ESC European Society of Cardiology

European Heart Journal Open (2023) **3**, 1–8
https://doi.org/10.1093/ehjopen/oead024

ORIGINAL ARTICLE
Coronary artery disease

The association between sodium intake and coronary and carotid atherosclerosis in the general Swedish population

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Received 3 September 2022; revised 11 February 2023; accepted 8 March 2023; online publish-ahead-of-print 30 March 2023

Handling Editor: Maciej Banach

Editorial for this article: *Eur Heart J Open 2023*; https://doi.org/10.1093/ehjopen/oead025

Aims

A high intake of salt raises blood pressure and the risk of cardiovascular disease. Previous studies have reported on the association between salt intake and carotid stenosis, but the association with coronary atherosclerosis has not been reported. Therefore, this project aimed at studying the association between salt intake and both carotid and coronary atherosclerosis in a contemporary community-based cohort.

Methods and results

Estimated 24-h sodium excretion (est24hNa) was calculated by the Kawasaki formula for participants of two sites (Uppsala and Malmö) of the Swedish Cardiopulmonary bioImage Study, who underwent a coronary computed tomography ($n = 9623$) and measurement of coronary artery calcium score (CACS, $n = 10\,289$). Carotid ultrasound was used to detect carotid plaques ($n = 10\,700$). Ordered logistic regression was used to calculate odds ratios (OR) per 1000 mg increase in est24hNa. We also investigated potential J-formed associations using quintiles of est24hNa. Increased est24hNa was associated with increased occurrence of carotid plaques [OR: 1.09, $P < 0.001$, confidence interval (CI): 1.06–1.12], higher CACS (OR: 1.16, $P < 0.001$, CI: 1.12–1.19), and coronary artery stenosis (OR: 1.17, $P < 0.001$, CI: 1.13–1.20) in minimal adjusted models. Associations were abolished when adjusting for blood pressure. When adjusting for established cardiovascular risk factors (not including blood pressure), associations remained for carotid plaques but not for coronary atherosclerosis. There was no evidence of J-formed associations.

Conclusion

Higher est24hNa was associated with both coronary and carotid atherosclerosis in minimal adjusted models. The association seemed mainly mediated by blood pressure but to some degree also influenced by other established cardiovascular risk factors.

The work was performed at the Department of Neurobiology, Care Sciences and Society (NVS), Family Medicine and Primary Care Unit, Karolinska Institute, Huddinge, Sweden And Center for Clinical Research Dalarna, Uppsala University, Sweden

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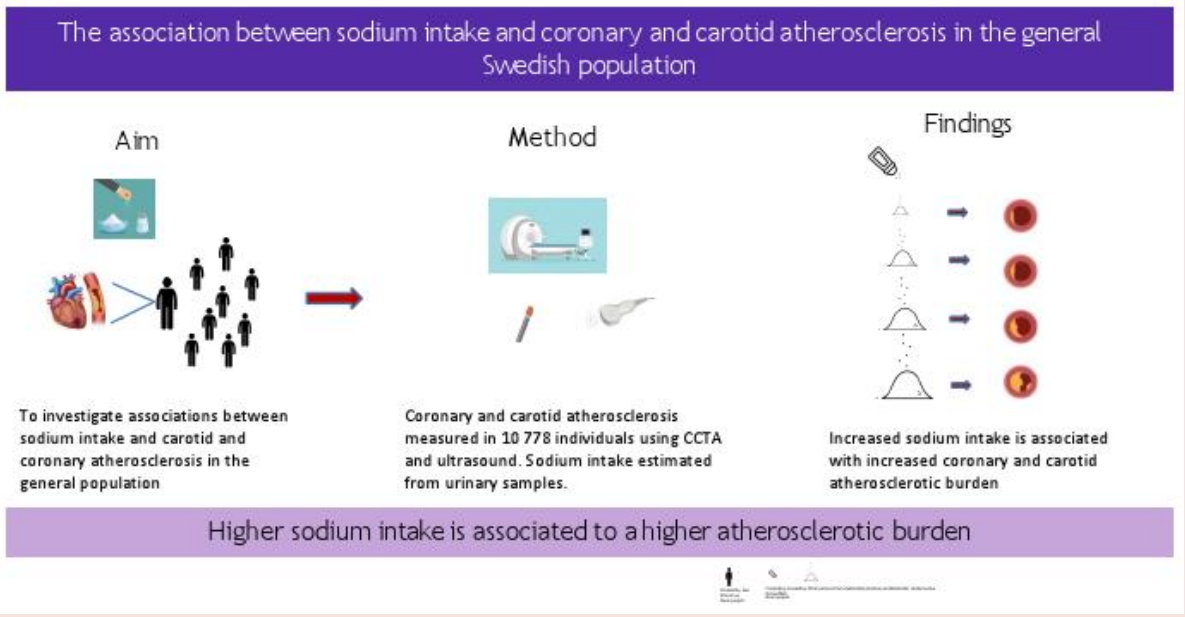
Graphical Abstract



Keywords Sodium • Salt • Hypertension • Cardiovascular disease • Atherosclerosis

Introduction

Previous studies have concluded that a diet with a high intake of salt raises blood pressure[1–5] and the risk for cardiovascular disease (CVD)[6,7] and mortality.[8,9] Efforts to favour behavioural changes to reduce salt intake are effective[10] and have been shown to reduce blood pressure.[11] The underlying pathological processes that cause CVD starts decades prior to clinically overt disease,[12] and a better understanding of these processes in order to improve disease prevention could have a major public health impact. Several previous studies have reported association between salt intake with various markers for vascular damage such as arterial stiffness, endothelial dysfunction, and inflammation.[13,14] Some have investigated associations with manifest peripheral atherosclerosis,[15–17] but whether salt intake associates with coronary atherosclerosis has not been reported previously. The Swedish Cardiopulmonary bioImage Study (SCAPIS) is a unique cohort from the general population in Sweden with detailed characterization of atherosclerosis in the coronary arteries as well as in the carotid arteries.[18] We therefore aimed at studying the association between estimated sodium intake and both carotid and coronary atherosclerosis in this cohort. As a second step, we also investigated these associations in individuals with normal blood pressure or without known atherosclerotic CVD.

Method

We used the Swedish cohort SCAPIS,[18] a population-based study of 30 154 participants in the age range of 50–64 years. The participants were recruited through mail invitations sent out to a random sample within the target population. Each participant visited the screening centre during 2–3 days, and the examinations included blood and urine samples, questionnaires, clinical examinations, and computed tomography imaging. The biological samples were collected at the time of examination and were frozen in −80°C until analysis. The study is being conducted at six university hospitals with approximately 5000 participants in each node. There was a possibility for each node to add on investigations to the core program, making use of the available extensive infrastructure. The baseline investigations were completed in 2018. We used the Uppsala ($n = 5033$) and Malmö ($n = 6140$) nodes for this study where we had analysed urinary sodium and creatinine in addition to the core protocol (*Figure 1*).

The SCAPIS-multicentre study was approved by the ethical review board at Umeå University, Sweden (number 2010–228–31 M), and the analysis of urine samples was approved by the ethical boards at Uppsala University and Lund University, Sweden (number EPN Uppsala University 2016/387 and 2018/315; Lund university 2016/1031).

Coronary atherosclerosis

The coronary atherosclerotic burden was measured with coronary computed tomography angiography (CCTA) and coronary artery calcium score (CACS) according to Agatston (Somatom Definition Flash, Siemens Medical Solutions). Details regarding cardiac imaging have previously been described.[18]

Individual readers assessed 18 segments of coronary arteries for stenosis. The degree of luminal obstruction in the artery was judged visually as above or below 50%. We defined the finding of a stent in a vessel or coronary artery bypass graft (CABG) as a stenosis significant stenosis >50%. 'Calcium blooming', where dense calcifications made it impossible for the reader to evaluate, was defined as a non-significant stenosis <50%. Missing values, for example, due to technical problems, were excluded. The outcome was defined as categorical ordinal values of 'no stenosis', 'non-significant stenosis (<50%)', and 'significant stenosis (>50%)'.

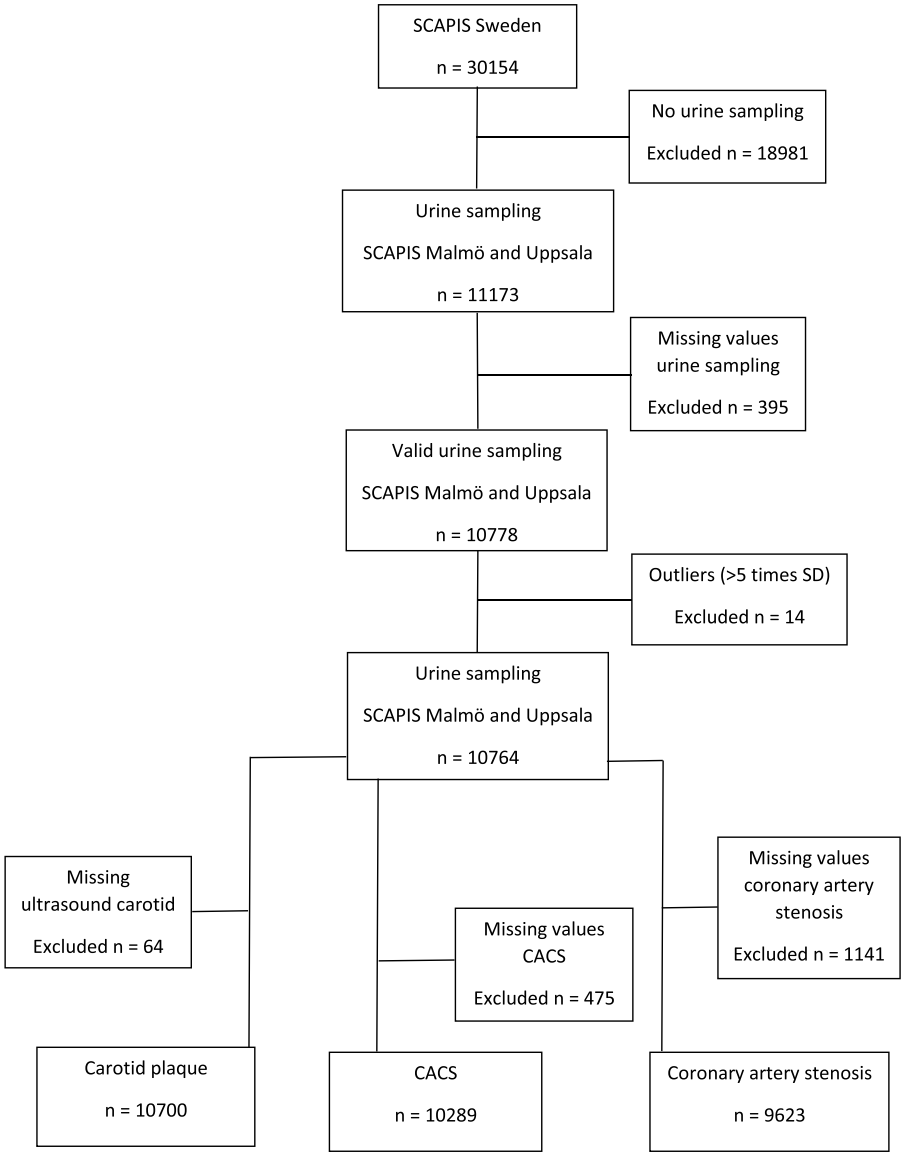


Figure 1 CONSORT flow chart of the included and excluded participants from Swedish Cardiopulmonary bioImage Study.

Non-contrast enhanced images were used to measure the total amount of calcifications in each artery and were summed to a total CACS according to international standards.[19] We divided the sum from CACS into five categories usually used in clinical practise (0, 1–9, 10–99, 100–399, and >399).

Carotid atherosclerosis

The carotid arteries of the participants were examined with ultrasound (Siemens Acuson S2000 ultrasound scanner equipped with a 9L4 linear transducer) at inclusion, and the images were examined online. Several different operators performed the examination at each site. A significant plaque was defined as a focal protrusion[20] of >50% or 0.5 mm of the surrounding intima media thickness or a thickness >1.5 mm measured from the intima–lumen interface to the media–adventitia interface. The result was provided as categorical ordinal values of 'no plaque', 'plaque in one vessel', and 'plaque in both vessels'. Participants with missing values were excluded from this part of the study.

Blood pressure

Systolic and diastolic brachial artery blood pressure was obtained by automatic measurements in the supine position after a 5-min rest. The average value of two measurements from the arm with the highest mean blood pressure was used. Use of antihypertensive medication during the last 2 weeks was self-reported in questionnaires from the examination.

Estimation of sodium intake

The urinary samples were collected as a second morning void at the time of examination. Sodium intake was estimated by calculating the estimated 24-h sodium excretion (est24hNa) through the Kawasaki formula.[19]

$$\text{est24hNa(mg/day)} = 22.99 \times 16.3\sqrt{X_{Na}}$$

where

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

SMU_{Na} (mmol/L),
SMU_{Cr} (mg/L),
Male: PreCr-excretion (mg/day) = −12.63 × age + 15.12 × weight + 7.39 × height (cm) − 79.9,
Female: PreCr-excretion (mg/day) = −4.72 × age + 8.58 × weight + 5.09 × height (cm) − 74.5.

To minimize the impact of outliers, we excluded participants with an est24hNa deviating by more than five standard deviations from the mean.

As a validation of the result from the Kawasaki formula, we compared quintiles of est24hNa with sodium calculated from a food frequency questionnaire.[21]

Statistical analysis

Participants with missing values for urinary analyses (sodium and/or creatinine) were excluded ($n = 395$) (*Figure 1*). One participant had missing value for weight that was imputed using the median value prior to calculating est24hNa with the Kawasaki formula. Missing values for covariates were assumed to be missing at random and imputed using multiple imputation with 20 imputations and the result pooled according to 'Rubin's rule'.[22] For the categorical data (e.g. smoking, diabetes mellitus, and 'on antihypertensive medication'), we used multiple imputation with a ordered logistic regression model for smoking and a multinomial logistic regression model for diabetes mellitus an antihypertensive medication. For the continuous data, we used a linear regression model. For participants with missing values for diabetes (from the questionnaire), a valid measurement of haemoglobin A1c (HbA1c) ≥ 48 mmol/L or fasting *p*-glucose ≥ 7 mmol/L was classified as having diabetes mellitus ($n = 14$).

In our primary analyses, we modelled est24hNa as a continuous variable (expressed per 1000 mg increase). However, since some previous studies have detected a J-formed curve, showing an association with increasing risk for CVD in both high and low intake of salt, we also divided the sample into quintiles of est24hNa and compared the atherosclerosis measures in the lowest quintile to the others.

We used regression analyses to study the association between systolic and diastolic blood pressure and est24hNa. Since the data for the categories of CACS (cCACS), carotid plaque, and CCTA are ordinal, we used ordered logistic regression analysis to analyse association between est24hNa and the different levels of manifest atherosclerosis. Multivariable adjustments were made in three models:

A. Site (node where participants were investigated, Uppsala or Malmö).
B. Site + age + sex.
C. Site + age + sex + (resting systolic blood pressure + resting diastolic blood pressure + self-reported hypertension medication)—as we made the a priori assumption that blood pressure levels would be the most important factor mediating associations between salt intake and atherosclerosis.

As an extra analysis, we added a multivariable adjustment (Model D) to Model B to investigate the impact from potential confounders/mediators other than blood pressure.

D. Body mass index (BMI = weight/length^2), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), diabetes mellitus (doctor diagnosed or self-reported), smoking (current, ex-smoker, and never), and estimated glomerular filtration rate (eGFR calculated from the Lund–Malmö formula).

We performed interaction analyses for site, age, and sex and also stratified for sex since previous studies have reported sex-specific differences in salt intake and cardiovascular risk.[23–25]

To further study the effect of pre-existing diseases and medications, we did three subgroup analyses. First, we excluded participants with hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, self-reported antihypertensive medication, and self-reported diagnosis of hypertension). Second, we excluded participants with known atherosclerosis [self-reported CABG or percutaneous coronary intervention (PCI), myocardial infarction, peripheral artery disease, and stroke]. Third, we excluded participants with antihypertensive medications and medications for heart failure to rule out possible effect of diuretics on the results.

STATA (StataCorp LLC) version 17 was used to perform the analyses.

Results

A total of 10 778 participants with valid results for the urinary data were included in the study. Fourteen participants deviated more than five SD from the mean of est24hNa and were excluded, leaving a total of 10 764 participants for further analysis (*Figure 1*). Baseline characteristics of the participants are presented in *Table 1* and *Table 2*. Women had a lower est24hNa compared to men (mean value 2925 mg vs. 3642 mg; $P < 0.001$). Systolic and diastolic blood pressure, BMI, prevalence of diabetes mellitus, HDL, and eGFR all increased, and cholesterol decreased with increasing quintiles of est24hNa (*Table 1*). There was a positive, significant association between est24hNa and systolic blood pressure (Model A, coefficient 1.74, $P < 0.001$) and diastolic blood pressure (Model A, coefficient 0.92, $P < 0.001$).

Carotid plaques

A total of 10 700 participants had valid results for the carotid ultrasound (64 participants excluded due to missing values) (*Figure 1*). The odds ratio (OR) increased with increasing quintile of est24hNa with no sign of a J-formed association (see Supplementary material online, *Table S1*). There was a significant association between higher est24hNa and burden of carotid plaques in the minimal adjusted Model A (site) (OR: 1.09, $P < 0.001$) and Model B (site, age, and sex) (OR: 1.03, $P < 0.001$). When further adjusting for blood pressure (Model C), the significant association was abolished (*Table 3*).

When adding established cardiovascular risk factor (without blood pressure) to Model B (Model D), the association between carotid plaques and est24hNa remained statistically significant (OR: 1.04; CI: 1.01–1.07; $P = 0.017$).

Coronary artery calcium score

A total of 10 289 participants had valid results for measurement of CACS ($n = 475$ excluded) (*Figure 1*). There was no sign of a J-formed association (see Supplementary material online, *Table S1*) between the est24hNa and cCACS. A significant association between est24hNa and cCACS was seen in the minimal adjusted Model A (OR: 1.16, $P < 0.001$) as well as Model B (OR: 1.038, $P = 0.016$). When adjusting for blood pressure (Model C), the significant association was abolished (*Table 3*).

When adding established cardiovascular risk factor (without blood pressure) to Model B (Model D), the association between est24hNa and cCACS was lost (OR: 1.01; CI: 0.98–1.04; $P = 0.643$).

Coronary artery stenosis

A total of 1141 participants were excluded due to missing values in the readings of the CCTA images (included $n = 9623$) (*Figure 1*). The OR in

Table 1 Baseline characteristics of the participants in quintiles (Q1–Q5) of increasing estimated 24-h sodium excretion with standard deviations ($n = 10\,764$)

	Total	Q1	Q2	Q3	Q4	Q5
est24hNa (mg/24 h)	3267 (1314)	1640 (425)	2507 (185)	3131 (185)	3822 (232)	5235 (951)
Women ($n = 5627$)	2925 (1175)	1631 (426)	2496 (185)	3120 (187)	3804 (229)	5130 (850)
Men ($n = 5137$)	3642 (1355)	1663 (422)	2524 (185)	3145 (183)	3837 (233)	5284 (990)
Age (years)	57.6	57.6	57.6	57.6	57.5	57.5
Systolic blood pressure (mmHg)	124 (16)	122 (16)	123 (16)	124 (16)	126 (16)	128 (16)
Diastolic blood pressure (mmHg)	76 (10)	75 (10)	75 (10)	76 (10)	77 (10)	78 (10)
Hypertension %	30.6	28.5	28.5	27.3	30.9	37.9
BMI (kg/m^2)	27.2 (4.5)	26.0 (4.3)	26.6 (4.4)	26.9 (4.3)	27.6 (4.3)	28.6 (4.8)
Cholesterol (mmol/L)	5.6 (1.1)	5.7 (1.1)	5.6 (1.1)	5.6 (1.0)	5.5 (1.0)	5.4 (1.1)
LDL (mmol/L)	3.6 (0.9)	3.6 (1.0)	3.6 (0.9)	3.6 (1.0)	3.6 (0.9)	3.5 (0.9)
HDL (mmol/L)	1.6 (0.5)	1.7 (0.5)	1.6 (0.5)	1.6 (0.5)	1.5 (0.4)	1.5 (0.4)
eGFR (mL/min/1.73 m^2)	78 (10)	76 (10)	77 (10)	78 (10)	78 (10)	80 (10)
Diabetes mellitus (yes %)	5.1	4.3	4.9	5.2	4.5	6.7
Smoking status (%)						
Never	48	52	56	54	52	
Former	37	34	32	34	35	
Current	15	14	12	12	13	

Table 2 Estimated 24-h sodium excretion in the different groups of atherosclerosis [mean (standard deviation)]

		est24hNa (mg/24 h)
Carotid plaques		
	None	3178 (1340)
	One	3292 (1340)
	Two	3365 (1362)
CACS		
	0	3167 (1229)
	1–9	3341 (1352)
	10–99	3355 (1351)
	100–399	3527 (1502)
	>399	3566 (1533)
Coronary stenosis		
	None	3164 (1220)
	<50%	3380 (1383)
	>50%	3574 (1450)

the quintiles of est24hNa showed a linear pattern with no sign of a J-formed association (see Supplementary material online, *Table S1*). There was a significant association between higher est24hNa and risk of coronary artery stenosis in the minimal adjusted Model A (OR: 1.17, $P < 0.001$) and Model B (OR: 1.04, $P = 0.020$). After adjusting for blood pressure (Model C), the association was abolished (*Table 3*).

When adding established cardiovascular risk factor (without blood pressure) to Model B (Model D), there was no longer an association between est24hNa and coronary artery stenosis (OR: 1.01; CI: 0.98–1.04; $P = 0.643$).

Stratified and subgroup analyses

Associations between est24hNa and carotid plaques, CACS, and coronary artery stenosis were similar as the original result when excluding participants with antihypertensive medication or medication for heart failure ($n = 2106$; OR: 1.08, 1.15, and 1.15, respectively; $P < 0.001$), hypertension ($n = 3404$; OR: 1.07, 1.16, and 1.16, respectively; $P < 0.001$) or known pre-existing atherosclerotic disease ($n = 356$; OR: 1.09, 1.16, and 1.17, respectively; $P < 0.001$).

When the analyses were stratified with respect to sex, the significant associations between est24hNa and carotid plaques, cCACS, and coronary artery stenosis were only seen among men in Models A and B (see Supplementary material online, *Table S2*), but there was no statistically significant effect modification by sex ($P > 0.13$ for all outcomes).

The association between est24hNa and the different indices of carotid and coronary atherosclerosis was similar when only including participants that had data on all three indices ($n = 9623$, data not shown).

We noticed minor violations against the proportional odds assumption for a few covariates in the separate studies. We did a sensitivity analysis using a generalized ordered logistic regression model that did not alter the results.

Discussion

Main findings

The main finding from this study is that increased sodium excretion had a significant association with carotid atherosclerosis as well as atherosclerotic stenosis in the coronary arteries and overall coronary artery calcification reflected by CACS in minimal adjusted models (site, age, and sex). As the association was abolished when adjusting for blood pressure, our interpretation is that the increase in blood pressure from sodium intake, even below the level that currently defines arterial hypertension, is an important factor that mediates the interplay between salt intake and the atherosclerotic process. As we observed an association in individuals with normal blood pressure, one possible explanation for these findings is that the detrimental pathological

Table 3 The odds ratio for the association between estimated 24-h sodium excretion (per 1000 mg) and finding of atherosclerosis (95% confidence intervals and *P*-values)

Study	Model A	*P*	Model B	*P*	Model C	*P*	Model D to Model B	*P*
Carotid plaques[a]	1.09 (1.06–1.12)	<0.001	1.03 (1.00–1.06)	0.028	1.00 (0.98–1.03)	0.815	1.04 (1.01–1.07)	0.017
CACS[b]	1.16 (1.12–1.19)	<0.001	1.04 (1.01–1.07)	0.016	1.01 (0.98–1.04)	0.663	1.01 (0.98–1.04)	0.643
Coronary artery stenosis[c]	1.17 (1.13–1.20)	<0.001	1.04 (1.01–1.07)	0.020	1.01 (0.97–1.04)	0.750	1.01 (0.98–1.04)	0.643

[a]Findings of carotid plaques with ultrasound in 'none', 'one', or 'two' carotid vessels.
[b]Coronary Artery Calcification Score divided into groups 0, 1–9, 10–99, 100–399, and >399.
[c]Findings of coronary artery stenosis (lumen obstruction >50%, <50%, no stenosis) with coronary computed tomography angiography.

processes begin already prior to the development of hypertension. However, due to the observational, cross-sectional design of the study, no causal relationships can be established. Adjusting the result for several other well-known risk factors for arteriosclerosis (adding Model D to Model B) also abolished the results for CACS and coronary artery stenosis, indicating confounding or other pathways salt mediates its harmful effects. Interestingly, this was not the case for carotid plaques, which still yielded a significant result after multifactor adjustment. Stratifying for sex showed higher est24hNa among men, and the associations were only seen among men (although there was no significant interaction by sex).

Comparison with previous studies

Previous epidemiological studies have led to the consensus that a high intake of salt increases the risk for atherosclerosis,[26] which is in line with the results from this study. Yet, as far as we know, this is the first study reporting the association between sodium excretion and sub-clinical coronary atherosclerosis measured with computed tomography in a general population. Since some previous epidemiological studies and meta-analyses have suggested a J-formed curve,[8,25,27–34] where the cardiovascular risk also increases with a low salt intake, a heated debate has taken place in the last decade.[35–37] However, we did not find evidence of a J-formed association in this study. The lowest occurrence of atherosclerosis, both carotid and coronary, was found in the lowest quintiles of sodium excretion (Q1) and then increasing in a linear fashion.

Three previous studies have addressed the question of carotid atherosclerosis and salt intake or sodium excretion. Dai *et al.*[38] found a positive association between findings of carotid stenosis and increasing urinary–sodium–creatinine ratio in 3290 healthy adults. Mazza *et al.*[17] found a positive association between sodium intake (combination of 7-day register and 24-h recall) and carotid atherosclerosis in 108 elderly women. Both these studies are in line with our results. In a study by Tsirimiagkou *et al.* in 2021,[16] the probability of finding femoral plaques showed a reverse association to salt intake (24-h recall) among women but not in men. Similar results were found for carotid plaques, although not statistically significant. This contrasts with our results where we found a positive association to carotid plaques, particularly in men. In the same study, measured arterial stiffness seemed positively associated with salt intake. The authors argue that there may be different pathological processes for low and high salt intake, explaining their apparently divergent findings.

Biological explanations

There is a consensus that a high salt intake raises the blood pressure.[36] The reason behind this is not fully known in its details, but theories include altered salt handling by the kidneys, vascular dysfunction, sympathetic nervous dysfunction, and immune system involvement.[39] The association between high blood pressure and the atherosclerotic process is well-established, and high blood pressure is considered the leading cause of the development of CVD.[40] Salt's ability to raise blood pressure is the most commonly used explanation of how salt exerts its pathological processes on our vessels, and in this study, the blood pressure seemed to be the most important mediating factor to the association between salt intake and atherosclerosis. But other studies have concluded that salt may have a direct blood pressure-independent detrimental effect on our vessels, leading to increased arterial stiffness and endothelial dysfunction.[14,41] These findings could explain the results from other epidemiological studies where the association between salt intake and CVD remains significant after careful adjustments for blood pressure. The reason for this is not fully understood, but reduced availability to nitric oxide through the production of reactive oxygen species as a response to salt intake could explain endothelial dysfunction induced by salt loading.[41] Independent of blood pressure, salt intake can induce cascades of molecular signalling, ending up in the production of transforming growth factor β (TGF-β) that promotes reduced vascular compliance. Nitric oxide also serves as negative feedback of TGF-β.[42] Evidence also suggests damaging of the glycocalyx of extracellular matrix, initiating cell stiffening.[14] Residual confounding due to the inherent variability of blood pressure levels over time may also be an explanation.

When we included several known risk factors for CVD in the multivariable model (but not blood pressure), there was still a significant association between salt intake and carotid, but not coronary arteriosclerosis. The explanation for these divergent findings could be that the female participants have a higher prevalence of arteriosclerosis in the carotids than in the coronary arteries, more comparable to men, so that adjustment for sex does not have such a pronounced effect in the analyses using carotid plaques as the outcome. The reason for this is not clear since the coronary and carotid atherosclerotic processes share the same pathological processes and risk factors,[43] and as far as we know, this should not differ between sexes. One speculation could be of technical reason since the carotids were investigated by ultrasound.

There are, however, possible explanations for the overall sex difference. For example, evidence suggests that women handle sodium load differently from men by a more active renal endothelin-1 natriuretic system,[44] which gives a greater ability to maintain sodium homeostasis. There are also well-known sex differences in atherosclerotic burden, where women have a known lower prevalence, possibly due to protective effect of oestrogen before menopause.[45] This has also previously been reported in SCAPIS.[46]

Strengths and limitations

The greatest strength of this study is the contemporary cohort with detailed characterization of the study participants. The measurements of coronary atherosclerosis and carotid plaques are state-of-the-art, and considering this, the number of participants is high.

A limitation is that we used the Kawasaki formula to estimate 24-h sodium excretion from spot urinary sodium samples. The Kawasaki

formula has been not only validated[47,48] but also criticized.[37,49] In the debate on whether a J-formed curve between sodium intake and cardiovascular risk truly exists, the Kawasaki formula has often been blamed for creating biased results.[36,50,51] One popular theory has been that the constituent variables in the formulae by itself have associations to the cardiovascular outcome and therefore create the J-curve.[36] It is, however, hardly proved. When the participants in this study are divided into quintiles according to est24hNa, the blood pressure increases with increasing salt intake (*Table 1*). The same goes for BMI, which has an established positive association with salt intake[52–54] (*Table 1*). We also used dietary sodium data from food frequency questionnaires to plot against est24hNa. The result confirmed that reported sodium intake was increasingly higher from the lowest to the highest quintile of est24hNa (see Supplementary material online, *Figure S1*). Also, we did not find any J-formed curve in this material rendering it unlikely that the formula itself has caused the J-formed associations in previous studies. We, therefore, believe that the Kawasaki formula is good enough to estimate salt intake at a population level. However, we do not think the Kawasaki formula is accurate enough to conclude 'safe levels' of salt intake in milligrams on an individual level.

Other limitations include unknown generalizability to other populations, residual confounding, and the observational, cross-sectional design of the study where causal relationships cannot be established.

Conclusion

In this study from the general Swedish population, est24hNa was associated to both cardiac and carotid atherosclerosis in minimal adjusted models, even in participants with normal blood pressure and without known CVD. The association seemed mainly mediated by blood pressure (even in the normal range) but to some degree also influenced by other established risk factors.

Ethical statement

The SCAPIS-multicentre study was approved by the ethical review board at Umeå University, Sweden (number 2010–228–31 M), and the add-on collection of urine was approved by the ethical board at Uppsala University and Lund University, Sweden (number EPN Uppsala University 2016/387 and 2018/315; Lund University 2016/1031).

Lead author biography

Jonas Wuopio is a specialist in internal medicine, Mora county hospital, Sweden, and a doctoral researcher at Karolinska Institute, Department of Neurobiology and Care Sciences and Clinical Research Center, Falun, Sweden, Uppsala University. Research interest includes molecular epidemiology, markers for predicting future disease, and the relationship between sodium and the atherosclerotic process.

Data availability

The personal data in SCAPIS are of sensitive nature and therefore cannot be made freely available. However, by contacting the corresponding author or study organization (www.scapis.org), sharing of data can be arranged for reproducing study results and procedures.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

The main funding body of The Swedish CArdioPulmonary bioImage Study (SCAPIS) is the Swedish Heart-Lung Foundation. The study is also funded by the Knut and Alice Wallenberg Foundation, the Swedish Research Council and VINNOVA (Sweden's Innovation agency), the University of Gothenburg and Sahlgrenska University Hospital, Karolinska Institutet and Stockholm County Council, Linköping University and University Hospital, Lund University and Skåne University Hospital, Umeå University and University Hospital, and Uppsala University and University Hospital.

Conflict of interest: J.Ä. declares that he has received lecturing fees from AstraZeneca and Novartis and has served on advisory boards for AstraZeneca and Boehringer Ingelheim, unrelated to the present study. None of the other authors have any conflicts of interest to declare.

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