Estimated salt intake and risk of atrial fibrillation in a prospective community-based cohort

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Abstract. Wuopio J, Orho-Melander M, Ärnlöv J, Nowak C (Mora County Hospital, Mora; Clinical Research Center, Falun; Lund University, Malmö; Dalarna University, Falun; Karolinska Institutet, Huddinge, Sweden). Estimated salt intake and risk of atrial fibrillation in a prospective community-based cohort (Original). *J Intern Med* 2021; **289**: 700–708.

Introduction. Hypertension predisposes to atrial fibrillation (AF) – a major risk factor for ischaemic stroke. Since a high dietary salt consumption is associated with hypertension, we investigated the association between urinary sodium excretion as a marker for dietary sodium intake and risk of new-onset AF in community-dwelling adults.

Method. The UK Biobank includes 40- to 69-year-old British residents recruited 2006–2010. Participants were divided into sex-specific quintiles according to 24-hour sodium excretion estimated based on spot samples with the Kawasaki equation. We excluded participants with AF at baseline. Cox regression adjusted for cardiovascular risk factors was used to assess associations with risk of AF, using the third quintile as reference.

Results. A total of 257 545 women and 215 535 men were included. During up to 10 years' follow-up, 2221 women and 3751 men were diagnosed with AF. There was a tendency for an increased risk of AF in the lowest and highest quintiles of estimated daily salt intake in both women and men. In the fully adjusted model, significant associations were seen amongst men in the lowest and highest quintiles of sodium excretion (hazard ratio, HR_{Qv1}, 1.20; 95% CI, 1.08–1.32, $P < 0.001$, and HR_{Qv5} 1.15, 95% CI, 1.03–1.27, $P = 0.011$).

Conclusion. We found evidence for a U-shaped association between estimated daily salt intake and AF risk amongst men. A suggestive J-shaped association in women was not statistically confirmed, but analyses were likely underpowered. Our results suggest that above a certain physiological minimum level progressively higher salt intake is associated with increasing risk of AF.

Keywords: atrial fibrillation, blood pressure, dietary salt, hypertension, Kawasaki formulae, sodium excretion.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance. It is a major risk factor for arterial thromboembolism and is associated with a fivefold increase in risk of stroke and a twofold increased risk for all-cause mortality [1, 2]. Arterial hypertension is an important precursor and comorbidity in AF, further raising thromboembolic risk and complicating treatment of AF [3-5]. Increased dietary salt intake is associated with raised blood pressure [6-9]. There is, however, an ongoing debate about how much daily salt intake contributes to cardiovascular risk [10, 11], and

whether even too little salt in a typical diet can have adverse consequences [12-16]. To our knowledge, there is only one large prospective study assessing the association between estimated daily salt intake and risk of new-onset AF [17]. No sizable, community-based study on AF risk using urinary sodium excretion to estimate daily salt intake has been reported. Evidence-based dietary guidance on recommended salt intake is crucial for the prevention of hypertension and AF, and representative, contemporary studies are needed.

Here, we aim to study the association between estimated daily salt consumption and 10-year risk

of new-onset AF in the UK Biobank sample of middle-aged adults without a history of AF at baseline.

Methods

Study material and population

We used the data from the UK Biobank (project ID 42176), a longitudinal cohort study of about 500 000 British residents. The participants were recruited between April 2006 and December 2010 and underwent detailed assessments at one of 22 centres in Scotland, England and Wales. Data from the UK Biobank can be obtained for legitimate research purposes in the interest of public health upon application (https://www.ukbiobank.ac.uk/register-apply/). All participants have provided written informed consent and the UK Biobank has received ethical approval from the relevant institutions in the UK. Participants with AF at baseline (self-reported in nurse-led interview, or hospital episode statistics diagnosis ICD-9: 427/ICD-10: I48 before baseline assessment) were excluded ($n = 4,216$), as were participants who had withdrawn consent ($n = 1,290$). A detailed description of the cohort and assessment is available elsewhere [18]. Participants provided midstream spot urine samples, and we used urine sodium and creatinine measurements to estimate 24-hour dietary sodium intake. Measurements were carried out using Beckman Coulter assays on a Beckman Coulter Ltd AU4500 analyser. The enzymatic method was used to measure creatinine levels (analytical range 88 to 44200 umol L^{-1}). The ISE ion selective electrode method was used to measure urinary sodium levels (analytical range 10 to 400 mmol L^{-1}). Ethnicity was coded as European or non-European. Hypertension was included as a binary variable based on self-reported diagnosis, hypertension medication and/or resting assessment centre blood pressure above 140/90 mmHg. Current tobacco smoking status was based on self-report. Body mass index (BMI) was defined as body weight in kg divided by height in m^2 and included as a continuous variable. Alcohol abuse was defined as self-reported in nurse-led interview or hospital diagnoses according to ICD-9 (303, 303.9, 305.0, 357.5, 571.0) or ICD-10 (F10, G62.1, G72.1, K70). Diabetes was defined as self-reported diabetes, diabetes medication and/or hospital diagnosis (ICD-9: 250, ICD-10: E11). Total plasma cholesterol was measured with an enzymatic Beckman Coulter assays in a Beckman Coulter AU5800 analyser. Kidney function

(estimated glomerular filtration rate, eGFR) was estimated using the CKD-EPI formula based on plasma creatinine (assessed by enzymatic Beckman Coulter assay), age, and ethnicity. We used the Kawasaki formula to estimate 24-h sodium excretion [19]:

Predicted 24-hour sodium excretion (mg day^{-1}) = $16.3 \times \sqrt{X_{Na}}$

Where,

$$X_{Na} = \frac{SMU_{Na}}{SMU_{Cr}} \times (PreCr - excretion)$$

SMU_{Na} (mmol L^{-1}); SMU_{Cr} (mg L^{-1}).

Male: PreCr-excretion (mg day^{-1}) = $-12.63 \times$ Age + $15.12 \times$ Weight + $7.39 \times$ Height (cm) – 79.9

Female: PreCr-excretion (mg day^{-1}) = $-4.72 \times$ Age + $8.58 \times$ Weight + $5.09 \times$ Height (cm) – 74.5

To minimize the impact of outliers, we excluded participants with an estimated urinary sodium excretion deviating by more than five standard deviations from the sex-specific mean. Participants were divided into five quintiles according to sex-specific estimated sodium excretion.

Outcomes

Atrial fibrillation or atrial flutter was defined as ICD-10 codes I48 (I48.0–I48.9) in the hospital admissions codes.

Statistical analyses

As previous studies [20, 21] consistently reported sex-specific differences in salt intake and its relationship with cardiovascular physiology, we carried out separate analyses in women and men. Adjusted Cox proportional hazards models were used to estimate hazard ratios for incident AF in each sex-specific quintile of salt intake, using the third (middle) quintile as a reference as there may be an increased risk of AF associated with both, too little and too much salt intake [22]. We used time since baseline assessment as time scale and participants were followed until the first diagnosis of AF or censoring at the last date of follow-up (31st March 2017) or death. We assessed three different Cox models adjusting for the following variables:

A Age, ethnicity (European/non-European)

B Age, ethnicity, hypertension (diagnosis, self-reported, on treatment, systolic blood pressure and diastolic blood pressure >140/90 mmHg),

C Age, ethnicity, hypertension, smoking (yes/no), BMI (kg m^{-2}), type 2 diabetes (yes/no), alcohol abuse (yes/no), total cholesterol (mmol L^{-1}), eGFR (mL min^{-1} 1.73 m^{-2})

The proportional hazards and linearity assumptions were assessed using Schoenfeld and Martingale residuals plots. We report unadjusted p-values and define Bonferroni-corrected statistical significance as $P < 0.05/6$ (three models for each gender). Analyses were carried out in R version 3.3, and the code is available on request from the corresponding author.

Results

We included 257 545 women and 215 535 men in the study. Baseline characteristics per quintile of estimated salt intake are shown in Table 1. During a mean follow-up of 8.2 ± 1.0 years (median 8.2, max. 10 years), 2221 women and 3751 men received a first diagnosis of AF. The overall incidence rate was 21.4 per 10 000 person-years in men and 10.6 per 10 000 person-years in women. Sex-specific hazard ratios are shown in Figure 1 and Table 2. Amongst women, there was a tendency for a J-shaped association in the minimally adjusted model A, with the lowest AF risk in the second quintile and the highest risk in the fifth quintile. These associations, however, were not statistically significant and further attenuated with progressive adjustment for cardiovascular risk factors (Table 2).

Amongst men, both the lowest and the highest quintiles of estimated salt intake were associated with increased risk of AF, regardless of adjustment for cardiovascular risk factors (Table 2). In the fully adjusted model, there was a U-shaped relationship, with the highest risk of AF at the extremes of estimated daily salt intake (hazard ratios and 95% confidence intervals 1.20 [1.08–1.32], $P = 5 \times 10^{-4}$, and 1.15 [1.03–1.27], $P = 0.011$, for the first and fifth quintiles of estimate salt intake, respectively). Sensitivity analyses with additional adjustment for urinary potassium concentration and following the exclusion of participants with impaired kidney function (eGFR < 60; 2.26% of

female and 2.33% of male participants) did not affect the results materially with regards to effect size, direction and statistical significance.

Discussion

In this prospective observational study of 473 080 community-dwelling British adults, urinary sodium excretion – a proxy for dietary salt intake – had a U-shaped association with risk of new-onset AF during up to 10 years of follow-up in men. That is, both very low and very high estimated daily sodium intake were associated with raised AF risk. Amongst women, we found a tendency for a J-shaped association in the model adjusted for age and ethnicity only (e.g. a slightly raised risk on the lowest, and a more strongly raised risk of AF in the highest quintile of sodium excretion), which was, however, no longer evident after full adjustment for established cardiovascular risk factors.

To our knowledge, we report the largest study to date in the general population assessing the association between estimated daily salt intake and risk of AF. It is also the first large study to use urinary sodium excretion to estimate salt intake instead of relying on self-report via questionnaires or food diaries, which can be biased [23]. A smaller Finnish study by Pääkkö et al. has addressed the same question [17]. Using questionnaires to estimate salt intake in 716 persons, they found that higher self-reported sodium intake was associated with a raised risk of AF over 19 years' follow-up. Our study in a much larger sample and 10 years of follow-up confirms the association between high salt intake and raised AF risk. The association between very low sodium intake and AF risk in men in our study was not reported by Pääkkö et al. [17]. Possible explanations could be the different sample sizes, target populations, follow-up periods and assessment methods (self-report versus spot urine measurements).

In a study from 2013, Marketou et al. [24] studied the association between sodium and potassium excretion and premature supraventricular and ventricular contractions in 255 persons with well-controlled hypertension. They found a weak correlation (r = 0.2) between sodium excretion and premature ventricular contractions but did not find a correlation with premature supraventricular contractions [24]. This cardiac electrical instability associated with sodium excretion is at least in part in line with our results.

Table 1. *Baseline characteristics according to quintile (Qv) of estimated salt intake amongst women (W) and men (M). Unless indicated otherwise, mean and standard deviation are shown*

	Qv1	Qv2	Qv3	Qv4	Qv5
N					
W	51 442	51 546	51 563	51 565	51 429
M	42 919	43 102	43 161	43 238	43 115
Atrial fibrillation, *n* (%)					
W	502 (1.0%)	399 (0.8%)	416 (0.8%)	438 (0.9%)	466 (0.9%)
M	868 (2.0%)	730 (1.7%)	663 (1.5%)	729 (1.7%)	761 (1.8%)
AF incidence rate per 10 000 person-years					
W	12	9.5	9.9	10.4	11
M	25.1	20.9	18.9	20.7	21.5
Estimated 24-hour sodium excretion, g d^{-1}					
W	2.4 (0.4)	3.2 (0.2)	3.8 (0.2)	4.3 (0.2)	5.4 (0.7)
Age, years					
M	2.8 (0.5)	3.78 (0.19)	4.40 (0.17)	5.05 (0.21)	6.26 (0.76)
W	57.5 (7.9)	56.6 (7.9)	56.2 (7.9)	56.0 (8.0)	55.4 (8.1)
M	58.6 (7.8)	57.4 (8.0)	56.7 (8.2)	56.0 (8.2)	54.9 (8.3)
Hypertension, *n* (%)					
W	24 257 (47.2%)	23 979 (46.6%)	24 929 (48.5%)	26 453 (51.4%)	29 637 (57.6%)
M	26 053 (60.7%)	25 674 (59.8%)	26 320 (61.3%)	27 460 (64.0%)	29 690 (69.2%)
eGFR, mL min^{-1} 1.73 m^{-2}					
W	87.0 (14.2)	89.4 (13.2)	90.9 (12.9)	92.2 (12.5)	94.8 (12.2)
M	86.6 (14.0)	88.9 (13.0)	90.4 (12.8)	92.0 (12.6)	94.7 (12.7)
Current smokers, *n* (%)					
W	4539 (8.8%)	4438 (8.6%)	4318 (8.4%)	4564 (8.9%)	4909 (9.5%)
M	5462 (12.7%)	4999 (11.6%)	5137 (12.0%)	5342 (12.5%)	5795 (13.5%)
Type 2 diabetes, *n* (%)					
W	2221 (4.3%)	1928 (3.7%)	1890 (3.7%)	2202 (4.3%)	2993 (5.8%)
M	3547 (8.3%)	3069 (7.2%)	3040 (7.0%)	3270 (7.6%)	4404 (10.3%)
BMI, kg m^{-2}					
W	26.6 (4.9)	26.5 (4.8)	26.7 (4.9)	27.2 (5.1)	28.3 (5.8)
M	27.1 (4.0)	27.3 (3.9)	27.6 (4.0)	28.0 (4.1)	29.0 (4.8)
LDL-C, mmol L^{-1}					
W	3.6 (0.9)	3.6 (0.9)	3.7 (0.9)	3.6 (0.9)	3.6 (0.9)
M	3.4 (0.9)	3.5 (0.9)	3.5 (0.9)	3.5 (0.8)	3.5(0.9)
HDL-C, mmol L^{-1}					
W	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.3)
M	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
Triglycerides, mmol L^{-1}					
W	1.6 (0.9)	1.5 (0.8)	1.5 (0.9)	1.6 (0.9)	1.6 (0.9)
M	1.9 (1.1)	1.9 (1.1)	2.0 (1.1)	2.0 (1.2)	2.1 (1.2)
eGFR < 60, *n* (%)					
W	2001 (3.9%)	1185 (2.3%)	910 (1.8%)	726 (1.4%)	550 (1.1%)
M	1662 (3.9%)	1016 (2.4%)	806 (1.9%)	640 (1.5%)	561 (1.3%)

Table 1 (*Continued*)

	Qv1	Qv2	Qv3	Qv4	Qv5
Lipid treatment, *n* (%)					
W	5958 (11.6%)	4945 (9.6%)	4747 (9.2%)	5012 (9.7%)	5951 (11.6%)
M	9743 (22.7%)	8251 (19.2%)	7954 (18.5%)	7767 (18.1%)	8776 20.4%)
Systolic blood pressure, mmHg					
W	134.7 (19.7)	135.6 (19.8)	136.9 (20.1)	138.4 (20.3)	140.7 (20.9)
M	140.6 (18.9)	141.8 (18.3)	142.4 (18.2)	143.7 (18.2)	145.6 (18.4)
Diastolic blood pressure, mmHg					
W	79.4 (10.5)	79.8 (10.4)	80.5 (10.4)	81.2 (10.5)	82.6 (10.6)
M	82.4 (10.8)	83.3 (10.5)	83.8 (10.4)	84.7 (10.3)	85.9 (10.4)

In another study in the UK Biobank, Zanetti et al. [25] found an inverse relationship between the ratio of urinary sodium and urinary potassium (uNA/uK) and AF, which stands somewhat in contrast to our results. However, disturbance in the potassium balance is far more arrhythmogenic than fluctuances in the sodium homeostasis [26], which could explain some of the discrepant results. Another explanation is that we used the Kawasaki formula instead of the unadjusted ratio between uNa/uK [19]. Even though associated with some biases, we believe that relating urinary spot sample concentrations of sodium to the concentration of urinary creatinine gives a more reliable, concentration-adjusted estimate than isolated spot measurements of two urinary electrolytes. Interestingly, Zanetti et al. [25] found positive effects between raised uNa/uK and increased blood pressure in both, observational analysis and Mendelian randomization studies. Another UK Biobank study [27] reported suggestive causal effects between raised urinary sodium excretion and increased diastolic blood pressure, as well as between raised urinary potassium and lower systolic blood pressure in Mendelian randomization analysis. However, the authors caution about large inconsistencies in their results depending on which Mendelian randomization methods was used [27]. Altogether, it appears that genetically predicted urinary sodium excretion could be a causal risk factor for raised blood pressure. Any causal effect on AF, however, remains uncertain.

High blood pressure is one of the most important risk factors for AF [4,28], and excessive sodium intake is strongly associated with raised blood pressure [6, 7], including in the UK Biobank [8]. The mechanisms by which hypertension contributes to AF are not fully elucidated, but probably involve structural and functional changes in the cardiac atria followed by electrophysiological disturbances [4, 28]. High sodium intake, in turn, leads to raised blood pressure mediated mainly by raised intracellular osmolality and the release of antidiuretic hormone from the posterior pituitary. Chronically high sodium intake upregulates brain-derived neurotrophic factor in the supraoptic vasopressin neurones, which in turn diminishes the physiological capacity of baroreceptors to respond to raised blood pressure with an inhibition of antidiuretic hormone release [29]. In our study, additional adjustment for hypertension at baseline assessment did not alter the association between sodium intake and AF risk substantially, suggesting that hypertension was not a major confounder. However, the limited number of AF cases in our comparatively 'healthy' sample [30] did not allow us to stratify analyses by, for example, hypertension status, and studies with higher power and longer follow-up are needed to dissect out the role of hypertension in the relationship between sodium intake and AF. Further adjustments for other cardiovascular risk factors attenuated the association in men somewhat, implying that these risk factors together explain some of interplay between sodium intake and AF.

Apart from effects through hypertension and conventional cardiovascular risk factors, the association between salt intake and AF risk might be driven by sodium-induced prolongation of the cardiac QT-interval. A prolonged QT-interval has been shown to predict the development of AF, and longer QTc intervals increase the heart's vulnerability to ventricular dysrhythmias [31]. Prolonged QTc intervals also reflect the atrial effective

Table 2. *Hazard ratios for incident atrial fibrillation according to quintile (Qv) of estimated salt intake. Model A adjusts for age and ethnicity, model B adjusts for age, ethnicity and hypertension; and model C adjusts for age, ethnicity, hypertension, smoking, BMI, diabetes mellitus, ongoing alcohol abuse, total cholesterol and eGFR-creatinine*

|	Qv1	Qv2	Qv3	Qv4	Qv5
Women					
A	1.03 (0.91–1.16) $P = 0.674$	0.89 (0.78–1.02) $P = 0.086$	ref	1.03 (0.91–1.17) $P = 0.632$	1.14 (1.01–1.29) $P = 0.039$
B	1.04 (0.90–1.18) $P = 0.554$	0.91 (0.79–1.04) $P = 0.172$		1.05 (0.92–1.19) $P = 0.492$	1.12 (0.99–1.28) $P = 0.079$
C	1.05 (0.92–1.19) $P = 0.466$	0.93 (0.81–1.07) $P = 0.313$		1.03 (0.90–1.18) $P = 0.638$	1.02 (0.89–1.16) $P = 0.767$
Men					
A	1.16 (1.05–1.27) $P = 0.003$	1.03 (0.93–1.14) $P = 0.558$		1.12 (1.02–1.24) $P = 0.023$	1.26 (1.14–1.39) $P = 5.0 \times 10^{-6}$
B	1.17 (1.06–1.29) $P = 0.002$	1.05 (0.95–1.17) $P = 0.313$		1.11 (1.00–1.23) $P = 0.056$	1.25 (1.13–1.39) $P = 1.9 \times 10^{-5}$
C	1.20 (1.08–1.32) $P = 5.0 \times 10^{-4}$	1.08 (0.98–1.20) $P = 0.136$		1.09 (0.98–1.21) $P = 0.112$	1.15 (1.03–1.27) $P = 0.011$
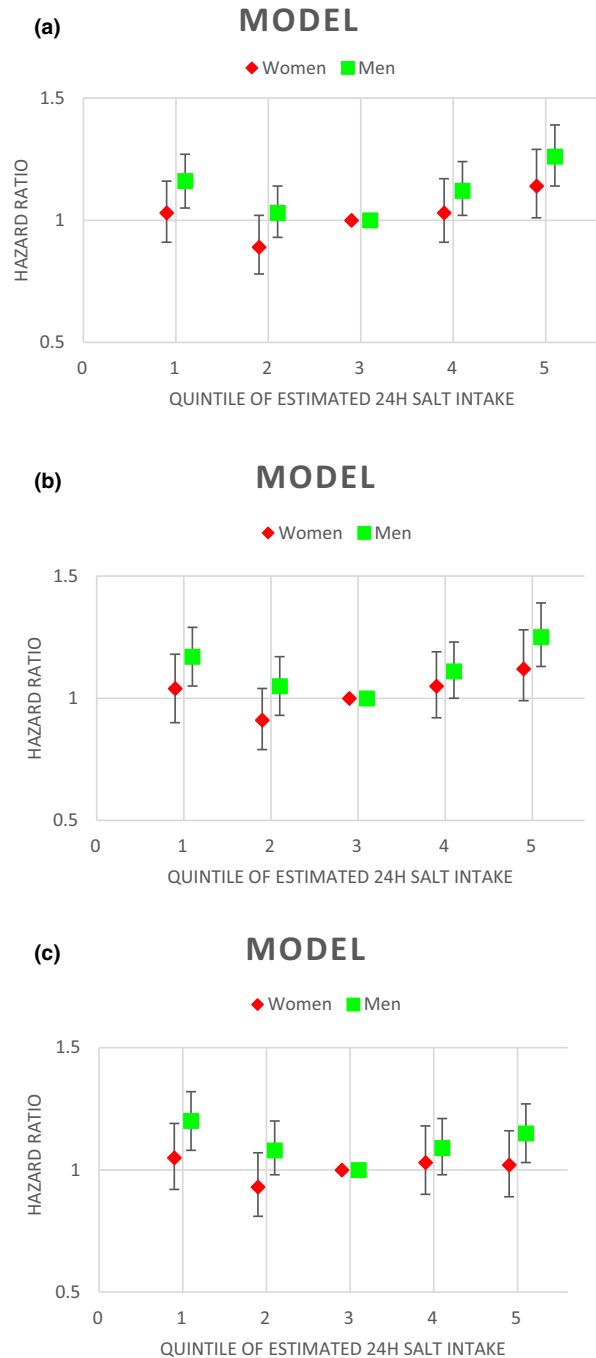
Figure 1 *Hazard ratios for incident atrial fibrillation according to quintile (Qv) of estimated salt intake. Model A adjusts for age and ethnicity, model B adjusts for age, ethnicity and hypertension; and model C adjusts for age, ethnicity, hypertension, smoking, BMI, diabetes mellitus, ongoing alcohol abuse, total cholesterol and eGFR-creatinine.*

refractory period (AERP) [32], and a prolonged AERP is associated with an increased risk of AF [33]. A high sodium intake may affect QT-interval length. In one study, participants given a high sodium diet for seven days had prolonged QT-intervals and QT-dispersion (the difference between the longest and shortest QT-interval) reflecting electrical heterogeneity and electrical instability [34]. Potential mechanisms could comprise changes in the arterial wall, such as endothelial dysfunction, arterial stiffness, excess sympathetic tone and left ventricular hypertrophy. We were unable to assess the role of QTc length in our study, as ECG data are currently only available for a sub-sample of the UK Biobank participants.

In our study, an increased risk of AF was associated with a very low estimated salt intake amongst men. A possible explanation could be a higher sympathetic tone associated with a low intake of salt. For example, a low intake of salt is associated with a slightly higher heart rate [16], possibly driven by increased plasma levels of norepinephrine [14]. This increased sympathetic tone is in turn associated with AF [35]. A low salt intake also stimulates the renin-angiotensin-aldosterone system (RAAS) [14], which has also been associated with AF [36]. However, this association has only been established in people with hypertension or heart failure, rendering RAAS activation unlikely as an explanation.

Clinical implications

Dietary recommendations from international medical societies include a low salt consumption with the aim of reducing cardiovascular risk [37, 38]. Currently, these guidelines do not include a lower limit or 'minimum' recommended salt intake, which has led to debate [39-42] since some studies have pointed to a possibly increased cardiovascular risk with a very low salt intake [13, 22]. Our study provides additional tentative evidence for an increased risk of AF associated with a low sodium consumption, at least in men, which is in contrast to the current dietary guidelines were a lower limit is lacking. Our results are otherwise in line with the previously reported association between high salt intake and raised cardiovascular risk. Hypertension did not appear to be a major explanatory factor for the link between high salt intake and raised AF risk in our study. A U-shaped or J-shaped association with AF risk is biologically appealing, as hyponatremia is associated with

excess mortality and morbidity [43, 44] and J-shaped associations with cardiovascular risk are common for electrolytes (for example calcium [45] and potassium [46].

Strengths and limitations

Strengths of our study include the large sample size, in-depth phenotyping of participants, 10 years of follow-up, and using actual sodium excretion to estimate salt intake instead of relying on self-report. Limitations include a possible 'healthy volunteer' bias [30], limited power and unknown generalizability to non-European populations. Most participants were under 60 years of age and the incidence of AF was low. There is also a risk of bias in the estimation of sodium excretion based on spot urine samples with the Kawasaki formula, which may overestimate sodium excretion compared with 24-hour urine sodium excretion [47]. The Kawasaki formula might also provide biased results in the lower sodium excretion range [48]. However, a previous study in the UK Biobank that also applied the Kawasaki equation to estimate salt intake found the expected associations with blood pressure [8]. Given the downsides of using dietary questionnaires and self-reported salt intake, we believe the spot urine sample Kawasaki formula provides a reasonable proxy for estimating actual salt intake in our epidemiological study.

Conclusion

We found a U-shaped association between estimated dietary sodium intake and risk of AF amongst men. A suggestive J-shaped association in women was not statistically confirmed, but analyses were likely underpowered. The result of an increased risk of AF with a very low salt intake does not support lowering salt intake to an absolute minimum level, but remains to be confirmed in independent studies.

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Author contribution

Jonas Wuopio: Conceptualization (equal); Methodology (equal); Validation (equal); Writing-original draft (lead); Writing-review & editing (equal). **Marju Orho Melander:** Validation (supporting); Writing-

review & editing (supporting). **Johan Ärnlöv:** Conceptualization (equal); Methodology (equal); Supervision (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Christoph Nowak:** Conceptualization (equal); Data curation (lead); Formal analysis (lead); Methodology (equal); Resources (lead); Software (equal); Supervision (equal); Validation (equal); Writing-original draft (supporting); Writing-review & editing (equal).

Conflicts of interest

The authors declare that no conflicts of interest exist.

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