Urinary sodium excretion, blood pressure and risk of future cardiovascular disease and mortality in subjects without prior cardiovascular disease

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Abstract

Hypertension is a risk factor for cardiovascular disease. Increased urinary sodium excretion, representing dietary sodium intake, is associated with hypertension. Low sodium intake has been associated with increased mortality in observational studies. Further studies should assess if confounding relationships explain associations between sodium intake and outcomes. We studied UK Biobank participants (n=457,484, mean age 56.3 years, 44.7% male) with urinary electrolytes and blood pressure data. Estimated daily urinary sodium excretion was calculated using Kawasaki formulae. We analysed associations between sodium excretion and blood pressure in subjects without cardiovascular disease, treated hypertension or diabetes mellitus at baseline (n=322,624). We tested relationships between sodium excretion, incidence of fatal and non-fatal cardiovascular disease, heart failure and mortality. Subjects in higher quintiles of sodium excretion were younger, with more males and higher body mass index. There was a linear relationship between increasing urinary sodium excretion and blood pressure. During median follow-up of 6.99 years there were 11932 deaths (1125 cardiovascular deaths) with 10717 nonfatal cardiovascular events. There was no relationship between quintile of sodium excretion and outcomes. These relationships were unchanged after adjustment for comorbidity or excluding subjects with events during first two years follow-up. No differing risk of incident heart failure (1174 events) existed across sodium excretion quintiles**.** Urinary sodium excretion correlates with elevated blood pressure in subjects at low cardiovascular risk. No pattern of increased cardiovascular disease, heart failure or mortality risk was demonstrated with either high or low sodium intake.

Key words: Sodium, blood pressure, cardiovascular disease, heart failure, diet

Background

Hypertension is a modifiable risk factor for development of cardiovascular disease (CVD), the leading cause of death in high income countries[1, 2]. Large cohort studies showed associations between high sodium consumption and raised blood pressure[3-5]. Clinical trials have demonstrated that reduction in sodium intake leads to lowering of blood pressure[6-8] and international guidelines advocate a dietary sodium intake of 1.5-2.4g per day[9]. However, observational cohort studies (in approximately 3,600 to 102,000 participants) consistently demonstrate J-shaped relationships between sodium intake and CVD risk whereby very low sodium intake is associated with higher cardiovascular risk[10-12]. In the PURE study (n ~ 101,945), both low (<3 g/day) and high (>6 g/day) sodium intakes were associated with higher risk of CVD. Some observational data controversially suggest that salt intake relates positively to life expectancy[13]. Thus, conventional dietary guidance on reduction of sodium intake conflicts with observational population data regarding CVD risk, even after correction for baseline CVD, blood pressure and cholesterol[10].

One explanation often proposed is of 'reverse causality' where subjects with comorbid conditions (e.g. hypertension, heart failure) have low sodium intake either as recommended therapy or are malnourished due to poor dietary (and sodium) intake. This explanation becomes less robust in large cohort studies using appropriate statistical analysis to account for comorbidities and baseline individual cardiovascular risk profile[3, 10, 14]. We aimed to test if 'reverse causality' accounted for 'J shaped' relationships between sodium intake and CVD and/or mortality.

Materials and Methods

UK Biobank data are available on application to the UK Biobank for data access (http://www.ukbiobank.ac.uk/), and authors have returned derived data to UK Biobank as per their requirements. Between April 2007 and December 2010, over 500,000 participants were recruited by UK Biobank, and had baseline measurements recorded at one of 22 assessment centres in Scotland, England or Wales, as described elsewhere[15]. UK Biobank received ethical approval from the North West Multi-center Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment, which was conducted in accord with the principles of the Declaration of Helsinki.

Ethnicity was coded as white, South Asian, black or other, with white used as the referent group. Body mass index (BMI) was calculated as weight(kg)/height^2(m). Smoking status was self-reported and categorised as never, former or current smoker, and area-based sociodemographic status was derived from postcode of residence, using Townsend score[16], where higher scores relate to greater deprivation. Diagnosis by a doctor of diabetes mellitus (DM), stroke, myocardial infarction (MI), transient ischaemic attack (TIA) or brain haemorrhage were self-reported at baseline. Family history of CVD (stroke or heart disease in participant's mother, father or sibling) was self-reported.

A mid-stream urine sample collected was refrigerated between 2 and 8^{O}C until potentiometric measurement for sodium and potassium content using a Beckman Coulter (UK) Ltd AU5400 analyser. Sodium and potassium concentrations (in mmol/L) were capped at sex-specific mean ± 4 standard deviations. Kawasaki formulae[17] were

used to convert spot sodium and potassium measurements into estimated 24-hour excretion (eNa^{24h} and eK^{24h}, in g/day). Two resting blood pressure measurements were taken, according to a standard operating procedure (http://biobank.ctsu.ox.ac.uk/showcase/docs/Bloodpressure.pdf) at least 1 minute apart, by trained staff, using either an automated sphygmomanometer with an appropriate cuff size relative to the participant's arm, or manually if an automated reading was not possible. Mean systolic (SBP) and diastolic (DBP) blood pressures were calculated and used to derive an estimated mean arterial blood pressure (MABP); MABP = (SBP+2*DBP)/3, and pulse pressure PP = (SBP-DBP). Lean body mass as fat free mass was derived from whole-body bio-impedance measures using the Tanita BC418MA body composition analyser. For full data collection protocols refer to UK Biobank online (http://www.ukbiobank.ac.uk).

The process for generation of the cohort for analysis is shown in figure S1. Charlson co-morbidity index was calculated for all subjects[18], and a secondary analysis was conducted after excluding those participants with Charlson score greater than zero. Use of diuretics and blood pressure medications, were detected by searching medicines reported by participants in the 63rd revision of the British National Formulary.

CVD events (MI, stroke, heart failure admission ICD10 codes I20-23, I24.1, I25.2, I60, I61, I62, I63 or I64) were identified by linkage with routine hospital data, and date and cause of death (where appropriate) were obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales, and the NHS Central Register Scotland for participants from Scotland. All-cause mortality (ACM) was defined as death from all causes. Start of follow-up was date of assessment, and end of follow-up for mortality endpoints was recorded as the

end of data collection for the assessment centre attended (30/11/2015 for centres in Scotland, 31/1/2016 for centres in England/Wales), or date of death, whichever came first. For nonfatal outcomes, end of follow-up was date of death, first date of hospitalisation for nonfatal CVD, or end of follow-up.

Statistical Analyses

We excluded participants hospitalised within 30 days of assessment or those missing blood pressure measurements from all analyses. Continuous variables (age, BMI (or lean body mass), Townsend deprivation score, eNa^{24h}) were summarized as mean ± standard deviation or median ± inter-quartile range (Q1, Q3) if the distribution skewed. Categorical variables (sex, ethnicity, family history of CVD, smoking status) were summarized as numbers and percentages. MABP and eNa^{24h} were divided into sex-specific quintiles to lessen impact of outliers. Independent variables were examined for differences across quintiles of eNa^{24h} and MABP. Differences between means or groups were tested using ANOVA, Kruskal-Wallis or Pearson's chi-squared tests for Normal, skewed continuous or categorical variables, respectively.

Blood Pressure Models

Associations of MABP with sex-specific quintiles of eNa^{24h} were examined using sex-specific unadjusted linear regression models. Each model was then adjusted for the following; age, lean body mass, ethnicity, family history of CVD, smoking status, eK^{24hr} and deprivation score. Linearity of associations were further explored using restricted cubic splines (data not shown).

Cardiovascular Disease Models

Associations of fatal or nonfatal CVD, or ACM with eNa^{24h} were examined using eNa^{24h} in sex-specific quintiles in Cox proportional hazard models. In these main analyses we excluded those with treated hypertension, baseline CVD, or baseline diabetes (Fig S1). All models were adjusted for age, Townsend deprivation index, eK^{24hr}, MABP (used as continuous variable), smoking status, ethnicity, lean body mass, family history of CVD, rheumatoid arthritis, atrial fibrillation and a binary variable for Charlson comorbidity score >0. We checked for effect mediation by MABP through models that did not adjust for this variable. The proportional hazard assumption was checked by visual inspection of Schöenfeld residuals.

To minimise effect of reverse causality on predictors of early CVD events, we performed additional landmark sensitivity analyses, analysing events occurring after two years follow up. Further sensitivity analyses were conducted excluding participants with Charlson comorbidity index of greater than zero.

Incident heart failure was treated as specific event of interest, on the basis that excess sodium ingestion may lead to sodium and water retention triggering heart failure. Cox proportional hazard models used to test for associations with eNa^{24hr} quintiles, using the methods as for other CVD events.

All analyses were performed using STATA 14 (StataCorp LP, College Station, USA). A p-value of <0.05 was considered statistically significant.

Results

Baseline demographics, blood pressure and urinary sodium excretion in all subjects and those without comorbid disease

Baseline characteristics for all subjects categorised by quintile of MABP are shown in Table 1. Subjects in the highest MABP quintiles were more likely to be older, have greater BMI and lean body mass, a higher prevalence of family history of CVD, less likely to have a positive smoking history, reside in an area of greater socioeconomic deprivation and have greater eNa^{24h} excretion. When categorised by quintiles of eNa^{24h} excretion (Table 2), subjects in the highest eNa^{24h} quintiles were younger, had higher BMI and lean body mass, lower prevalence of family history of CVD, lower smoking prevalence, more likely to reside in areas of lower socioeconomic deprivation and have higher MABP. Excluding those with treated hypertension, baseline CVD, or DM did not substantially attenuate these results (Supplementary Tables S1, S2). In regression models assessing relationships between eNa^{24h} and MABP performed in subjects without CVD, DM or treated hypertension, there were linear relationships between increasing quintiles of eNa^{24h} and increased MABP in both females and males (Figure 1). These associations were consistent before and after adjustment for baseline characteristics and were similar when restricted to subjects with Charlson score of zero to minimise influence of residual confounding.

Relationship between urinary sodium excretion, future CVD events, heart failure admissions and all-cause mortality in subjects without baseline CVD

In 322,624 subjects without baseline CVD, DM and treated hypertension over median follow-up time of 6.99 years (IQR 6.29-7.64 years) there were 6742 deaths, 3016 of

which were in women (44.7%). There were 740 fatal CVD events in men and 364 in women, and 6972 nonfatal CVD events in men and 3739 in women.

There was no association between quintiles of eNa^{24hr} and risk of CVD events or ACM in any model (Figure 2). These relationships were unaffected by adjustment for self-reported chronic kidney disease or statin use (Supplementary Figure 2). These relationships did not change either after limiting the adjustment model to not include MAPB as a potential effect mediator, or following landmark analysis excluding subjects who died within 2 years of follow up, or after substituting lean body mass with conventional body mass index (Supplementary Figure 3). Data on the incidence of subtypes of CVD (myocardial infarction, ischaemic and haemorrhagic stroke) are shown in Supplementary Table 3 and Supplementary Figure 4.

There were 283 incident heart failure hospitalisations during follow up in the 322,624 participants without baseline CVD, DM or treated hypertension. There were no statistically significant differences in risk of incident heart failure across eNa^{24hr} quintiles in either males of females (Figure 3).

Discussion

In a large prospective cohort study we demonstrate a consistent relationship between estimated urinary sodium excretion as a marker of sodium intake and elevation in blood pressure. These relationships were present both in the whole cohort and when restricted to subjects free of baseline comorbidity, specified by restricting analysis to those without baseline CVD, DM or treated hypertension and with Charlson comorbidity score of zero. These findings are consistent with other cohort studies, interventional clinical trials and meta-analyses[3-8].

The mechanisms by which dietary sodium contribute to raised blood pressure have been reviewed extensively elsewhere[19]. Sodium excess have been associated with excess activation of the sympathetic nervous system, increased vascular tone, and endothelial dysfunction as well as end organ damage with left ventricular hypertrophy, glomerulosclerosis, and arteriolosclerosis. In industrialised countries, diets rich in sodium and low in potassium are the norm. Processed meals are rich in sodium. Societies following a 'non-industrialised' diet low in sodium have very low prevalence (<1%) of hypertension[20-22]. Meta-analyses demonstrate that reduction in dietary sodium intake is associated with average reduction in SBP of 3-5.4mmHg in hypertensive subjects[7, 8]. Our data add weight to the hypothesis that reduction of dietary sodium intake may lead to lower blood pressure. Unfortunately, we do not have long term blood pressure changes to assess the influence of sodium intake on development of hypertension.

The relationship between sodium excretion and future non-fatal CVD and ACM is more complex and essentially showed no strong relationship between higher or lower sodium intake with risk of mortality or CVD. These null relationships did not appear to be altered by adjustment for comorbid disease using the Charlson

comorbidity index. The landmark analysis excluding subjects who died within two years of follow-up showed similar lack of a relationship between sodium excretion and risk of CVD death. This refutes the perception that reverse causality underpins relationships whereby those with the lowest sodium intake have greater mortality risk due to underlying (perhaps undiagnosed) disease.

Our results demonstrating a lack of straightforward linear relationships between high sodium intake and increased risk of mortality of CVD are broadly in keeping with other studies. Whilst much public policy and conventional advice focuses on benefits of reduction of sodium intake on future cardiovascular health, large cohort studies, including subjects with comorbidities associated with increased CVD risk such as chronic kidney disease and diabetes, have demonstrated there is a nadir of sodium consumption below which increased risk of future CVD and/or ACM increases[12, 23-27]. Alternatively, lower sodium intake may risk via activation of the renin-angiotensin-aldosterone system to maintain sodium and water homeostasis exposing the cardiovascular system to the deleterious effects of aldosterone[28]. As heart failure represents a syndrome of renal salt avidity driving fluid retention, in the setting of cardiac dysfunction[29], we specifically analysed the influence of sodium intake on incidence of heart failure hospitalisation. However, we could find no evidence that sodium excretion as a marker for sodium intake was associated with incident heart failure, albeit in a small number of events. Alternatively, if renal sodium avidity was expected to be a driver for future heart failure, one might expect lower sodium excretion to precede future heart failure events, but this was not the case. Unlike PURE, we do not demonstrate any association with low sodium excretion on CVD events or ACM supporting the notion that public health policy reducing sodium intake in healthy individuals is not harmful and will be associated reduced blood pressure. It

may take longer follow up than this study to demonstrate the benefits of sodium reduction on CVD events in low risk individuals.

Only a large randomised trial of differing sodium intake targets will address what the optimal sodium intake should be in an industrialised nation. In the face of public health advice, competing pressures from the food industry and trends towards a diet based on convenience foods, such a trial would be challenging to implement, and would require regular monitoring to ensure participants complied with the 'prescribed' sodium intake. Experts have designated this such a pressing issue that undertaking such a trial in institutionalised environments such as prisons may be justified[30].

There are limitations to this study. The population recruited to UK Biobank were volunteers and therefore may not be representative of older or more comorbid populations. As observational data, we describe associations, and cannot infer causal relationships. We used the Kawasaki formula to estimate daily sodium excretion. Estimating sodium excretion from a single urine sample may be inaccurate. We chose to use the Kawasaki formula to allow comparability between studies as it is felt to be the least biased of a number of estimation algorithms for estimating 24h sodium excretion[31]. The relationship between sodium and fatal and non-fatal CVD was not in keeping with perceived wisdom that lower sodium intake leads to lower risk of CVD. Sodium intake was linearly associated with blood pressure, reducing the probability that exposure misclassification biased results to the null. The absence of serum biochemistry is limitation although out with electrolyte disorders, serum sodium is homeostatically maintained in a physiological range in the face of a wide dietary intake. There was no assessment of salt sensitivity in this study which would provide more detailed insight into which groups are at greater risk from increased dietary salt intake[32]. Finally, recent sodium balance studies demonstrate that relationships

between dietary sodium intake and urinary excretion are not as simple as previously thought with cyclical handling of sodium over several days and sequestering of sodium in organs such as skin and muscle[33-36]. Whilst this opens new paradigms of thought on sodium homeostasis, for large cohort epidemiological research, using estimates of sodium intake and excretion from spot urine and derivation from sodium: creatinine ratio is widely accepted[10, 17].

Perspectives

In summary, we confirm the relationship between increasing sodium intake and blood pressure is linear, but there is a fairly limited relationship between salt intake and risk of fatal/non-fatal CVD and ACM in subjects at low cardiovascular risk. Based on these observational data from a large cohort, we there is no strong relationship of high or low sodium excretion, as a marker of dietary salt intake, with increased risk of cardiovascular events or death. These data may further inform public health debate around recommended dietary daily sodium intake.

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Novelty and significance

1. **What is new?** We demonstrate that in a very large cohort of subjects at low risk of cardiovascular disease, urinary sodium excretion as a marker for salt intake is linearly associated with blood pressure, but with no relationship between sodium excretion and cardiovascular events or mortality
2. **What is relevant?** Current public health advice to reduce sodium intake is likely to lead to lower blood pressure and is unlikely to be harmful in low risk individuals. Based on these findings, it is less clear that this has benefits on cardiovascular events over follow up of approximately seven years.
3. **Summary.** Lower urinary sodium excretion correlated with reduced blood pressure in subjects at low cardiovascular risk, but this was not associated with reduced cardiovascular events.

Figure Legends

Fig 1. Linear regression analyses describing the association between MABP and sex-specific quintiles of eNa^{24h} in unadjusted (A&C) and fully adjusted models (B&D), using all participants (A&B, n=322624), and excluding participants with a Charlson score of greater than zero (C&D, n=160920). All plots exclude participants with baseline CVD, DM or treated hypertension.

Fig 2. Adjusted hazard ratios of sex-specific quintiles of eNa^{24h} on the risk of all-cause mortality (A&B) and fatal or non-fatal cardiovascular disease events (C&D) in all participants (A&C, n=322624) and excluding participants with a Charlson score of greater than zero (B&D, n=160920). All plots exclude participants with baseline CVD, DM or treated hypertension.

Fig 3. Adjusted hazard ratios of sex-specific quintiles of eNa^{24h} on incident heart failure in 322624 UK Biobank participants, excluding those with baseline CVD, DM or treated hypertension.

Factor		MABP mmHg, quintiles					P
		1	2	3	4	5	
		(50.7-88.7, n=51400) (48.3-93.7, n=41586)	(89-95.7, n=51218) (94-100.3, n=41446)	(96-102, n=49240) (100.7-106.3, n=40772)	(102.3-110, n=51163) (106.7-113.7, n=40642)	(110.3-174.7, n=49993) (114-177.7, n=40024)	
Age (years)		52.92 (8.06) 54.45 (8.54)	55.08 (8.08) 55.52 (8.40)	56.50 (7.82) 56.41 (8.19)	57.73 (7.53) 57.32 (7.89)	58.75 (7.19) 58.15 (7.53)	<0.001 <0.001
Ethnic background	**White**	46785(91.4) 37102(89.8)	47076 (92.3) 37715 (91.6)	45242 (92.2) 37307 (92.0)	47071 (92.4) 37466 (92.7)	45829 (92.0) 37032 (93.0)	<0.001 <0.001
	South Asian	735 (1.4) 957 (2.3)	677 (1.3) 807 (2.0)	677 (1.4) 758 (1.9)	653 (1.3) 673 (1.7)	679 (1.4) 545 (1.4)	
	Black	660 (1.3) 724 (1.8)	742 (1.5) 610 (1.5)	803 (1.6) 571 (1.4)	932 (1.8) 585 (1.4)	1155 (2.3) 636 (1.6)	
	Other	3011 (5.9) 2553 (6.2)	2529 (5.0) 2057 (5.0)	2326 (4.7) 1922 (4.7)	2274 (4.5) 1692 (4.2)	2136 (4.3) 1610 (4.0)	
Body mass index (kg/m^2)		24.70 (3.95) 26.14 (3.82)	26.27 (4.59) 27.35 (3.97)	27.31 (5.07) 28.00 (4.16)	28.08 (5.30) 28.45 (4.21)	28.76 (5.66) 28.80 (4.29)	<0.001 <0.001
Lean body mass (kg)		43.53 (4.33) 62.30 (7.42)	44.17 (4.71) 63.52 (7.61)	44.62 (5.05) 63.98 (7.77)	44.90 (5.20) 64.21 (7.87)	45.19 (5.50) 64.17 (7.99)	<0.001 <0.001
FH CVD		26162(50.9) 20451(49.2)	28586 (55.8) 21184 (51.1)	29067 (59.0) 21356 (52.4)	31471 (61.5) 22401 (55.1)	31378 (62.8) 22367 (55.9)	<0.001 <0.001
Smoking status	**Never**	30075 (58.6) 21726 (52.3)	30555 (59.7) 21298 (51.4)	29646 (60.3) 20391 (50.1)	30863 (60.4) 19975 (49.2)	30904 (61.9) 19246 (48.1)	<0.001 <0.001
	Former	15501 (30.2) 13564 (32.7)	15726 (30.7) 14581 (35.2)	15237 (31.0) 15460 (38.0)	16303 (31.9) 16092 (39.6)	15572 (31.2) 16330 (40.8)	
	Current	5754 (11.2) 6243 (15.0)	4887 (9.6) 5521 (13.3)	4300 (8.7) 4873 (12.0)	3943 (7.7) 4537 (11.2)	3475 (7.0) 4418 (11.0)	
Townsend		-1.25 (3.08)	-1.37 (3.02) -1.27 (3.15)	-1.37 (3.02) -1.34 (3.10)	-1.39 (3.01) -1.41 (3.07)	-1.43 (2.99) -1.38 (3.07)	<0.001

deprivation index		-1.07 (3.26)					<0.001
Estimated Na^{24hr} (g)		3.57 (2.92, 4.26) 4.16 (3.43, 4.93)	3.68 (3.01, 4.39) 4.32 (3.60, 5.08)	3.75 (3.06, 4.47) 4.41 (3.65, 5.18)	3.82 (3.11, 4.56) 4.46 (3.69, 5.23)	3.92 (3.21, 4.67) 4.53 (3.75, 5.31)	<0.001 <0.001
Rheumatoid Arthritis		563 (1.1%) 263 (0.6%)	656 (1.3%) 271 (0.7%)	698 (1.4%) 281 (0.7%)	781 (1.5%) 291 (0.7%)	831 (1.7%) 335 (0.8%)	<0.001 0.005
Atrial Fibrillation		130 (0.3%) 302 (0.7%)	108 (0.2%) 214 (0.5%)	120 (0.2%) 224 (0.5%)	116 (0.2%) 174 (0.4%)	115 (0.2%) 230 (0.6%)	0.68 <0.001
Baseline CVD		3736 (7.3%) 6484 (15.6%)	7459 (14.6%) 9208 (22.2%)	11021 (22.4%) 12066 (29.6%)	16639 (32.5%) 15759 (38.8%)	22991 (46.0%) 19520 (48.8%)	<0.001 <0.001
Antihypertensive medications		2592 (5.0%) 4936 (11.9%)	5420 (10.6%) 7010 (16.9%)	7984 (16.2%) 8884 (21.8%)	11600 (22.7%) 10955 (27.0%)	13824 (27.7%) 11644 (29.1%)	<0.001 <0.001
Diabetes Mellitus		1200 (2.3%) 2534 (6.1%)	1755 (3.4%) 2777 (6.7%)	2010 (4.1%) 2854 (7.0%)	2207 (4.3%) 2649 (6.5%)	1894 (3.8%) 2128 (5.3%)	<0.001 <0.001

Table 1. Distribution of variables by quintiles of MABP in women (upper) and men (lower) among all included UK Biobank participants. Numbers in parentheses are percentages for ordinal variables, standard deviations for continuous variables, or Q1 and Q3 for skewed variables. Tests of differences between groups are $\chi^2$and One way ANOVA

Factor		Estimated Urinary Sodium Excretion g/day, quintiles					P
		1	2	3	4	5	
		(0.71-2.89, n=47830) (0.74-3.43, n=38193)	(2.89-3.48, n=47829) (3.43-4.08, n=38193)	(3.48-4.01, n=47829) (4.08-4.66, n=38193)	(4.01-4.66, n=47829) (4.66-5.35, n=38193)	(4.66-7.00, n=47829)(5.35-7.00, n=38192)	
Age, years		57.37 (7.88) 58.10 (7.86)	56.45 (7.93) 57.11 (8.05)	56.07 (7.95) 56.43 (8.18)	55.84 (7.98) 55.77 (8.22)	55.31 (8.07) 54.71 (8.32)	<0.001 <0.001
Ethnic background	**White**	44421 (93.2%) 34916 (91.9%)	44256 (92.9%) 35163 (92.5%)	44116 (92.5%) 35039 (92.2%)	43912 (92.2%) 35040 (92.2%)	43179 (90.7%) 34602 (91.1%)	<0.001 <0.001
	South Asian	410 (0.9%) 644 (1.7%)	464 (1.0%) 563 (1.5%)	494 (1.0%) 606 (1.6%)	669 (1.4%) 696 (1.8%)	1057 (2.2%) 787 (2.1%)	
	Black	700 (1.5%) 586 (1.5%)	765 (1.6%) 556 (1.5%)	806 (1.7%) 587 (1.5%)	787 (1.7%) 542 (1.4%)	804 (1.7%) 577 (1.5%)	
	Other	2110 (4.4%) 1830 (4.8%)	2178 (4.6%) 1720 (4.5%)	2262 (4.7%) 1762 (4.6%)	2280 (4.8%) 1713 (4.5%)	2558 (5.4%) 2005 (5.3%)	
Body mass index (kg/m^2)		26.48 (4.82) 26.99 (3.91)	26.40 (4.73) 27.18 (3.82)	26.67 (4.85) 27.44 (3.91)	27.09 (5.07) 27.91 (4.08)	28.05 (5.65) 28.69 (4.54)	<0.001 <0.001
Lean body mass by impedance (kg)		43.97 (4.74) 62.15 (7.49)	43.97 (4.71) 62.68 (7.33)	44.27 (4.82) 63.29 (7.46)	44.57 (4.96) 64.06 (7.63)	45.33 (5.37) 65.39 (8.06)	<0.001 <0.001
Family history of CVD		28404 (59.4%) 20815 (54.5%)	27682 (57.9%) 20395 (53.4%)	27647 (57.8%) 20069 (52.5%)	27446 (57.4%) 19988 (52.3%)	27525 (57.5%) 19521 (51.1%)	<0.001 <0.001
Smoking status	**Never**	28754 (60.2%) 19292 (50.6%)	29186 (61.1%) 19743 (51.7%)	29098 (60.9%) 19632 (51.4%)	28840 (60.4%) 19105 (50.1%)	28094 (58.8%) 18573 (48.7%)	<0.001 <0.001
	Former	14917 (31.2%) 14051 (36.8%)	14539 (30.4%) 14025 (36.7%)	14692 (30.7%) 14018 (36.7%)	14788 (30.9%) 14332 (37.6%)	15151 (31.7%) 14528 (38.1%)	
	Current	4111 (8.6%) 4818 (12.6%)	4060 (8.5%) 4402 (11.5%)	4000 (8.4%) 4508 (11.8%)	4159 (8.7%) 4713 (12.4%)	4531 (9.5%) 5047 (13.2%)	

Townsend deprivation index		-1.48 (2.98) -1.32 (3.17)	-1.50 (2.96) -1.49 (3.06)	-1.45 (2.97) -1.44 (3.05)	-1.37 (3.01) -1.35 (3.07)	-1.16 (3.11) -1.10 (3.17)	<0.001 <0.001
MABP (mmHg)		97.00 (89.00, 105.67) 101.67 (93.67, 110.00)	97.67 (89.67, 106.67) 102.33 (94.67, 110.67)	98.67 (90.33, 107.33) 103.00 (95.33, 111.00)	99.67 (91.33, 108.33) 104.00 (96.33, 112.00)	101.33 (93.00, 110.00) 105.00 (97.67, 113.00)	<0.001 <0.001
Rheumatoid Arthritis		803 (1.7%) 335 (0.9%)	579 (1.2%) 258 (0.7%)	636 (1.3%) 234 (0.6%)	542 (1.1%) 241 (0.6%)	727 (1.5%) 252 (0.7%)	<0.001 <0.001
Atrial Fibrillation		138 (0.3%) 321 (0.8%)	105 (0.2%) 211 (0.6%)	97 (0.2%) 210 (0.5%)	107 (0.2%) 164 (0.4%)	96 (0.2%) 161 (0.4%)	0.029 <0.001
Baseline CVD		11807 (24.7%) 12497 (32.7%)	10112 (21.1%) 10499 (27.5%)	10308 (21.6%) 10471 (27.4%)	11176 (23.4%) 11194 (29.3%)	14124 (29.5%) 12867 (33.7%)	<0.001 <0.001
Antihypertensive medications		7741 (16.2%) 8670 (22.7%)	6251 (13.1%) 6864 (18.0%)	6611 (13.8%) 6932 (18.1%)	7476 (15.6%) 7571 (19.8%)	10425 (21.8%) 9355 (24.5%)	<0.001 <0.001
Diabetes Mellitus		1624 (3.4%) 2423 (6.3%)	1410 (2.9%) 2075 (5.4%)	1440 (3.0%) 2080 (5.4%)	1627 (3.4%) 2208 (5.8%)	2145 (4.5%) 2792 (7.3%)	<0.001 <0.001

Table 2. Distribution of variables by quintiles of Na^{24h} in women (upper) and men (lower) among all included UK Biobank participants

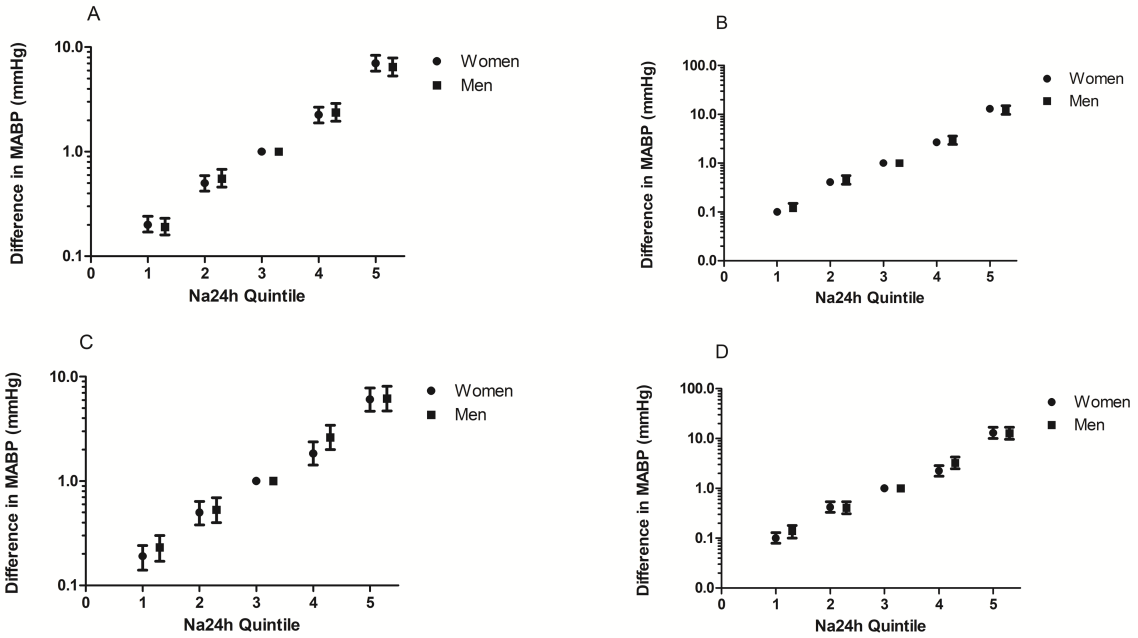
A
B
C
D
Difference in MABP (mmHg)
Na24h Quintile
Women
Men
10.0
1.0
0.1
100.0
0.0
0
1
2
3
4
5

Figure 1

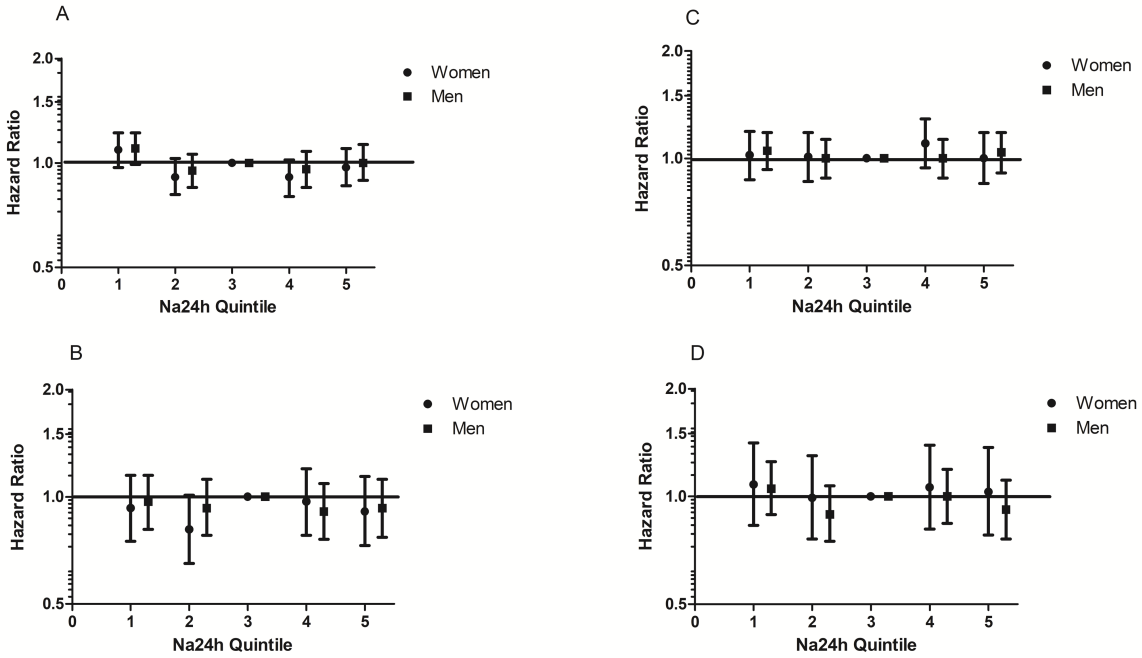
A
Hazard Ratio
2.0
1.5
1.0
0.5
0
1
2
3
4
5
Na24h Quintile
Women
Men
C
Hazard Ratio
2.0
1.5
1.0
0.5
0
1
2
3
4
5
Na24h Quintile
Women
Men
B
Hazard Ratio
2.0
1.5
1.0
0.5
0
1
2
3
4
5
Na24h Quintile
Women
Men
D
Hazard Ratio
2.0
1.5
1.0
0.5
0
1
2
3
4
5
Na24h Quintile
Women
Men

Figure 2

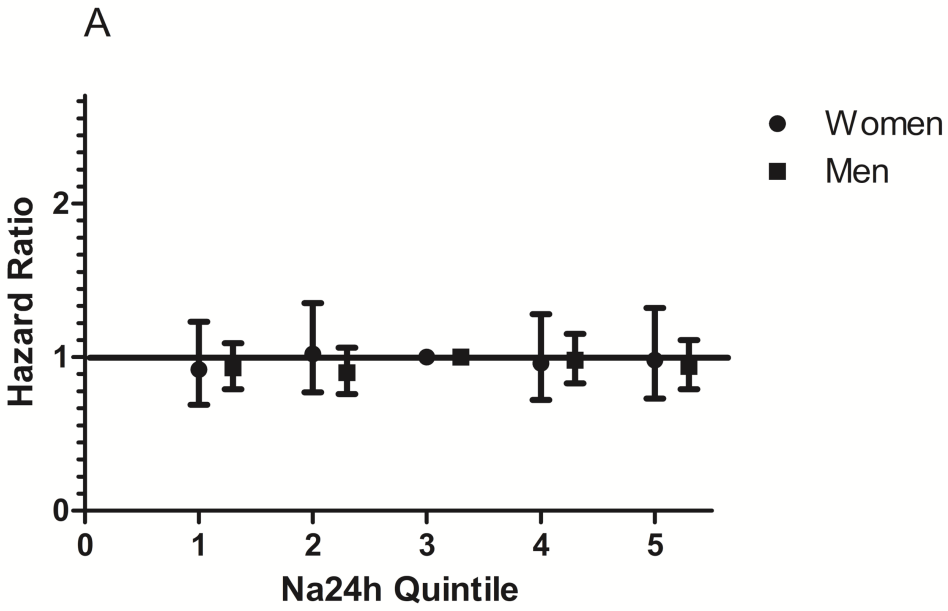

Figure 3

Urinary sodium excretion, blood pressure and risk of future cardiovascular disease and mortality in subjects without prior cardiovascular disease

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Data Supplement

Supplementary Tables

S1. Distribution of variables by quintiles of MABP in women (upper) and men (lower) among UK Biobank participants excluding those with treated hypertension, baseline CVD, and DM.

Factor		MABP mmHg, quintiles					P
		1	2	3	4	5	
		(50.7-87, n=37820)(50-92.3, n=28480)	(87.3-93.3, n=36881)(92.7-98.3, n=26560)	(93.7-99.7, n=39070)(98.7-204, n=27100)	(100-107, n=36156)(104.3-111, n=26738)	(107.3-174.7, n=36708)(111-175.7, n=27111)	
Age (years)		52.16 (7.86) 53.18 (8.32)	53.88 (7.98) 53.94 (8.32)	55.23 (7.90) 54.73 (8.29)	56.42 (7.70) 55.68 (8.11)	57.97 (7.39) 57.03 (7.89)	<0.00 <0.00
Ethnic background	**White**	34444 (91.4%) 25397 (89.7%)	33914 (92.3%) 24205 (91.6%)	36107 (92.8%) 24897 (92.5%)	33534 (93.2%) 24679 (92.8%)	34089 (93.3%) 25195 (93.5%)	<0.00 <0.00
	South Asian	519 (1.4%) 598 (2.1%)	458 (1.2%) 454 (1.7%)	473 (1.2%) 419 (1.6%)	406 (1.1%) 415 (1.6%)	421 (1.2%) 343 (1.3%)	
	Black	442 (1.2%) 492 (1.7%)	490 (1.3%) 364 (1.4%)	493 (1.3%) 345 (1.3%)	483 (1.3%) 330 (1.2%)	572 (1.6%) 342 (1.3%)	
	Other	2263 (6.0%) 1812 (6.4%)	1875 (5.1%) 1393 (5.3%)	1825 (4.7%) 1269 (4.7%)	1575 (4.4%) 1164 (4.4%)	1456 (4.0%) 1061 (3.9%)	
Body mass index (kg/m^2)		24.24 (3.54) 25.48 (3.34)	25.50 (4.10) 26.58 (3.51)	26.32 (4.47) 27.15 (3.62)	27.11 (4.79) 27.63 (3.79)	27.91 (5.21) 28.13 (3.96)	<0.00 <0.00
Lean body mass by impedance (kg)		43.35 (4.16) 62.01 (7.15)	43.88 (4.44) 63.13 (7.37)	44.18 (4.71) 63.55 (7.45)	44.47 (4.87) 63.75 (7.60)	44.73 (5.19) 63.67 (7.74)	<0.00 <0.00
Family history of CVD		18527 (49.0%) 13204 (46.4%)	19409 (52.6%) 12760 (48.0%)	21731 (55.6%) 13178 (48.6%)	20967 (58.0%) 13704 (51.3%)	21969 (59.8%) 14224 (52.5%)	<0.00 <0.00
Smoking status	**Never**	22265 (58.9%) 15736 (55.3%)	22138 (60.1%) 14483 (54.6%)	23775 (60.9%) 14459 (53.5%)	22007 (60.9%) 14042 (52.6%)	22708 (62.0%) 13795 (51.0%)	<0.00 <0.00
	Former	11259 (29.8%) 8503 (29.9%)	11040 (30.0%) 8373 (31.6%)	11764 (30.2%) 9139 (33.8%)	11165 (30.9%) 9537 (35.7%)	11234 (30.7%) 10160 (37.5%)	
	Current	4246 (11.2%) 4198 (14.8%)	3657 (9.9%) 3679 (13.9%)	3478 (8.9%) 3450 (12.8%)	2938 (8.1%) 3124 (11.7%)	2707 (7.4%) 3114 (11.5%)	
Townsend deprivation index		-1.30 (3.05) -1.15 (3.20)	-1.43 (2.99) -1.39 (3.08)	-1.49 (2.96) -1.47 (3.01)	-1.51 (2.93) -1.49 (3.01)	-1.58 (2.91) -1.54 (2.97)	<0.00 <0.00
Estimated 24hour sodium excretion (g/day)		3.56 (2.92, 4.24) 4.15 (3.44, 4.91)	3.66 (3.00, 4.36) 4.31 (3.61, 5.06)	3.73 (3.07, 4.42) 4.39 (3.68, 5.12)	3.78 (3.11, 4.48) 4.44 (3.71, 5.19)	3.87 (3.19, 4.58) 4.52 (3.77, 5.27)	<0.00 <0.00

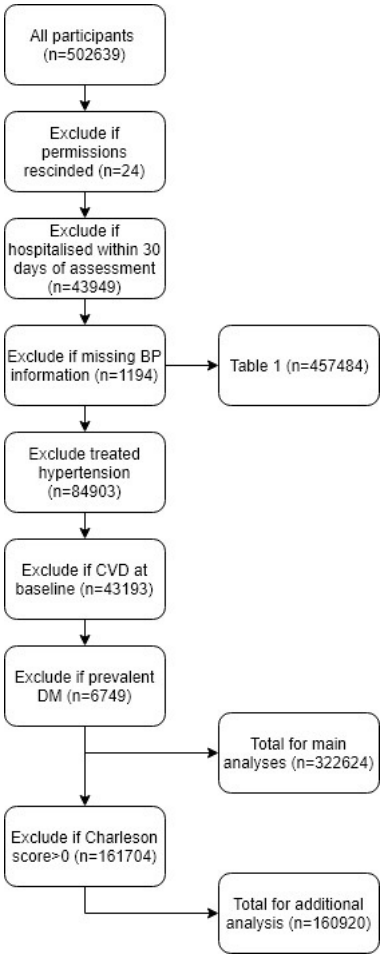
S2. Distribution of variables by quintiles of Na^{24h} in women (upper) and men (lower) among UK Biobank participants excluding those with treated hypertension, baseline CVD, and DM.

Factor		Estimated Urinary Sodium Excretion g/day, quintiles					P
		1	2	3	4	5	
		(0.7-2.9, n=35488)(0.8-3.5, n=25685)	(2.9-3.5, n=35488)(3.5-4.1, n=25685)	(3.5-4.0, n=35488)(4.1-4.6, n=25685)	(4.0-4.6, n=35488)(4.6-5.3, n=25685)	(4.6-7.0, n=35487)(5.3-7.0, n=25685)	
Age (years)		56.37 (7.98) 56.81 (8.07)	55.63 (7.97) 55.93 (8.18)	55.16 (7.94) 55.17 (8.24)	54.81 (7.96) 54.31 (8.22)	53.82 (7.96) 52.78 (8.10)	<0.001 <0.001
Ethnic background	**White**	33203 (94.0%) 23664 (92.7%)	32988 (93.3%) 23702 (92.8%)	32911 (93.1%) 23627 (92.5%)	32715 (92.6%) 23571 (92.3%)	32186 (91.1%) 23239 (91.0%)	<0.001 <0.001
	South Asian	258 (0.7%) 354 (1.4%)	301 (0.9%) 307 (1.2%)	314 (0.9%) 356 (1.4%)	447 (1.3%) 441 (1.7%)	754 (2.1%) 518 (2.0%)	
	Black	352 (1.0%) 322 (1.3%)	482 (1.4%) 323 (1.3%)	498 (1.4%) 365 (1.4%)	470 (1.3%) 348 (1.4%)	439 (1.2%) 350 (1.4%)	
	Other	1525 (4.3%) 1194 (4.7%)	1593 (4.5%) 1216 (4.8%)	1646 (4.7%) 1192 (4.7%)	1708 (4.8%) 1184 (4.6%)	1934 (5.5%) 1422 (5.6%)	
Body mass index (kg/m^2)		25.70 (4.34) 26.22 (3.46)	25.79 (4.34) 26.59 (3.46)	26.02 (4.43) 26.83 (3.60)	26.31 (4.60) 27.22 (3.74)	27.01 (5.06) 27.80 (4.08)	<0.001 <0.001
Lean body mass by impedance kg		43.63 (4.51) 61.66 (7.16)	43.72 (4.48) 62.38 (7.12)	43.98 (4.55) 62.99 (7.24)	44.24 (4.70) 63.70 (7.39)	44.87 (5.03) 64.96 (7.81)	<0.001 <0.001
Family history of CVD		20107 (56.7%) 13286 (51.7%)	19563 (55.1%) 12887 (50.2%)	19698 (55.5%) 12689 (49.4%)	19268 (54.3%) 12574 (49.0%)	19061 (53.7%) 12134 (47.2%)	<0.001 <0.001
Smoking status	**Never**	21512 (60.7%) 13761 (53.6%)	21776 (61.4%) 14017 (54.6%)	21809 (61.5%) 13993 (54.5%)	21467 (60.6%) 13643 (53.2%)	20913 (59.0%) 13312 (51.9%)	<0.001 <0.001
	Former	10803 (30.5%) 8581 (33.4%)	10604 (29.9%) 8637 (33.7%)	10621 (30.0%) 8534 (33.3%)	10781 (30.4%) 8758 (34.1%)	10961 (30.9%) 8717 (34.0%)	
	Current	3133 (8.8%) 3314 (12.9%)	3065 (8.6%) 3008 (11.7%)	3026 (8.5%) 3128 (12.2%)	3199 (9.0%) 3247 (12.7%)	3558 (10.0%) 3612 (14.1%)	
Townsend deprivation index		-1.59 (2.93) -1.47 (3.08)	-1.59 (2.90) -1.59 (2.99)	-1.54 (2.91) -1.53 (3.00)	-1.47 (2.96) -1.42 (3.02)	-1.25 (3.06) -1.21 (3.10)	<0.001 <0.001
MABP (mmHg)		94.67 (87.33, 103.00) 99.33 (92.00, 107.33)	95.67 (88.00, 104.00) 100.33 (93.33, 108.00)	96.33 (88.67, 104.67) 101.00 (94.00, 109.00)	97.00 (89.67, 105.67) 102.00 (94.67, 109.67)	98.33 (90.67, 106.67) 102.67 (95.67, 110.67)	<0.001 <0.001

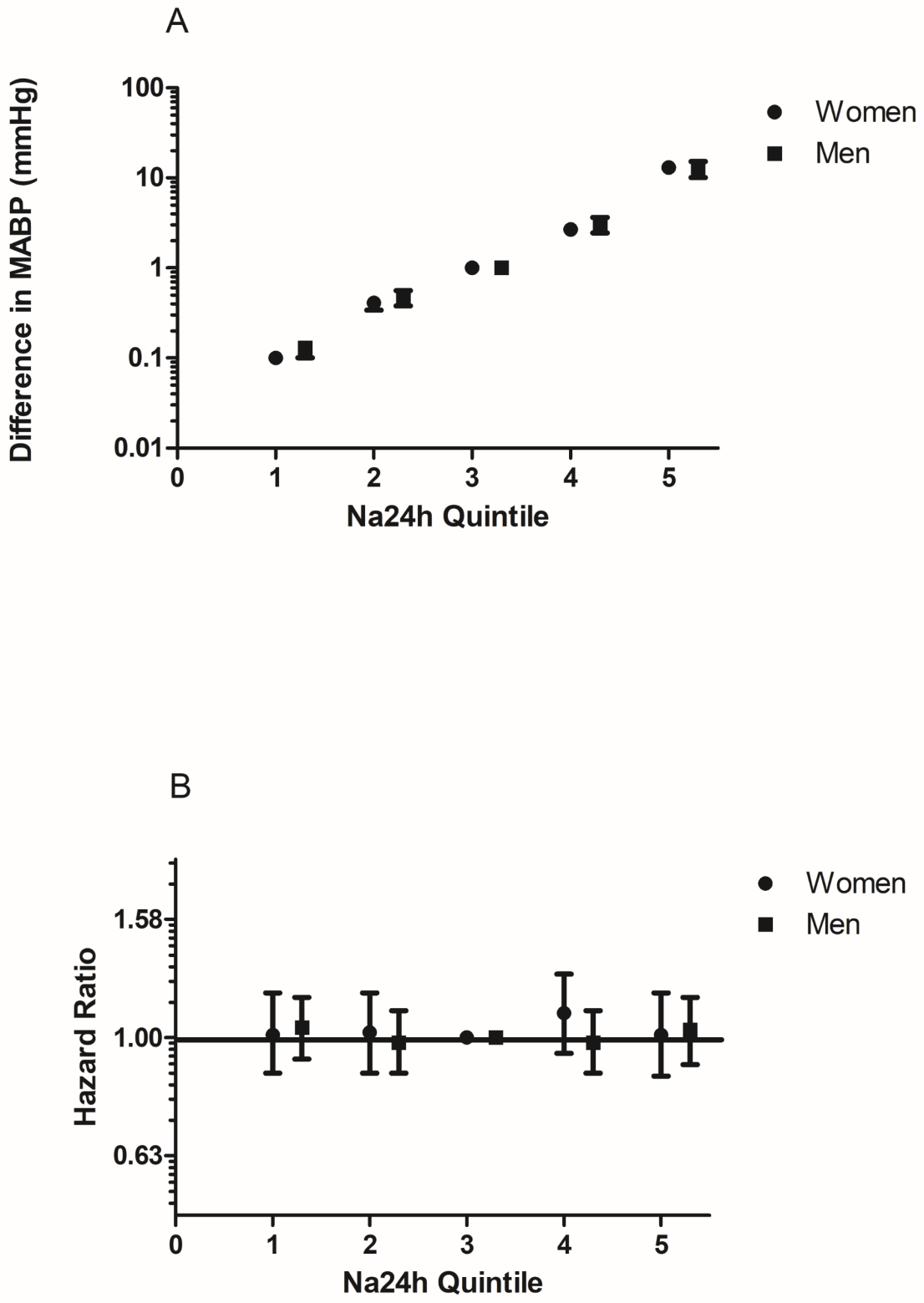
S3. Incidence rates for different disease outcomes per 100,000 person years among all UK Biobank participants, by quintile of eNa^{24h}.

Outcome	**Quintile of eNa^{24h}**	**Incidence rate per 100000 person years**	**Lower 95% Confidence Interval**	**Upper 95% Confidence Interval**
CVD	1	141.56	127.40	157.29
	2	127.81	114.41	142.78
	3	130.36	116.83	145.46
	4	139.00	125.02	154.54
	5	121.90	108.90	136.45
All-cause mortality	1	278.96	258.83	300.65
	2	215.96	198.35	235.13
	3	227.96	209.87	247.61
	4	203.92	186.87	222.52
	5	209.90	192.64	228.70
Myocardial Infarction	1	39.14	32.04	47.81
	2	39.50	32.37	48.19
	3	41.03	33.76	49.87
	4	36.45	29.65	44.82
	5	36.63	29.83	44.99
Haemorrhagic stroke	1	23.63	28.27	30.57
	2	23.19	17.89	30.07
	3	21.10	16.08	27.70
	4	28.34	22.42	35.82
	5	27.76	21.93	35.15
Ischaemic stroke	1	46.50	38.70	55.87
	2	31.75	25.43	39.64
	3	34.11	27.54	42.24
	4	31.59	25.30	39.44
	5	29.78	23.71	37.40

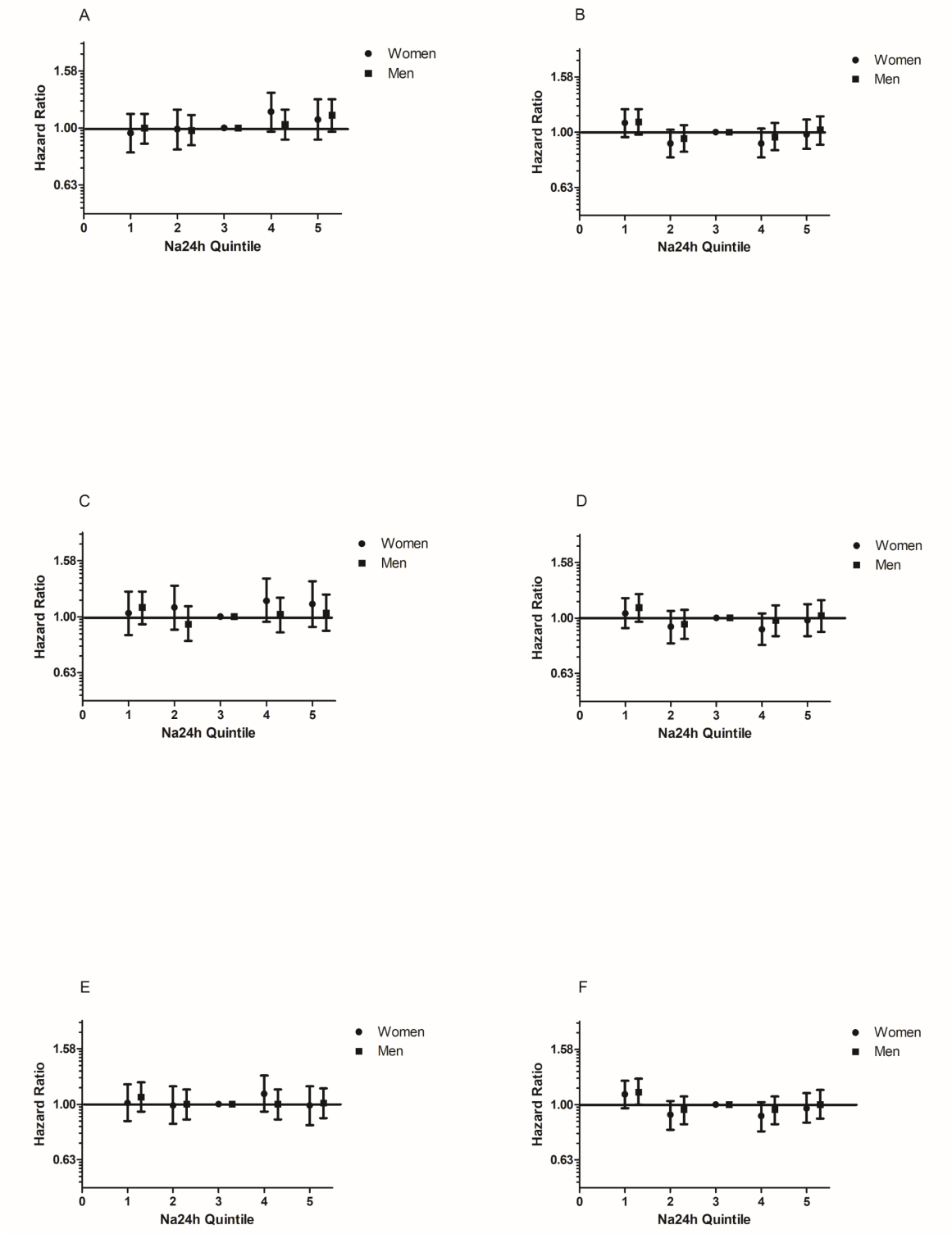
Supplementary figures



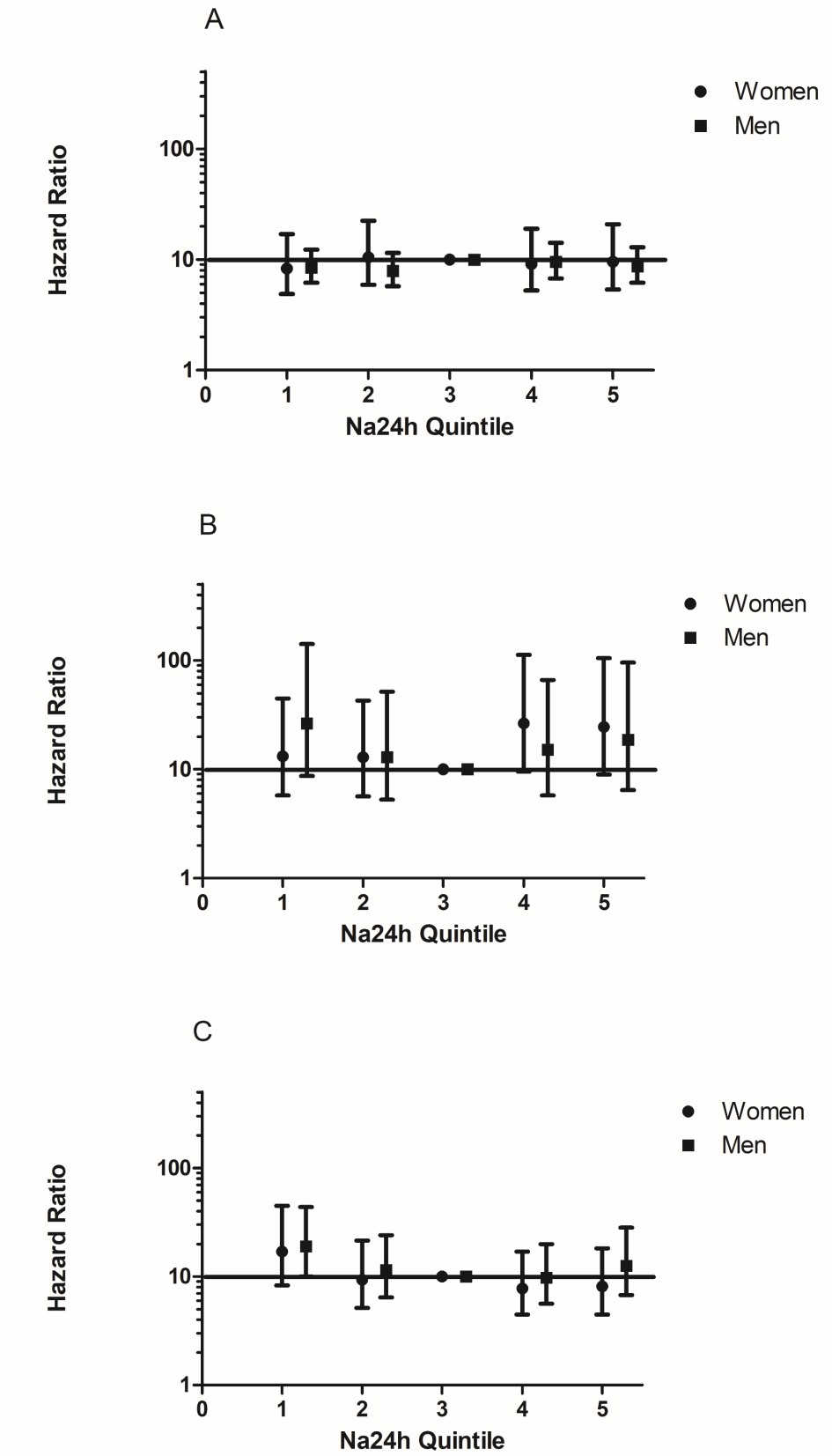
S1 Flow Diagram demonstrating generation of the cohort from UK Biobank for the whole cohort analyses (Table 1 and 2) and by excluding those with baseline CVD, DM or treated hypertension.



S2 Adjusted (including chronic kidney disease and statin use) linear regression analyses describing the association between MABP and sex-specific quintiles of eNa^{24h} (A) and adjusted hazard ratios of sex-specific quintiles of eNa^{24h} on the risk of CVD (B)



S3 Adjusted hazard ratios of sex-specific quintiles of eNa^{24h} on fatal or non-fatal cardiovascular disease events (A, C, E) or all-cause mortality (B, D, F), without adjustment for MABP (A, B, n=322624), after exclusion of the first two years of follow-up (C, D, n=322624), and after substituting lean body mass with continuous body mass index (E, F, n=322624). All plots exclude participants with baseline CVD, DM or treated hypertension.



S4 Adjusted hazard ratios of sex-specific quintiles of eNa^{24h} on the risk of myocardial infarction (A) and haemorrhagic stroke (B), and ischaemic stroke (C) in all participants (n=322624). All plots exclude participants with baseline CVD, DM or treated hypertension.