension Society, Chinese Regional Office of the World Hypertension League, George Institute for Global Health, Hypertension Canada, International Council of Cardiovascular Prevention and Rehabilitation, International Society of Hypertension, International Society of Nephrology, Resolve to Save Lives, WHO Collaborating Centre on Population Salt Reduction, WHO Collaborating Centre on Nutrition Policy for Chronic Disease Prevention and the World Hypertension League* provides recommendations on assessing sodium intake with urine studies [24]. This International Health Research Community is unequivocal in affirming that spot urine samples (including morning fasting samples) should not be used to assess an individual's sodium intake as they have large random and systematic errors and are not reproducible. Liu *et al.* refer mainly to the validation study from PURE in China that concluded, 'A more accurate method should be developed to estimate the 24-h urinary sodium excretion from spot urine for assessment of sodium intakes in the Chinese population' [31]. In the original PURE study validation, the error between the mean Kawasaki estimated 24-h urine sodium and the mean measured 24-h urine sodium was relatively small. However, the majority of measured 24-h urine sodium samples were incomplete, hence the average error cannot be accurately assessed. Further, the formula to assess completeness was altered by the authors, without

scientific rationale or overt disclosure, resulting in many 'incomplete' 24-h urine samples being classified as 'complete' and the spot samples were a part of the 24-h urine sample itself (thereby correlating a sample against itself). Furthermore, the PURE validation study confirmed very large systematic and random error between individual spot urine estimates of 24-h urine sodium and the measured 24-h urine sodium. An independent validation study from China reported that of all the estimating equations, the Kawasaki equation estimates of 24-h urine sodium had the highest misclassification of quartile 24-h urine sodium (63% misclassification), with more than 50% of participants having a difference of more than 40% from 24-h urine sodium and the largest mean bias (1347 mg) [32]. Gross inaccuracies of individuals estimated sodium excretion using the Kawasaki equation have been reported in other validation studies from China including the citations used by Liu *et al.;* the degree of error in estimating 24-h sodium varies with the level of measured 24-h sodium in all the validation studies [33–35]. There is also 'extreme' intraindividual variability of estimates of 24-h urine from spot samples when the Kawasaki equation is used [36–38]. The Kawasaki and other estimating equations contain many variables that are strong independent cardiovascular risk factors (e.g. age, sex, body weight, urine creatinine), yet Liu *et al.* make highly controversial conclusions attributing the equation results solely to the sodium variable. Surprisingly, Liu *et al.* ignore reports that demonstrate that the Kawasaki equation distorts the association of dietary sodium to mortality creating a spurious J-curve and that the equation remains associated with mortality even when a constant sodium value is used [39,40].

Claims based on inappropriate research methods, and that are not supported by the best quality evidence

Claim 1 (paragraph 1) regarding 'tissue stores'

Liu *et al.* state: '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, than spot urines' [3]. Liu *et al.*'s assertion regarding sodium stores does not have supporting evidence. To our knowledge, there are no comparative studies assessing the association of types of spot urine samples and long-term sodium stores. Indeed, considerable evidence indicates the Liu *et al.* assertion is incorrect. Long-term body sodium stores, as such, have not yet been related to human disease. The very high random and systematic error, and lack of reproducibility of spot urine samples in estimating 24-h urine sodium make it unlikely that the samples reflect total body sodium 'stores'. Further, the morning fasting spot urine samples are affected by nocturnal voids, which occur in 69% of people aged 40 years or older; consequently a fasting morning void is often not an overnight collection [41]. Many of the PURE participants would have voided in the night, given that study participants were enrolled at 35–70 years of age. Sodium in early morning samples is also influenced by the 'morning surge' of hormones that are associated with wakening and influence sodium excretion, and by variable dehydration associated with overnight fasting. Dehydration impacts the fractional excretion of sodium relative to creatinine and alters the estimated 24-h urine sodium by equations [42]. In addition, as noted below, overnight collections have greater disagreement with 24-h urine samples than other forms of spot samples. Liu *et al.* assert that 'fasting morning urine samples, reflect overnight basal excretion, and is likely a better indicator of long-term sodium stored in tissues in the body [3] than other spot urines' could be misinterpreted by readers who are not methodological and content experts in the area. There is no consistent evidence that supports increased validity of using fasting morning spot urine samples versus other subtypes of spot urine samples. We do not understand why Liu *et al.* made such a statement.

Claim 2 (paragraph 3) related to the statement that sodium intake affects cardiovascular disease but not through blood pressure

Liu *et al.* [3] controversially claim that the effects of sodium intake on cardiovascular disease are largely independent of BP. Specifically, Liu *et al.* state, 'Previous studies showed that the effects of sodium intake on cardiovascular events is largely unrelated to the effects of sodium intake on BP'.

This claim contrasts with reports from leading scientific groups that concluded that dietary sodium largely acts through BP changes [10,17]. The causal link between BP and cardiovascular disease is one of the most established evidence-based cause-and-effect link in clinical medicine. The cause-and-effect link between dietary sodium and BP is also very strong. The link between dietary sodium and cardiovascular disease is supported by meta-analyses of randomized controlled trials and by meta-analyses of high-quality cohort studies (as noted elsewhere in our critique). These long-term studies are consistent with and support the consensus that a reduction in dietary sodium reduces cardiovascular disease to the extent predicted through BP lowering. Since the publication by Liu *et al.,* two landmark studies have been published in the *New England Journal of Medicine* supporting the effectiveness of reducing dietary sodium on cardiovascular disease outcomes. Neal *et al.* performed a RCT reporting that a low sodium salt (with partial replacement of sodium by potassium) reduced BP, cardiovascular disease and death compared with regular salt (with linear associations related to reduction in sodium and also to increase in potassium) [43]. Ma *et al.* performed a meta-analysis of cohort studies that defined sodium intake with multiple 24-h urine collections reporting sodium intake above 1846 mg/day was linearly associated with cardiovascular disease [44]. Neither study showed a lower limit where reduction in dietary sodium is not associated with a linear reduction in cardiovascular disease.

Claim 3 (paragraph 2) that low sodium intake is associated with higher mortality

Liu *et al.* [3] state, 'A meta-analysis, involving 270 000 people from 23 cohort studies, showed that both (<2.7 g/day) low and high sodium intake (>5 g/day) are associated with higher mortality'.

The claim that less than 2.7 g/day sodium intake results in higher mortality is based on flawed research interpretation and methods with multiple errors (e.g. reverse causality) [7]. To meet the International Health Research Community standard, researchers must use multiple nonconsecutive 24-h urine samples to define an individual's usual sodium intake [24]. A single 24-h urine sample has been reported to cause an inaccurate association (J-curve) with cardiorenal events relative to the linear association found with multiple 24-h urine samples taken over time [45]. Meta-analyses of randomized controlled trials show that reducing dietary sodium in the range of 2300 to 4100 mg/day has a linear association with CVD events. One low bias cohort study identified by the National Academy of Science, Engineering and Medicine report shows the linearity continues below 2300 mg/day [10]. Indeed, a series of meta-analyses of cohort studies that used specific criteria to exclude low-quality research reported lower rates of CVD with lower levels of sodium consumption [22,46]. Liu *et al.* select studies that the National Academy of Science, Engineering and Medicine confirm are at high risk of bias and which are the source of spurious J curves to support the controversial conclusion in an apparent attempt to contradict higher quality evidence. Liu *et al.*'s selection of low-quality studies as justification for their surprising claim could be misinterpreted by many readers.

Claim 4 (paragraph 5) regarding the validity of the Kawasaki equation and fasting morning spot urine tests

Liu *et al.* [3] claim that several studies find the Kawasaki equation to be the most valid method of estimating 24-h urine sodium when using a fasting morning spot urine sample in Chinese adults and that 'the study' we cited used nonfasting urines. In fact, we did not cite an isolated study but a systematic review and meta-analysis of all the available literature examining the accuracy of spot urine samples and equations to estimate 24-h urine sodium. This review and meta-analysis is relevant to criticize the use of the Kawasaki equation and fasting morning urine samples as it found that six variables were associated with greater inaccuracies in estimating 24-h urine sodium including: use of the Kawasaki equation; overnight urine sampling; and Asian populations [47]. The systematic review and meta-analysis were rich in having had 22 comparisons of overnight and 16 morning void urine samples. The very few validation studies that specify whether the first morning void spot samples were fasting or not show similar inaccuracies in predicting an individual's sodium intake and lack of reproducibility as other types of spot samples [35,38].

Liu *et al.* use a correlation coefficient to validate the accuracy of the Kawasaki equation ignoring a landmark publication by Bland and Altman that explains that, in the circumstances that we are debating, '*The use of correlation is misleading because correlation measures linearity, rather than equality*' [3,48].

Liu *et al.* [3] indicate that the WHO uses a spot urine sample to assess population average sodium intake, citing a relatively old WHO report. But that report states

> Where possible and feasible, 24-hour urine collection should be used to establish the baseline, with a target sample of at least 150–200 people for each separate population group (e.g. sex, age group, ethnicity, rural or urban residency, socioeconomic status) for whom consumption is being assessed [49]. Depending on objectives and resources, countries may also resort to using spot urines given its potential for lower costs and reduced complexity of implementation.

Liu *et al.*'s claim is inappropriate as the issue in their study is associating individual sodium intake to disease and not population average intake, which is the focus of the WHO reference. The health and scientific community have strongly recommended against the use of spot urine samples in the context of assessing an individual's sodium intake especially in associating estimates of sodium intake with disease outcomes [24].

Further, the WHO has not endorsed the spot urine test as the gold standard for determining average sodium intake for populations and has never recommended spot urine samples to assess an individual's sodium intake. The WHO has merely acknowledged that low resourced studies might need to resort to lower quality methods for financial and logistic reasons to assess the average population sodium intake. More recent studies demonstrate the unreliability of using spot urine samples and equations in monitoring even mean changes in 24-h urine sodium excretion and specifically in China [50,51].

Conclusion

We reiterate our letter's statement: major international health and scientific organizations have expressed concern that apparent controversies about reducing dietary sodium are related to low-quality research [4,12,13,17,30]. The use of spot urine samples (including first morning fasting samples) with estimating equations has been widely recommended not to be used [24,29]. 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 and have been shown to cause a spurious J curve between estimated sodium intake and mortality [24]. This is the position of the International Health Research Community based on the existing science. In response to our letter detailing the problems of their research, Liu *et al.* fundamentally miscategorized the nature of the debate as being a minor spat between research groups whereas one group opposes the scientific consensus opinion, will not correct obvious error and continues to repeat unsupported claims. Liu *et al.*'s reply also contains a surprising number of inaccuracies, statements and claims that are not supported by the best quality scientific evidence. Many of these claims and statements have been reiterated in previous manuscripts by several of the coauthors. These statements and claims do not impact national and international nutrition recommendations that are based on the repeated, thorough, independent scientific reviews by multiple governmental and nongovernmental scientific organizations.

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†The views expressed herein are not necessarily the views or the stated policy of World Health Organization (WHO), and the presentation of material does not imply the expression of any opinion on the part of WHO.

Conflicts of interest

N.R.C.C. reports personal fees from Resolve to Save Lives (RTSL), The Pan American Health Organization, and the World Bank, outside the submitted work; and is an unpaid member of World Action on Salt, Sugar and Health and an unpaid consultant on dietary sodium and hypertension control to numerous governmental and non-governmental organizations. N.R.C.C. chaired the International Consortium for Quality Research on Dietary Sodium/Salt (TRUE) which is an unpaid voluntary position. F.J.H. is an unpaid member of Action on Salt, and World Action on Salt, Sugar and Health (WASSH). F.J.H. is partially funded by the National Institute for Health Research (NIHR) and the Medical Research Council (MRC). F.P.C. is Past-President, British & Irish Hypertension Society (2017–9) (unpaid); Member, Action on Salt and World Action on Salt, Sugar and Health (unpaid); Head, World Health Organization (WHO) Collaborating Centre for Nutrition (unpaid); Senior Advisor, WHO (refunds for travel, accommodation, per-diem); OMRON Academy (speaker fees, travel, accommodation, expenses); Annual Royalties from Oxford University Press (OUP) for two books on topics unrelated to salt. G.A.M. is the unpaid Chair of Action on Salt, Sugar and Health, World Action on Salt, Sugar and Health (WASSH) and Blood Pressure UK. G.A.M. is partially funded by the National Institute for Health Research (NIHR) and the Medical Research Council (MRC). M.W. is a consultant to Amgen, Freeline and Kyowa Kirin. J.R.G. reports no conflicts of interest. I.M. reports research funding from AbbVie Canada, Medimmune, Regeneron, Boehringer.

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Rho kinase inhibition: from hypertension to cardiovascular–renal remodeling and more

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The activation of Rho kinase (ROCK), the target of the GTPase RhoA, by vasopressors stimuli, such as Angiotensin II (Ang II) and Endothelin (ET)-1, is an essential mechanism involved in the pathophysiology of hypertension and cardiovascular–renal remodeling [1,2]. It includes the modulation of myosin light chain phosphorylation through inhibition of myosin phosphatase, the contribution to the increase of calcium sensitization in smooth muscle contraction, the downregulation of endothelial nitric oxide synthase (eNOS), whereas the inhibition of ROCK results in reduction of blood pressure and activation of antiremodeling defenses including upregulation of NO system [1,2].

Recently, Li *et al*. [3] in a recent article published in the *Journal of Hypertension* have added another piece of knowledge regarding the likely beneficial effect, during antitumoral therapy, of ROCK inhibition for hypertension and cardiovascular remodeling induced by tyrosin kinase inhibitors (TKIs) targeting endothelial growth factors. Exploring the role of RhoA/ROCK signaling pathway in a rat model of apatinib-induced hypertension, Li *et al*. [3] have, in fact, provided evidence suggesting that the activation of the RhoA/ROCK