Chronic Disease Outcomes (and Issues): Perspectives from My Involvement on DRI, Dietary Guidelines and AHA Committees

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Outline

- DRI for Sodium
- Sodium Guidance in the US (IOM, DG, AHA)
- Recurring issues
  - Trials w/ surrogate outcomes vs observational studies w/ clinical outcomes
  - Progressive dose response, no threshold
- New [heightened importance] issues
  - Absolute vs calorie adjusted goals (or both)
  - Methodological ‘landmines’ in cohort studies
  - Urine excretion of electrolytes, ‘Bronze Standard’
    - Group vs individual level estimation
    - High intra-individual variation, unrelated to diet
Because the relationship between sodium intake and blood pressure is progressive and continuous without an apparent threshold, it is difficult to precisely set a UL, especially because other factors (weight, exercise, potassium intake, dietary pattern, and alcohol intake) also affect BP.

Among certain groups of individuals who are most sensitive to the blood pressure effects of increased sodium intake (e.g., the elderly, African Americans, individuals with hypertension, and diabetics), their UL may be lower. These groups also experience an especially high incidence of blood pressure-related cardiovascular disease.
### Upper Limit (UL) for Sodium by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Upper Limit (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 m</td>
<td>-</td>
</tr>
<tr>
<td>1-3 yr</td>
<td>1,500</td>
</tr>
<tr>
<td>4-8 yr</td>
<td>1,900</td>
</tr>
<tr>
<td>9-13 yr</td>
<td>2,200</td>
</tr>
<tr>
<td>14-18 yr</td>
<td>2,300</td>
</tr>
<tr>
<td>19-50 yr</td>
<td>2,300</td>
</tr>
<tr>
<td>51+ yr</td>
<td>2,300</td>
</tr>
</tbody>
</table>
## Timeline – Sodium Guidance in the US

<table>
<thead>
<tr>
<th>Year</th>
<th>Report</th>
<th>[Recommendation]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>IOM DRI</td>
<td>UL: 2,300 mg but maybe lower in certain groups (elderly, HTN, DM, AA) AI:1,500 mg</td>
</tr>
<tr>
<td>2005</td>
<td>DG Adv Committee 2005</td>
<td>&lt; 2,300 mg, others benefit from lower intake</td>
</tr>
<tr>
<td>2005</td>
<td>DG 2005</td>
<td>&lt; 2,300 mg</td>
</tr>
<tr>
<td>2006</td>
<td>AHA Lifestyle</td>
<td>&lt; 2,300 mg (interim)</td>
</tr>
<tr>
<td>2010</td>
<td>DG Adv Committee 2010</td>
<td>&lt; 1,500 mg</td>
</tr>
<tr>
<td>2010</td>
<td>DG 2010</td>
<td>&lt; 1,500 mg in 51+, HTN, DM, AA, CKD &lt; 2,300 mg</td>
</tr>
<tr>
<td>2010</td>
<td>AHA 2020 Strategic Goals</td>
<td>&lt; 1,500 mg (aspirational)</td>
</tr>
<tr>
<td>2014</td>
<td>AHA/ACC [NHLBI] Lifestyle</td>
<td>&lt; 2,400 mg</td>
</tr>
<tr>
<td>2015</td>
<td>DG Adv Committee 2015</td>
<td>&lt; 2,400 mg, as in AHA/ACC</td>
</tr>
<tr>
<td>2015</td>
<td>DG 2015</td>
<td>&lt; 2,300 mg, the UL</td>
</tr>
</tbody>
</table>
Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction
The American Heart Association’s Strategic Impact Goal Through 2020 and Beyond

Donald M. Lloyd-Jones, MD, ScM, FAHA, Chair;
Yuling Hong, MD, MSc, PhD, FAHA*; Darwvson Labarthe, MD, MPH, PhD, FAHA*;
Darwish Moazzamian, MD, DrPH, FAHA; Lawrence J. Appel, MD, MPH, FAHA;
Linda Van Horn, PhD, RD, FAHA; Kurt Greenlund, PhD*; Stephen Daniels, MD, PhD, FAHA;
Graham Nichol, MD, MPH, FAHA; Gordon F. Tomaselli, MD, PhD, FAHA; Donna K. Arnett, PhD, FAHA;
Gregg C. Fonarow, MD, FAHA; P. Michael Ho, MD, PhD; Michael S. Lauer, MD, FAHA;
Frederick A. Masoudi, MD, MPH; Rose Marie Robertson, MD, FAHA; Véronique Roger, MD, FAHA;
Lee H. Schawarman, MD, FAHA; Paul Sorlie, PhD; Clyde W. Yancy, MD, FAHA;
Wayne D. Rosamond, PhD, FAHA; on behalf of the American Heart Association Strategic Planning Task Force
and Statistics Committee

Abstract—This document details the procedures and recommendations of the Goals and Metrics Committee of the Strategic Planning Task Force of the American Heart Association, which developed the 2020 Impact Goals for the organization. The committee was charged with defining a new concept, cardiovascular health, and determining the metrics needed...
In the context of DASH-style dietary pattern and energy balance:

1) Fruit and vegetables ≥ 4.5 cups/day
2) Fish ≥ two 3.5-oz servings/wk
3) Fiber-rich whole grains ≥ three 1-oz servings/day
4) Sodium <1500 mg/day
5) Sugar-sweetened beverages ≤ 450 kcal (36 oz)/wk

“Intake goals are expressed for a 2000-kcal diet and should be scaled accordingly for other levels of caloric intake”
Calories
Estimated Mean Daily Sodium Intake in US, by Age/Sex Group, 2011-2

- Male
- Female

+ Recommended upper limit of intake for adults
++ Recommended intake for blacks, hypertensives, and middle- and older-aged adults
+++ Needed to replace obligatory losses (Dahl, 1958)
Estimated Mean Daily Calorie Intake in US, by Age/Sex Group, 2011-2
Correlation (r) Between Individuals’ Mean Daily Self-Reported Intake of Sodium, Potassium, and Calories

<table>
<thead>
<tr>
<th></th>
<th>Sodium (mg)</th>
<th>Potassium (mg)</th>
<th>Calories (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mg)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>0.64</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>0.81</td>
<td>0.73</td>
<td>1</td>
</tr>
</tbody>
</table>

Correlation (rho) between Sodium, Potassium, and Calories.
As Sodium Intake Is Reduced, So is Blood Pressure

Sacks, NEJM 2001;344:3

Typical Diet

-6.7
p<.0001

DASH Diet

-3.0
P<.0001

Systolic Blood Pressure

Lower 1,500
Intermediate 2,400
Higher 3,300

Average Achieved Sodium Level: mg/d
Intermediate Sodium Level by Kcal in Level in DASH Sodium Feeding Study
Sodium Targets by Kcal in Level in DASH Sodium Feeding Study

![Graph showing sodium targets by Kcal intake level in the DASH Sodium Feeding Study. The graph displays sodium intake in mmol/d for different Kcal intake levels, categorized as Low, Intermediate, and High. The categories are: 1600, 2100, 2600, 3100, and 3600 Kcal. The graph uses color coding (Green for Low, Yellow for Intermediate, and Red for High) to represent the sodium intake levels.](image-url)
Saturated Fat Intake (gmd) by kcal Level to Achieve Saturated Fat Goals of 7% and 14% in the DASH Feeding Studies
Effects of Absolute Intake of Sodium (mg/d) and Sodium Density (mg/kcal) on BP

- To be presented at AHA Epi/Lifestyle Meeting, March 2017

- Qualitative results
  - Both absolute Na intake and Na density were directly associated with blood pressure
Uncertainties about Calorie Adjustment

- Whether to adjust dietary recommendations
  - Considerations: scientific, practical, tradition
- Can a standardized approach be developed
- Which nutrients to adjust
- If yes, how to adjust:
  - kcal intake
  - body mass index
  - age
  - ? other
Measurement of Electrolyte Intake and Other Methodological Issues
Urinary Recovery of Potassium is Incomplete and Differs by Race and Diet: Percent of K Intake that is Excreted

<table>
<thead>
<tr>
<th></th>
<th>% Excreted</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>End of run-in</td>
<td>74 ± 25</td>
<td>67 ± 24</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>End of intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control diet</td>
<td>73 ± 27</td>
<td>74 ± 24</td>
<td>0.838</td>
<td></td>
</tr>
<tr>
<td>F/V diet</td>
<td>60 ± 21</td>
<td>53 ± 19</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>DASH diet</td>
<td>69 ± 17</td>
<td>50 ± 18</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Turban, JASN 2008;19:1396
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

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

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

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
Extremely High Variation in Urinary Na Excretion, even on a Constant Intake, in a Cosmonaut Related to Physiologic Variation

Rakova, Cell Metabolism, 2013;17;125–131
Examples of Results of Cohort Studies Published after DRI
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

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>HR</td>
<td>1.8</td>
<td>1.94</td>
<td>1.48</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Na (mg/d)</th>
<th>Energy Intake (kcal)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (Lowest)</td>
<td>1,501</td>
<td>1,282</td>
<td>25.8</td>
</tr>
<tr>
<td>2nd</td>
<td>2,483</td>
<td>1,762</td>
<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>
</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
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
Estimated Sodium Excretion (from 1 ‘spot’ early morning void) and Risk of Death or CVD Events in PURE Study (n=101,945)
Direct, Progressive Relationship of CVD with Urinary Sodium Excretion* in 2,275 Individuals with Prehypertension

Cook, Circ 2014:129:981

*Based on 24 hr urine collections (median = 5)
Conclusion

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.