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Sodium Intake, Blood Pressure and Cardiovascular Disease

Moo-Yong Rhee, MD, PhD[1], and Yun-Jeong Jeong, MD[2]

[1]Cardiovascular Center, Dongguk University Ilsan Hospital, Goyang, Korea
[2]Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Korea

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Correspondence to
Moo-Yong Rhee, MD, PhD
Cardiovascular Center, Dongguk University Ilsan Hospital, 27, Dongguk-ro, Ilsandong-gu, Goyang 10326, Korea.
E-mail: mooyong_rhee@dumc.or.kr

ORCID iDs
Moo-Yong Rhee
https://orcid.org/0000-0002-1595-3627
Yun-Jeong Jeong
https://orcid.org/0000-0001-9144-7403

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Rhee MY has received lecture honoraria from Pfizer Inc., LG Life Sciences Ltd, Boehringer Ingelheim Pharma GmbH & Co. KG., Hanmi Pharm. Co. Ltd., Yuhan Co. Ltd., Boryung Pharmaceutical Co. Ltd., Fees for consulting from Hanmi Pharm. Co. Ltd., and research grant from Boryung Pharmaceutical Co. Ltd. and Dong-A Pharmaceutical Co., Ltd.
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ABSTRACT

Sodium intake reduction has been emphasized because sodium adversely impacts health, especially blood pressure (BP), and the cardiovascular (CV) disease risk. However, data obtained from several cohort studies have raised questions regarding the effects of high sodium intake on BP and the CV disease risk. In the present study, we systematically reviewed the literature to evaluate these associations. Studies showing negative associations between urine sodium and BP and CV outcomes relied on estimated 24-hour urine sodium from spot urine that is inappropriate for determining sodium intake at an individual level. Furthermore, controversy about the association between 24-hour urine sodium and BP may have been caused by different characteristics of study populations, such as age distribution, ethnicity, potassium intake and the inclusion of patients with hypertension, the different statistical methods and BP measurement methods. Regarding the association between sodium intake and the CV disease risk, studies showing negative or J- or U-shaped associations used a single baseline measurement of 24-hour urine sodium in their analyses. However, recent studies that employed average of subsequently measured 24-hour urine sodium showed positive, linear associations between sodium intake and CV outcomes, indicating that controversies are caused by the different sodium intake measurement methods and analytic designs. In conclusion, the study shows that positive associations exist between sodium intake and BP, CV outcomes, and mortality, and that the argument that reducing sodium intake is dangerous is invalid. Sodium intake reduction should be recommended to all, and not limited to patients with hypertension or CV disease.

Keywords: Sodium intake; Urine; Blood pressure; Cardiovascular

INTRODUCTION

Excessive sodium intake has been shown to have major impacts on blood pressure (BP) and the risk of cardiovascular (CV) disease,[1)2)] and to increase the risk of stroke,[3)] left ventricular hypertrophy,[4)] the progression of renal disease,[5)] renal stones and osteoporosis[6)] and possibly the risk of stomach cancer.[7)] Accordingly, the World Health Organization (WHO) and many countries are making efforts to reduce sodium intakes.

Nevertheless, some scientists argue reducing sodium intake to or below the recommended level is dangerous,[8)9)] and that there is no clear evidence that sodium intake reduction

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Conceptualization: Rhee MY; Data curation: Rhee MY, Jeong YJ; Formal analysis: Rhee MY, Jeong YJ; Investigation: Jeong YJ; Project administration: Rhee MY; Writing - original draft: Rhee MY, Jeong YJ; Writing - review & editing: Rhee MY, Jeong YJ.

decreases the incidence of CV diseases.[10] However, these studies have methodologic limitations that warrant consideration.

In this article, we review recent publications on the assessment of salt intake and on the associations between high sodium intake and BP and the risk of CV diseases.

MEASUREMENT OF SALT INTAKE

Sodium intake is usually measured using a dietary survey-based or urine collection methods. Dietary survey-based methods rely on food intakes determined by questionnaire or interview, and subsequently, nutrient intakes are calculated using food composition tables. Dietary surveys are commonly used in large population surveys because they are convenient and readily applicable. However, they may result in inaccurate estimations of dietary sodium intake because of their inherent limitations, such as reporting errors, inaccurate or incomplete food composition tables, missing data, and coding errors.[11-13] In addition, the use of dietary surveys makes it difficult to compare sodium intakes between countries, studies, and surveys because of the different dietary survey methods and food composition tables used.

Therefore, measurement of 24-hour urine sodium is recommended as a gold standard method of sodium intake estimation because of its accuracy and consistency. However, multiple 24-hour urine collection is needed to obtain accurate results because of large day-to-day variations in sodium intakes.[14] In a recent study, the means of three to seven 24-hour urinary sodium measurements during the study periods showed a linear association with mortality, but baseline 24-hour urinary sodium showed no relationship with mortality.[15] These findings indicate multiple subsequent 24-hour urine collection should be used to assess the risk of future CV events rather that single baseline 24-hour urine sodium. However, many studies have used single or double 24-hour urine collection because multiple collection of 24-hour urine without any loss of urine in population survey is much difficult.

Because 24-hour urine collection requires skills and resources in large scaled population health survey, considerable efforts have been made to use spot urine in the estimation of sodium intake, and WHO recommend the use of spot urine to estimate sodium intake in low and middle income countries.[16] Furthermore, the latest Prospective Urban Rural Epidemiology (PURE) study, which challenged the need to reduce sodium intake to or below the recommended level, used a spot urine collection method to estimate sodium intake.[8,9] Many formulae have been developed and are widely used for the estimation of sodium intake, but despite its convenience and low cost, the calculation of 24-hour urine sodium based on spot urine should be considered with caution because of inaccuracy.

To explore the validity of the spot urine method, we performed a systematic review of published studies. The electronic database of PubMed from publication date of January 2014 to September 2019 was searched using applicable terms (search terms in **Appendix 1**). The inclusion criteria used were as follows: human, sodium intake measured by 24-hour urine collection (single or multiple), sodium intake calculated by single or multiple spot urine collection, and comparison between measured and calculated urine sodium level. Potentially eligible articles were identified, and full texts were then reviewed. Eighteen eligible studies were identified (**Table 1**).[17-34]

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Table 1. Studies that evaluated the validity of spot urine collection method for the estimation of sodium intake

Authors, year	Country	Population	Sample size	Mean age, years (SD)/age range	Men (%)	Measured 24-hour urine sodium (mmol/day)	Equation	Estimated 24-hour urine sodium (mmol/day)	Use at population level	Use at individual level	Notes
Ji et al., 2014[17]	UK (White women)	General	297	51	297 (44.1)	129.9	Tanaka	129.9	Not recommended	Not recommended	- Over-estimation at lower level and under-estimation at higher level
							Arithmatic	113.6			
	UK (White men)					174.9	Tanaka	174.9			
							Arithmatic	130.2			
	UK (African women)	General	326	52	125 (38.3)	145.9	Tanaka	146.2			
							Arithmatic	121.1			
	UK (African men)					170.9	Tanaka	170.4			
							Arithmatic	133.8			
	UK (South Asian women)	General	292	50	154 (52.7)	129.8	Tanaka	129.8			
							Arithmatic	114.1			
	UK (South Asian men)					161.4	Tanaka	161.4			
							Arithmatic	120.8			
Mente et al., 2014[18]	11 countries (India, China, Colombia, Argentina, Brazil, Malaysia, South Africa, Turkey, Canada, Sweden, UAE)	General	1,083	56.6 (9.4)/ 35–70	451 (41.6)	179	Kawasaki	192.6	Recommended	Commended	- Over-estimation at lower level and under-estimation at higher level
							INTERSALT	141.6			
							Tanaka	155.2			
Toft et al., 2014[19]	Denmark	General	473	51.9/ 28–74	102 (21.6)	150	Tanaka	156	Recommended	Recommended	- Internal validation
							Danish model	140			
Rhee et al., 2014[20]	Korea	General	224	51.0 (10.9)	89 (29.7)	165.3	Kawasaki	195.5	Not recommended	Not recommended	- Over-estimation at lower level and under-estimation at higher level
							Tanaka	153.1			
							INTERSALT	131.7			
							Linear equation	159.6	Recommended		
							Quadratic equation	160.1			
							Cubic equation	164.4			
McLean et al., 2014[21]	New Zealand (Dunedin)	General	98	35.6/ 18–64	30 (30.6)	150.4	PAHO and measured Cr	156.3	Recommended	Not recommended	- Small sample size and young, patients on diuretics are excluded
							PAHO and Milton cCr	172.7			
							INTERSALT	126.4	Recommended		
							Tanaka	157			
							Kawasaki	198.9			
Kelly et al., 2015[22]	Ireland	Workers	50	37.7/ 18–64	32 (64)	138	Arithmetric (morning)	136	Recommended	Not recommended	- Small sample size
							Tanaka (morning)	129			
							Kawasaki (morning)	157			
							INTERSALT (morning)	125			
							Arithmetric (evening)	168			
							Tanaka (evening)	147			
							Kawasaki (evening)	187			
							INTERSALT (evening)	132			
Han et al., 2015[23]	China (Beijing)	Hypertensives	222	58.4 (14.5)	99 (45)	147.9	Kawasaki (SMU)	145.8	Recommended	Recommended	- Over-estimation at lower level and under-estimation at higher level
							Tanaka (SMU)	178.8			
							Kawasaki (PM)	219.5			
							Tanaka (PM)	169.3			
Peng et al., 2016[24]	China (Shanxi)	General	116	53.2 (8.1)	37 (31.9)	275.8	Kawasaki	243.6	Not recommended	Not recommended	- Substudy of PURE, patients on diuretics are excluded
							INTERSALT	154.2			
							Tanaka	175.6			
Whitton et al., 2016[25]	Singapore	General (Chinese, Malay, Indian)	140	49.4 (14.9)	57 (41)	125	INTERSALT	N/A	Recommended		- Validation was performed in small population (n=70)
							Singapore Health 2	N/A	Not recommended		
							Tanaka	N/A	Not recommended		

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Table 1. (Continued) Studies that evaluated the validity of spot urine collection method for the estimation of sodium intake

Authors, year	Country	Population	Sample size	Mean age, years (SD)/age range	Men (%)	Measured 24-hour urine sodium (mmol/day)	Equation	Estimated 24-hour urine sodium (mmol/day)	Use at population level	Use at individual level	Notes
Polonia et al., 2016[26]	Portugal	General	2,339	51.1 (16.9)	1,118 (47.8)	176.2	Tanaka	N/A	Not recommended	Not recommended	- Low correlation and ICC - Over-estimation at lower level and under-estimation at higher level
							Kawasaki	N/A			
							INTERSALT	N/A			
							NHANES	N/A			
Ma et al., 2017[27]	China (Shaanxi)	Individuals with elevated risk of stroke	365	67.5 (6.8)	155 (42.5)	162	Kawasaki	193.92	Not recommended		- Kawasaki and Tanaka methods were used while the INTERSALT method underestimated 24-hour sodium excretion
							INTERSALT	129.97			
							Tanaka	378.74			
Vidal-Petiot et al., 2017[28]	France (Paris)	Patients undergoing evaluation of renal function	1,018	51 (14)	617 (61)	157.6	Kawasaki	168.3		Not recommended	- Over-estimation at lower level and under-estimation at higher level - 71% were on antihypertensive drugs
							INTERSALT	128.7			
							Tanaka	134.8			
Allen et al., 2017[29]	USA (Chicago)	General	554	60.3 (9.1)/ 45–79	253 (45.7)	143.1	INTERSALT	138.6		Not recommended	-
							Tanaka	157.1			
							Kawasaki	190.5			
							Mage	165.3			
Rhee et al., 2017[30]	Korea	General	175	46.2 (12.7)	68 (38.9)	161.3	Kawasaki	185.3	Not recommended	Not recommended	- Over-estimation at lower level and under-estimation at higher level
							Tanaka	147			
							INTERSALT	126.5			
							Quadratic equation	149.2			
							Equation using 3 SU	158.4			
Zhou et al., 2017[31]	China (Dexing)	General	141	51.1 (8.2)	8 (5.7)	220.8	Kawasaki	246.1		Not recommended	- Mostly women
							INTERSALT	143.6			
							Tanaka	183.7			
Jędrusik et al., 2018[32]	Poland	Mostly hypertensives (92%)	335	55 (16)*/ 16–94	135 (40.3)	160.3	Tanaka	149.2	Not recommended	Not recommended	- Over-estimation and under-estimation - Hospitalized patients
							Kawasaki	189.7			
							PAHO	148.3			
Zhang et al., 2019[33]	China	General (healthy)	85	32.2 (11.1)/ 18–60	32 (37.6)	198.2	Kawasaki	231.6	Not recommended	Not recommended	- Patients taking diuretics are excluded
							INTERSALT	136.5			
							Tanaka	193.9			
							SunSMU	156.7			
							SunPM	188.9			
Emeville et al., 2019[34]	French	General	193	50.1 (16.5)	102 (52.8)	123.3	INTERSALT	108	Recommended	Not recommended	- Over-estimation at lower level and under-estimation at higher level

Cr = creatinine; ICC = intraclass correlation coefficient; INTERSALT = International Cooperative Study on Salt, Other Factors, and Blood Pressure; Milton = age- and sex-specific measured 24-hour creatinine excretion from 24-hour urine samples collected in the New Zealand Milton Study; N/A = not available; PAHO = Pan American Health Organization; PM = post meridiem; PURE = Prospective Urban Rural Epidemiology; SD = standard deviation; SMU = second morning urine; SU = spot urine.
*Age before exclusion.

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Thirteen studies concluded that calculation result from spot urine could not be recommended in the estimation of 24-hour urine sodium estimation at an individual level because of tendencies of underestimation at high sodium intake and over-estimation at low sodium intake.[17)20-22)24)26)28-34)] Even the study of Mente et al.[18)] showed a tendencies to over-estimate at low sodium intake and under-estimate at high sodium intake although they did not comment about that finding. In terms of 24-hour urine sodium estimation at a population level, eight studies suggested the use of spot urine collection method for the estimation of sodium intake at the population level.[18-23)25)34)] However, the result of calculated sodium intake from spot urine may be inappropriate at the population level as the various formulae produced inconsistent bias between measured and estimated 24-hour urine. For example, the bias between measured and estimated 24-hour urine sodium (as determined using Kawasaki formula) ranged from −32.2 to 84.5 mmol/day. Even in the largest study conducted on this topic by Mente et al.,[18)] the bias between measured and estimated 24-hour urine sodium level (calculated using the Kawasaki formula) was not small (bias=13.6 mmol/day, 7.8% of average 24-hour urine sodium of study population).

Inaccurate estimation of 24-hour urine sodium level by formulae using spot urine sodium concentration may have inherent problem considering the method to develop formulae. Most of these formulas were developed using regression models in specific populations. Therefore, estimated 24-hour urine sodium values may depend on the mean of 24-hour urine sodium in the population used for formula development, and thus, calculated 24-hour urine sodium do not accurately reflect values in populations with different characteristics from the formula development population.

We evaluated this hypothesis. Populations of studies that were conducted in year 2012,[20)] 2014,[30)] and from 2013 to 2014[35)] were combined and analyzed. The method to determine the completeness of 24-hour urine collection was described elsewhere.[20)30)35)] Among 1,115 participants, 791 had a valid 24-hour urine collection and spot urine sample (**Table 2**). Study population was divided by septiles of 24-hour urine sodium level. The means of measured 24-hour urine sodium and estimated 24-hour urine sodium (calculated using the Kawasaki

Table 2. Demographic and clinical characteristic of study population

Variables	Values
Number of subject	
Total	791
Study 2012, number (% and total number of primary study)	325 (64.7, 502)
Study 2013–2014, number (% and total number of primary study)	192 (68.8, 279)
Study 2013, number (% and total number of primary study)	274 (82.0, 334)
Age (years)	50.5±11.9
Men	315 (39.8)
Body weight (kg)	62.5±10.7
Height (cm)	162.7±8.2
Hypertension	253 (32.0)
Use of antihypertensive drugs	90 (11.4)
Diabetes	50 (6.3)
Serum sodium (mmol/L)	140.4±6.6
Serum potassium (mmol/L)	4.4±0.4
Serum creatinine (mg/dL)	0.80±0.16
24-hour urine sodium (mmol/day)	161.3±63.2
Estimated 24-hour urine sodium (by Kawasaki formula) (mmol/day)	190.0±53.2
Estimated 24-hour urine sodium (by Danish formula) (mmol/day)	156.9±37.2
24-hour urine potassium (mmol/day)	63.0±24.3

Populations of study in 2012, 2013–2014 and 2014 were combined. Data are expressed as mean±standard deviation or number (%) not otherwise specified.

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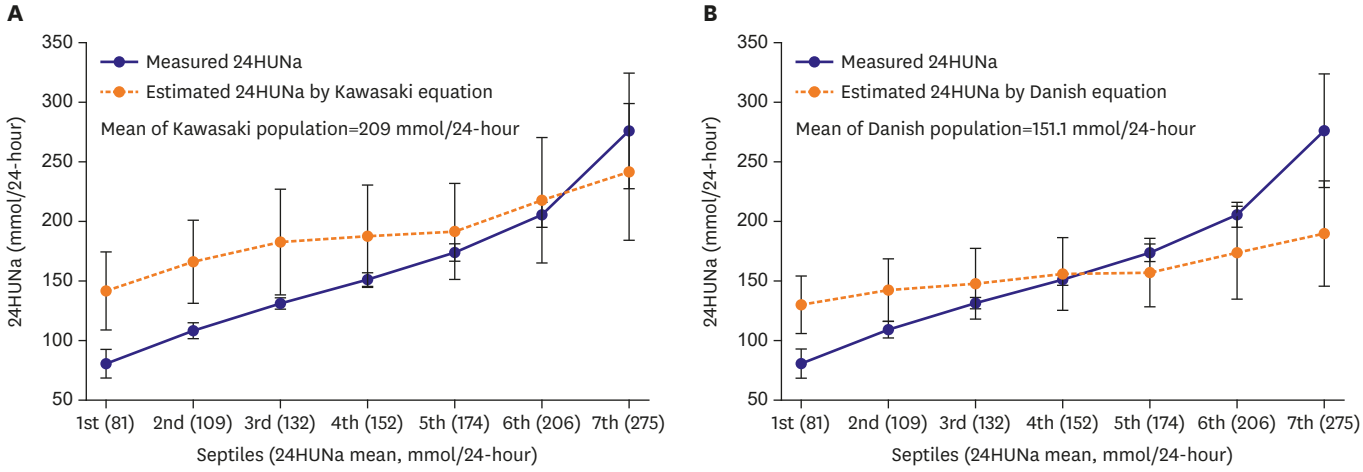

Figure 1. Comparison between measured and estimated 24HUNa in septile groups divided according to measured 24HUNa. Estimated 24-hour urine sodium was calculated by using previously suggested equations. (A) Kawasaki, and (B) Danish equation. When the 24HUNa is calculated by applying the formulas to groups with smaller 24HUNa than that of formula development population, there is a tendency of overestimation of population mean 24-hour urine sodium. On the other hands, in groups with greater 24-hour urine sodium than that of the formula development population, there is a tendency of underestimation of 24-hour urine sodium.
24HUNa = 24-hour urine sodium excretion.

and Danish formula) were compared (**Figure 1**). When the 24-hour urine sodium excretion is calculated by applying the formulas to groups with smaller 24-hour urine sodium excretion than that of formula development population, there is a tendency of overestimation of 24-hour urine sodium. On the other hands, in groups with greater 24-hour urine sodium than that of the development population, there is a tendency of underestimation of 24-hour urine sodium. This phenomenon has been observed in many studies that validated spot urine collection methods. Some studies that validated the Kawasaki formula showed if mean measured 24-hour urine sodium in the validation population was lower than that in the population used to develop Kawasaki formula (209 mmol/day), mean estimated 24-hour urine sodium in the validation population was higher than mean measured 24-hour urine sodium,.[18][20-22][27-30][32][33] and conversely, if mean measured 24-hour urine sodium in the validation population was higher than that in development population, mean estimated 24-hour urine sodium in the validation population was lower than mean measured 24-hour urine sodium.[24] However, many large studies are needed to verify our hypothesis and find method for accurate estimation of 24-hour urine from spot urine in a population level.

SODIUM INTAKE AND BLOOD PRESSURE

Many intervention studies have reported sodium intake reduction lowers BP and has a profound effect in individuals with hypertension.[36] Furthermore, this effect was observed even after modest sodium intake reduction.[37] However, the majority of intervention studies were conducted over the short- or medium-term and few long-term studies have been undertaken, presumably because long-term dietary intervention studies are much more difficult to perform. In a previous study,[38] we found 5 dietary intervention studies performed over more than 6 months.[39-43] Four of these studies reported lowering sodium intake significantly lowered BP.[39-42] In the Trials of Hypertension Prevention (TOHP) II study, the effect of sodium intake reduction on BP was observed, and although the effect declined with time, it remained significant until 36 months and reduced the incidence of hypertension.[41] On the other hand, a study performed in young healthy nulliparous pregnant

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women concluded a low sodium diet had no effect on BP or on the incidence of gestational hypertension.[43]

The International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) was a representative population-based cross-sectional study that evaluated the relationship between salt intake and blood pressure.[44] This study showed that 24-hour urine sodium and BP were significantly related, but unfortunately, did not determine whether BP reductions were dose-dependently related to 24-hour urine sodium levels.

To investigate the dose-dependent effect of sodium intake on BP in population-based epidemiological studies, we searched PubMed from January 2009 to September 2019 for cross-sectional studies that evaluated the relationship between BP and sodium intake (search terms in **Appendix 2**). The inclusion criteria used were as follows: human, sodium intake measured by 24-hour urine collection (single or multiple), and BP data (casual or ambulatory). We identified 374 articles. Studies used spot urine collection to estimate 24-hour urine sodium or a dietary survey-based method were excluded for the reasons mentioned above. Titles and abstracts were screened, potentially eligible articles were identified, and the full text were reviewed. As a result, 15 studies were eligible for analysis (**Table 3**).[45-59] Of these 15 studies, 9 reported a significant association between sodium intake and BP,[45-53] and 6 studies found no significant association.[54-59] Jackson et al. analyzed data obtained from 766 participants in the National Health and Nutrition Examination Survey (2014) conducted in the United States,[51] and reported significant, dose-dependent associations between BP and 24-hour urine sodium (positive association) and potassium (negative association). On the other hand, a study by Mente et al.[55] performed as part of the Prospective Urban Rural Epidemiological (PURE)-Canadian study found no linear association between BP and 24-hour urine sodium excretion. The differences between these studies were; 1) determination method of complete 24-hour urine collection, 2) 24-hour urine potassium excretion, and 3) ethnicity. Mente et al.[55] used para-aminobenzoic acid to determine complete 24-hour urine collection but did not use it in individual over 65 years old, and thus, it was not clear whether complete 24-hour urine collection was performed in those over 65-years old. The most obvious difference between the 2 studies was that the study population of Mente's study[55] had a higher potassium intake and a lower urine sodium-to-potassium ratio than those of Jackson's study had[51] (sodium-to-potassium ratios were 1.93 vs 2.98, respectively). In a study by Xu et al.[49] on 2,281 Chinese individuals, a significant linear association was observed between BP and 24-hour urine sodium excretion. In this study, average 24-hour urine potassium was 25.3 mmol/day and the urine sodium-to-potassium ratio was 6.8. In a previous study, we found a significant association between urinary sodium-to-potassium ratio and BP.[53] These findings suggest that high potassium intake and a low sodium-to-potassium ratio may reduce the effect of sodium intake on BP. Furthermore, ethnicity may have contributed to result disparities. The population studied by Jackson et al. included more than 10% African-Americans, but the population studied by Mente et al.[55] included 9.1% non-Europeans (the proportion of Black people was not reported). BP response to sodium intake is not as uniform as response to antihypertensive drugs, which can be explained by sodium sensitivity. In general population, 20–50% of individuals exhibit sodium sensitivity,[60] and the condition is highly prevalent in Black people, those with hypertension or metabolic syndrome, and in older people and women.[61] Therefore, the inclusion of a large number of sodium resistant individuals might blur the dose-dependent effect of sodium intake on BP. As an example, Mohammadifard et al.[57] included young and healthy individuals without diabetes, hypertension, a history of diuretic use, or renal

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Table 3. Cross-sectional epidemiologic studies that evaluated the association between sodium intake and blood pressure

Authors, year	Country	Number	Participants	Age range (years)	Mean (SD) age (years)	Mean (SD) urine sodium (mmol/day)	BP measurement method	Findings	Notes
Angell et al., 2014[45]	USA (New York)	1,656	General, 41.8% men	≥18	N/A	140.8	OBP	Significant linear association with SBP	26.6% was black, 35.6% was hypertensive
Xu et al., 2014[46]	China (Yantai)	191	General, 51.3% men	18–69	42.3 (13.5)	201.5 (77.7)	OBP	Significant linear association with SBP	
Rodrigues et al., 2015[47]	Brazil (Vitória)	272	General, 47.4% men	18–69	44 (14)	176.5 (70.9)	OBP	Significant association with SBP	Positive association between salt and systolic BP was more striking when salt intake was greater than 9 g/d
Ndanuko et al., 2017[48]	Australia (Illawarra)	327	General, 27% men	25–54	43.6 (8)	139 (median)	OBP, supine	Significant linear association with SBP	Over-weighted BMI 25–40 kg/m^2
Xu et al., 2017[49]	China (Fushan, Gaomi, Xinyl, Ganyu)	2,281	General, 49.8% men	18–69	42.1 (13.4)	166.9 (25.6)	OBP	Significant association with SBP	Sodium intake was estimated from 24-hour urine sodium by using PC-SIDE
Glatz et al., 2017[50]	Swiss (Vaud, Geneva, Valais, Fribourg, Luzern, Basel, Zürich, St Gallen, Ticino)	1,336	General, 48.7% men	>15	German 48.8 (18), French 47.8 (18.1), Italian 45.3 (18.4)	156.8	OBP	Significant association with SBP	Participants in eight predefined sex- and age-strata (men and women aged 15–29, 30–44, 45–59 and ≥60 years)
Jackson et al., 2017[51]	USA (National)	766	General, 48.4% men	20–69	43.6	Hypertensive 162.6 mmol/day, prehypertensive 154.5 mmol/day, Optimal 159.0 mmol/day	OBP	Significant linear association with SBP and DBP	Sodium intake was estimated from 24-hour urine sodium by using measurement error model to account day-to-day variation, National Health and Nutrition Examination Survey
Maseko et al., 2018[52]	South Africa [Johannesburg (Soweto)]	547	General, 36.7% men	>18	45.3 (18.5)	105.6 (78.4)	ABP	Significant association with SBP and DBP in normal BMI participants	44.9% of 1,219 recruited participants were included in the analysis
Kim et al., 2019[53]	Korea (Goyang, Paju, Seoul, Chuncheon, Gyeongju)	740	General, 41.1% men	20–70	48 (median)	153.9 (median)	ABP	Significant linear or non-linear association with SBP and DBP in older ages	
McLean et al., 2015[54]	New Zealand (Dunedin, Wellington)	299	General, 48.5% men	18–64	N/A	147.2 (63.1)	OBP	No association	24-hour urine sodium was entered as a dependent variable
Mente et al., 2016[55]	Canada (Vancouver, Hamilton, Ottawa, and Quebec City)	1,700	General, 49.4% men	37–72	59.6 (9.0)	144.6 (63.8)	OBP	No association	90.9% European 21.9% Hypertensives
Mizéhoun-Adissoda et al., 2016[56]	Benin (Bohicon, Tanvè)	354	General, 48.5% men	25–64	43.0 (11.3)	173.9 (82.6)	OBP	No association	Participants rested throughout the 24-hour period in the health care center
Mohammadifard et al., 2017[57]	Iran (Isfahan)	796	Non-hypertensive adults, 43.3% men	>18	38.9 (11.4)	176.9 (72.0)	OBP	No association	Young healthy individuals without diabetes, hypertension, history of using diuretics, renal insufficiency
Vallejo et al., 2017[58]	Mexico (Mexico City)	711	General, 32.1% men	20–50	37.4 (9.0)	137	OBP	No association	
Chen et al., 2018[59]	Norway (Oslo)	159	General	20–67	40.3 (11.1)	137.9 (61.3)	OBP	No association	Immigrants of Somalis from east Africa

ABP = ambulatory blood pressure; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; N/A = not available; OBP = office measured blood pressure; SBP = systolic blood pressure; SD = standard deviation; PC-SIDE = PC Software for Intake Distribution Estimation.

insufficiency (i.e. large number of sodium resistant individuals may be included), and reported no association between sodium intake and BP. In terms of statistical analysis, we

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used multiple regression with restricted cubic splines,[53] and found a non-linear (curvilinear) association between 24-hour urine sodium excretion and BP, which contrasts with that found by Mente et al.[55] and others. In addition, BP measurement methods might have contributed to result disparities. We previously reported a significant linear association between 24-hour urine sodium and nighttime BP and a curvilinear association with daytime BP in older individuals (≥55 years old).[53] Accordingly, the different relations between sodium intake and BP in cross-sectional studies might be caused by study population, statistical method, and/or BP measurement differences.

SODIUM INTAKE AND CARDIOVASCULAR DISEASE

Although the association between sodium intake and BP is generally accepted, relations between the effects of sodium intake on CV events and mortality have been debated. Few long-term intervention trials have evaluated the effect of sodium intake on CV outcomes and studies conducted have lacked the statistical power to access the relation between CV events and sodium intake. A long-term maintenance of dietary sodium intakes in large populations is difficult for cost and ethical reasons, especially in high risk patients. Although the phase I and II TOHP did not include CV outcomes as primary efficacies, they did perform long-term follow-ups (over 20 years) to determine CV outcomes, after the original studies had been terminated.[62] This long-term study showed a linear increase in all-cause mortality of 12% for every 1 g/day increase in sodium consumption and no evidence of a J-shaped or nonlinear relation.[63] On the other hand, the Trial of Nonpharmacologic Intervention in the Elderly (TONE) study showed no difference between the CV event rates in a reduced sodium intervention group and a usual lifestyle intervention group.[64] However, a meta-analysis that included data from the TOHP I, TOHP II, and TONE studies showed sodium intake reduction significantly reduced CV events.[65] Stolarz-Skrzypek et al.[66] reported an inverse association between 24-hour urine sodium and risk of CV mortality in a general population and in individuals with hypertension without CV disease. Actually, several cohort studies have reported different associations between sodium intake and CV outcomes.

We searched cohort studies that evaluated association between sodium intake and CV outcomes in PubMed from 2009 to 2019 (search terms in **Appendix 3**) and initially identified 619 articles. We included studies that used 24-hour urine collection method to determine sodium intakes and excluded studies that used spot urine collection or a dietary survey. Titles and abstracts were screened and potentially eligible articles were identified and reviewed full text in detail. Of the 10 studies included (**Table 4**), 5 studies[66-70] used single 24-hour urine sodium measurements at baseline and the other 5 studies[63,71-74] used averages of subsequently measured multiple 24-hour urine sodium measurements to estimate sodium intake. The five studies performed using single 24-hour urine sodium measurements showed inverse,[66] J- or U-shaped associations,[67,70] a positive association,[68] or no association[69] with CV outcomes. However, in the 5 studies that used average of subsequently measured multiple 24-hour urine sodium,[63,71-74] high 24-hour urine sodium excretion was associated with a higher risk of CV outcomes and 24-hour urine sodium excretion and CV outcomes were found to be linearly associated.

The different results may be explained by the difference in measurement methods of sodium intake, a single measurement of 24-hour urine sodium or subsequently multiple measurement of 24-hour urine sodium. A single 24-hour urine sodium measurement at baseline cannot reflect day-to-day variations in sodium intake. For example, many people change their dietary

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habits during follow-up in cohort studies. In a study by Olde Engberink et al.,[74] 50% of subjects showed more than 0.8 g (34 mmol) difference between sodium intake at baseline and averages of subsequent measurements taken over 5 years, and 50% subjects were classified into different sodium intake groups when long-term 24-hour urine sodium measurements were used to classify sodium intake groups rather than single baseline measurements. Similarly, the hazard

Table 4. Cohort studies that evaluated the association between sodium intake and cardiovascular outcomes

Authors, year	Country	Population	Sample size	Mean age (age range)	Follow up duration (median years)	Estimation of sodium intake	Outcome
Stolarz-Skrzypek et al., 2011[66]	Northern Belgium	General and hypertensive (without CV disease)	3,681	40.9	7.9	- A single 24-hour urine collection at baseline - Criteria of a complete urine collection: N/A	- CV deaths decreased across increasing tertiles for 24-hour urinary sodium: low tertile (death rate, 4.1%; 95% CI, 3.5–4.7), medium tertile, (death rate, 1.9%; 95% CI, 1.5–2.3); and high tertile (death rate, 0.8%,95% CI, 0.5–1.1; p<0.001). - The risk of CV mortality was inversely associated with 24-hour urinary sodium (p=0.02) and the HR in the low tertile was 1.56 (95% CI, 1.02–2.36; p=0.04).
Thomas et al., 2011[67]	Finland	Adults with type 1 diabetes without ESRD	2,807	39	10	- A single 24-hour urine collection at baseline - Criteria of a complete urine collection: N/A	- Urinary sodium excretion was nonlinearly associated with all-cause mortality (individuals with the highest daily urinary sodium excretion, as well as the lowest excretion, had reduced survival, p<0.001). - Urinary sodium excretion was inversely associated with the cumulative incidence of ESRD (p<0.001).
Joosten et al., 2014[68]	Netherlands	Adults free of CV and kidney disease (PREVEND study)	7,543	(28–75)	10.5	- A single 24-hour urine collection at baseline - Criteria of a complete urine collection: N/A	- Each 1-g/day increment in sodium excretion was associated with an increased risk for CHD 1) In subjects with hypertension (adjusted HR, 1.14; 95% CI, 1.01–1.28; n=2,363) and 2) In subjects with NT-proBNP concentrations above the sex-specific median (adjusted HR, 1.16; 95% CI, 1.03–1.30; n=3,771).
Cook et al., 2014[71]	USA	Pre-hypertensive	2,275 not in a sodium reduction intervention	(30–54)	10–15	- Mean of subsequent multiple 24-hour urine sodium measurement: 1) 5 (lifestyle interventions) or 7 (nutritional supplement interventions) scheduled collections during 18 months in TOHP I 2) 3 or up to 5 scheduled collections during 3 years in TOHP II	- Compared to those with sodium excretion of 3,600 to <4,800 mg/24-hr, risk for those with sodium <2,300 mg/24-hr was 32% lower after multivariable adjustment (HR, 0.68; 95% CI, 0.34–1.37, p for trend=0.13). - There was a linear 17% increase in risk per 1,000 mg/24-hr (p=0.05).
Singer et al., 2015[69]	USA	Participants in a work site hypertension program	3,505	52±10	18.6	- A single 24-hour urine collection at baseline 1) After the medication washout period 2) Subjects were instructed to follow their usual diet while avoiding "excessively salty foods" for a period of 4–5 days preceding the collection	- Sodium intake was 1) Not significantly associated with all CV mortality (QI vs. QIV: HR, 1.00; 95% CI, 0.71–0.42; p=0.99). 2) Significantly associated with non-CV disease mortality (QI vs. QIV: HR, 0.57; 95% CI, 0.41–0.80; p=0.001), 50% was cancers. 3) No U- or J-shape association.
Cook et al., 2016[63]	USA	Pre-hypertensive adults	3,011	43	24 (more extended follow-up of TOHP)	- Mean of subsequent multiple 24-hour urine sodium measurements: 1) 5 (lifestyle interventions) or 7 (nutritional supplement interventions) scheduled collections during 18 months in TOHP I 2) 3 or up to 5 scheduled collections during 3 years in TOHP II	- Direct linear association between average sodium intake and mortality. - HR, 1.12 per 1,000 mg/24-hr (95% CI, 1.00–1.26; p=0.05). - No J-shaped association.

(continued to the next page)

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Table 4. (Continued) Cohort studies that evaluated the association between sodium intake and cardiovascular outcomes

Authors, year	Country	Population	Sample size	Mean age (age range)	Follow up duration (median years)	Estimation of sodium intake	Outcome
Mills et al., 2016[72]	USA	Patients with mild to moderate CKD: eGFR of 20–70 mL/min/1.73 m^2	3,757	58	6.8	- Cumulative mean of three 24-hour urinary sodium excretion: the baseline visit and the first 2 annual follow-up visits	- HR of the highest quartile compared with the lowest quartile: 1.36 (95% CI, 1.09–1.70; p=0.007) for composite CV disease events, 1.34 (95% CI, 1.03–1.74; p=0.03) for heart failure, and 1.81 (95% CI, 1.08–3.02; p=0.02) for stroke after multivariable adjustment. - Significant linear association between urinary sodium excretion and composite CV disease.
Polonia et al., 2016[73]	Portugal	Hypertensives, treated	608	54.1±14.3	7.2	- A single 24-hour urine collection at baseline - Average of first and second 24-hour urine collections within a 3-month period whenever possible	- Urine sodium above the median (189 mmol sodium/day) predicted CV events with HR, 2.99 (95% CI, 1.75–5.13; p<0.001) with worse CV event-free survival rates (log rank statistics of 17.44, p<0.001). - HR, 1.09 (95% CI, 1.06–1.12; p<0.001) for each 10 mmol increase of urine sodium.
Olde Engberink et al., 2017[74]	Netherlands	Subjects with an eGFR >60 mL/min/1.73m^2	574	47	16.2	- A single baseline collection or 24-hour urine - The average of samples collected during a 1-, 5-, and 15-year follow-up	- High 24-hour sodium excretion was associated with a higher risk for CV events and mortality (1-year HR, 1.80; 95% CI, 1.03–3.13; 5-year HR, 1.73; 95% CI, 1.00–2.99).
Lelli et al., 2018[70]	Italy	Community dwelling older people (≥65 years)	920	74.5	9	- A single 24-hour urine collection at baseline	- A bi-modal association between sodium excretion and mortality, with risk increasing only below sodium excretion of 6.25 g/day (HR, 1.12; 95% CI, 1.04–1.22). - No association between 24-hour sodium excretion and 9-year incidence of CV diseases (adjusted risk ratio, 0.96; 95% CI, 0.90–1.02).

CHD = coronary heart disease; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; N/A = not available; Q = quintile; TOHP = Trials of Hypertension Prevention.

ratios of CV events and mortality were altered by up to 85% when average of subsequently measured long-term 24-hour urine sodium measurements were used.

In the present review, we excluded studies that estimated sodium intakes from spot urine measurements using formulae, although the estimation of 24-hour urine sodium from spot urine is inexpensive and easily performed in large populations. Several large-scale studies have evaluated the association between sodium intake and CV outcomes and mortality using estimated 24-hour urine sodium values calculated in this manner, and these studies have consistently found paradoxical J- or U-shaped associations between sodium intake and CV outcomes and mortality.[8][9][75] However, in addition to the reasons as mentioned above, a recently published study demonstrated the inappropriateness of using estimated dietary sodium intake from spot urine when investigating the association between sodium intake and mortality.[76] In this study, a significant linear association was reported between the averages of subsequently measured 24-hour urine sodium and mortality, but J- or U-shaped relationships were found between estimated 24-hour urine sodium levels using spot urine and mortality.

CONCLUSION

The findings of the present systematic review can be summarized as follows:

1) The spot urine collection method is inaccurate and should not be recommended to measure sodium intake at the individual level, and further studies for its use to measure

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sodium intake at the population level are required.
2) High sodium intake is positively associated with BP.
3) Associations between high sodium intake and CV outcomes are significant, but reverse causality cannot be ruled out.

Although many studies have reported no, inverse, or J- or U-shaped associations of sodium intake with BP, CV outcomes, and mortality, these studies used biased methods to determine sodium intakes. This review convincingly shows sodium intake is associated with BP, CV outcomes, and mortality and invalidates the argument that reducing sodium intake is dangerous and unnecessary. Therefore, we conclude that sodium intake reduction should be generally recommended and not limited to patients with hypertension or CV disease.

REFERENCES

1. He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* 2009;23:363-84.
PUBMED | CROSSREF
2. Adrogué HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* 2007;356:1966-78.
PUBMED | CROSSREF
3. Nagata C, Takatsuka N, Shimizu N, Shimizu H. Sodium intake and risk of death from stroke in Japanese men and women. *Stroke* 2004;35:1543-7.
PUBMED | CROSSREF
4. Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. *Circulation* 1994;89:1041-50.
PUBMED | CROSSREF
5. Cianciaruso B, Bellizzi V, Minutolo R, et al. Salt intake and renal outcome in patients with progressive renal disease. *Miner Electrolyte Metab* 1998;24:296-301.
PUBMED | CROSSREF
6. Cappuccio FP, Kalaitzidis R, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. *J Nephrol* 2000;13:169-77.
PUBMED
7. Tsugane S, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004;90:128-34.
PUBMED | CROSSREF
8. Mente A, O'Donnell M, Rangarajan S, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. *Lancet* 2018;392:496-506.
PUBMED | CROSSREF
9. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med* 2014;371:612-23.
PUBMED | CROSSREF
10. Adler AJ, Taylor F, Martin N, Gottlieb S, Taylor RS, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2014:CD009217.
PUBMED | CROSSREF
11. Rhee MY. High sodium intake: review of recent issues on its association with cardiovascular events and measurement methods. *Korean Circ J* 2015;45:175-83.
PUBMED | CROSSREF
12. Espeland MA, Kumanyika S, Wilson AC, et al. Statistical issues in analyzing 24-hour dietary recall and 24-hour urine collection data for sodium and potassium intakes. *Am J Epidemiol* 2001;153:996-1006.
PUBMED | CROSSREF
13. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. *Int J Epidemiol* 2009;38:791-813.
PUBMED | CROSSREF

14. Luft FC, Fineberg NS, Sloan RS. Estimating dietary sodium intake in individuals receiving a randomly fluctuating intake. *Hypertension* 1982;4:805-8.
PUBMED | CROSSREF

15. He FJ, Campbell NR, Ma Y, MacGregor GA, Cogswell ME, Cook NR. Errors in estimating usual sodium intake by the Kawasaki formula alter its relationship with mortality: implications for public health. *Int J Epidemiol* 2018;47:1784-95.
PUBMED | CROSSREF

16. The WHO STEPwise approach to noncommunicable disease risk factor surveillance [Internet]. Geneva: World Health Organization; 2017 [cited 2019 October 10]. Available from: http://www.who.int/chp/steps/en/

17. Ji C, Miller MA, Venezia A, Strazzullo P, Cappuccio FP. Comparisons of spot vs 24-h urine samples for estimating population salt intake: validation study in two independent samples of adults in Britain and Italy. *Nutr Metab Cardiovasc Dis* 2014;24:140-7.
PUBMED | CROSSREF

18. Mente A, O'Donnell MJ, Dagenais G, et al. Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. *J Hypertens* 2014;32:1005-14.
PUBMED | CROSSREF

19. Toft U, Cerqueira C, Andreasen AH, et al. Estimating salt intake in a Caucasian population: can spot urine substitute 24-hour urine samples? *Eur J Prev Cardiol* 2014;21:1300-7.
PUBMED | CROSSREF

20. Rhee MY, Kim JH, Shin SJ, et al. Estimation of 24-hour urinary sodium excretion using spot urine samples. *Nutrients* 2014;6:2360-75.
PUBMED | CROSSREF

21. McLean R, Williams S, Mann J. Monitoring population sodium intake using spot urine samples: validation in a New Zealand population. *J Hum Hypertens* 2014;28:657-62.
PUBMED | CROSSREF

22. Kelly C, Geaney F, Fitzgerald AP, Browne GM, Perry IJ. Validation of diet and urinary excretion derived estimates of sodium excretion against 24-h urine excretion in a worksite sample. *Nutr Metab Cardiovasc Dis* 2015;25:771-9.
PUBMED | CROSSREF

23. Han W, Sun N, Chen Y, Wang H, Xi Y, Ma Z. Validation of the spot urine in evaluating 24-hour sodium excretion in Chinese hypertension patients. *Am J Hypertens* 2015;28:1368-75.
PUBMED | CROSSREF

24. Peng Y, Li W, Wang Y, et al. Validation and assessment of three methods to estimate 24-h urinary sodium excretion from spot urine samples in Chinese adults. *PLoS One* 2016;11:e0149655.
PUBMED | CROSSREF

25. Whitton C, Gay GM, Lim RB, Tan LW, Lim WY, van Dam RM. Evaluation of equations for predicting 24-hour urinary sodium excretion from casual urine samples in Asian adults. *J Nutr* 2016;146:1609-15.
PUBMED | CROSSREF

26. Polonia J, Lobo MF, Martins L, Pinto F, Nazare J. Estimation of populational 24-h urinary sodium and potassium excretion from spot urine samples: evaluation of four formulas in a large national representative population. *J Hypertens* 2017;35:477-86.
PUBMED | CROSSREF

27. Ma W, Yin X, Zhang R, et al. Validation and assessment of three methods to estimate 24-h urinary sodium excretion from spot urine samples in high-risk elder patients of stroke from the rural areas of Shaanxi province. *Int J Environ Res Public Health* 2017;14:1211.
PUBMED | CROSSREF

28. Vidal-Petiot E, Joseph A, Resche-Rigon M, et al. External validation and comparison of formulae estimating 24-h sodium intake from a fasting morning urine sample. *J Hypertens* 2018;36:785-92.
PUBMED | CROSSREF

29. Allen NB, Zhao L, Loria CM, et al. The validity of predictive equations to Estimate 24-hour sodium excretion: the MESA and CARDIA urinary sodium study. *Am J Epidemiol* 2017;186:149-59.
PUBMED | CROSSREF

30. Rhee MY, Kim JH, Shin SJ, et al. Estimating 24-hour urine sodium from multiple spot urine samples. *J Clin Hypertens (Greenwich)* 2017;19:431-8.
PUBMED | CROSSREF

31. Zhou L, Tian Y, Fu JJ, et al. Validation of spot urine in predicting 24-h sodium excretion at the individual level. *Am J Clin Nutr* 2017;105:1291-6.
PUBMED | CROSSREF

https://doi.org/10.4070/kcj.2020.0042

32. Jędrusik P, Symonides B, Gaciong Z. Comparison of three formulas to estimate 24-hour urinary sodium and potassium excretion in patients hospitalized in a hypertension unit. *J Am Soc Hypertens* 2018;12:457-69.
PUBMED | CROSSREF

33. Zhang Y, Peng Y, Li K, Peng X. Assessing whether a spot urine specimen can predict 24-h urinary sodium excretion accurately: a validation study. *J Hypertens* 2019;37:99-108.
PUBMED | CROSSREF

34. Emeville E, Lassale C, Castetbon K, et al. Estimating sodium intake from spot urine samples at population level: a validation and application study in French adults. *Br J Nutr* 2019;122:186-94.
PUBMED | CROSSREF

35. Rhee MY, Lee SY, Oh SW, et al. *Study for the Effect of Natrium Intake on the Prevalence of Cardiovascular Disease*. Cheongju: Ministry of Food and Drug Safety; 2014.

36. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev* 2017:CD004022.
PUBMED | CROSSREF

37. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ* 2013;346:f1325.
PUBMED | CROSSREF

38. Rhee OJ, Rhee MY, Oh SW, et al. Effect of sodium intake on renin level: Analysis of general population and meta-analysis of randomized controlled trials. *Int J Cardiol* 2016;215:120-6.
PUBMED | CROSSREF

39. Whelton PK, Appel L, Charleston J, et al. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA* 1992;267:1213-20.
PUBMED | CROSSREF

40. Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation* 1994;89:1023-31.
PUBMED | CROSSREF

41. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997;157:657-67.
PUBMED | CROSSREF

42. Takahashi Y, Sasaki S, Okubo S, Hayashi M, Tsugane S. Blood pressure change in a free-living population-based dietary modification study in Japan. *J Hypertens* 2006;24:451-8.
PUBMED | CROSSREF

43. van Buul BJ, Steegers EA, van der Maten GD, et al. Dietary sodium restriction does not prevent gestational hypertension: a Dutch two-center randomized trial. *Hypertens Pregnancy* 1997;16:335-46.
CROSSREF

44. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988;297:319-28.
PUBMED | CROSSREF

45. Angell SY, Yi S, Eisenhower D, et al. Sodium intake in a cross-sectional, representative sample of New York city adults. *Am J Public Health* 2014;104:2409-16.
PUBMED | CROSSREF

46. Xu J, Wang M, Chen Y, et al. Estimation of salt intake by 24-hour urinary sodium excretion: a cross-sectional study in Yantai, China. *BMC Public Health* 2014;14:136.
PUBMED | CROSSREF

47. Rodrigues SL, Souza Júnior PR, Pimentel EB, et al. Relationship between salt consumption measured by 24-h urine collection and blood pressure in the adult population of Vitória (Brazil). *Braz J Med Biol Res* 2015;48:728-35.
PUBMED | CROSSREF

48. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, O'Donnell KM, Batterham MJ. Relationship between sodium and potassium intake and blood pressure in a sample of overweight adults. *Nutrition* 2017;33:285-90.
PUBMED | CROSSREF

49. Xu J, Chen X, Ge Z, et al. Associations of usual 24-hour sodium and potassium intakes with blood pressure and risk of hypertension among adults in China's Shandong and Jiangsu provinces. *Kidney Blood Press Res* 2017;42:188-200.
PUBMED | CROSSREF

50. Glatz N, Chappuis A, Conen D, et al. Associations of sodium, potassium and protein intake with blood pressure and hypertension in Switzerland. *Swiss Med Wkly* 2017.147:w14411.
PUBMED | CROSSREF

51. Jackson SL, Cogswell ME, Zhao L, et al. Association between urinary sodium and potassium excretion and blood pressure among adults in the United States: National Health and Nutrition Examination Survey, 2014. *Circulation* 2018;137:237-46.
PUBMED | CROSSREF

52. Maseko M, Mashao M, Bawa-Allah A, Phukubje E, Mlambo B, Nyundu T. Obesity masks the relationship between dietary salt intake and blood pressure in people of African ancestry: the impact of obesity on the relationship between sodium and blood pressure. *Cardiovasc J Afr* 2018;29:172-6.
PUBMED | CROSSREF

53. Kyung Kim M, Kwon M, Rhee MY, et al. Dose-response association of 24-hour urine sodium and sodium to potassium ratio with nighttime blood pressure at older ages. *Eur J Prev Cardiol* 2019;26:952-60.
PUBMED | CROSSREF

54. McLean R, Edmonds J, Williams S, Mann J, Skeaff S. Balancing sodium and potassium: estimates of intake in a New Zealand adult population sample. *Nutrients* 2015;7:8930-8.
PUBMED | CROSSREF

55. Mente A, Dagenais G, Wielgosz A, et al. Assessment of dietary sodium and potassium in Canadians using 24-hour urinary collection. *Can J Cardiol* 2016;32:319-26.
PUBMED | CROSSREF

56. Mizéhoun-Adissoda C, Houinato D, Houehanou C, et al. Dietary sodium and potassium intakes: data from urban and rural areas. *Nutrition* 2017;33:35-41.
PUBMED | CROSSREF

57. Mohammadifard N, Khaledifar A, Khosravi A, et al. Dietary sodium and potassium intake and their association with blood pressure in a non-hypertensive Iranian adult population: Isfahan salt study. *Nutr Diet* 2017;74:275-82.
PUBMED | CROSSREF

58. Vallejo M, Colín-Ramírez E, Rivera Mancía S, et al. Assessment of sodium and potassium intake by 24 h urinary excretion in a healthy mexican cohort. *Arch Med Res* 2017;48:195-202.
PUBMED | CROSSREF

59. Chen SL, Dahl C, Meyer HE, Madar AA. Estimation of salt intake assessed by 24-hour urinary sodium excretion among Somali adults in Oslo, Norway. *Nutrients* 2018;10:900.
PUBMED | CROSSREF

60. Shin SJ, Lim CY, Rhee MY, et al. Characteristics of sodium sensitivity in Korean populations. *J Korean Med Sci* 2011;26:1061-7.
PUBMED | CROSSREF

61. Elijovich F, Weinberger MH, Anderson CA, et al. Salt sensitivity of blood pressure: a scientific statement from the American Heart Association. *Hypertension* 2016;68:e7-46.
PUBMED | CROSSREF

62. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the Trials of Hypertension Prevention (TOHP). *BMJ* 2007;334:885-8.
PUBMED | CROSSREF

63. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the Trials of Hypertension Prevention. *J Am Coll Cardiol* 2016;68:1609-17.
PUBMED | CROSSREF

64. Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med* 2001;161:685-93.
PUBMED | CROSSREF

65. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet* 2011;378:380-2.
PUBMED | CROSSREF

66. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA* 2011;305:1777-85.
PUBMED | CROSSREF

67. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care* 2011;34:861-6.
PUBMED | CROSSREF

68. Joosten MM, Gansevoort RT, Mukamal KJ, et al. Sodium excretion and risk of developing coronary heart disease. *Circulation* 2014;129:1121-8.
PUBMED | CROSSREF

69. Singer P, Cohen H, Alderman M. Assessing the associations of sodium intake with long-term all-cause and cardiovascular mortality in a hypertensive cohort. *Am J Hypertens* 2015;28:335-42.
PUBMED | CROSSREF

70. Lelli D, Antonelli-Incalzi R, Bandinelli S, Ferrucci L, Pedone C. Association between sodium excretion and cardiovascular disease and mortality in the elderly: a cohort study. *J Am Med Dir Assoc* 2018;19:229-34.
PUBMED | CROSSREF

71. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. *Circulation* 2014;129:981-9.
PUBMED | CROSSREF

72. Mills KT, Chen J, Yang W, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA* 2016;315:2200-10.
PUBMED | CROSSREF

73. Polonia J, Monteiro J, Almeida J, Silva JA, Bertoquini S. High salt intake is associated with a higher risk of cardiovascular events: a 7.2-year evaluation of a cohort of hypertensive patients. *Blood Press Monit* 2016;21:301-6.
PUBMED | CROSSREF

74. Olde Engberink RH, van den Hoek TC, van Noordenne ND, van den Born BH, Peters-Sengers H, Vogt L. Use of a single baseline versus multiyear 24-hour urine collection for estimation of long-term sodium intake and associated cardiovascular and renal risk. *Circulation* 2017;136:917-26.
PUBMED | CROSSREF

75. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA* 2011;306:2229-38.
PUBMED | CROSSREF

76. He FJ, Ma Y, Campbell NR, MacGregor GA, Cogswell ME, Cook NR. Formulas to estimate dietary sodium intake from spot urine alter sodium-mortality relationship. *Hypertension* 2019;74:572-80.
PUBMED | CROSSREF

APPENDIX 1

Search terms for validation study of spot urine collection method (n=301)

#1 (salt[Text Word]) OR sodium[Text Word]
#2 (urine[Text Word]) OR urinary[Text Word]
#3 ((((24 hour*[Text Word]) OR 24-hr*[Text Word]) OR 24-h*[Text Word]) OR 24-hour*[Text Word]) OR 24 hr*[Text Word]
#4 ((((((spot[Text Word]) OR casual[Text Word]) OR random[Text Word]) OR timed[Text Word]) OR morning[Text Word]) OR fractional[Text Word]) OR afternoon[Text Word]
#5 (((#1) AND #2) AND #3) AND #4
#6 (("2014/01/01"[Date - Publication]: "2019/09/30"[Date - Publication])) AND #5

APPENDIX 2

Search terms of salt intake and blood pressure in cross-sectional epidemiologic studies (n=374)

#1 (salt[Text Word]) OR sodium[Text Word]
#2 (urine[Text Word]) OR urinary[Text Word]
#3 intake[Text Word]
#4 blood pressure[Text Word]
#5 (((#1) AND #2) AND #3) AND #4
#6 ((#5) AND ("2009/01/01"[Date - Publication]: "2019/09/30"[Date - Publication])) NOT intervention

APPENDIX 3

Search terms of salt intake and cardiovascular outcome (n=619)

#1 (salt[Text Word]) OR sodium[Text Word]
#2 (urine[Text Word]) OR urinary[Text Word]
#3 (((((((((cardiovascular[Text Word]) OR coronary[Text Word]) OR cerebrovascular[Text Word]) OR stroke[Text Word]) OR myocardial[Text Word]) OR heart failure[Text Word]) OR outcome[Text Word]) OR heart[Text Word]) OR transient ischemic attack[Text Word]) OR mortality[Text Word]
#4 ((((24 hour*[Text Word]) OR 24-hr*[Text Word]) OR 24-h*[Text Word]) OR 24-hour*[Text Word]) OR 24 hr*[Text Word]
#5 (((#1) AND #2) AND #3) AND #4
#6 (("2009/01/01"[Date - Publication]: "2019/09/30"[Date - Publication])) AND #19

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