LOW SODIUM INTAKE: CARDIOVASCULAR HEALTH BENEFIT OR RISK?

Suzanne Oparil, MD
Distinguished Professor of Medicine, Professor of Cell, Developmental and Integrative Biology
Director, Vascular Biology and Hypertension Program, Division of Cardiovascular Disease
Co-chair, “Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8)”
University of Alabama at Birmingham, Birmingham, Alabama
Past President, American Heart Association (AHA)
Past President, American Society of Hypertension (ASH)

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Faculty Disclosure
Suzanne Oparil, MD

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CDC Recommendations for Dietary Sodium

- All American adults should consume < 2,300 mg of sodium per day.
- The following should consume < 1,500 mg of sodium per day.*
  51 years of age or older.
  African American, Hypertensive, Diabetic or have Chronic Kidney Disease.

- *This applies to about half of U.S. population and the majority of adults...

http://www.cdc.gov/salt/, October 2013
THE CONTENDING VIEWS

• ADVOCATES contend that because ↓ing Na⁺ will ↓ average BP (a CVD surrogate), it will prevent CVD

• SKEPTICS argue altering only one of many physiological surrogates renders the health outcome unpredictable

What is known about Na⁺ intake, and its reduction, and BP

• Usual intake ~ 3.6gms = 160mols
• Normal renal function - reducing Na⁺ does not influence BP
• However, average BP Δ ↓ 1-5mmHg/100 mmols
  – varies by BP, race, age
  – heterogeneous - including rise
  – attenuates over time

Meta-analysis of Salt Restriction Trials

Mean change in BP with 100 meq/day reduction in salt intake

Midgley et al, JAMA 1996
Other RCT Demonstrated consequences of sodium restriction

- Increases renin-angiotensin-aldosterone system activity
  - PRA x 3.6 fold
  - Aldosterone x 3.2 fold
- Decreases insulin sensitivity
- Increases sympathetic nerve activity
- Increases triglycerides
- Decreases blood pressure

+ Unanticipated Consequences

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The NEW ENGLAND JOURNAL of MEDICINE

Association of Urinary Sodium and Potassium Excretion with Blood Pressure

Population Urban Rural Epidem. (PURE) Study: Systolic BP by Na Intake (N=102,216)

- 102,216 participants: aged 35-70, enrolled from 667 communities in 18 countries
- Na intake estimated by morning fasting urine method, extensively validated previously in 11 countries
- Standardized BP measurements using automated device
- Regression analyses
  - Association of Na with BP levels: overall & key subgroups
  - Adjusted for age, sex, geography, education, BMI, alcohol
PURE: 157,543 from 667 communities in 18 countries from 5 continents

% with Na intake at current guidelines

**Observed Na intake:**
- 3.3% with Na < 2.3 g/d;
- 0.6% with Na < 1.5 g/d

**Usual Na intake:**
- 0.2% with Na < 2.3 g/d;
- 0% with Na < 1.5 g/d

Systolic BP by sodium intake (N=102,216)

Adjusted for age, sex, geographic region, BMI, education, and alcohol intake
Diastolic BP by sodium intake (N=102,216)

Adjusted for age, sex, geographic region, BMI, education, and alcohol intake

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**ORIGINAL ARTICLE**

**Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events**

Martin O'Donnell, M.B., Ph.D., Andrew Mente, Ph.D., Sumathy Rangarajan, M.Sc., Matthew J. McQueen, M.B., Ph.D., Xingyu Wang, Ph.D., Lisheng Liu, M.D., Hou Yan, Ph.D., Shun Fu Lee, Ph.D., Prem Mony, M.D., Anitha Devanath, M.D., Annika Rosengren, M.D., Patricio Lopez-Jaramillo, M.D., Ph.D., Rafael Diaz, M.D., Alvaro Alvarez, M.D., Ph.D., Fernando Lanas, M.D., Khalid Yusoff, M.B., B.S., Romina Iqabal, Ph.D., Rafal Ilow, Ph.D., Nasrin Mohammadi, M.Sc., Sadi Guler, M.D., Afzal Hussain Yusufi, M.D., Lamhe Kruger, Ph.D., Ria Yusuf, Ph.D., Jepheth Chifamba, M.Phil., Conrad Kaboli, Ph.D., Gilles Dagenais, M.D., Scott A. Lear, Ph.D., Koon To, M.B., Ph.D., and Salim Yusuf, D.Phil., for the PURE Investigators.

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**PURE Study (Sodium Intake and CVD)**

- **Population**
  - General population (n=101,945 with urine samples for measurement)
  - Prior history of CVD: n=8485 (8.3%)
- **Exposure**: Mean sodium excretion 4.93g/day (SD 1.7)
  - Fasting morning urine
  - Formula-derived 24 hour urinary estimate (Kawasaki formula)
- **Outcomes**: CV death, non-CV death, stroke, MI and CHF (n=3,317)
  - All outcomes were independently adjudicated
  - Follow-up: 3.7 years (95% completed follow-up)
- **Statistical Analyses**
  - Multivariable logistic regression with generalized estimating equation models
  - Analytic approaches to address confounding and reverse causality

Yusuf et al Lancet 2011
Composite: Cardiovascular Events
(17 Countries, N=101,945; 3,317 events)

Sodium Excretion and Risk of Death or CV Events

Primary Outcome

Sodium and Risk of Death or CV

PowerPoint Slide

Potassium Excretion (PURE)

Primary Composite Outcome
SUMMARY

- Vast majority of global population consume more than 2g of sodium per day (different regions, different diets and different sources of sodium)
- There is a significant association between sodium intake and blood pressure, most evident at higher intake ranges
- Three-quarters of population consumed moderate sodium intake range (3-6g/day) which was associated with lowest risk of death and CVD
- Excess CV risk of high sodium intake (>6g/day) was mostly observed in those with hypertension
- Low sodium intake (<3g/day) was not associated with lower risk than moderate sodium intake, despite lower blood pressure
- Higher potassium was associated with lower risk of CVD

CONCLUSIONS

- Findings support reducing high sodium intake (>6g/day) to moderate intake levels
- Moderate sodium intake (3-6g/day) appears optimal (for those with hypertension, target the lower end of range)
- Casts considerable uncertainty about whether low sodium intake (<3g/day) results in net clinical benefit, and calls for definitive randomized controlled trials
- Adopt a healthy dietary pattern, rich in foods containing potassium (fruit and vegetables) with moderate sodium intake

Relationship of risk and nutrient intake, showing the 3 principal Dietary Reference Intakes.
Overview

- Most of the global population consumes 3 to 6 g of sodium per day (7.5 to 15.0 g of salt)
- Guidelines recommend a maximum sodium intake of 1.5 to 2.4 g/day, but achieving this target will require substantial change in diet for most people
- No large randomized trial conducted to show reduced cardiovascular disease (CVD) risk with low sodium intake
- Prospective cohort studies have shown inconsistent results; many included people at high CV risk, who were not representative of general population
- Potassium may modify effect of sodium on CVD risk
- How PURE study informs:
  - Association between sodium intake and blood pressure
  - Association between sodium intake and CVD + mortality
  - International context
- Addresses need for large-scale prospective cohort studies in general populations employing standardized methodology in international cohort

Sodium Intake in Populations: Assessment of Evidence

Released May 14, 2013

IOM Statement of Task

Evaluate the results, study design and methodological approaches to assessing the relationship between sodium and health outcomes in literature since 2003.

- Evaluate potential benefits/adverse impacts of reduced population sodium intake (i.e., 1,500 – 2,300 mg/day) in the general population and population subgroups (e.g., those with hypertension, prehypertension, those 51 ≥ years of age, African Americans; with diabetes, CKD and congestive heart failure).
- Comment on implications for population-based strategies to reduce sodium intake.
- Identify data and methods gaps and suggest ways to address them.
Overarching Findings

- Many populations evaluated were outside the US
  - included groups that consumed mean levels of sodium much higher than the average amount consumed by adults in the US
- The quantity and quality of relevant studies was less than optimal
  - limitations associated with quantitative measures of sodium intake
  - potential for spurious findings related to incorrect measurement and reverse causality
- Variability in the types and quality of the measures used, therefore measures could not reliably be calibrated across studies

Findings & Conclusions

**General Population**

**Finding 1** Results from studies linking dietary sodium intake with direct health outcomes were highly variable in methodological quality, particularly in assessing sodium intake. The range of limitations included over- or under-reporting of intakes or incomplete collection of urine samples. In addition, variability in data collection methodologies limited the Committee’s ability to compare results across studies.

**Conclusion 1** Given methodological flaws and limitations, the evidence indicates a positive relationship between higher levels of sodium intake and CVD risk. This is consistent with existing evidence on BP as a surrogate indicator of CVD risk.

**General Population Cont’d**

**Finding 2** Evidence from studies on direct health outcomes was insufficient and inconsistent regarding an association between sodium intake below 2,300 mg per day and benefit or risk of CVD outcomes (including stroke and CVD mortality) or all-cause mortality in the general US population.

**Conclusion 2** Evidence from studies on direct health outcomes is inconsistent and insufficient to conclude that lowering sodium intakes below 2,300 mg/day either increases or decreases risk of CVD outcomes (including stroke and CVD mortality) or all-cause mortality in the general U.S. population.
**Population Subgroups**

**Finding 2** In addition to inconsistencies in sodium intake measures, methodological flaws included the possibility of confounding and reverse causality. No relevant evidence was found on health outcomes for other population subgroups considered (i.e., persons ≥ 51 years, and African Americans). In studies that explored interactions, race, age, or the presence of hypertension or diabetes did not change the effect of sodium on health outcomes.

**Population Subgroups**

**Conclusion 2** While the current literature provides some evidence for adverse health effects of low sodium intake among individuals with diabetes, CKD, or preexisting CVD, the evidence on both the benefit and harm is not strong enough to indicate that these subgroups should be treated differently from the general U.S. population. Thus, the evidence on direct health outcomes does not support prior recommendations to lower sodium intake within these subgroups to ≤ 1,500 mg/day.

**IMPLICATIONS FOR POPULATION BASED STRATEGIES**

- The available evidence on associations between sodium intake and direct health outcomes is consistent with population-based efforts to lower excessive dietary sodium intakes, but it is not consistent with efforts that encourage lowering of dietary sodium in the general population to 1,500 mg/day.
- The evidence reviewed also suggests that dietary sodium intake may affect heart disease risk through pathways in addition to blood pressure.
Conclusion 2: With the exception of CHF patients, the current body of evidence addressing the association between low sodium intake and health outcomes in the population subgroups considered is limited. The evidence available is inconsistent and limited in its approaches to measuring sodium intake. The evidence also is limited by small numbers of health outcomes and the methodological constraints of observational study designs, including the potential for reverse causality and confounding.

Population Subgroups

IOM Conclusions 2013
- BP no longer acceptable surrogate for health outcomes of dietary sodium
- Recognized heterogeneity in association of Na+
  - Results in High and Low salt settings differ
  - Potential harm at High and Low ends
  - Did not identify “Target” range
  - Insufficient evidence to support <2300, and warned against <1500
  - Specifically did not endorse CDC Guidelines

BACKGROUND GUIDANCE
- this U-shaped distribution of risk is explicitly cited in the IOM’s guidance documents
- and is taken as the basic model for all nutrients in standard textbooks of nutritional epidemiology
Further research may shed more light on the association between lower (1,500 to 2,300 mg) levels of sodium and health outcomes in the general population and subpopulations.

The committee was not asked to draw conclusions about a specific target range of dietary sodium. Other factors also precluded specifying a such range. These included methodologic problems in assessing sodium intake and difficulty calibrating those measures across different approaches to measuring intake and different study designs.

With regard to implications for population-based efforts, the IOM committee finds that:

- Available evidence on associations between sodium intake and direct health outcomes is consistent with population-based efforts to lower excessive dietary sodium intake.
- The evidence on health outcomes is not consistent with efforts that encourage lowering dietary sodium in the general population to 1,500 mg/day.
- There is no evidence on health outcomes to support treating population subgroups differently from the general US population.

Observational studies linking Dietary Sodium Intake to Blood Pressure and Cardiovascular Events

- In normotensive persons, a 1.2 mmol (3.68 G) reduction in sodium intake produces a 1.2 mmHg reduction in Systolic BP.
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