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, and to increase the risk of stroke, left ventricular hypertrophy, the progression of renal disease, renal stones and osteoporosis and possibly the risk of stomach cancer. 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, and that there is no clear evidence that sodium intake reduction
decreases the incidence of CV diseases. 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.

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. 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. These findings indicate multiple subsequent 24-hour urine collection should be used to assess the risk of future CV events rather than 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. 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. 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).
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 | 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<sup>17</sup> | UK (White women) | General | 297 | 51 (44.1) | 129.9 | Tanaka Arithmetic | 129.9 | Not recommended | Not recommended | Over-estimation at lower level and under-estimation at higher level |
| | UK (White men) | General | 297 | 51 (44.1) | 174.9 | Tanaka Arithmetic | 174.9 | Not recommended | Not recommended | |
| | UK (African women) | General | 326 | 52 (38.3) | 145.9 | Tanaka Arithmetic | 145.9 | Recommended | Recommended | |
| | UK (African men) | General | 292 | 50 (52.7) | 129.8 | Tanaka Arithmetic | 129.8 | Not recommended | Not recommended | |
| | UK (South Asian women) | General | 292 | 50 (52.7) | 161.4 | Tanaka Arithmetic | 161.4 | Recommended | Recommended | |
| | UK (South Asian men) | General | 292 | 50 (52.7) | 161.4 | Tanaka Arithmetic | 161.4 | Recommended | Recommended | |
| Mente et al., 2014<sup>18</sup> | 11 countries (India, China, Colombia, Argentina, Brazil, Malaysia, South Africa, Turkey, Canada, Sweden, UAE) | General | 1,083 | 56.6 (9.4)/35–70 | 451 | Kawasaki INTERSALT | 192.6 | Recommended | Recommended | Over-estimation at lower level and under-estimation at higher level |
| Toft et al., 2014<sup>19</sup> | Denmark | General | 473 | 51.9/28–74 | 150 | Tanaka Danish model | 156 | Recommended | Recommended | Internal validation |
| Rhee et al., 2014<sup>20</sup> | Korea | General | 224 | 51.0 (10.9) | 165.3 | Kawasaki INTERSALT | 195.5 | Not recommended | Not recommended | Over-estimation at lower level and under-estimation at higher level |
| McLean et al., 2014<sup>21</sup> | New Zealand (Dunedin) | General | 98 | 35.6/18–64 | 150.4 | PAHO and measured Cr INTERSALT Tanaka Kawasaki | 156.3 | Recommended | Recommended | Small sample size and young, patients on diuretics are excluded |
| Kelly et al., 2015<sup>22</sup> | Ireland | Workers | 50 | 37.7/18–64 | 138 | Arithmetric (morning) Tanaka (morning) Kawasaki (morning) INTERSALT (morning) Arithmetric (evening) Tanaka (evening) Kawasaki (evening) INTERSALT (evening) | 156 | Recommended | Recommended | Small sample size |
| Han et al., 2015<sup>23</sup> | China (Beijing) | Hypertensives | 222 | 58.4 (14.5) | 147.9 | Kawasaki (SMU) Tanaka (SMU) Kawasaki (PM) Tanaka (PM) | 145.8 | Recommended | Recommended | Over-estimation at lower level and under-estimation at higher level |
| Peng et al., 2016<sup>24</sup> | China (Shanxi) | General | 116 | 53.2 (61) | 275.8 | Kawasaki INTERSALT Tanaka | 243.6 | Not recommended | Not recommended | Substudy of PURE, patients on diuretics are excluded |
| Whitten et al., 2016<sup>25</sup> | Singapore | General (Chinese, Malay, Indian) | 140 | 49.4 (14.9) | 125 | INTERSALT Singapore Health 2 Tanaka | N/A | Recommended | Recommended | Validation was performed in small population (n=70) |

(continued to the next page)
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 | 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<sup>26</sup> | Portugal | General | 2,339 | 51.1 (16.9) / 118 (47.8) | 176.2 | Tanaka | N/A | Not recommended | Not recommended | - Low correlation and ICC |
| Ma et al., 2017<sup>27</sup> | China (Shaanxi) | Individuals with elevated risk of stroke | 365 | 67.5 (6.8) / 155 (42.5) | 162 | Kawasaki | INTERSALT | N/A | N/A | - Kawasaki and Tanaka methods were used while the INTERSALT method underestimated 24-hour sodium excretion |
| Vidal-Petiot et al., 2017<sup>28</sup> | France (Paris) | Patients undergoing evaluation of renal function | 1,018 | 57 (14) / 617 (67) | 157.6 | Kawasaki | INTERSALT | 168.3 | Not recommended | - Over-estimation at lower level and under-estimation at higher level |
| Allen et al., 2017<sup>29</sup> | USA (Chicago) | General | 554 | 60.3 (9.1) / 253 (45.7) | 143.1 | INTERSALT Tanaka | 138.6 | 157.1 | 190.5 | - 7% were on antihypertensive drugs |
| Rhee et al., 2017<sup>30</sup> | Korea | General | 175 | 46.2 (12.7) / 68 (38.9) | 161.3 | Kawasaki | INTERSALT Tanaka | 185.3 | 147 | 149.2 | |
| Zhou et al., 2017<sup>31</sup> | China (Dexing) | General | 141 | 51.1 (8.2) / 8 (5.7) | 220.8 | Kawasaki | INTERSALT Tanaka | 246.1 | 143.6 | 183.7 | - Mostly women |
| Jędrusik et al., 2018<sup>32</sup> | Poland | Mostly hypertensives (92%) | 335 | 55 (16) / 168 (16) / 135 (40.3) | 160.3 | Kawasaki | INTERSALT Tanaka | 149.2 | 189.7 | - Over-estimation and under-estimation |
| Zhang et al., 2019<sup>33</sup> | China (healthy) | General | 85 | 32 (11.2) / 32 (37.6) | 198.2 | Kawasaki | INTERSALT Tanaka SunSMU SunPM | 231.6 | 136.5 | 193.9 | - Patients taking diuretics are excluded |
| Emeville et al., 2019<sup>34</sup> | France | 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.
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.\textsuperscript{17,20-22,24,26,28-34} Even the study of Mente et al.\textsuperscript{18} showed 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.\textsuperscript{18,20-23,25,34} 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.,\textsuperscript{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,\textsuperscript{20} 2014,\textsuperscript{30} and from 2013 to 2014\textsuperscript{35} were combined and analyzed. The method to determine the completeness of 24-hour urine collection was described elsewhere.\textsuperscript{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                              | 791                                         |
| Total                                          |                                             |
| 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.
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 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.

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.

SODIUM INTAKE AND BLOOD PRESSURE

Many intervention studies have reported sodium intake reduction lowers BP and has a profound effect in individuals with hypertension. Furthermore, this effect was observed even after modest sodium intake reduction. 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, we found 5 dietary intervention studies performed over more than 6 months. Four of these studies reported lowering sodium intake significantly lowered BP. 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. On the other hand, a study performed in young healthy nulliparous pregnant
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 study55) had a higher potassium intake and a lower urine sodium-to-potassium ratio than those of Jackson’s study had51) (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, MohammadiFarz et al.57) included young and healthy individuals without diabetes, hypertension, a history of diuretic use, or renal...
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 | 24% was black, 35.6% was hypertensive |
| 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 | Participants were included in the analysis |
| 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/m² |
| 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 model |
| 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% (19), French 47.8% (18), Italian 45.3% (18.4) | 156.8 | OBP | 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 | 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 | 44.9% of 1,219 recruited participants were included in the analysis |
| Kim et al., 2019 (53) | Korea (Goyang, Paju, Seoul, Chuncheon, Gyeonggi) | 740 | General, 41.3% men | 20–70 | 48 (median) | 153.9 (median) | ABP | Significant linear or non-linear association with SBP and DBP in normal BMI participants | 24-hour urine sodium was entered as a dependent variable |
| 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 | 90.9% European, 21.9% Hypertensives |
| 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 | Participants rested throughout the 24-hour period in the health care center |
| Mizéhoun-Adissoda et al., 2016 (56) | Benin (Bohicon, Tanvi) | 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) | 771 | General, 32.1% men | 20–50 | 37.4 (9.0) | 137 | OBP | No association | Immigrants of Somalis from east Africa |
| Chen et al., 2018 (59) | Norway (Oslo) | 159 | General | 20–67 | 40.3 (11.1) | 137.9 (61.3) | OBP | No association | Insufficient (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 |

**Notes:** 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.
used multiple regression with restricted cubic splines, and found a non-linear (curvilinear) association between 24-hour urine sodium excretion and BP, which contrasts with that found by Mente et al. 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). 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. 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. 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. However, a meta-analysis that included data from the TOHP I, TOHP II, and TONE studies showed sodium intake reduction significantly reduced CV events. Stolarz-Skrzypek et al. 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 used single 24-hour urine sodium measurements at baseline and the other 5 studies 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, J- or U-shaped associations, a positive association, or no association with CV outcomes. However, in the 5 studies that used average of subsequently measured multiple 24-hour urine sodium, 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...
habits during follow-up in cohort studies. In a study by Olde Engberink et al., 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 | 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; 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 | 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 | 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; p=0.10). |
| Cook et al., 2014 | 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 | 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, 0.71–1.42; 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. | - Direct linear association between average sodium intake and mortality. - HR, 1.32 per 1,000 mg/24-hr (95% CI, 1.00–1.62; p=0.05). - No J-shaped association. |
| Cook et al., 2016 | 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 | - Sodium intake was 1) Not significantly associated with all CV mortality (QI vs. QIV: HR, 1.00; 95% CI, 0.71–1.42; 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. | - Direct linear association between average sodium intake and mortality. - HR, 1.32 per 1,000 mg/24-hr (95% CI, 1.00–1.62; p=0.05). - No J-shaped association. |
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. 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. 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
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.

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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