Health Benefits of Lowering Sodium Intake in the US

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The Johns Hopkins University
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Disclosure

• Research
  – McCormick Foundation
Outline

• Benefits of Lowering Sodium Intake

• Methodological Challenges
  – Measurement of blood pressure
  – Measurement of sodium Intake
  – Cohort studies
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
Critical Facts: (1) 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
Mean Systolic BP Rises with Age (U.S. Women)

SBP Rise with Age = ~0.6 mmHg per year

Burt, Hypertension 1995;26:60.
Critical Facts: (2) Costs of the BP Epidemic

- Projected direct (medical) costs of CVD in 2030 in billions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CVD</td>
<td>$818b</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$200b</td>
</tr>
<tr>
<td>CHD</td>
<td>$106b</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>$77b</td>
</tr>
<tr>
<td>Stroke</td>
<td>$95b</td>
</tr>
<tr>
<td>[Hypertension as risk factor]</td>
<td>$389b</td>
</tr>
</tbody>
</table>

Heidenreich PA. Circulation. 2011;123:933-44
### Types of Evidence Linking Sodium Intake to Blood Pressure

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Over 50 population studies</td>
</tr>
<tr>
<td>Migration</td>
<td>Several, e.g. Kenya</td>
</tr>
<tr>
<td>Genetic</td>
<td>All defects identified so far impair the ability of the kidney to excrete salt.</td>
</tr>
<tr>
<td>Animal</td>
<td>All forms of hypertension are caused or aggravated by salt</td>
</tr>
<tr>
<td></td>
<td>No study has documented increased CVD risk from reduced sodium</td>
</tr>
<tr>
<td>Trials</td>
<td>Children: ~10 trials, one trial in infants</td>
</tr>
<tr>
<td></td>
<td>Adults: &gt; 50 trials, 10 dose-response</td>
</tr>
<tr>
<td>Population</td>
<td>Northern Japan</td>
</tr>
<tr>
<td>Interventions</td>
<td>Finland</td>
</tr>
<tr>
<td></td>
<td>Portuguese villages</td>
</tr>
</tbody>
</table>
As Sodium Intake Is Reduced, So is Blood Pressure

Systolic Blood Pressure

8.9 mmHg from low Na + DASH

Sodium Level: mg/d per day

Typical Diet

-6.7 p<.0001

DASH Diet

-3.0 P<.0001

Sacks, NEJM 2001;344:3
Factors Associated with Greater BP Reduction from Lower Sodium Intake

• Fixed factors
  – African-Americans
  – Middle and older-aged persons
  – Genetic Factors
  – Individuals with:
    • Hypertension
    • Diabetes
    • Chronic Renal Insufficiency

• Modifiable
  – Low potassium intake
  – Poor quality diet
<table>
<thead>
<tr>
<th></th>
<th>General</th>
<th>High Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of US Adults</td>
<td>52%</td>
<td>48%**</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>2,300</td>
<td>1,500</td>
</tr>
<tr>
<td>Sodium (mmol)</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>Salt (g), [Sodium Chloride]</td>
<td>5.8</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*African-Americans, Adults ≥ 51 yrs, Hypertensives, and Diabetics

**MMWR 2011, Vol 60, No. 41
Reduced Sodium Intake Has Greater BP Effects in African-Americans

African-Americans

Non-African-Americans

-8 †

-4.5 †

-5.1

-2.2

Systolic BP

Diastolic BP

† P-interaction < 0.05

Vollmer, Ann Int Med 2001;135:1019
Reduced Sodium Intake Has Greater BP Effects in Hypertensives

Hypertensives

Non-Hypertensives

Systolic BP

Diastolic BP

† P-interaction < 0.05

Vollmer, Ann Int Med 2001;135:1019
Dose Response Trial in Hypertensives

MacGregor, 1989 (20 hypertensive)
Reduced Sodium Intake Has Greater BP Effects in Middle- and Older-Aged Persons than Younger Persons

Age > 45

- 7.5 †

Age ≤ 45

- 5.3

- 2.8

† P-interaction < 0.05

Vollmer, Ann Int Med 2001;135:1019
Dose Response in Elderly with Isolated Systolic Hypertension

Johnson, 2001 (n=15 elderly with isolated systolic hypertension)
Trials of Sodium Reduction in Patients with Diabetes

- 13 trials with 254 individuals
  - 75 individuals with type 1 diabetes
  - 158 individuals with type 2 diabetes

- Duration
  - median: 1 week, range: 5 days to 12 wks

*Suckling RJ, Cochrane Review, 2010 Dec 8;(12):CD006763*
# BP Reductions from Lowering Sodium Intake: Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>-7.1</td>
<td>-6.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-3.1</td>
<td>-2.9</td>
</tr>
<tr>
<td>Median Na (mg/d)</td>
<td>4,700</td>
<td>2,900</td>
</tr>
</tbody>
</table>

*Median Na Reduction*  

* Suckling RJ, Cochrane Review, 2010 Dec 8;(12):CD006763
<table>
<thead>
<tr>
<th></th>
<th>Children¹</th>
<th>Non-HTN²</th>
<th>HTN²</th>
<th>Resistant HTN³</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>-1.2</td>
<td>-2.0</td>
<td>-5.0</td>
<td>-22.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-1.3</td>
<td>-1.0</td>
<td>-2.7</td>
<td>-9.1</td>
</tr>
<tr>
<td>Na (mg/d) Reduction</td>
<td>n/a</td>
<td>1,700</td>
<td>1,800</td>
<td>2,300</td>
</tr>
</tbody>
</table>

¹He, HTN 2006;48:861 ²Cochrane Review, 2006; ³Pimenta, HTN 2009;54:475
Population-Based Strategy

SBP Distributions

After Intervention

Before Intervention

Reduction in SBP mmHg

Reduction in BP

<table>
<thead>
<tr>
<th>Reduction in SBP mmHg</th>
<th>% Reduction in Mortality Stroke</th>
<th>% Reduction in Mortality CHD</th>
<th>% Reduction in Mortality Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-6</td>
<td>-4</td>
<td>-3</td>
</tr>
<tr>
<td>3</td>
<td>-8</td>
<td>-5</td>
<td>-4</td>
</tr>
<tr>
<td>5</td>
<td>-14</td>
<td>-9</td>
<td>-7</td>
</tr>
</tbody>
</table>

Estimated Annual Number of Prevented Heart Attacks from Population-Wide Sodium Reduction

Bibbins-Domingo, NEJM 2010;362:590
Estimated Annual Number of Prevented Heart Attacks from Population-Wide Sodium Reduction

- Sodium Reduction: 400 mg/d
- Sodium Reduction: 1200 mg/d
- Drug Therapy for HTN
- Smoking Cessation (50%)
- Weight Loss (5%)

Bibbins-Domingo, NEJM 2010;362:590
Sodium Reduction Lowers CVD Risk: Meta-Analysis of Trials

Methodological Issues
Blood Pressure: High Degree of Random Error (Noise)

- Huge within-person variability in blood pressure
- Reduced by:
  - Standardized technique
  - Multiple visits
  - Multiple measurements (e.g. ambulatory BP)

**Implication**: Impossible to classify individuals as ‘salt sensitive’
Distribution of Systolic BP Change in Non-Hypertensive Adults (Pre-Post) in Response to Reduced Sodium Intake

Miller, J Chronic Dis 40, 1987
Distribution of Systolic BP Differences Between Two Periods When Participants Ate the Same Diet/Same Sodium

Obarzanek, HTN 2003;42:459
Distribution of Systolic BP Differences Between Two Periods with Different Sodium Levels (~ 70 mmol/d)

Obarzanek, HTN 2003;42:459
Major Methodological Challenges in Observational Studies that Relate Sodium Intake to CVD

- Random error in sodium assessment
- Systematic error in sodium assessment
- Potential for reverse causality
- Major analytic issue, e.g. under-adjustment
- Potential for residual confounding

26 studies with 31 independent samples
On average, 2.5 issues/study
AHA Presidential Advisory

Sodium, Blood Pressure, and Cardiovascular Disease
Further Evidence Supporting the American Heart Association Sodium Reduction Recommendations

Paul K. Whelton, MB, MD, MSc, FAHA, Chair; Lawrence J. Appel, MD, MPH, FAHA; Ralph L. Sacco, MD, MSc, FAHA; Cheryl A.M. Anderson, PhD, MPH, MS, FAHA; Elliott M. Antman, MD, FAHA; Norman Campbell, MD; Sandra B. Dunbar, RN, DSN, FAHA; Edward D. Frohlich, MD, FAHA; John E. Hall, PhD, FAHA; Mariell Jessup, MD, FAHA; Darwin R. Labarthe, MD, MPH, PhD, FAHA; Graham A. MacGregor, MB, BCH; Frank M. Sacks, MD, FAHA; Jeremiah Stamler, MD, FAHA; Dorothea K. Vafiadis, MS, FAHA; Linda V. Van Horn, PhD, RD, LD, FAHA

Abstract—Recent reports of selected observational studies and a meta-analysis have stirred controversy and have become the impetus for calls to abandon recommendations for reduced sodium intake by the US general population. A detailed review of these studies documents substantial methodological concerns that limit the usefulness of these studies in setting, much less reversing, dietary recommendations. Indeed, the evidence base supporting recommendations for reduced sodium intake in the general population remains robust and persuasive. The American Heart Association is committed to improving the health of all Americans through implementation of national goals for health promotion and disease prevention, including its recommendation to reduce dietary sodium intake to <1500 mg/d. (Circulation. 2012;126:00-00.)

Key Words: AHA Scientific Statements ■ sodium ■ diet ■ prevention
Random and Systematic Error in Measuring Na Intake

- **Random error**
  - Reason: high day-to-day variability of Na within an individual
  - Impact: bias to the null
- **Systematic error**
  - Reason: underreporting of intake from 24 hr recalls OR incomplete urine collection
  - Impact: potential for paradoxical relationship
- Both types of errors – extremely common
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
Correlations of Sodium with Indices of Completeness

Diet Studies: Correlation of sodium and calorie
0.80 in NHANES\textsuperscript{1}
0.73 in PREMIER\textsuperscript{2} trial

Urine Studies: Correlations of Sodium with creatinine excretion
0.56 in PREMIER\textsuperscript{2} trial

\textsuperscript{1}Dietary Guidelines Scientific Advisory Committee, 2010
\textsuperscript{2}Unpublished
Random Error in Na Measurement Attenuates the Relationship of Na Intake on CVD Risk
Random Error in Na Measurement Attenuates the Relationship of Na Intake on CVD Risk
Systematic Error in Na Measurement Attenuates the Relationship of Na Intake on CVD Risk
Systematic Error in Na Measurement Could Lead to J-Shaped or Inverse Relationship of Na Intake with CVD Risk
Special Article

Biases in the Identification of Risk Factor Thresholds and J-Curves

Ian C. Marschner¹,², R. John Simes², and Anthony Keech²

¹ Asia Biometrics Center, Pfizer Australia, Sydney, Australia.
² National Health and Medical Research Council Clinical Trials Center, University of Sydney, Sydney, Australia.

Received for publication March 15, 2006; accepted for publication April 9, 2007.

For some diseases, there has been controversy about whether key risk factors are related linearly to the occurrence of disease events. This issue has important implications for strategies to modify risk factors, since nonlinear threshold or J-curve associations imply that risk factor modification is not beneficial beyond a certain level. This paper considers whether nonlinear risk factor associations can arise spuriously from selection mechanisms common in prospective cohort studies. Using theory, simulation, and cohort data, the authors show that selecting individuals based on their prior disease status leads to the primary risk factor being negatively confounded with other residual risk factors. If this confounding combines with effect modification between the primary and residual risk factors, as exists in cardiovascular disease, then the aggregate effect is nonlinear distortion of the risk factor relation. Such distortion can produce an apparent threshold or J-curve relation, even if the true underlying relation is linear. The authors conclude that nonlinear risk factor associations observed in primary or secondary prevention cohorts should be interpreted with caution because they may be consistent with an un-
Observational Study with Systematic Error in Na Assessment: NHANES II
Case of Systematic Error Leading to Bias: Increased CVD Mortality in Persons with Lowest Na (by Quartile of Na Intake in mg/d)

P=0.03
Q1 vs Q4

1st: 1.8
2nd: 1.94
3rd: 1.48
4th: 1

Na Quartile of based on mg of Na/d

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

<table>
<thead>
<tr>
<th>Quartile of Sodium Intake:</th>
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<th>2nd</th>
<th>3rd</th>
<th>4(^{th}) (Highest)</th>
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<tr>
<td>Na (mg/d)</td>
<td>1,501</td>
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<tr>
<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
Evidence of Contamination in a Cohort Study (NHANESIII) Reporting Increased Mortality in Persons with Low Sodium Intake on 24Hr Dietary Recall Quartile of Sodium Intake: 

<table>
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<td>2,938</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8</td>
<td>26.4</td>
<td>26.3</td>
<td>26.6</td>
</tr>
</tbody>
</table>

Evidence of Massive Underreporting of Calorie Intake Leading to Systematic Error in Estimate or Sodium Intake

¹Cohen, JGIM 2008;23:1297-302
Reduced Systematic Error from Use of Na/Kcal Ratio as Exposure instead of Na/d

- 1st: Hazard Ratio (HR) = 1.25
- 2nd: Hazard Ratio (HR) = 0.9
- 3rd: Hazard Ratio (HR) = 0.9
- 4th: Hazard Ratio (HR) = 1

P = 0.26
Q1 vs Q4

Na Quartile of based on mg of Na/Kcal

1Cohen, JGIM 2008;23:1297-302
Extremely low levels are most likely the result of extreme undercollection.
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>
</tr>
</tbody>
</table>
Arguments Made by Those who Oppose Sodium Reduction

- Clinical trial of sodium reduction with hard clinical outcomes is needed
- Only ‘salt sensitive’ persons should reduce their salt intake
- Sodium reduction might be harmful

Such trials are impossible because of logistical, financial and ethical considerations.

No test available. Irrelevant given the massive scope of the blood pressure epidemic.

Extremely unlikely: 1) major methodological limitations of cohort studies + 2) over-interpretation of biomarkers
Trials of Sodium Reduction in Heart Failure by Paterna

- **Participants**
  - Hospitalized NYHA Class III Heart Failure
  - Intensive medication regimens
    - 100% ACEI
    - 100% Lasix
    - 85% Spironolactone

- **Medical management**
  - Unconventional, leading to untreated longterm volume depletion

Paterna, Am J Card 2009:103:93
No Effect of Reducing Sodium Intake on LDL Cholesterol

Harsha, Hypertension 2004;43;393
Key Points to Remember

- The estimated benefits of sodium reduction are substantial and warrant major public health efforts to reduce salt intake.

- Major methodological issues limit the usefulness of available cohort studies as a basis for guiding policy, much less reversing recommendations.