Estimated 24-Hour urinary sodium excretion and incident cardiovascular disease and mortality among 398,628 individuals in UK Biobank

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Abstract

Aims To explore the association between estimated 24h urinary sodium excretion (surrogate for sodium intake) and incident cardiovascular disease and mortality.

Methods 398,628 UK Biobank Study participants (40-69 years), recruited between 2006 and 2010, with no history of cardiovascular disease, renal disease, diabetes or cancer, and cardiovascular events and mortality recorded during follow-up. Hazard ratios between 24h sodium excretion were estimated from spot urinary sodium concentrations across incident cardiovascular disease and its components, and all cause and cause-specific mortality.

Results In restricted cubic splines analyses, there was little evidence for an association between estimated 24h sodium excretion and cardiovascular disease, coronary heart disease or stroke; hazard ratios for cardiovascular disease (95% confidence intervals) for the 15th and 85th percentiles (2.5 g/day and 4.2 g/day respectively) compared to the 50th percentile of estimated sodium excretion (3.2 g/day) were 1.05 (1.01, 1.10) and 0.96 (0.92, 1.00) respectively. An inverse association was observed with heart failure but that was no longer apparent in sensitivity analysis. A J-shaped association was observed between estimated sodium excretion and mortality.

Conclusions Our findings do not support a J-shaped association of estimated sodium excretion with cardiovascular disease events, although such an association was apparent for all cause and cause-specific mortality across a wide range of diseases. Reasons for this discrepancy are unclear; methodological limitations, including use of estimating equations based on spot urinary data, need to be considered in interpreting our findings.

Keywords: Urinary sodium, cardiovascular diseases, blood pressure, risk
Introduction

Studies from epidemiology, animal models and clinical trials have shown a significant, direct association of sodium intake (mostly as sodium chloride, common salt) with blood pressure\textsuperscript{1},\textsuperscript{2}, the leading modifiable cause of morbidity and mortality from cardiovascular diseases worldwide\textsuperscript{3}, but there is debate as to the shape of the relationship between sodium and cardiovascular disease. Several studies have suggested that this relationship may be curvilinear (‘J’-shaped)\textsuperscript{4-8} although results of these studies have been criticized on methodological grounds, including inadequate measurement of sodium intake, use of unrepresentative cohorts and patient populations, confounding and reverse causality\textsuperscript{9,10}. US Dietary Guidelines recommend a reduction in sodium intakes to <2.3 g/day sodium (6 g/day salt) or <1.5 g/day sodium (5 g/day salt) among adults at high risk of cardiovascular disease\textsuperscript{11}, although this and other guidelines have been called into question\textsuperscript{12,13}. At the same time, analysis from the Global Burden of Disease\textsuperscript{14} study as well as other comprehensive overviews\textsuperscript{15} show that virtually every nation in the world, and each age and sex group within these nations, exceeds the optimal sodium intake levels whether modest (2–2.4 g/day) or low (1.20–1.5 g/day) target intakes are designated as optimal. To further inform the public health debate, we analyzed data from UK Biobank, the largest population-based study with measurements of urinary sodium excretion and subsequent occurrence of cardiovascular disease and mortality.

Methods

Study Design and Participants

UK Biobank includes 502,628 volunteers aged 40–69 years at baseline recruited through United Kingdom National Health Service registers. Participants attended one of 20 dedicated assessment centers nationally during 2006 to 2010\textsuperscript{16}. Representativeness of the UK Biobank
The sample has been previously investigated\textsuperscript{17}. Following informed consent, participants completed a computer-based questionnaire on life-course exposures, medical history and treatments and underwent a standardized portfolio of clinical measurements including weight using an electronic weighing scale (Tanita BC-418), height, with body mass index (BMI) derived as weight (kg) divided by height squared (m\textsuperscript{2}). A casual (‘spot’) urine was obtained at the end of a ~2-hour visit and stored at -80\textdegree C. Sodium and potassium concentrations were measured at the UK Biobank laboratory from stored urine aliquots by the Ion Selective Electrode (potentiometric) method using Beckman Coulter AU5400. Analytical range for sodium was 2-200mmol/L and 10-400mmol/L for potassium\textsuperscript{18}. Urine creatinine was measured via an enzymatic method (88-44200μmol/L)\textsuperscript{18}.

**Data analyses**

A statistical analysis plan with pre-planned statistical analysis steps was developed before data analysis. Both retrospective and prospective data linkage to electronic health records are available in UK Biobank including hospital episode statistics data on diagnoses and operations, and cause of death data through the Office for National Statistics. Our primary outcomes were (i) incident cardiovascular disease (coronary heart disease, stroke or heart failure) based either on first admission to hospital or death certificate only and (ii) each of these diseases considered separately during follow up (2006-2016). In secondary analyses, we separately examined fatal and non-fatal first presentation of cardiovascular disease, as well as all-cause and cause-specific (circulatory, cancer, any other) mortality during follow up (Supplementary Table 1). Our primary exposure was 24h sodium excretion (g/d) estimated from the spot urinary concentration values based on the sex-specific INTERSALT equations that included spot urinary sodium and creatinine concentrations, age, age\textsuperscript{2} and BMI, and Western Europe intercept\textsuperscript{19} (Methods in the Online-Only Data Supplement). We selected the
INTERSALT equations as they were the least prone to bias in a study comparing different predictive equations, including the Kawasaki equation, and unlike the Kawasaki equation, were developed using non-fasting spot urine samples as obtained in UK Biobank\textsuperscript{14,20}.

After exclusions (those who had withdrawn, were pregnant, had missing data or prevalent cardiovascular disease, renal disease, diabetes or cancer at baseline) data on N=398,628 individuals remained for analysis (Figure S1 in the Online-Only Data Supplement). Cox proportional hazards regression models were used to study the association between estimated sodium excretion and events, with age as the time metric. Potential non-proportional hazards were assessed by fitting interactions between sodium excretion and time-scale. We used restricted cubic splines to account for potential non-linear associations, with an internal knot at the median of the sodium distribution, and boundary knots at minimum and maximum values, allowing for the possibility of non-linear associations throughout the range of sodium excretion (we also allowed for additional knots at the 33\textsuperscript{rd} and 67\textsuperscript{th} centiles, which did not improve model fit assessed by the Akaike Information Criterion). Tests of linear and non-linear terms were based on the likelihood ratio test. We present an overall $P$-value for a likelihood ratio test that compares models including covariates, with and without the sodium parameter. We also investigated interactions between sodium excretion and sex in the regression models.

We adjusted regression models for sex, birth cohort in 5-year groups, urinary potassium concentration (mmol/L, log base 2 transformation), smoking (current, past, never), alcohol intake (estimated g/day from self-report data on type and quantity of alcohol, with imputation by bootstrap resampling for incomplete data), Townsend Deprivation Index\textsuperscript{21} (an area-level score based on residential postcode as a measure of socioeconomic status), BMI (g/m$^2$) and
sedentary behavior (sum [hours/day] spent (i) driving, (ii) using a computer and (iii) watching television). We also present an additional model excluding adjustment for BMI from the aforementioned covariates as BMI is already included in the sodium estimation equations and introduction of all terms in the model might create multicollinearity and other biases.

We performed sensitivity analyses to guard against reverse causation from change of diet/urinary electrolyte excretion as a consequence of illness or treatment. We excluded from analyses participants who died or had a cardiovascular event during the first two years of follow-up (N=4,056) or were on anti-hypertensive medication (N=68,194) (which may interfere with the pattern of sodium excretion\(^{22}\)) (N=327,704 in sensitivity analysis).

Finally, we calculated the intra-class correlation coefficients for a subsample of UK Biobank participants with repeated measurements (baseline and ~ 5 years later, N=15,809) for both spot urinary sodium concentration and estimated 24h sodium excretion, to evaluate test-retest reliability\(^{23}\).

Because of the number of outcomes and tests performed we considered \(P\) less than 0.005 for the main analysis as strong evidence for an association and \(P\) less than 0.0005 for interaction tests. All analyses were performed (DCM) using R version 3.4.3.

**Results**

Characteristics of the 398,628 UK Biobank participants contributing to this analysis are shown in Table 1.
Table 1 Baseline characteristics and incident events (2006 to 2016) for UK Biobank participants.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Overall (N= 398,628)</th>
<th>Males (N= 179,195)</th>
<th>Females (N= 219,433)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), yrs</td>
<td>55.9(8.1)</td>
<td>55.9(8.2)</td>
<td>55.8(8)</td>
</tr>
<tr>
<td>Smoking, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>40978(10)</td>
<td>22087(12)</td>
<td>18891(9)</td>
</tr>
<tr>
<td>Past</td>
<td>132489(33)</td>
<td>65195(36)</td>
<td>67294(31)</td>
</tr>
<tr>
<td>Never</td>
<td>225170(56)</td>
<td>91918(51)</td>
<td>133252(61)</td>
</tr>
<tr>
<td>Alcohol, mean (SD), g/day</td>
<td>2.9(1.5)</td>
<td>2.6(1.4)</td>
<td>3.1(1.5)</td>
</tr>
<tr>
<td>Body Mass Index, mean (SD), kg/m²</td>
<td>27.3(4.7)</td>
<td>27.7(4.1)</td>
<td>26.9(5.1)</td>
</tr>
<tr>
<td>Waist circumference, mean (SD), cm</td>
<td>89.7(13.2)</td>
<td>96.3(11.1)</td>
<td>84.2(12.3)</td>
</tr>
<tr>
<td>Antihypertensive medication, N (%)</td>
<td>68198(17)</td>
<td>34322(19)</td>
<td>33876(15)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mmHg</td>
<td>140.3(20.6)</td>
<td>143.9(19.2)</td>
<td>137.3(21.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mmHg</td>
<td>84.2(11.3)</td>
<td>86.5(11)</td>
<td>82.3(11.1)</td>
</tr>
<tr>
<td>Sedentary lifestyle, mean (SD), hr/day</td>
<td>4.4(2.5)</td>
<td>5.0(2.7)</td>
<td>4.0(2.2)</td>
</tr>
<tr>
<td>Townsend Deprivation Index, mean (SD)</td>
<td>-1.4(3)</td>
<td>-1.4(3.1)</td>
<td>-1.4(3)</td>
</tr>
<tr>
<td>Urinary sodium concentration, mean (SD), mmol/L</td>
<td>77.8(44.7)</td>
<td>89.8(46.2)</td>
<td>68.0(40.9)</td>
</tr>
<tr>
<td>Estimated 24h sodium excretion, mean (SD), g/d</td>
<td>3.3(0.8)</td>
<td>4.0(0.6)</td>
<td>2.8(0.5)</td>
</tr>
<tr>
<td>Urinary potassium concentration, mean (SD), mmol/L</td>
<td>63.0(33.9)</td>
<td>68.3(34.0)</td>
<td>58.8(33.2)</td>
</tr>
<tr>
<td>Urinary creatinine concentration, mean (SD), mmol/L</td>
<td>8.82(5.76)</td>
<td>10.89 (6.06)</td>
<td>7.13(4.89)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident events and deaths</th>
<th>Overall (N= 398,628)</th>
<th>Males (N= 179,195)</th>
<th>Females (N= 219,433)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident composite Cardiovascular Disease, N (%)</td>
<td>11451(3)</td>
<td>7549(4)</td>
<td>3902(2)</td>
</tr>
<tr>
<td>Incident Coronary Heart Disease, N (%)</td>
<td>6323(2)</td>
<td>4516(3)</td>
<td>1807(1)</td>
</tr>
<tr>
<td>Incident Stroke, N (%)</td>
<td>2181(&lt;1)</td>
<td>1220(&lt;0.5)</td>
<td>861(&lt;0.5)</td>
</tr>
<tr>
<td>Incident Heart Failure, N (%)</td>
<td>377(&lt;0.5)</td>
<td>226(&lt;0.5)</td>
<td>151(&lt;0.5)</td>
</tr>
<tr>
<td>All-cause mortality, N (%)</td>
<td>7647(2)</td>
<td>4570(3)</td>
<td>3076(1)</td>
</tr>
<tr>
<td>Circulatory disease mortality, N (% of deaths)</td>
<td>1456(19)</td>
<td>1027(22)</td>
<td>429(14)</td>
</tr>
<tr>
<td>Cancer mortality, N (% of deaths)</td>
<td>4415(58)</td>
<td>2417(53)</td>
<td>1998(65)</td>
</tr>
<tr>
<td>Other cause mortality, N (% of deaths)</td>
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<td>---------------------------------------</td>
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</tr>
<tr>
<td>Respiratory, N (% of deaths)</td>
<td>434(6)</td>
<td>272(6)</td>
<td>162(5)</td>
</tr>
<tr>
<td>Digestive, N (% of deaths)</td>
<td>313(4)</td>
<td>227(5)</td>
<td>86(3)</td>
</tr>
<tr>
<td>Nervous system, N (% of deaths)</td>
<td>267(3)</td>
<td>147(3)</td>
<td>120(4)</td>
</tr>
<tr>
<td>Accidental or other external, N (% of deaths)</td>
<td>228(3)</td>
<td>159(3)</td>
<td>69(2)</td>
</tr>
<tr>
<td>Other, N (% of deaths)</td>
<td>533(7)</td>
<td>321(7)</td>
<td>212(7)</td>
</tr>
</tbody>
</table>

* CVD: death certificate or hospital admission (diagnoses and procedures) codes for coronary heart disease, stroke or heart failure (Appendix Table 1).

Mean (SD) spot urinary sodium concentration was 77.8 (44.7) mmol/L and mean (SD) estimated 24h urinary sodium was 3.3 (0.8) g/d, with higher values in men than in women.

During a median follow up period of 5 years 11 months, 11,451 (3%) participants experienced a cardiovascular event (10,707 hospital admissions and 744 deaths), of whom 6,323 (59%) had a diagnosis of coronary heart disease, 2,181 (20%) a stroke and 377 (4%) heart failure. Overall, 7,647 (2%) deaths occurred by the end of follow-up, of which 1,456 (19%) were attributed to a circulatory cause and there were 4,415 (58%) cancer deaths.

Urinary sodium and potassium concentrations were strongly and positively correlated (Spearman r=0.47). Estimated 24h sodium excretion was positively associated with socioeconomic deprivation (r=0.06), sedentary behavior (r=0.22) and, as expected, strongly correlated with BMI (r=0.46) since BMI was included in the predictive equations. The intra-class correlation coefficient between baseline and second measurement ~5 years later was 0.36 for spot urinary sodium concentration, and 0.80 for estimated 24h sodium excretion (that includes age and BMI in the equations).

**Urinary sodium excretion and cardiovascular disease**
Unadjusted analysis showed a strong linear association between estimated 24h urinary sodium excretion and cardiovascular disease (Figure S2 in the Online-Only Data Supplement). With multiple adjustment for confounders, estimated 24h urinary sodium excretion did not show evidence of association with cardiovascular or coronary heart disease (Figure 1). The hazard ratios (95% confidence intervals) for cardiovascular disease for the 15th (2.5 g/day) and 85th percentiles (4.2 g/day) compared to the 50th percentile of sodium excretion (3.2g/day) were 1.05 (1.01, 1.10) and 0.96 (0.92, 1.00) respectively and they were 0.98 (0.92, 1.05) and 1.04 (0.97, 1.10) in sensitivity analyses that excluded the first two years of follow up and participants receiving blood pressure treatment at baseline (Table 2). When analyses were subdivided to fatal and non-fatal cardiovascular disease events, only the fatal events showed suggestion of J-shaped association with estimated 24h sodium excretion, but this was no longer apparent in sensitivity analyses (Figure S3 in the Online-Only Data Supplement).
Table 2 Hazard Ratios (HR) and 95% CI from Cox models with restricted cubic splines shown for different centiles relative to the median. Corresponding restricted cubic splines are shown on Figures 1 and 3.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N cases</th>
<th>Percentile</th>
<th>Estimated 24h sodium excretion g/d</th>
<th>HR</th>
<th>95% Lower CI</th>
<th>95% Upper CI</th>
<th>HR</th>
<th>95% Lower CI</th>
<th>95% Upper CI</th>
</tr>
</thead>
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<tr>
<td>Cardiovascular disease</td>
<td>11451</td>
<td>15%</td>
<td>2.51</td>
<td>1.05</td>
<td>1.01</td>
<td>1.10</td>
<td>0.99</td>
<td>0.93</td>
<td>1.05</td>
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<td>Cardiovascular disease</td>
<td>11451</td>
<td>50%</td>
<td>3.21</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
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<td>0.96</td>
<td>0.92</td>
<td>1.00</td>
<td>1.04</td>
<td>0.98</td>
<td>1.10</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>6323</td>
<td>15%</td>
<td>2.51</td>
<td>0.96</td>
<td>0.90</td>
<td>1.02</td>
<td>0.92</td>
<td>0.84</td>
<td>1.01</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>6323</td>
<td>50%</td>
<td>3.21</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Coronary Heart Disease</td>
<td>6323</td>
<td>85%</td>
<td>4.21</td>
<td>1.00</td>
<td>0.94</td>
<td>1.06</td>
<td>1.03</td>
<td>0.95</td>
<td>1.12</td>
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<tr>
<td>Stroke</td>
<td>2181</td>
<td>15%</td>
<td>2.51</td>
<td>1.12</td>
<td>1.03</td>
<td>1.23</td>
<td>1.06</td>
<td>0.93</td>
<td>1.21</td>
</tr>
<tr>
<td>Stroke</td>
<td>2181</td>
<td>50%</td>
<td>3.21</td>
<td>1.00</td>
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<td>Stroke</td>
<td>2181</td>
<td>85%</td>
<td>4.21</td>
<td>0.94</td>
<td>0.86</td>
<td>1.03</td>
<td>1.09</td>
<td>0.95</td>
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<td>1.42</td>
<td>1.19</td>
<td>1.69</td>
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<tr>
<td>Heart failure</td>
<td>377</td>
<td>85%</td>
<td>4.21</td>
<td>0.71</td>
<td>0.59</td>
<td>0.87</td>
<td>0.99</td>
<td>0.70</td>
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<td>All-cause mortality</td>
<td>7647</td>
<td>15%</td>
<td>2.51</td>
<td>1.24</td>
<td>1.18</td>
<td>1.29</td>
<td>1.19</td>
<td>1.12</td>
<td>1.27</td>
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<tr>
<td>All-cause mortality</td>
<td>7647</td>
<td>50%</td>
<td>3.21</td>
<td>1.00</td>
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<td>1.00</td>
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<tr>
<td>All-cause mortality</td>
<td>7647</td>
<td>85%</td>
<td>4.21</td>
<td>0.89</td>
<td>0.85</td>
<td>0.93</td>
<td>0.92</td>
<td>0.86</td>
<td>0.98</td>
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<tr>
<td>Circulatory disease mortality</td>
<td>1456</td>
<td>15%</td>
<td>2.51</td>
<td>1.33</td>
<td>1.21</td>
<td>1.46</td>
<td>1.23</td>
<td>1.06</td>
<td>1.43</td>
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<td>50%</td>
<td>3.21</td>
<td>1.00</td>
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<td>1.00</td>
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</tr>
<tr>
<td>Mortality Type</td>
<td>N</td>
<td>%</td>
<td>HR</td>
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<td>95% CI High</td>
<td>95% CI Low</td>
<td>95% CI High</td>
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<td>85%</td>
<td>4.21</td>
<td>0.84</td>
<td>0.76</td>
<td>0.93</td>
<td>0.86</td>
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<td>1.07</td>
<td>1.01</td>
<td>1.15</td>
<td>1.10</td>
<td>1.01</td>
<td>1.19</td>
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<td>Cancer mortality</td>
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<td>85%</td>
<td>4.21</td>
<td>0.98</td>
<td>0.91</td>
<td>1.05</td>
<td>0.99</td>
<td>0.91</td>
<td>1.09</td>
</tr>
<tr>
<td>Other death</td>
<td>1175</td>
<td>15%</td>
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<td>1.48</td>
<td>1.37</td>
<td>1.61</td>
<td>1.38</td>
<td>1.23</td>
<td>1.55</td>
</tr>
<tr>
<td>Other death</td>
<td>1175</td>
<td>50%</td>
<td>3.21</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Other death</td>
<td>1175</td>
<td>85%</td>
<td>4.21</td>
<td>0.76</td>
<td>0.69</td>
<td>0.83</td>
<td>0.82</td>
<td>0.72</td>
<td>0.93</td>
</tr>
</tbody>
</table>

The baseline hazard is stratified for sex and birth cohort, and the model is adjusted for potassium excretion, alcohol intake, smoking (current, past, never), sedentary lifestyle (hours sitting watching television, use of computer or sitting), Townsend deprivation index and body mass index.
For stroke, there was only weak evidence for associations with estimated 24h sodium excretion, more marked (direct) at high sodium levels in sensitivity analyses. However, there was an inverse association of estimated 24h sodium excretion with incident heart failure; hazard ratios (95% confidence intervals) for the 15th (2.5 g/day) and 85th percentiles (4.2 g/day) compared to the 50th percentile of sodium excretion (3.2g/day) were 1.42 (1.19, 1.69) and 0.71 (0.59, 0.87) respectively (Table 2), which was no longer significant in the sensitivity analyses (Figure 1 and Table 2).

As BMI is already included in the 24h sodium excretion estimation equations, we also examined models without further adjustment for BMI. With multiple adjustment for all other covariates, estimated 24h urinary sodium excretion was directly and linearly associated with cardiovascular disease ($P=2\times10^{-16}$) and also showed strong upward association with coronary heart disease ($P=1\times10^{-13}$) and heart failure ($P=7\times10^{-8}$), with similar patterns of association in sensitivity analyses (Figure 2).

Overall, there was no evidence for interaction by sex. Stronger associations in women for cardiovascular disease, stroke and heart failure were only seen in analyses not adjusted for BMI, which were substantially weakened in sensitivity analyses (Figures S5 and S6 in the Online-Only Data Supplement).

**Estimated 24h urinary sodium excretion and mortality**

We found an association of low levels of estimated 24h sodium excretion with higher total mortality, also mortality from circulatory diseases and any other cause, but less so for cancer
mortality in unadjusted and adjusted for confounders analyses (Figure S7 in Online-Only Data Supplement and Figure 2). These associations remained in sensitivity analysis (Figure 2, Table 2) and were little affected after exclusion of BMI from the models (Figure S8 in Only-Only Data Supplement). There was evidence for sex interaction in the mortality analyses, with both genders showing evidence for curvilinear associations with estimated sodium excretion (Figures S9 and Figure S10 in the Online-Only Data Supplement).

Discussion

Statement of principal findings

In the largest study to date on urinary sodium excretion and disease outcomes, with highly standardized measurements from a single population, we found no evidence of J-shaped association between estimated 24h sodium excretion and cardiovascular events. However, as others have reported 4-8, we did observe a curvilinear association with all-cause and cause-specific mortality, and this finding merits careful consideration.

Comparison with other studies

While direct associations of sodium intake with blood pressure, and blood pressure with cardiovascular disease, are well established based on results of both observational studies and randomized controlled trials2.11.24-29, the relationship between sodium and cardiovascular disease has proved more controversial. In the absence of well-powered trial data30, there is a reliance on observational studies, which are prone to confounding, reverse causation and other biases10. In the present study, leveraging the UK Biobank large sample size, we guarded against reverse causation both through exclusion of prevalent cases of various diseases and sensitivity analyses. Although we did not find evidence for a J-shaped association with cardiovascular events, there
was an inconsistency between first presentation as either a fatal or non-fatal event; for fatal events, there was an apparent J-shaped association with estimated urinary sodium excretion, which disappeared in sensitivity analyses, suggesting either possible reverse causation or lower power of those analyses.

For stroke, in sensitivity analyses, there was suggestion of a curvilinear association, with higher estimated 24h sodium excretion associated with higher risk of stroke, in agreement with recent evidence from the PURE study. An inverse association of heart failure with estimated sodium excretion was substantially attenuated and no longer statistically significant in sensitivity analyses, as was also the case in the EPIC-NORFOLK study. Heart failure is associated with sodium retention and reduced sodium excretion which may explain our findings in sensitivity analyses, as excluding events over the first two years is likely to have excluded some individuals with early and undiagnosed heart failure.

For mortality, we showed a curvilinear association of estimated sodium excretion with all cause, circulatory diseases and other cause mortality, a mixed group of diseases including respiratory, digestive, nervous system, accidental causes and other causes of death. Any causal interpretation of these findings would need to encompass how low sodium is causally associated with mortality, but not cardiovascular events, and how this could pertain across a wide range of diseases. We are unaware of a single mechanism of low sodium intake that could explain such a differential effect between mortality and incidence of CVD and on such a wide range of diseases including accidental deaths.

Several hypotheses have been suggested to support adverse effects of low sodium intake. Sodium is the principal cation of the extracellular fluid with an essential role in regulating extracellular fluid and plasma volumes. Neuroscience studies have suggested a central control of
sodium appetite that may maintain a certain intake of this nutrient\textsuperscript{34}. It has been proposed that since the mean sodium intake across most populations varies little – for example, the mean estimated intake in our population is close to the mean intake across many other study populations – sodium intake is under tight physiological control\textsuperscript{14,15,35}. However, counterarguments include a) anthropological studies which indicate that humans evolved on a very low sodium diet and adapted for salt retention rather than salt excretion of a very high current intake (> 10 times the physiological need of 8–10 mmol/day\textsuperscript{1}), b) very low sodium intakes observed in populations where access to sodium was limited\textsuperscript{35} and c) the fact that public health interventions have successfully modified sodium intake\textsuperscript{36}. Excessively low sodium diets may result in a physiological response to maintain sodium homeostasis, including activation of the renin-angiotensin-aldosterone system (RAAS)\textsuperscript{37}. While RAAS has known effects on the cardiovascular system including on levels of catecholamines and blood lipids, evidence for adverse effects on cardiovascular health comes largely from small (<50 participants) and short-term studies on participants with hypertension\textsuperscript{26} and it is unclear what mechanisms may be operating on other systems that might lead to fatal events. While studies have reported other putative adverse effects of sodium reduction including dizziness, headache, insulin sensitivity and muscle cramping\textsuperscript{38-40}, again those studies have limitations and are insufficient to support firm conclusions of adverse effects\textsuperscript{41}.

**Strengths and weaknesses of the study**

Our study was based on a large sample with highly standardized measurements from a single population; however, only spot urine collection was available while the gold standard for sodium intake estimation is a 24h collection or timed overnight collections\textsuperscript{10}. Other studies have also suggested a curvi-linear association with all-cause mortality\textsuperscript{4,6,8} but also relied on predictive...
equations to estimate 24h sodium excretion from spot or first morning void urinary data. The use of such equations has been criticized as they produce biased estimates of 24h urine excretion, with over-estimation at lower sodium intake levels and under-estimation at higher levels\textsuperscript{20,42}. In the Trials of Hypertension Prevention follow-up, measurement of sodium excretion averaged over up to seven 24-hour urine collections suggested a direct linear association between sodium and mortality, whereas use of predictive equations introduced a spurious J-shaped relationship, indicating the potential for bias when estimating equations are used.\textsuperscript{42} UK Biobank includes a highly selected population with around 5\% response rate, a higher social class distribution and lower mortality rates than the general population\textsuperscript{17}. It is therefore possible that unaccounted biases, including collider bias\textsuperscript{43}, may have distorted associations between sodium excretion and outcomes in either direction. Finally, given the observational nature of the data, the observed associations may reflect residual confounding or some other source of bias, including reverse causality\textsuperscript{9,10}, despite our attempts to account for such effects by excluding prevalent cases of cardiovascular and kidney disease. Consequently, our results apply to seemingly healthy populations and we did not examine the effect of sodium excretion in individuals with established disease.

Conclusions

In conclusion, our results do not support a J-shaped association between sodium excretion and incident cardiovascular disease. There was an apparent curvilinear association with all-cause and cause-specific mortality; this occurred across a wide range of diseases including accidental causes and therefore it is unclear whether the associations may be causal or reflect potential biases e.g. from use of spot urine data and 24h urine predictive equations. Given these
uncertainties, large follow-up studies with 24h urine collections as well as well-powered trial
data of sodium reduction and cardiovascular events and mortality are urgently needed. Such
trials are currently underway in China\textsuperscript{44} and have been proposed in the USA\textsuperscript{30}.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Figure 1

Hazard ratio of composite cardiovascular disease (CVD), coronary heart disease (CHD), stroke and heart failure (HF) as a function of estimated 24h sodium excretion. A) Main analysis and B) Sensitivity analysis excluding participants on BP medication and first 2 years of follow up.

Sodium excretion is modelled using restricted cubic splines with two degrees of freedom. The hazard ratio is relative to the median sodium excretion. CVD is defined from death certificate or hospital admission (diagnoses and procedures) codes for CHD, stroke or heart failure (Appendix Table 1). The baseline hazard is stratified for sex and birth cohort, and the model is adjusted for potassium excretion, alcohol intake, smoking (current, past, never), sedentary lifestyle (hours sitting watching television, use of computer or sitting), Townsend deprivation index and body mass index. The overall P-value and the P-value for non-linearity are shown. Right and left shaded areas mark the values up to the 2.5th percentile, and above the 97.5th percentile.

Figure 2

Hazard ratio of composite cardiovascular disease (CVD), coronary heart disease (CHD), stroke and heart failure (HF) as a function of estimated 24h sodium excretion with models not adjusted for body mass index. A) Main analysis and B) Sensitivity analysis excluding participants on BP medication and first 2 years of follow up. Sodium excretion is modelled using restricted cubic splines with two degrees of freedom. The hazard ratio is relative to the median sodium excretion. CVD is defined from death certificate or hospital admission (diagnoses and procedures) codes for CHD, stroke or heart failure (Appendix Table 1). The baseline hazard is stratified for sex and birth cohort, and the model is adjusted for potassium excretion, alcohol intake, smoking (current, past, never), sedentary lifestyle (hours sitting watching television, use of computer or sitting), Townsend deprivation index and body mass index. The overall P-value and the P-value for non-linearity are shown. Right and left shaded areas mark the values up to the 2.5th percentile, and above the 97.5th percentile.
and Townsend deprivation index. The overall $P$-value and the $P$-value for non-linearity are shown. Right and left shaded areas mark the values up to the 2.5th percentile, and above the 97.5th percentile.

**Figure 3**

Hazard ratio of all-cause mortality, circulatory disease mortality (CVD mortality), cancer mortality and mortality from other causes as a function of estimated 24h sodium excretion.

Sodium excretion is modelled using restricted cubic splines with two degrees of freedom. A) Main analysis and B) Sensitivity analysis excluding participants on BP medication and first 2 years of follow up. The hazard ratio is relative to the median sodium excretion. Main causes of death are shown in Table 1. The baseline hazard is stratified for sex and birth cohort, and the model is adjusted for potassium excretion, alcohol intake, smoking (current, past, never), sedentary lifestyle (hours sitting watching television, use of computer or sitting), Townsend deprivation index and body mass index. The overall $P$-value and the $P$-value for non-linearity are shown. Right and left shaded areas mark the values up to the 2.5th percentile, and above the 97.5th percentile.