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Association between urinary sodium excretion and all-cause mortality: a cohort study in a Chinese community-based population

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Abstract

Background The association between sodium intake and mortality risk in the general population remains controversial. We aimed to explore the association between sodium intake and all-cause mortality in a Chinese community-based population.

Methods A total of 6510 individuals from a Chinese community-based cohort were enrolled. 24-hour urinary sodium excretion was estimated using the Kawasaki formula. Cox proportional hazards models were used to determine the association of estimated urinary sodium excretion and spot urinary sodium with all-cause mortality.

Results With a mean follow-up of 3.13 years, 65 participants (1.0%) experienced all-cause mortality. The association between estimated urinary sodium excretion and all-cause mortality appeared to be J-shaped (P for non-linearity = 0.009). Individuals were grouped in quartiles according to estimated urinary sodium excretion and spot urinary sodium. After adjusting for risk factors, the fourth quartile of estimated urinary sodium excretion (> 5.75 g/day) was associated with an increased risk of mortality compared to the second quartile (3.90 to 4.76 g/day) (hazard ratio 2.94; 95% confidence interval, 1.27–6.83). Subgroup analyses revealed that current drinking status (P for interaction = 0.005) may serve as a potential modifying factor influencing the association between estimated urinary sodium excretion and all-cause mortality. There was no association between spot urinary sodium and all-cause mortality.

Conclusions Higher estimated urinary sodium excretion significantly increased all-cause mortality risk compared to moderate levels. Extremely low estimated urinary sodium excretion showed a similar trend. It is important for individuals with high sodium intake to reduce consumption to lower mortality risk.

Clinical trial number Not applicable.

Keywords Urinary sodium excretion, Spot urinary sodium, Sodium intake, Mortality

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Introduction

Numerous large clinical studies have established a clear linear relationship between high sodium consumption and elevated blood pressure [1], and high sodium intake also leads to an increased risk of cardiovascular disease (CVD) [2, 3]. However, there remains significant controversy regarding the relationship between sodium intake and mortality [4]. In earlier years, a prospective cohort study from Finland [5] and the TOHP study [6] found a significant linear positive correlation between sodium intake and all-cause mortality. However, studies utilizing the NHANES database have shown that low sodium intake may also increase the risk of all-cause mortality [7]. In recent years, the PURE study and several studies utilizing the UK Biobank database have indicated that the relationship between sodium intake and mortality risk is not a simple linear one, but rather a non-linear J-shaped or U-shaped association [8, 9]. Nevertheless, some cohort studies also reported that no significant association between sodium intake and death [10, 11]. Summarizing the current evidence, due to differences in assessment methods, the heterogeneity of study subjects, and variations in trial designs, the relationship between sodium intake and the risk of all-cause mortality remains unclear and appears to be quite complex.

Given the complex relationship with mortality, effective tools for assessing an individual's sodium intake are crucial [12]. Almost all dietary sodium consumption is eliminated through urine, making urinary sodium excretion a widely accepted method for assessing sodium intake [13]. Multiple 24 h urinary sodium collections are regarded as the gold standard method for accurately reflecting the recent individual daily sodium intake [14]. However, owing to the cumbersome operations and high costs, its application in clinical practice is challenging. Utilizing a single urine sample to calculate the estimated 24 h urinary sodium excretion through formulas is simple and easily accessible and shows a good correlation with actual 24 h urinary sodium measurements [15]. Among these, the Kawasaki formula has shown the best consistency with actual measured urinary sodium excretion in several validation studies involving Chinese populations [16, 17]. Therefore, the 24 h urinary sodium excretion estimated utilizing the Kawasaki formula can serve as a valuable approach for evaluating sodium intake.

Although spot urinary sodium concentration is typically regarded as inadequate for reflecting individual sodium intake due to significant variability, it offers advantages in terms of simple, convenient, and easily accessible [18]. As an indicator derived directly from a single urine sample, spot urinary sodium concentration serves as a straightforward tool for clinical and research applications. Previously, only one study focused on a diabetic population found that lower spot urinary sodium

concentrations were associated with higher mortality risks [19]. Another study utilizing the UK Biobank database indicated that there was no significant association between spot urinary sodium concentration and CVD risk in the general population [20]. Therefore, we would like to help bridge the knowledge gap regarding the direct impact of spot urinary sodium concentration on mortality risk in the general population.

Sodium has a broad range of physiological functions in the human body, and variations in sodium intake can have different effects on various physiological processes [21]. Additionally, the variability in sodium sensitivity among different populations indicates that the impact of sodium consumption on health may not be consistent [22]. This further underscores the necessity for context-specific evaluations. Being among the countries with the highest levels of individual sodium consumption globally, where adults consistently consume 4.1–4.4 g/day, China faces a significant disease burden attributed to excessive sodium consumption [23, 24]. This intake level represents more than double the WHO recommended limit of <2 g/day, yet studies on this topic remain relatively limited [25]. Moreover, there are currently no studies that investigated the relationship between spot urinary sodium concentration and all-cause mortality among general individuals. Therefore, this study is conducted in a Chinese population to investigate the association between estimated urinary sodium excretion and spot urinary sodium levels and the risk of all-cause mortality. The findings of this study would offer additional evidence regarding these associations and support further development of public health strategies and recommendations regarding sodium intake.

Methods

Study design and population

A flow chart showing the process used to select the study participants is provided in Fig. 1. Participants in this study were sourced from an observational atherosclerosis cohort established between December 2011 and April 2012 by Peking University First Hospital across multiple communities in Shijingshan District, Beijing, China [26]. A total of 6568 participants underwent unified cross-sectional follow-up from September to December 2018, during which standardized institutional questionnaires and physical examination data, and morning fasting blood and urine samples were collected. For the current analysis, individuals with missing information on sex, age, body mass index (BMI), urinary sodium, and urinary creatinine were excluded. Ultimately, 6510 participants from this follow-up were included, who had complete relevant data. Written informed consent was provided by all participants. This study was reviewed and approved by the Ethics Committee of Peking University First Hospital and

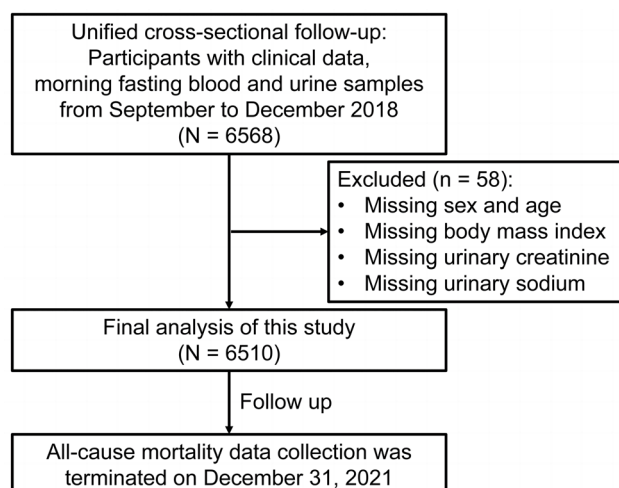


Fig. 1 Flowchart of the study design, population, and follow-up

the Office of Human Genetic Resources Administration of China.

Collection of clinical data

Baseline standardized questionnaires were completed by all participants in the above atherosclerosis cohort survey [26], which included demographic information, lifestyle risk factors, comorbidities, and detailed medication history. Current smoking was defined as currently smoking at least one cigarette per day for more than half a year, and current drinking was defined as currently consuming alcohol at least once a week for more than half a year. Body composition metrics, including height, weight, and BMI were gathered by professional personnel adhering to standardized protocols. Peripheral brachial blood pressure was measured using an Omron electronic sphygmomanometer (HEM-7130). Three successive measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained on the right arm while the participant was seated and at rest. Finally, the means of these three determinations were used for the analyses.

Hypertension was defined as a brachial SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, or self-reported history of hypertension, or current use of antihypertensive medications. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) > 3.37 mmol/L, total cholesterol > 5.18 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L, triglycerides > 1.7 mmol/L, self-reported history of dyslipidemia, or current use of antilipidemic medications. Diabetes mellitus was defined as fasting blood glucose ≥ 7.0 mmol/L, 2-hour postprandial blood glucose ≥ 11.1 mmol/L during an oral glucose tolerance test, self-reported history of diabetes mellitus, or current use of antidiabetic medications.

Laboratory measurement

After fasting overnight for ≥ 12 h, trained personnel collected the first-morning peripheral venous blood samples. Fasting blood glucose, 2-hour postprandial blood glucose during an oral glucose tolerance test, total cholesterol, triglycerides, LDL-C, and HDL-C were determined by a Hitachi 7180 automatic biochemistry analyzer. Serum creatinine was measured using the Jaffe method on the same analyzer. The estimated glomerular filtration rate (eGFR) was computed utilizing the CKD-EPI formula [27]. After fasting overnight for ≥ 12 h, the first-morning urine samples (approximately 15 mL for each sample) of the subject were also collected and centrifuged within 30 min by the trained personnel. Urinary creatinine and sodium levels were measured by an AU5800 automatic biochemical analyzer (Beckman, USA).

Estimated urinary sodium excretion was calculated using the Kawasaki formula [16], a method that has demonstrated robust validation across various demographic groups [15]. Kawasaki formula is as follows [16]. Firstly, calculate predicted 24 h urinary creatinine excretion (PreCr) by applying the subsequent formula: $\text{PreCr (mg/d)} = (a \times \text{weight (kg)}) + (b \times \text{height (cm)}) - (c \times \text{age (years)}) - d$. (For males, $a = 15.12$, $b = 7.39$, $c = 12.63$, $d = 79.9$; For females, $a = 8.58$, $b = 5.09$, $c = 4.72$, $d = 74.95$). Then, calculate the estimated 24 h urinary sodium excretion by applying the subsequent formula: $\text{estimated 24 h urinary sodium excretion} = 0.023 \times [16.3 \times \text{spot urinary sodium (mmol/L)} \times \text{PreCr (mg/d)} \div (113.12 \times \text{urinary creatinine (mmol/L)})]^{0.5}$.

Ascertainment of endpoint

The endpoint is all-cause mortality. For the current analysis, endpoint event collection was terminated on December 31, 2021. The mortality data utilized in this study was sourced from the Cause of Death Database maintained by The Chinese Center for Disease Control and Prevention-National Mortality Surveillance System [28].

Statistical analysis

Normally distributed continuous variables are represented as mean $\pm$ standard deviation (SD) and the Analysis of Variance is utilized to evaluate differences across multiple groups. Non-normally distributed continuous variables are represented as median (interquartile range [IQR]) and the Kruskal-Wallis test is utilized to evaluate differences across multiple groups. Categorical variables are represented as counts (percentages) and the chi-square test is utilized to evaluate differences across multiple groups. A generalized additive model employing the spline smoothing function was applied to investigate the association between estimated urinary sodium excretion and spot urinary sodium and the risk of all-cause

mortality with adjustments for potential confounders. Participants were classified into four groups based on the quartile distribution of estimated urinary sodium excretion and spot urinary sodium concentration, respectively. Kaplan-Meier survival curves were utilized to depict the temporal distribution of endpoint event rates in the different groups and the log-rank tests were employed to compare the variations between these groups. Both univariable and multivariable Cox proportional hazards models are used with the second quartile (Q2) group as the reference, which was determined through spline smoothing curves as the group with the lowest all-cause mortality risk associated with estimated urinary sodium excretion. Adjusted model 1 was adjusted for age and sex. Adjusted model 2 was further adjusted for BMI, eGFR, hypertension, diabetes, dyslipidemia, CVD, anti-hypertensive medications, antidiabetic medications, and antilipidemic medications based on model 1. Subgroup analysis was conducted for key characteristics that might modify the association, which were stratified by sex (male or female), age (≤ 65 or > 65 years), BMI (≤ 24 , 24 to < 28 , or > 28 kg/m²), renal function (low or high which is based on eGFR for dichotomous grouping), current smoking status (yes or no), current drinking status (yes or no), hypertension (yes or no), diabetes mellitus (yes or no), dyslipidemia (yes or no), antihypertensive medications (yes or no), antidiabetic medications (yes or no), antilipidemic medications (yes or no). Interaction effects were formally assessed using likelihood ratio tests comparing

models with versus without multiplicative interaction terms. Since the overall trends for the third quartile (Q3) and Q4 group are similar, they are combined into a single group (Q3 + Q4) in subgroup analysis to more effectively observe potential modifying factors. A significance level of $P < 0.05$ is considered statistically significant. All analyses were performed utilizing R software (version 4.1.0, <http://www.R-project.org>).

Results

Baseline characteristics

A total of 6510 participants were included, with a mean age of 62.53 ± 7.76 years, and 4271 were female (65.6%). The mean ($\pm$ SD) estimated urinary sodium excretion was 4.9 ± 1.4 g/d, and the mean ($\pm$ SD) spot urinary sodium was 13.97 ± 48.69 mmol/L. Baseline characteristics of all participants grouped by quartiles of estimated urinary sodium excretion calculated using the Kawasaki formula are summarized in Table 1.

As estimated urinary sodium excretion increased, participants tended to be older, with higher peripheral systolic and diastolic blood pressure. Additionally, participants with higher estimated urinary sodium excretion were more likely to be male, current smokers, current drinkers, have hypertension, diabetes mellitus, and baseline cardiovascular diseases.

Table 1 Baseline characteristics of estimated urinary sodium excretion quartile group

	Total	Q1 (< 3.90 g/d)	Q2 (3.90–4.76 g/d)	Q3 (4.77–5.75 g/d)	Q4 (> 5.75 g/d)	P value
N	6510	1628	1627	1627	1628	
Age (years)	62.00 [57.00, 66.00]	61.00 [56.00, 65.00]	61.00 [57.00, 66.00]	62.00 [58.00, 67.00]	63.00 [59.00, 68.00]	< 0.001
Male	2239 (34.4%)	354 (21.7%)	482 (29.6%)	599 (36.8%)	804 (49.4%)	< 0.001
Current smoking	914 (14.2%)	162 (10.0%)	225 (14.1%)	233 (14.5%)	294 (18.4%)	< 0.001
Current drinking	674 (10.5%)	114 (7.1%)	159 (9.9%)	160 (9.9%)	241 (14.9%)	< 0.001
BMI (kg/m ²)	25.07 [23.03, 27.29]	24.12 [22.07, 26.23]	24.80 [22.92, 26.88]	25.39 [23.38, 27.50]	25.99 [23.92, 28.18]	< 0.001
Systolic blood pressure (mmHg)	132.33 [121.33, 143.67]	128.33 [117.00, 139.67]	130.67 [120.67, 142.00]	134.00 [122.67, 145.00]	136.33 [125.92, 148.00]	< 0.001
Diastolic blood pressure (mmHg)	78.67 [72.33, 85.33]	76.67 [70.67, 83.67]	78.67 [72.67, 84.67]	78.67 [73.00, 85.67]	80.33 [74.00, 86.33]	< 0.001
Heart rate (beats/min)	76.67 [69.33, 84.67]	77.33 [70.16, 86.00]	76.33 [69.00, 84.00]	76.33 [69.33, 84.33]	76.67 [69.33, 84.67]	0.011
Hypertension	3586 (55.1%)	753 (46.3%)	850 (52.3%)	908 (55.8%)	1050 (66.1%)	< 0.001
Diabetes mellitus	1927 (29.7%)	398 (24.5%)	432 (26.6%)	482 (29.7%)	615 (37.8%)	< 0.001
Hyperlipidemia	5237 (80.6%)	1330 (81.7%)	1315 (81.1%)	1295 (79.7%)	1297 (79.8%)	0.067
Cardiovascular disease	444 (7.0%)	95 (5.9%)	83 (5.2%)	107 (6.7%)	159 (10.0%)	< 0.001
eGFR (ml/min/1.73m ²)	95.22 [87.77, 100.51]	95.53 [87.81, 100.69]	95.70 [89.08, 100.95]	95.18 [87.32, 100.52]	94.62 [87.33, 99.98]	0.012
Estimated urinary sodium excretion (g/d)	4.90 ± 1.42	3.24 ± 0.53	4.34 ± 0.24	5.24 ± 0.29	6.78 ± 0.96	< 0.001
Spot urinary sodium (mmol/L)	113.97 ± 48.69	82.26 ± 35.79	108.43 ± 41.89	123.96 ± 45.87	141.24 ± 49.65	< 0.001

All data in n (%), mean $\pm$ standard deviation or median [interquartile range]. The P value indicates the comparison of differences among the four groups. BMI, body mass index; eGFR, estimated glomerular filtration rate

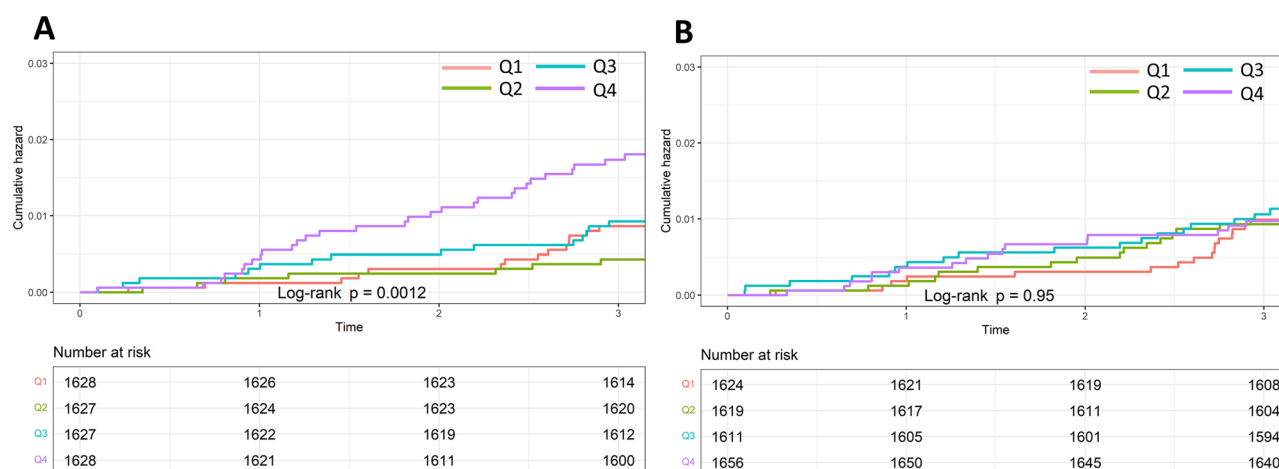


Fig. 2 Kaplan-Meier survival curves for all-cause mortality with estimated urinary sodium excretion (A) and spot urinary sodium (B) levels divided into quartiles

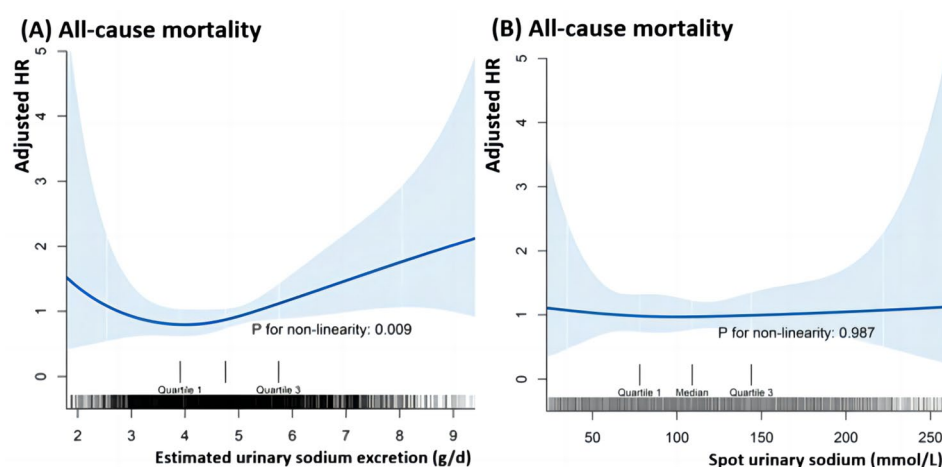


Fig. 3 Splines of the association of estimated urinary sodium excretion (A) and spot urinary sodium (B) with all-cause mortality. The line represents the fitted curve for estimated urinary sodium excretion or spot urinary sodium and all-cause mortality, with the shaded area indicating the 95% confidence interval. Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, antihypertensive medications, antidiabetic medications, antilipidemic medications, and estimated glomerular filtration rate

Urinary sodium excretion and all-cause mortality

The mean follow-up time was 3.13 ± 0.18 years. During the follow-up period, 65 participants (1.0%) experienced all-cause mortality.

The Kaplan-Meier survival curve demonstrated that after categorizing baseline estimated urinary sodium excretion into quartiles, there were varying risks of all-cause mortality across the groups ($P=0.0012$, log-rank test), with the lowest risk observed in the Q2 group (Fig. 2A). However, for spot urinary sodium, the Kaplan-Meier survival curve did not demonstrate significant differences among the four groups when categorized into quartiles ($P=0.95$, log-rank test) (Fig. 2B).

A risk curve for all-cause mortality was plotted with estimated urinary sodium excretion as a continuous variable, showing a U-shaped association (P for non-linearity = 0.009) (Fig. 3A). However, there was no association

between spot urinary sodium and all-cause mortality (Fig. 3B).

For estimated urinary sodium excretion, compared with the Q2 group (3.90–4.76 g/d), the fourth quartiles (Q4) group (>5.75 g/d) had a significantly increased risk of all-cause mortality (hazard ratio [HR] 2.94; 95% confidence interval [CI], 1.27–6.83) (Table 2). There were no statistically significant associations between different spot urinary sodium groups and the risk of all-cause mortality (Table 2).

Subgroup analysis

Figure 4 presents the results of the subgroup analysis for the association between estimated urinary sodium excretion and all-cause mortality, based on multivariable adjusted Model 2. Using the Q2 group as a reference, the association between estimated urinary sodium excretion

Table 2 Association of estimated urinary sodium excretion and spot urinary sodium with all-cause mortality

	N	Event (%)	Unadjusted model		Adjusted model 1*		Adjusted model 2**	
			HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Estimated urinary sodium excretion								
Q2 (3.90–4.76 g/d)	1627	7 (0.4)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q1 (< 3.90 g/d)	1628	14 (0.9)	2.00 (0.81,4.96)	0.134	2.13 (0.86,5.28)	0.103	1.83 (0.72,4.68)	0.205
Q3 (4.77–5.75 g/d)	1627	15 (0.9)	2.15 (0.88,5.27)	0.095	1.75 (0.71,4.31)	0.220	1.69 (0.68,4.21)	0.258
Q4 (> 5.75 g/d)	1628	29 (1.8)	4.17 (1.83,9.51)	<0.001	3.00 (1.31,6.88)	0.009	2.94 (1.27,6.83)	0.012
Spot urinary sodium								
Q2 (78–109mmol/L)	1619	15 (0.9)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Q1 (< 78mmol/L)	1624	16 (1.0)	1.06 (0.53,2.15)	0.867	1.21 (0.60,2.45)	0.600	1.21 (0.58,2.52)	0.609
Q3(110–144mmol/L)	1611	18 (1.1)	1.21 (0.61,2.40)	0.590	1.27 (0.64,2.52)	0.497	1.29 (0.63,2.63)	0.489
Q4(> 144mmol/L)	1656	16 (1.0)	1.04 (0.52,2.11)	0.904	1.08 (0.53,2.20)	0.828	1.12 (0.53,2.36)	0.761

*Adjusted model 1: Adjusted for age and sex; **Adjusted model 2: Further adjusted for body mass index, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, antihypertensive medications, antidiabetic medications, antilipidemic medications, and estimated glomerular filtration rate based on Model 1. CI, confidence interval; HR, hazard ratio

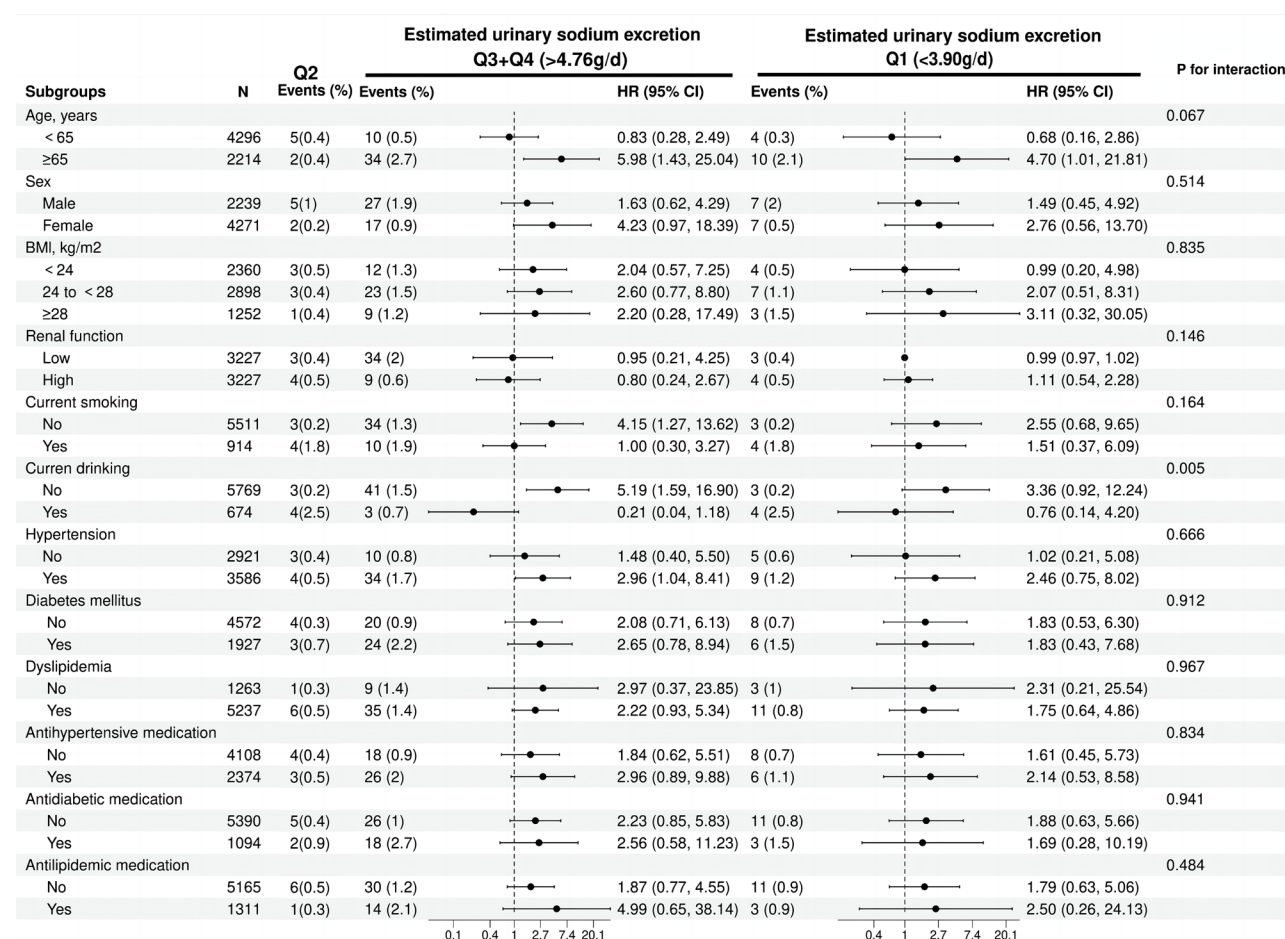


Fig. 4 Subgroup analysis of the association between estimated urinary sodium excretion and all-cause mortality. Cox proportional hazard regression models were adjusted for age, sex, body mass index, estimated glomerular filtration rate, current smoking, current drinking, hypertension, diabetes mellitus, dyslipidemia, anti-hypertensive medication, antidiabetic medication, and antilipidemic medication. When a variable was assessed for its possible modification on the association of estimated urinary sodium excretion and all-cause mortality, the stratified variable was not adjusted repeatedly. CI, confidence interval; HR, hazard ratio

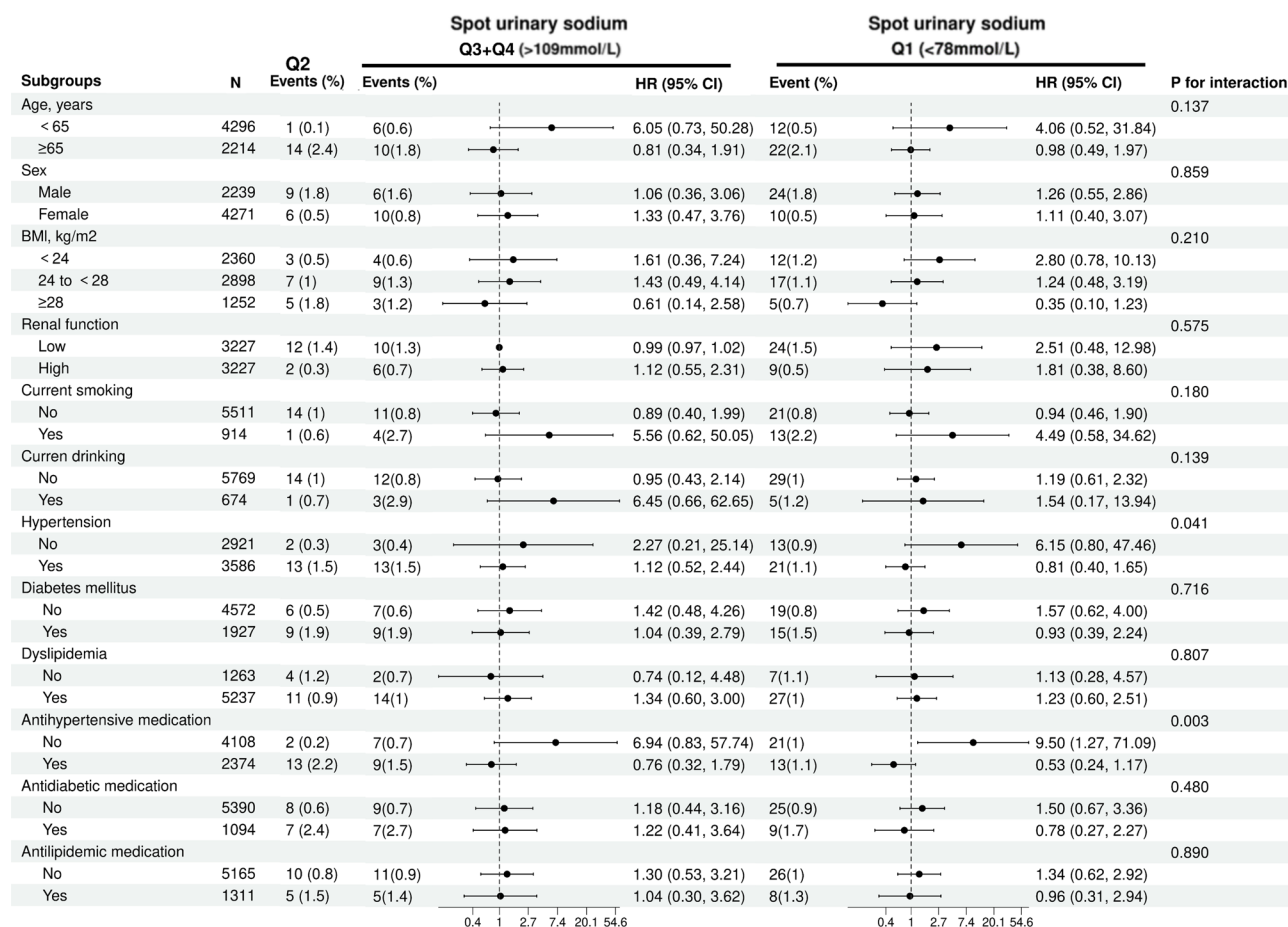


Fig. 5 Subgroup analysis of the association between spot urinary sodium and all-cause mortality. Cox proportional hazard regression models were adjusted for age, sex, body mass index, estimated glomerular filtration rate, current smoking, current drinking, hypertension, diabetes mellitus, dyslipidemia, anti-hypertensive medication, antidiabetic medication, and antilipidemic medication. When a variable was assessed for its possible modification on the association of spot urinary sodium and all-cause mortality, the stratified variable was not adjusted repeatedly. CI, confidence interval; HR, hazard ratio. CI, confidence interval; HR, hazard ratio

and all-cause mortality was generally consistent across subgroups stratified by age, sex, BMI, renal function, current smoking, hypertension, diabetes mellitus, dyslipidemia, antihypertensive medications, antidiabetic medications, antilipidemic medications. The association between estimated urinary sodium excretion and all-cause mortality varied according to current drinking status (P for interaction = 0.005). In individuals who do not currently drink, the risk of all-cause mortality was significantly higher in the Q3 + Q4 group (HR 5.19; 95% CI, 1.59–16.90), whereas no significant association was observed in those who currently drink (HR 0.21; 95% CI, 0.04–1.18).

Figure 5 presents the results of the subgroup analysis for the association between spot urinary sodium and all-cause mortality, based on multivariable adjusted Model 2. Hypertension (P for interaction = 0.041) and antihypertensive medications (P for interaction = 0.003) may serve as potential modifying factors. In individuals who were not using antihypertensive medications, the risk

of all-cause mortality was significantly elevated in the Q3 + Q4 group (HR 9.50; 95% CI, 1.27–71.09), whereas no significant association was observed in those who were using antihypertensive medications (HR 0.53; 95% CI, 0.24–1.17).

Discussion

This cohort study examined the associations of estimated urinary sodium excretion and spot urinary sodium with all-cause mortality risk and potential effect modifiers in a community-based Chinese population over a mean follow-up of 3.13 years. We found that estimated urinary sodium excretion > 5.75 g/day significantly increased the risk of death from any cause when compared with the reference range of 3.90–4.76 g/day. Extremely low estimated urinary sodium excretion trended towards an increased risk of all-cause mortality. And current drinking status was identified as a potential modifier of this association. By contrast, no significant association was

found between spot urinary sodium concentrations and all-cause mortality risk.

Comparison with previous studies

Numerous large cohort studies and randomized controlled trials have identified a significant positive linear relationship between sodium intake and blood pressure [1]. And most evidence indicated that excessive sodium intake was associated with an increased risk of CVD [3, 8, 29–31]. However, the association between sodium intake and mortality still remains highly inconclusive. A prospective cohort study in Finland and TOHP study both conducted in earlier years, found a linear positive correlation between sodium intake and all-cause mortality [5, 6]. In contrast, other earlier studies using the NHANES database and another large cohort study reported nearly opposite findings [7, 32]. Additionally, a meta-analysis including six studies found no association between sodium intake and all-cause mortality [3]. It should be noted that the sodium intake in these studies was determined by multiple 24 h urinary sodium collections or dietary surveys. However, recent evidence from numerous large cohort studies using the Kawasaki formula to estimate urinary sodium excretion such as ONTARGET and TRANSCEND study [31], PURE study [8], and several studies utilizing the UK Biobank database [9, 11], indicates a J-shaped or U-shaped relationship between sodium intake and all-cause mortality. Our study used the same estimation method and similarly found that both low and high sodium intake may increase the risk of all-cause mortality, especially in cases of high sodium intake. The aforementioned studies were predominantly large-scale investigations conducted abroad or across multiple countries. In contrast, our study focused solely on the Chinese community-based population for exploration, which minimized potential confounders related to ethnicity and diet. Furthermore, the follow-up period of our study (median 3.13 years) was notably shorter than that of other studies, resulting in a lower all-cause mortality and limiting our statistical power to assess the association between low sodium intake and mortality. However, this also suggested that the relationship between high sodium intake and increased mortality risk can become apparent within just three years. In summary, our study provided more evidence for the U-shaped association between sodium intake and mortality risk, especially for the Chinese population.

It is important to note that the range of sodium intake associated with the lowest risk of all-cause mortality remains contentious. Most existing guidelines recommend that the general population maintain a very low sodium intake, typically below 1.5, 2.0, or 2.3 g/day [25]. However, ONTARGET and TRANSCEND study, and PURE study both identified a sodium intake of 4–5.99 g/

day as associated with the lowest risk, particularly compared to higher intakes (>7.00 g/day) [8, 31]. Our findings in a community population in Beijing, China, revealed that individuals with sodium intake >5.75 g/day had a significantly higher risk of all-cause mortality compared to those with an intake of 3.90–4.76 g/day, aligning with this range. Overall, the association between sodium intake and the risk of all-cause mortality appears to be U-shaped or J-shaped rather than simply linear. Our findings, along with existing evidence, still support recommendations to limit sodium intake in Chinese high-consumption populations, as reducing sodium intake could have a significant impact on public health. However, the potential risks associated with very low sodium intake require further confirmation, and additional research is needed to determine the optimal range of sodium intake for the general population [4].

Exploring potential moderating factors that may affect the relationship between sodium intake and all-cause mortality is crucial. Our study found that the association between sodium intake and the risk of death from any cause varied according to drinking status, with a notable U-shaped association observed in current non-drinkers. Notably, even moderate alcohol consumption has been associated with a significant increase in cardiovascular and all-cause mortality risk [33]. And alcohol consumption may exacerbate salt sensitivity, thereby influencing blood pressure and albuminuria levels [34]. Meanwhile, drinking alcohol can increase diuresis, leading to an increase in plasma sodium levels [35]. Some studies have also observed increased alcohol intake seemed to be correlated with decreased urinary sodium excretion [34]. Consequently, the predetermined urinary sodium excretion grouping was not applicable to the drinking population, and alcohol consumption may confound the observed association between urinary sodium excretion and all-cause mortality. However, it is important to emphasize that due to the low incidence of outcome events and the relatively small sample size of the current drinking population, we must interpret this finding with caution.

Additionally, it is important to interpret the variations in study results within the context of differences in study design, subject populations, and sodium intake assessment methods. Although multiple 24-hour urinary sodium collections are the gold standard for urinary sodium excretion, their complex and cumbersome operation makes it difficult to apply in large-scale populations [14]. Urinary sodium excretion estimated from single spot urine samples has been well validated [16, 17]. While it may still lead to misclassification, it serves as a more convenient and feasible surrogate for sodium intake in large-scale studies and clinical practice [15]. Furthermore, like most previous observational studies [9],

our study cannot completely rule out the possibility of reverse causality. A previous study indicated that individuals with low sodium intake also had lower protein intake and were more likely to live alone, which could confound the true association between sodium intake and mortality [36]. Additionally, the average urinary sodium excretion in our cohort was significantly lower than the values reported in the PURE study involving Chinese communities but higher than those in the UK Biobank database [8, 9, 11]. This difference may reflect that, despite a decline in sodium intake in China in recent years, it remains relatively high by global standards [23]. Therefore, variations in baseline sodium intake levels and categorization criteria may influence the true relationship between sodium intake and mortality.

However, despite the ease and simplicity of obtaining spot urinary sodium in clinical settings, there is a scarcity of studies on the association between spot urinary sodium concentrations and mortality. Re et al. found no association between spot urinary sodium concentrations and CVD risk in the UK Biobank cohort [20]. Similarly, our studies yielded negative findings regarding all-cause mortality. Interestingly, we found that hypertension and antihypertensive medications may act as modifying factors. This might be attributed to the potential impacts of hypertension and antihypertensive therapy on sodium metabolism and excretion, leading to differing associations between spot urinary sodium levels and mortality risk in these populations [37]. In reality, the spot urinary sodium concentration depends not only on dietary salt intake but also on factors such as fluid intake, circadian rhythms, the volume and timing of urine collection, and the time since the last meal containing salt [38]. Spot urinary sodium measurements reflect the sodium content in a single urine sample, which can be influenced by renal filtration, concentration, and reabsorption mechanisms [16]. Re et al. also found a low correlation between on-site urinary sodium measurements and self-reported high-sodium food intake [20], which suggests that spot urinary sodium levels may not accurately represent individual sodium intake. However, our study found a U-shaped relationship between estimated urinary sodium excretion and all-cause mortality. Therefore, the estimated 24 h urinary sodium excretion is a more meaningful indicator for predicting all-cause mortality.

Potential biological mechanisms

Unlike CVD or cardiovascular death, all-cause death also involves other systemic diseases or any accidental causes of death, hence it has more complex underlying biological mechanisms. Sodium is strictly regulated by renal, endocrine, immune, and nervous systems to maintain serum sodium within the normal range [39]. The causal relationship between high sodium intake and increased

cardiovascular risk and mortality is supported by numerous biological mechanisms [40]. High sodium intake can increase the concentration of sodium ions in cerebrospinal fluid, which increases sympathetic nervous activity, leading to vascular constriction and elevated blood pressure [41]. Furthermore, other mechanisms such as volume expansion, altered renal function, sodium balance disorders, impaired responses of the renin-angiotensin-aldosterone system, and possibly inflammation could lead to the development of salt-sensitive hypertension [42]. In addition to mechanisms that affect blood pressure, research has indicated that excessive sodium consumption can induce oxidative stress and inflammatory responses, impair endothelial function, reduce the production of nitric oxide, increase vascular stiffness, and lead to fibrosis [42]. These factors are key determinants of target organ damage and may lead to various diseases of the kidneys, brain, blood vessels, and immune system. High sodium intake may also be associated with cellular senescence, injury, and death and may adversely affect health through complex interactions involving immune and microbial mechanisms [43–45].

Additionally, there is considerable evidence suggesting potential harm from low sodium intake. Sodium, as an essential nutrient, plays a vital role in various physiological processes [39]. Low sodium intake can activate the renin-angiotensin-aldosterone system [46], and elevated plasma renin levels are associated with increased cardiovascular and mortality risk [47]. Studies have also shown that low sodium intake can activate the sympathetic nervous system and impair reflex homeostatic control [48]. Low sodium intake may also lead to significant increases in triglycerides and cholesterol, especially LDL-C [46]. It is well known that LDL-C is a recognized risk factor for atherosclerosis and cardiovascular disease, and increased levels significantly increase the mortality risk. Moreover, reducing sodium intake has been shown to increase resting heart rate, which is a recognized risk factor for CVD and death [49]. Despite some controversy, low sodium intake appears to be associated with insulin resistance, which may further increase the risk of mortality [50]. Therefore, the above-mentioned adverse effects associated with low sodium intake may outweigh the benefits of blood pressure reduction, particularly in individuals who do not have hypertension or have low blood pressure.

Strengths and limitations

Our study has several strengths. First, it conducted a longitudinal cohort analysis within a Chinese community-based population, further exploring the association between sodium intake and health outcomes. Second, it provides supplementary evidence supporting higher sodium intake significantly increased the risk of death from any cause, particularly within the Chinese

population. And extremely low estimated urinary sodium excretion also showed a similar trend. Third, it investigated potential modifiers of the association between sodium intake and all-cause mortality. Finally, while our study did not show positive findings between spot urinary sodium and all-cause mortality, the limited published research on this topic means our findings add to the related evidence. The estimated 24 h urinary sodium excretion is a better indicator of all-cause mortality risk than spot urinary sodium.

However, this study also has some limitations. First, the relatively short follow-up period may have resulted in a low incidence of events, limiting our ability to assess the association between sodium intake and specific causes of death. This also resulted in a further reduction in sample size and event rate during subgroup analyses, which affects the robustness of the results. Second, the absence of 24 h urine samples and dietary sodium intake questionnaire data restricted our ability to explore differences in the accuracy of various sodium intake assessment methods concerning all-cause mortality. Third, this study used a single baseline measurement of urinary sodium excretion, which may not accurately reflect long-term sodium intake patterns. Fourth, the study had an observational cohort design, which meant that reverse causality could not be completely eliminated. Finally, the study was conducted in a community population in Beijing, and thus the generalizability of its findings to broader populations may be limited.

Conclusion

Our study indicates that in a Chinese community-based population, higher estimated urinary sodium excretion significantly increased the risk of all-cause mortality compared to moderate levels. Extremely low estimated urinary sodium excretion seemed to have a trend to increase the risk of all-cause mortality. And this association was more pronounced among the current non-drinking population. However, no association was observed between spot urinary sodium and the risk of all-cause mortality. Based on these findings, the estimated 24 h urinary sodium excretion calculated using a formula is a better indicator of the risk of all-cause mortality compared to spot urinary sodium. We recommend that measures be taken to reduce sodium consumption in populations with high sodium intake to help lower the all-cause mortality.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
IQR	Interquartile range

LDL-C	Low-density lipoprotein cholesterol
PreCr	Predicted 24h urinary creatinine excretion
SBP	Systolic blood pressure
SD	Standard deviation

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Author contributions

Conceptualization, Y.Z. and Y.G.; methodology, X.W., and Y.Z.; software, J.J.; validation, H.X., J.J., and Y.Z.; formal analysis, H.X, X.W., and F.F.; investigation, Y.Z.; resources, Y.Z. and Y.G.; data curation, H.X, X.W., and Y.Z.; writing—original draft preparation, H.X., and X.W.; writing—review and editing, F.F., Y.Z. and Y.G.; visualization, F.F., and H.X.; supervision, Y.Z., Y.G. and Y.H.; project administration, Y.H., Y.Z. and Y.G.; funding acquisition, Y.Z. All authors have read and agreed to the published version of the manuscript.

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Data availability

The authors will provide the raw data supporting the conclusions of this article upon request. The data are not publicly accessible at this time, because the authors are still conducting further exploration and analysis, and have opted not to disclose them publicly for the moment.

Declarations

Human Ethics and consent to participate

The study was approved by the Ethics Committee of Peking University First Hospital and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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