The Evidence for Populationwide Reduction in Sodium Intake: Why All the Fuss?

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Lawrence J Appel, MD, MPH
C. David Molina, Professor of Medicine
Director, Welch Center for Prevention, Epidemiology and Clinical Research
Johns Hopkins University School of Medicine

The Johns Hopkins University
Disclosure

• Research
  – McCormick Science Foundation
Magnitude of the BP Epidemic

- 54% of strokes and 47% of coronary heart disease events attributed to elevated BP\(^1\)
- 26% of adults worldwide (971 million) have hypertension\(^2\)
- Lifetime risk\(^3\) of developing hypertension is 90%

\(^1\)Lawes CM Lancet 2008;371:1513
\(^2\)Kearney Lancet 2005;305:217
\(^3\)Vasan JAMA 2002; 287:1003
Big Picture: Worldwide, Elevated BP is the Leading Cause of Preventable Deaths

Global health risks: [http://www.who.int/healthinfo/global_burden_disease](http://www.who.int/healthinfo/global_burden_disease), WHO, 12/09
As Sodium Intake Is Reduced, So is Blood Pressure

Optimal diet approach to lower BP combines sodium reduction and improved diet

Sacks, NEJM 2001

*P=0.03 for non-linearity, -2.1 vs -4.6 mmHg
Effects of Na Reduction on CVD Events
Sodium Reduction Lowers CVD Risk: Meta-Analysis of Trials

## Range of Estimated Mean Effects from 4% Na Reduction/Year for 10 Years: Life-years Added and Deaths Prevented over 10 Years

<table>
<thead>
<tr>
<th></th>
<th>Low Estimate</th>
<th>High Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years of life added</td>
<td>919,000</td>
<td>1,817,000</td>
</tr>
<tr>
<td>Total deaths</td>
<td>274,000</td>
<td>505,000</td>
</tr>
<tr>
<td>CHD Deaths</td>
<td>145,000</td>
<td>383,000</td>
</tr>
<tr>
<td>Stroke Deaths</td>
<td>30,000</td>
<td>83,000</td>
</tr>
<tr>
<td>Major CVD deaths</td>
<td>192,000</td>
<td>516,000</td>
</tr>
</tbody>
</table>

Coxson, HTN 2013;61:564-70
Study suggests link between fall in salt intake and drop in heart attack deaths

Research claims 15% drop in average daily consumption of salt in England between 2003 and 2011 played an important role in fewer stroke and coronary heart disease fatalities

Denis Campbell, health correspondent
The Guardian, Monday 14 April 2014 18.30 EDT
Jump to comments (200)
Why the fuss about sodium?

• Scientific issues specific to sodium
  – Methodologic ‘landmines’
  – Challenges of measuring sodium
  – Interpretation of low diet and low urinary sodium excretion
  – High cost of high quality sodium research in humans

• Other scientific issues, not specific to sodium
  – Interpretation of unexpected j-shaped relationships in observational studies
  – Implications of non-BP effects of BP reducing therapies
Why the fuss about sodium?

- Commercial interests
  - Cheap ingredient, increases profit

- Role of government

- Evidence to guide policy
  - Role of ‘surrogate outcomes’
  - Level of evidence for prevention policy when clinical trials with hard outcomes cannot be done
Methodological Issues
Is Sodium Reduction Harmful? Three Lines of Evidence

• Adverse effects on biomarkers
  – Plasma renin activity, sympathetic nervous system activity, glycemia, lipid levels

• Epidemiologic studies with inverse or j-shaped relationship

• Heart failure trials from a single center in Palermo, Italy
No Effect of Reducing Sodium Intake on LDL Cholesterol

Harsha, Hypertension 2004;43;393
Methodological Issues in Cohort Studies That Relate Sodium Intake to Cardiovascular Disease Outcomes

A Science Advisory From the American Heart Association

Laura K. Cobb, MS; Cheryl A.M. Anderson, PhD, MPH, MS; Paul Elliott, MBBS, PhD*; Frank B. Hu, MD, PhD; Kiang Liu, PhD; James D. Neaton, PhD; Paul K. Whelton, MB, MD, MSc; Mark Woodward, PhD; Lawrence J. Appel, MD, MPH, Chair; on behalf of the American Heart Association Council on Lifestyle and Metabolic Health

Background—The results of cohort studies relating sodium (Na) intake to blood pressure–related cardiovascular disease (CVD) are inconsistent. To understand whether methodological issues account for the inconsistency, we reviewed the quality of these studies.

Methods and Results—We reviewed cohort studies that examined the association between Na and CVD. We then identified methodological issues with greatest potential to alter the direction of association (reverse causality, systematic error in Na assessment), some potential to alter the direction of association (residual confounding, inadequate follow-up), and the potential to yield false null results (random error in Na assessment, insufficient power). We included 26 studies with 31 independent analyses. Of these, 13 found direct associations between Na and CVD, 8 found inverse associations, 2 found J-shaped associations, and 8 found null associations only. On average there were 3 to 4 methodological issues per study. Issues with greater potential to alter the direction of association were present in all but 1 of the 26 studies (systematic error, 22; reverse causality, 16). Issues with lesser potential to alter the direction of association were present in 18 studies, whereas those with potential to yield false null results were present in 23.

Conclusions—Methodological issues may account for the inconsistent findings in currently available observational studies relating Na to CVD. Until well-designed cohort studies in the general population are available, it remains appropriate to base Na guidelines on the robust body of evidence linking Na with elevated blood pressure and the few existing general population trials of the effects of Na reduction on CVD. (Circulation. 2014;129:00-00.)
Major Methodological Challenges in Observational Studies that Relate Sodium Intake to CVD

• Errors with Greatest Potential to Alter Direction of Association
  – Systematic error in sodium assessment
  – Reverse causality

• Errors with Some Potential to Alter Direction of Association
  – Residual confounding
  – Imbalance across groups
  – Low follow-up rate

• Errors with Potential to Lead to a False Null
  – Random error in sodium assessment
  – Insufficient power

26 studies with 31 independent samples
On average, 2.5 issues/study
Measurement of Na Intake

**Optimal**
- Multiple, high quality 24 hour urine collections

**Suboptimal**
- 24 hour urine collected with limited or no attention to quality control
- Spot, overnight or timed urines
- 24 hour dietary recalls
- Food frequency questionnaire
Case of Systematic Error Leading to Bias: Increased CVD Mortality in Persons with Lowest Na (by Quartile of Na Intake in mg/d)

Hazard Ratio (HR)

<table>
<thead>
<tr>
<th>Na Quartile of based on mg of Na/d</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
</tr>
</thead>
<tbody>
<tr>
<td>hazard ratio</td>
<td>1.8</td>
<td>1.94</td>
<td>1.48</td>
<td>1.0</td>
</tr>
</tbody>
</table>

P=0.03
Q1 vs Q4

1Cohen, JGIM 2008;23:1297-302
Evidence of Contamination in a Cohort Study\(^1\) (NHANES III) Reporting Increased Mortality in Persons with Low Sodium Intake on 24Hr Dietary Recall

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<th>Quartile of Sodium Intake:</th>
<th>1(^{st}) (Lowest)</th>
<th>2nd</th>
<th>3rd</th>
<th>4(^{th}) (Highest)</th>
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<td>Na (mg/d)</td>
<td>1,501</td>
<td>2,483</td>
<td>3,441</td>
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<td>Energy Intake (kcal)</td>
<td>1,282</td>
<td>1,762</td>
<td>2,152</td>
<td>2,938</td>
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\(^1\)Cohen, JGIM 2008;23:1297-302
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<th>BMI (kg/m²)</th>
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<tr>
<td>1st (Lowest)</td>
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<td>25.8</td>
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<tr>
<td>2nd</td>
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<td>26.4</td>
</tr>
<tr>
<td>3rd</td>
<td>3,441</td>
<td>2,152</td>
<td>26.3</td>
</tr>
<tr>
<td>4th (Highest)</td>
<td>5,497</td>
<td>2,938</td>
<td>26.6</td>
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Evidence of Massive Underreporting of Calorie Intake Leading to Systematic Error in Estimate of Sodium Intake

\(^1\)Cohen, JGIM 2008;23:1297-302
J-Shaped Relationship of Total Mortality with Urine Sodium Excretion in Patients with Type 1 Diabetes

Extremely low levels are most likely the result of extreme undercollection

Thomas, Diabetes Care 2011: 861-6
Example of Low Sodium Excretion Related to Under-collection

- 78 year old women, screened for a trial
  - No special diet
  - 172 pounds, 5’2”, BMI 31 kg/m²
- Two 24 hour urine collections required
  - Detailed instructions provided

<table>
<thead>
<tr>
<th>Urine</th>
<th>Lab Range</th>
<th>1st</th>
<th>2nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/24hr)</td>
<td>18</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Volume (ml/24hr)</td>
<td>800</td>
<td>725</td>
<td></td>
</tr>
<tr>
<td>Creatinine (g/24 hr)</td>
<td>.63 to 2.5</td>
<td>.41</td>
<td>.09</td>
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Unanticipated J-Shaped Relationship: An Investigation
All Cause Mortality in Persons with Incident Diabetes (All Participants)

All Cause Mortality in Persons with Incident Diabetes (Excluding Early Deaths)

All Cause Mortality in Persons with Incident Diabetes (Just Never Smokers)

All Cause Mortality in Persons with Incident Diabetes (Just Never Smokers, Excluding Early Deaths)

TOHP Phase 3: Observational Study with No Evidence of Biases Leading to Systematic Error
Direct, Progressive Relationship of CVD with Urinary Sodium Excretion* in 2,275 Individuals with Prehypertension

![Graph showing the relationship between sodium excretion and hazard ratio]

Cook, Circ 2014:129:981

*Based on 24 hr urine collections (median = 5)
Heart Failure Trials: The adverse impact of bad science on public policy
Effects of Lower (80 mmol/d) vs Usual (120 mmol/d) Sodium on Outcomes in Patients with Heart Failure

Readmissions

Log-rank = 0.001

Readmissions or Death

LogRank = 0.001

Peculiarities of 6 Heart Failure Trials

- Massive concurrent therapy
  - 100% High dose lasix (250 – 1000mg/d)
  - 100% ACEI (Captopril 75-150mg/d)
  - ~80% Spironolactone (25mg/d)

- Details of dietary intervention unclear
  - ? Just advice

- Funding source mentioned in 1/6 papers

- Trial registration: 1/6 papers

- Two sets of trials with possibly duplicate data leading to retraction of a meta-analysis, other papers with identical text
“raw data no longer available having been lost as a result of computer failure”
Recommendations
Sodium Intake
2010 Dietary Guidelines: Sodium Recommendation

- Reduce intake to less than 2300 mg/day
- Further reduce intake to 1500 mg/day for:
  - Adults ages 51+
  - African Americans ages 2+
  - People ages 2+ with high blood pressure, diabetes, or chronic kidney disease
Conclusion

• Elevated blood pressure is the leading cause of preventable death worldwide
• No (minimal) debate about lowering sodium intake to 2,300 mg/d
• Major methodological issues limit the usefulness of recent studies as a basis for guiding policy, much less reversing recommendations
Bottom Line (Unchanged)

• The estimated benefits of sodium reduction are substantial and warrant major public health efforts to reduce salt intake
• Prevailing recommendations align with best evidence and do not warrant any change in policy