Response to Invited Commentary

Elliott et al. Respond to “Quantifying Urine Sodium Excretion”

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In their commentary (1) on our article (2), de Boer and Kestenbaum briefly summarized recent research on the relationship between salt intake (estimated from urinary sodium excretion) and cardiovascular disease (CVD). They cite a recent article by O'Donnell et al. (3) in which casual urine samples were used to characterize individual sodium intakes and an apparent J-shaped association was observed between sodium intake and CVD risk. de Boer and Kestenbaum state that “a very low intake of dietary sodium may truly increase the risk of CVD” (1, p. 1193); in contrast, an editorial (4) accompanying the article by O'Donnell et al. and subsequent publications (5–7) have highlighted methodological concerns about interpretation of the study findings. These include the use of a clinical trial population with established CVD or diabetes; high rates of medication usage among trial participants; use of a single casual urine sample to estimate individual sodium intake; inclusion of participants with sodium intakes at the bottom end of the distribution who appeared to be sicker than the rest of the study population (reverse causality); and use of data sets not specifically designed to address the sodium-CVD relationship.

de Boer and Kestenbaum also cite studies purporting to show that “[d]ietary sodium restriction can lead to adverse biologic responses, including activation of the renin-angiotensin system, stimulation of the sympathetic nervous system, and unfavorable alterations to serum lipids” (1, p. 1193). These matters have been thoroughly examined as part of a systematic review undertaken by the World Health Organization to reassess guidelines on population sodium intakes (8, 9). The World Health Organization reaffirmed its previous advice that salt intake should be less than 5 g (85 mmol sodium) per day in adults and for the first time recommended a reduction in sodium intake to control blood pressure in children (8). The World Health Organization review found no evidence for adverse effects on physiological response to sodium reduction, including on the sympathetic nervous system or blood lipids (8, 9).

We agree with de Boer and Kestenbaum that the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) equations “now represent the best available method to estimate urine sodium excretion from casual urine samples” (1, p. 1194), although there are limitations. They suggest that simple transformations may improve model fit. We re-ran the equations using the natural logarithm of the urinary excretion values. This resulted in only modest improvement in model fit; the adjusted R^2 increased from 0.2659 (Table 1 of our original article) to 0.2684 in men, and from 0.2327 to 0.2418 in women. We confirm that addition of urine potassium concentrations did not meaningfully improve the models; with exclusion of potassium, the adjusted R^2 was reduced to 0.2636 in men and 0.2310 in women. We therefore agree with de Boer and Kestenbaum that urinary potassium can be excluded from the models and provide revised model estimates that exclude potassium in Table 1. We disagree with de Boer and Kestenbaum that inclusion of dummy variables for the 5 regions included in the models may inflate the community-level performance of the equation (1). We think it is important to include such an adjustment; by fitting a different intercept for each region, we reduce the impact of cross-region differences in levels of sodium excretion on the within-region associations of casual to 24-hour sodium excretion.

We restricted our analyses to Western populations in INTERSALT for which we had the most data and which are likely to be the most representative of the situation in North America and Europe. We therefore agree that the equations should be used with caution outside of these 2 settings and outside the age range for which the equations were developed (20–59 years).

Finally, we agree that single urinary measures of sodium excretion are limited for assessing individual (compared with population-wide) sodium intakes. We also concur that multiple urine collections are preferable and required to increase reliability and reduce the “regression-dilution” problem for studies of individuals (10, 11).

Table 1. Multiple Linear Regression Analyses of Sex-Specific Individual 24-Hour Urinary Sodium Excretion in Test and Validation Data Sets Combined, International Cooperative Study on Salt, Other Factors, and Blood Pressure, 1984–1987

Variable	Men (n = 2,841) ^a			Women (n = 2,852) ^b		
	β (SE)	Student's t Test	P Value	β (SE)	Student's t Test	P Value
Intercept (North America) ^c	23.51 (16.64)	1.41	0.2	3.74 (13.43)	0.28	0.8
Casual sodium, mmol/L	0.45 (0.02)	19.96	4.7×10^{-83}	0.33 (0.02)	18.45	6.6×10^{-72}
Casual creatinine, mmol/L	−3.09 (0.19)	−16.37	1.2×10^{-57}	−2.44 (0.17)	−14.01	3.6×10^{-43}
Age, years	0.22 (0.78)	0.28	1.5×10^{-40}	2.34 (0.65)	3.58	3.8×10^{-33}
Age ² , years ²	0.00 (0.01)	−0.27	0.8	−0.03 (0.01)	−3.62	3.5×10^{-4}
Body mass index ^d	4.16 (0.31)	13.55	0.8	2.42 (0.20)	12.15	3.0×10^{-4}
Region			2.9×10^{-6}			5.8×10^{-5}
Northern Europe	20.93 (4.46)	4.69	5.5×10^{-18}	14.47 (3.60)	4.02	2.2×10^{-6}
Eastern Europe	39.58 (4.55)	8.70	1.6×10^{-7}	17.02 (3.59)	4.75	2.7×10^{-12}
Southern Europe	20.86 (3.97)	5.25	1.7×10^{-4}	21.98 (3.13)	7.02	2.3×10^{-4}
Western Europe	14.60 (3.88)	3.76	0.2	11.38 (3.08)	3.69	0.8

Abbreviation: SE, standard error.

^a Adjusted $R^2 = 0.26$.

^b Adjusted $R^2 = 0.23$.

^c Coefficients for region are with respect to North America.

^d Weight (kg)/height (m)².

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