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Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation. 2014;129(9):981 - 989.

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

We know that hypertension is the leading cause of mortality worldwide, and projected to increase by 60% globally by 2025 [(1)]. We know within this disease burden, the relationship with cardiovascular disease, in particular stroke, is linear: as blood pressure increases, so does risk for coronary heart disease and stroke [(2)]. What we also know from an extensive body of intervention studies is that lowering sodium in the diet will reduce blood pressure [(3)].

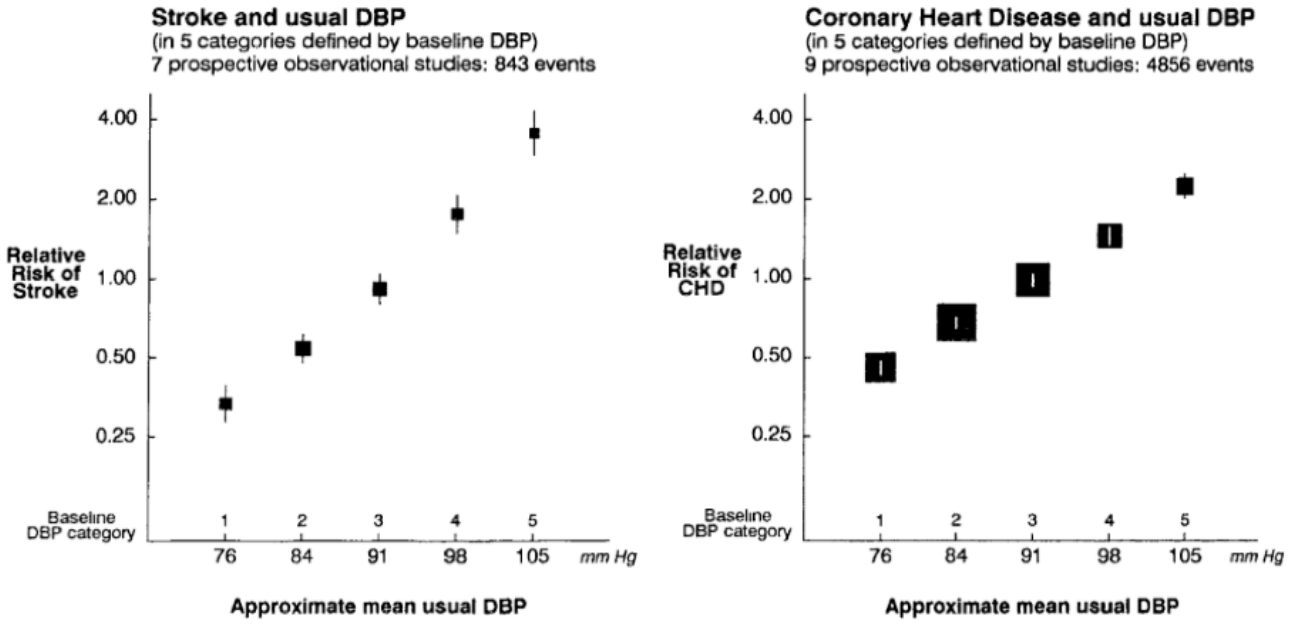

***Figure** from MacMahon et al. [(2)] indicating the relative risk of stroke **[left]** and coronary heart disease [right] per increasing quintiles of diastolic blood pressure: the increase in risk for both outcomes is linear as blood pressure increases.*

What we remain in debate over, however, is whether there are also risks to lower sodium intake, known as the 'J-shaped curve', where risk is lowest in the mid-level of intake, and increased at either extreme: low or high. There are also questions over it really is sodium that is the causal dietary factor, as high sodium diets are often low in other important micronutrients for blood pressure regulation, in particular potassium.

In all of this debate lies nutritional epidemiology, which is the only research design in nutrition science where "hard" endpoints, like a cardiovascular event or mortality, can be outcomes of interest, as the shorter duration of intervention studies mandates intermediate outcomes, like blood pressure or effects on the renin-aldosterone system.

Rarely, a study may combine the more precise measurements available in a shorter term randomised controlled trial [RCT], with an observational follow-up period after completion of the RCT, to look at longer term outcomes. The present study analysed the risk of cardiovascular disease 10-15yrs after completion of two RCTs which aimed to reduce blood pressure in participants with elevated blood pressure.

The Study

The Trials of Hypertension Prevention I [TOHP I] intervention study was an RCT conducted between 1988-1990 designed to test non-pharmacological means of lowering blood pressure, including weight loss, low-sodium diet, stress management, and supplementation, in participants with high-normal blood pressure. The Trials of Hypertension Prevention II [TOHP II] study subsequently began in 1992, and this time investigated the effects of weight loss alone, sodium restriction alone, and a combination of weight loss + sodium reduction, with a 3yr follow-up period. Multiple 24-hour urinary sodium excretions were collected over 18-months in TOHP I and 36-months in TOHP II.

The observational follow-up to assess cardiovascular disease, the Trials of Hypertension Prevention Follow-Up study, began in 2000, which was 10yrs and 5yrs following the completion of TOHP I and TOHP II, respectively.

2,974 *participants that had not been in an active low-sodium arm* of either TOHP I and TOHP II were included, and follow-up conducted by mail and telephone. If a cardiovascular event was reported, medical records were obtained with consent of the participant and reviewed by a medical doctor blinded to the participant' s treatment assignment during the study.

The primary endpoint was cardiovascular disease [CVD], [which included stroke, myocardial infarction, coronary artery bypass graft, coronary angioplasty, and death CVD]. The relevant exposure was mean urinary excretion* during the period of the TOHP I and TOHP II trials, for sodium and potassium, divided into quartiles of intake. Both sodium and potassium were analysed separately, and together in the same model. Creatinine excretion was also assessed, which provides a measurement of who complete urinary assessments were.

Hazard ratios were calculated for each quartile from the end of the original trial period, to the end of the follow-up period. The quartiles were: 1=<2300mg; 2= 2300mg to <3600mg; 3= 3600mg to <4800mg, and; 4= >4800mg/24hr. Because 3,600mg/d is the median level of sodium intake in the US population, this value - Quartile 3 - was taken as the reference category of intake for statistical analysis.

*Geek Box: Biomarkers in Dietary Assessment

The term "biomarker" means use of a specific biochemical measure that provides an indication of nutrient intakes. This isn't always as straightforward as "nutrient in = nutrient measured", because nutritional status is influenced by variations in the digestion, absorption, metabolism, distribution, and excretion of a nutrient, which differs from nutrients to nutrient. For example, when measuring fatty acids, whether it is red the phospholipid content of cell membranes, lipoproteins, or adipose tissue measured, each will provide different indications of dietary intake. Biomarkers may be classified according to what measurement they allow for. A biomarker for which there is a quantitative relationship between dietary intake and the value of the biomarker, such that absolute intake over a 24hr period can be measured accurately, is known as a "recovery biomarker". "Recovery" reflects the fact that all intake over a 24hr period is excreted, usually through urine, with minimal losses through other excretory pathways. These are very rare in nutrition science: only 24hr urinary sodium, 24hr urinary potassium, 24hr urinary nitrogen, and total energy measured by doubly-labeled water, are considered recovery biomarkers. The most commonly used biomarkers, which measuring the concentration of a nutrient in a plasma, red blood cells, adipose tissue, are known as "concentration biomarkers", as they are measuring the concentration of that particular nutrient in the circulation or tissue. The use of biomarkers is very attractive for nutritional epidemiology, as it allows for an objective assessment of the validity of dietary questionnaires, and quantification of intake that is independent of measurement error. However, there remain limitations to their application. First, there is not a reliable biomarker for every nutrient of interest to nutrition science. Secondly, many non-dietary factors may influence the status of a biochemical indicator, thus introducing a potential measurement error that is unrelated to actual dietary intake. Nonetheless, for exposures of interest like sodium, potassium, fatty acids, or total energy expenditure, biomarkers are reliable, and provide a means of quantifying accurate dietary intake.

Results: Follow-up information was available for 2275 participants, in which 193 confirmed CVD events occurred, including 27 CVD deaths. The median number of urinary excretion measures was 5 [range 1-7].

- ***Urinary sodium excretion:*** Median sodium excretion in all participants was 3630mg/24hr. 1.4% of participants had a median sodium intake <1,500mg/24hr, and 10% had <2,000mg/24hr. Median urinary sodium excretion was 3934mg/24hr in men and 3078mg/24hr in women.
- ***Urinary potassium:*** Median urinary potassium excretion in all participants was 2327mg/24hr. Median potassium excretion in men was 2502mg/24hr and 1952mg/24hr in women.
- ***CVD Events:*** Analysis of increases sodium per 1,000mg/24hr indicated a 17% increase [HR 1.17, 95% CI 1.00-1.36] in risk per 1,000mg, which was borderline significant [p=0.054]. The spline plot, a type of an analysis that plots data to look at linear relationships, indicated a significant nonlinear association between increasing sodium intake with CVD [p=0.044]. Compared to the reference category [>3600mg to <4800mg], intake of >2,300mg to <3,600mg/24hr was associated with a 25% reduction in risk [HR 0.75, 95% CI 0.50-1.11], and intake of <2,300mg/24hr associated with a 32% reduction in risk [HR 0.68, 95% CI 0.34-1.37], neither of which were statistically significant.

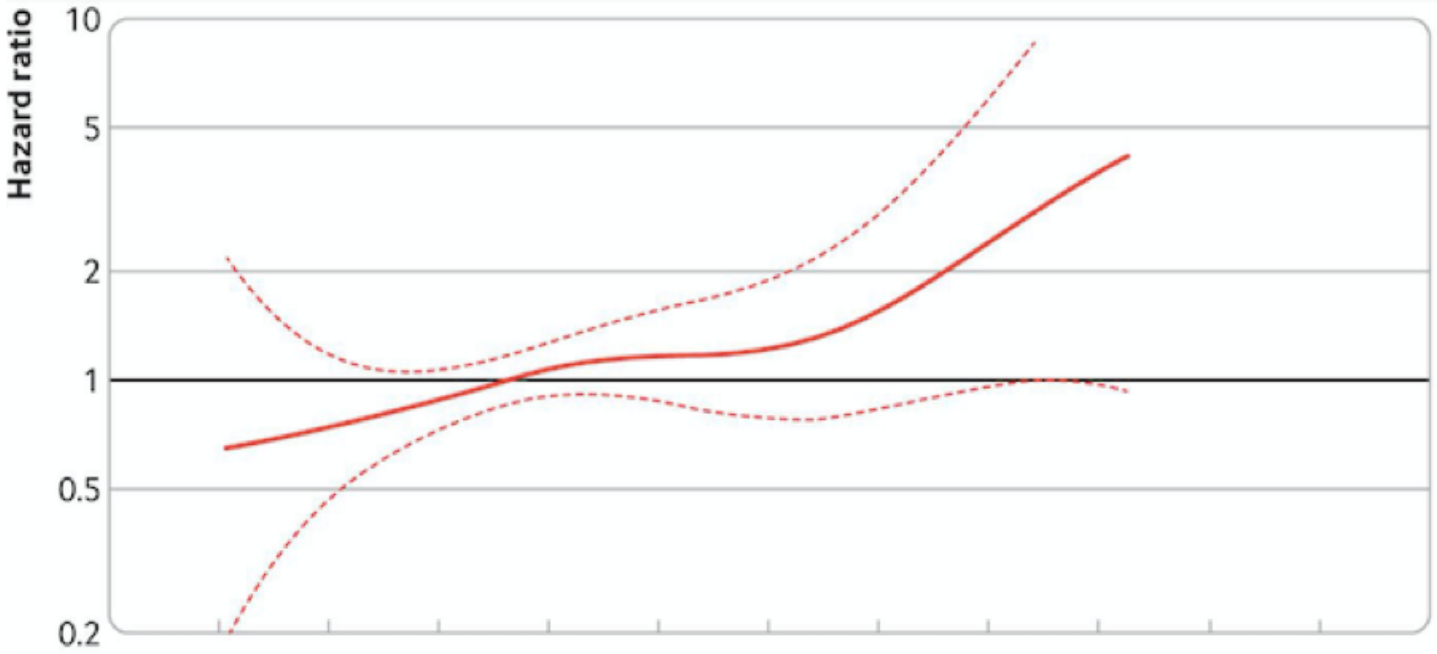

Figure *from paper: Spline curve illustrating nonlinear relationship between sodium levels of CVD risk. Each dash on the bottom reflects a 1,000mg increase, starting on the far left at 1,000mg intake of sodium. The mid-line is the mean sodium intake level in mg/24hr [the black finger bars on the bottom reflect the distribution of sodium intake in participants in the study. The main feature of the curve is that from compared to participants consuming 3600mg/24hr, participants consuming 2300mg/24hr and 1500mg/24hr were associated with 21% [HR 0.78] and 31% [HR 0.69] lower CVD risk, respectively.*

The Critical Breakdown

Pros: The gold standard for assessing sodium is multiple 24hr collections over a period of time, to account for within-person variability: with a median of 5 collections per participant, this is a more robust assessment of sodium intake that may reduce measurement error and bias. Participants were only included if they had not been in a sodium reduction arm of the intervention trials, thus reflecting habitual sodium intake. Measuring urinary creatinine levels allowed for assessment of sample completeness [see ***Key Characteristic***, below].

Cons: This is quite niche, but there was no adjustment for energy intake, which is usual practice in nutrition epidemiology. This is likely because in order to adjust for energy intake with urinary excretions, which is a recovery biomarker [***per the Geek Box, above***], a measure of energy intake using doubly-labeled water is required, which is incredibly expensive [and so may not be used]. Thus, the effects may not reflect sodium intake independent of total energy. The actual numbers of events was quite low, particularly with the data from TOHP II, e.g., only 18 events in 224 people with sodium intake >4,800mg, which may have influenced the overall significance of the findings, due to low statistical power.

Key Characteristic

Assessing reliability of recovery biomarkers can present challenges, in particular for whether the urinary samples gathered are in fact complete collections. While sodium levels exhibit high day-to-day variability in intake, and therefore high within-person variability in measuring sodium, creatinine levels in the body are produced at a constant rate, with very low variability. All of this creatinine is excreted from the body in urine under normal circumstances, and thus a measure of the creatinine levels in 24hr urinary samples provides an assessment of completeness of the sample collection. If creatinine levels in the sample are low, then it indicates an incomplete collection, and those participants data can be excluded. Analysing creatinine levels, and adjusting the sodium analyses for creatinine levels, indicated that multiple 24hr sodium measurements over a period of 18-36 months reduced within-person variability - and incomplete samples - in assessing sodium levels. In the analysis adjusted for creatinine, the results were largely similar. The measure of creatinine lends confidence to the accuracy of measurement of sodium levels.

*Geek Box: Urinary Samples in Nutritional Epidemiology

Per the Geek Box above, the key feature of urinary recovery biomarkers like sodium or potassium, is that urine is the primary means of excretion. This means that over a 24hr period, almost all sodium intake through the diet will ultimately be excreted through urine. However, this also means that the method of collection is very important. A spot urine sample, which is a single sample collected at particular time of day [which may be random, or planned, i..e, first void in the morning], may be appealing because it is easy for investigators to collect, and does not require a lot of compliance. However, it will inevitably fail to capture 24hr intake, and will be dependent on the timing of dietary intake and hydration status at that particular time of the day, leading to substantial measurement error. Particularly for sodium, it is important to obtain a full collection of all urine over a 24hr period. However, this is burdensome on investigators and participants. This may mean that a single 24hr collection is obtained in a study, however, the issue with this approach is that day-to-day intake in nutrients like sodium can vary substantially, and thus while it the 24hr collection may accurately reflect sodium intake that day, it only reflects that day. Thus, the variation between all participants will lead to measurement error. To overcome these limitations, the "gold standard" means of assessing sodium [or potassium] intake is to collect multiple 24hr urinary sample collections, and validation studies have indicated that up to 6 x 24hr collections per participant provides sufficient samples to correct for variation in individual intake [within-person error], and minimise variation from individual to individual in the study [between-person variation]. In assessing any epidemiological study that measures sodium intake, these differences in urinary samples are critical to interpreting the data.

Interesting Finding

The spline curve indicated a continued reduction in risk from 3,600mg to 2,300mg and 1,500mg/24hr. Studies that have found the 'J-shaped curve' have generally either used single 24hr sodium collections [4], or have often had participants in the low sodium groups with existing diabetes, heart disease, or hypertension, i.e., following a low sodium diet for disease management [5]. Salt intake has been romanticised as part of the ancestral revisionism of nutrients in the human diet, with some unfounded assumptions of high sodium intake, which seems to confuse the unquestionably essential role salt has played throughout human history, particularly for preservation purposes, with actual intake. However, actual human evolutionary requirements are tightly adapted to scarcity of salt intake, with homeostatic mechanisms designed to preserve relatively small amounts of sodium [6]. This is supported by analysis of 39 hunter-gatherer populations across Africa, Central and South America, Asia and the Pacific, which universally exhibit salt intake of <1,000mg/d, often less [7]. It may be that while sodium is essential, not unlike cholesterol levels, we simply don' t need that much.

Relevance

The TOHP is one of the more robust assessments of sodium intake in epidemiological research, and the primary findings from a statistically significant perspective relate to the increase in risk per 1,000mg/d increase in sodium, starting from 1,500mg, and the continued reduction in risk from 3,600mg to 2,300mg, to 1,500mg/24hr. However, the quartile comparisons were all non-significant, and the confidence intervals were so wide in the quartile analysis that they render those statistics practically meaningless. Nonetheless, the existence of a trend does not need statistical support, and with the robust methodology in assessing sodium intake, the continued reductions in risk as sodium intake is lower warrants attention. The lack of significance in the quartile ranges may reflect the relatively low number of events in each category.

An important factor with regard to hypertension is that for 90% of the condition, i.e., primary or 'essential' hypertension, there is no identified aetiology. Insofar as sodium is one factor that the literature clearly shows:

a) low levels in hunter-gatherer populations;
b) clear associations with BP at a whole-population level;
c) clear association between BP and CVD/AC mortality.

Then it has been prudent for public health policy to target reductions in sodium. However, evidence has accrued to demonstrate, from interventions, significant reductions in blood pressure with sodium reduction, and from epidemiology, reductions in CVD events and mortality in the population.

Application to Practice

When it comes to dietary sodium, it is common to hear "sure, too high is bad, but so is too low", i.e., the J-shaped curve. However, until better quality studies confirm this, we are left with an inference from traditional diets, physiology, interventions, and well-conducted sodium assessments in epidemiology, the advice for the general population of <6g/d salt - equivalent to 2,4000mg sodium - is reasonable.

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