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Wuopio J, Ling YT, Orho-Melander M, Engström G, Ärnlöv J. The association between sodium intake and coronary and carotid atherosclerosis in the general Swedish population. Eur Heart J Open. 2023 Mar 30;3(2):oead024.

What We Know, Think We Know, or Are Starting to Know

Of the exposure-outcome relationships that we have previously covered, sodium and cardiovascular disease [CVD] has most certainly been given its due. The backlog includes:

- **Research Lecture**: Sodium, Measurement Error, and the Unicorn-Shaped Curve.
- **Deepdive**: Of Salt and Stroke Risk: A SSaSSy Tale.
- **Deepdive**: Is Low Salt Intake Associated with Increased CVD Risk?
- **Deepdive**: Lower Sodium Intakes & Cardiovascular Disease Risk: a "J-Shaped Curve"?
- **Deepdive**: DASH Diet & Blood Pressure: Only Important in People with Hypertension?
- **Article**: Sodium & Cardiovascular Disease – When Good Science Meets Bad Thinking.

The importance of this topic relates to the strength of the relationship between salt in the diet and CVD outcomes, but to the fact that it has been trendy even in evidence-based nutrition to suggest that salt and sodium intake are not really a nutrient of concern beyond individuals with hypertension.

However, this line of reasoning ignores the temporality of this relationship, and the strength of the links in the causal chain. First, the data is overwhelming that hypertension is a causal risk factor for CVD, exhibiting a strong dose-response linear relationship with events and mortality [1,2]. Second is the linear relationship between sodium and blood pressure, which is clear when using multiple 24 h sodium excretion measurements* [see ***Geek Box** below for further details] [3,4]. Finally, the strong dose-response and linear relationship between sodium and CVD outcomes has crystallised with more recent evidence [5–7].

In the most recent synthesis of evidence from studies that estimated sodium intakes from multiple repeated 24 h sodium measurements, the risk of CVD events was 18% higher for each 1,000mg/d increase in sodium [5].

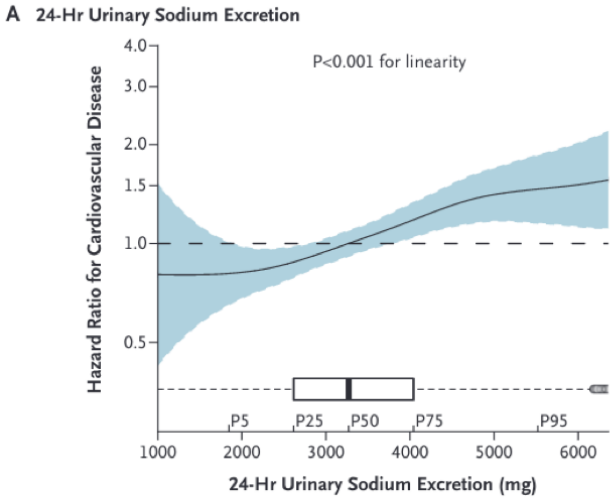


***Figure** from Ma et al. [5] indicating the linear increase in CVD risk with increasing sodium excretion levels, synthesising evidence from six studies that used multiple 24 h sodium measurements.*

Now, with all that said the chain of causation would appear to be sodium>hypertension >CVD, with the assumption that this chain is explained primarily by effects of elevated blood pressure on vascular function [8]. However, it is known that salt exerts other effects on the cardiovascular system, for example increased left ventricular size of the heart [i.e., a thickening of the wall of the main pumping chamber of the heart] [9].

What about atherosclerosis? We typically relate atherosclerosis to blood lipids, given LDL-cholesterol is the causal risk factor for this process and related CVD risk [10–12]. However, there have been some suggestions that dietary sodium may be associated with atherosclerosis [13]. The present study investigated this association in a Swedish cohort.

*Geek Box: Measuring Sodium in Nutrition Research

It is critical to understand sodium measurements in nutrition research in order to contextualise some of the findings in different studies. Sodium is a nutrient that tends to correlate quite poorly from dietary assessment methods such as food frequency questionnaires and other recall methods.

However, over up to 95% of ingested sodium is excreted in urine, which means that urinary sodium excretion has the potential to be an excellent biomarker for dietary intake of sodium. But this potential comes with a catch; to estimate actual daily 24 h intake of sodium would require collecting all urine excreted by an individual on that day. This is clearly burdensome on both investigators and participants, as well as costly to research.

Not only is this burdensome, however, there is also another catch, which is that sodium excretion is also highly variable from day-to-day in the same individual, i.e., within-person variation. This means that if only one single 24 h urine collection is taken, it will be unrepresentative of average [mean] intake in that individual. With one single 24 h urine collection estimates of sodium intake can vary by between 30–50% between individuals in a study.

As a result, researchers have employed other methods. For example, a "spot sample" is where the investigators take a single urine sample at a random point during the day – this will also vary widely from the true intake for that day, and therefore introduce a significant measurement error.

From such single "spot samples", researchers have attempted to construct mathematical formulas for estimating 24 h intake. Two widely used formulas are the Tanaka and Kawasaki formulas, respectively. However, these formulas are generally inaccurate and produce overestimations of risk at lower levels of estimated sodium and underestimations of risk at higher levels of estimated sodium.

The issue of sodium measurement is at the heart of the apparent controversy in the literature on sodium and CVD. To increase the reliability of estimates of sodium intake, multiple 24 h collections are required, with three in the same person being desirable as a minimum. To visualise and hear further discussion of the importance of the method of measuring sodium, I recommend you watch this Research Lecture.

The Study

The present study was a cross-sectional analysis from the Swedish Cardiopulmonary bioImage Study [SCAPIS], a population-based study of men and women aged between 50–64yrs. The participants in this study have undertaken clinical measurements of atherosclerosis of both the coronary and carotid arteries, including coronary artery calcification [CAC]. Blood pressure was also measured at a clinical examination.

Sodium intake was measured by taking a single sample in the morning, and by using the Kawasaki formula to estimate 24 h sodium intakes in each participant. The estimates from the Kawasaki formula were also compared to sodium intakes assessed using a food frequency questionnaire.

The study analysed the associations between estimated 24 h sodium and the presence of carotid artery plaques, coronary artery stenosis [i.e., a narrowing of the artery from fatty plaque build-up], and CAC scores. The associations between estimated 24 h sodium and both systolic and diastolic blood pressure were also analysed. The outcomes were presented as odds ratios [OR] with 95% confidence intervals [95% CI].

Results: 10,764 participants were included in the final analysis, of which 52% were women. Average estimated 24 h sodium intake was 2,925mg and 3,642mg in women and men, respectively.

***Association Between Sodium and Blood Pressure*:** Estimated 24 h sodium was significantly associated with a 1.74mmHg higher systolic and 0.92mmHg higher diastolic blood pressure.

***Association Between Sodium and Carotid Artery Plaque*:** After adjusting for blood pressure, there was no association between estimated 24 h sodium per 1,000mg and the presence of plaque in the carotid arteries [OR 1.00, 95% CI 0.98 – 1.03].

Adjusting for other CVD risk factors [e.g., blood cholesterol levels, BMI, smoking, etc.], but not including blood pressure, there was 4% higher odds [OR 1.04, 95% CI 1.01 – 1.07] for the presence of plaque in the carotid arteries per 1,000mg estimated sodium [discussed further under ***Interesting Finding***, below].

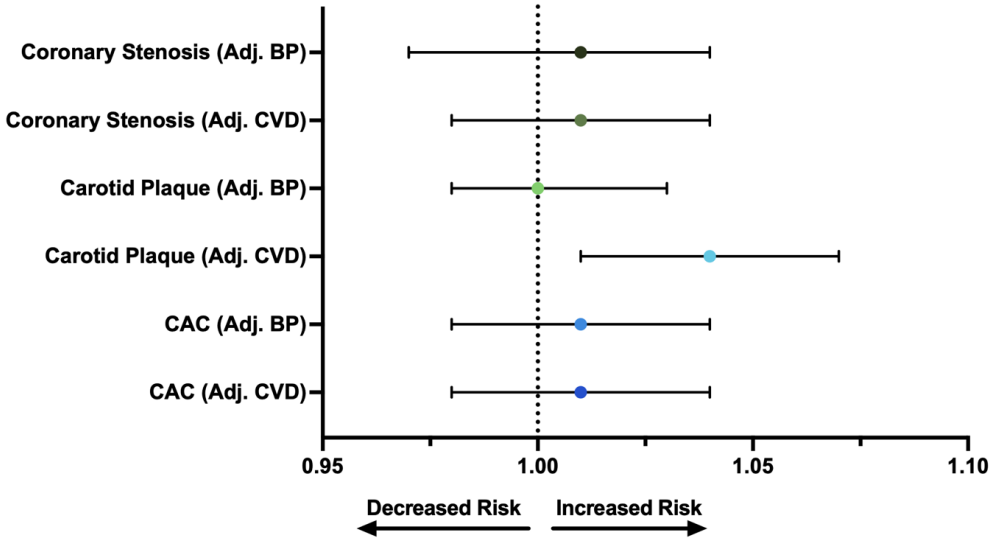
***Association Between Sodium CAC Scores*:** Estimated 24 h sodium was not significantly associated with CAC scores in any analysis, either adjusting for blood pressure or other CVD risk factors minus blood pressure [OR 1.01, 95% 0.98 – 1.04 for both analyses].

***Association Between Sodium and Coronary Artery Stenosis*:** Estimated 24 h sodium was not significantly associated with the presence of coronary artery stenosis in any analysis, either adjusting for blood pressure [OR 1.01, 95% 0.97 – 1.04] or other CVD risk factors minus blood pressure [OR 1.01, 95% 0.98 – 1.04].

The **figure below** illustrates the risk estimates for each of the main outcomes in the present study. "Adj. BP" = the analysis that adjusted for blood pressure only. "Adj. CVD" = the analysis that adjusted for other CVD risk factors minus blood pressure. The circles in each line represent the odds ratio, and the bars either side represent the confidence intervals.

Bear in mind that the scale of the X-axis was expanded to make the graph more presentable, however, these risk estimates are almost all in the range of noise; the odds ratios are 1.01 for four outcomes [i.e., 1% higher odds] and 1.00 for one outcome, while the confidence intervals are spread across 1.00.

All confidence intervals are also all >0.95 and <1.05 [except the carotid plaque analysis adjusted for CVD risk factors], indicating no clear signal for an association between estimated 24 h sodium and these markers of atherosclerosis.



The Critical Breakdown

Pros: The aims and objectives of the study were clearly stated. The major strength of the study is the assessment of atherosclerosis using imaging [computed tomography angiography for coronary artery stenosis and CAC scores] and ultrasound [for carotid artery plaque], both accurate methods. This allowed for precise characterisation of subclinical markers of atherosclerosis. Given the requirements for such measures, the same size of ~10,000 participants is commendable for a cohort study. The study was balanced for sex among participants. The study attempted to consider the potential for the Kawasaki formula estimates to result in a "J-shaped curve" by also analysing estimated sodium levels in quintiles [fifths], in addition to the main analysis which analysed sodium per 1,000mg increases [discussed further under ***Key Characteristic***, below].

Cons: The major limitation of the study is the use of estimated 24 h sodium intake based off a single urinary sodium "spot sample" and mathematical formula, and validation against a food frequency questionnaire [see ***Key Characteristic***, below]. The study is also cross-sectional in design, and as such only provides a snapshot in time and does not provide us with any insight into the temporal relationship between sodium intakes and atherosclerosis progression. The findings for blood pressure are presented unadjusted for age or sex, both factors which may influence blood pressure levels. The analysis by quintiles of estimated 24 h sodium was not presented with any confidence intervals, which limits the interpretation of this data. Similarly, the subgroup analyses the study conducted were not presented with confidence intervals, rendering their interpretation relatively meaningless.

Key Characteristic

If you've read the ***Geek Box** above, you probably could sense that this was coming; the estimates of sodium intake using the Kawasaki formula do not leave us with confidence in the accuracy of the sodium measures, and consequently in the associations from the analysis. So, what is the issue with an estimate of sodium from a single urinary spot sample using a formula such as the Kawasaki formula?

The Kawasaki formula uses sex-specific equations that also include age and weight, all factors which are themselves associated with blood pressure and thus may produce biased estimates of sodium intake [14]. An analysis that compared data from sodium measured from multiple 24 h urinary collections [3–7 in each participant] to various formulas for estimating sodium intake showed that, on average, the estimates from formulas differed from -78mg/d to 1,299mg/d [14]. Of particular note, the Kawasaki formula produced the most biased estimates in this analysis [14].

In the present study, the authors suggest that because estimated 24 h sodium was divided into quintiles, and the odds ratio increased with each increasing quintile, this indicated no "J-shaped curve" and thus the Kawasaki formula is valid for population-level analysis. But there are some issues with this interpretation, the first of which is that they did not present confidence intervals for this analysis, and this is an omission because the extent to which the confidence intervals overlapped would have been instructive because up to the third quintile the odds ratio were all modest.

Secondly, the authors also suggest that the validation of the estimated 24 h sodium against sodium intakes assessed from a food frequency questionnaire also support the use of the Kawasaki formula. Except, it is well established that estimating sodium intakes from such food-based dietary assessments is a poor method, because sodium is often added to foods/meals in addition to any sodium present in foods [15]. In the present study, in the highest quintile estimated dietary sodium intake was ~2,425mg/d, while estimated 24 h sodium using the Kawasaki formula was 5,235mg/d, indicating a substantial variance between these methods.

In effect, the central point the authors make is that because the Kawasaki formula didn't produce a "J-shaped curve" of risk estimates, it is valid; this is a real stretch, because the absence of any such curve does not mean the estimates of 24 h sodium are accurate, and ultimately it is accuracy that nutritional epidemiology so desperately seeks.

Interesting Finding

In each analysis, the adjustment for blood pressure abolished any significant associations that were present when only factoring in age and sex of participants. This indicates that the relationship between sodium and the respective atherosclerosis outcomes was explained by blood pressure, which at one level is unsurprising given the causal role of hypertension in CVD risk [1,2].

However, where it gets interesting is when we look at the actual blood pressure status of the participants in this study. Consider that optimal blood pressure is generally considered to be less than 120/80mmHg systolic/diastolic blood pressure, respectively; "normal" has been considered a 120-129mmHg systolic and 80-84mmHg diastolic blood pressure. In

the present study, average blood pressure was 124/76mmHg, indicating systolic blood pressure in the normal range and diastolic in the optimal range. Hypertension present in ~30% of participants.

Thus, even in this cohort of participants with relatively good blood pressure readings, it was blood pressure that explained the associations with the levels of atherosclerosis observed in the study. The reason this is interesting is because it reflects some previous research which showed that over 10yrs the risk of a CVD event was twice as high in the "normal" range when compared to the optimal range [16]. In this regard, perhaps somewhat similar to LDL-C, it may be that "normal" is not quite optimal for the role of blood pressure in cardiovascular health.

Relevance

The paper very much implies, indeed states in its graphical abstract, that *"higher sodium intake is associated with a higher atherosclerotic burden."* In their Discussion, they lead with this statement before stating *"...in minimally adjusted models"*, which meant the study site at which participants were measured, age and sex. However, as we can see from the **figure** above in the **Results** section, once adjusting for relevant moderating risk factors, these findings are largely in the range of noise and there is little confidence we can take in this association.

This is not to suggest no true relationship exists. Recall that adjustment for blood pressure abolished the associations between sodium and atherosclerosis markers, which would be consistent with the proposed causal chain: sodium > blood pressure > atherosclerosis. The first step in this chain, i.e., of the linear increase in blood pressure with higher sodium intakes, is at least clear in the evidence [3,4].

What is not clear is that this relationship is operative specifically in the case of atherosclerosis. In individuals with salt-sensitivity [i.e., exhibit very large blood pressure responses to salt], elevated atherosclerosis markers have been shown, specifically inflammatory markers and markers of vascular damage [17].

A 2011 study that used a single full 24 h urinary collection to measure sodium, which is still limited but better than a "spot sample" and formula-based guesstimate, showed an association between higher urinary sodium and carotid artery intima thickness that remained significant after adjusting for systolic blood pressure [18].

However, similar to the present study, this latter study was cross-sectional in design, and thus we are left with a lack of understanding for the temporal relationship between sodium, blood pressure, and progression of atherosclerosis.

Application to Practice

The specific research question being addressed in the present study was whether there was an association with specific markers of atherosclerosis such as carotid artery plaques or coronary artery stenosis. And while this study does not provide us with any substantive findings to take away, it should not distract from the well-established causal chain between sodium, hypertension, and CVD [1,5–7,19].

Bear in mind that 10% of deaths from CVD globally have been attributed to sodium intakes above 2,000mg/d [19]. And while there may be some individual exceptions

[e.g., athletes with high fluid replacement demands], the exceptions tend to prove the rule that maintaining a lower sodium intake is supported by an overwhelming and comprehensive body of evidence.

That said, to what extent sodium intakes may relate to atherosclerosis progression specifically remains to be established in better quality, prospective research.

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