Salt, Substitutes, and Strokes: Addressing Cardiovascular Diseases in Rural China through Sodium Reduction
Duke-NUS / Duke-Durham Bridging Symposium: Global Burden of Non-communicable Diseases with a focus on Vascular Disease

March 27, 2015

Lijing L. Yan, NCD program, Global Health Research Center, Duke Kunshan University
Our Menu

- **Cold appetizer**: CVD globally and in China
- **Hot appetizer**: salt consumption in rural China
- **Salad**: Salt substitutes and blood pressure
- **Main course**: CRHI-SRS
- **Dessert**: SSaSS
## Global Burden of Disease 2010: Years of Life Lost Rankings

<table>
<thead>
<tr>
<th>1990</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lower respiratory infections</td>
<td>1 Ischemic heart disease</td>
</tr>
<tr>
<td>2 Diarrheal diseases</td>
<td>2 Lower respiratory infections</td>
</tr>
<tr>
<td>3 Preterm birth complications</td>
<td>3 Stroke</td>
</tr>
<tr>
<td>4 Ischemic heart disease</td>
<td>4 Diarrheal diseases</td>
</tr>
<tr>
<td>5 Stroke</td>
<td>5 Malaria</td>
</tr>
<tr>
<td>6 Malaria</td>
<td>6 HIV/AIDS</td>
</tr>
<tr>
<td>7 COPD</td>
<td>7 Preterm birth complications</td>
</tr>
<tr>
<td>8 Protein-energy malnutrition</td>
<td>8 Road injury</td>
</tr>
<tr>
<td>9 Tuberculosis</td>
<td>9 COPD</td>
</tr>
<tr>
<td>10 Neonatal encephalopathy</td>
<td>10 Neonatal encephalopathy</td>
</tr>
</tbody>
</table>

## Rapid Health Transition in China: Years of Life Lost Rankings

<table>
<thead>
<tr>
<th>Year</th>
<th>Rank</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>1</td>
<td>Lower respiratory infections</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Drowning</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Neonatal encephalopathy</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Self-harm</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Preterm birth complications</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Road injury</td>
</tr>
<tr>
<td>2010</td>
<td>1</td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Road injury</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Liver cancer</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Stomach cancer</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Self-harm</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Lower respiratory infections</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Oesophageal cancer</td>
</tr>
</tbody>
</table>

Leading Causes of Death, China 2008

Urban

- Cerebrovascular Disease: 12.23
- Heart Disease: 19.62
- Malignant Neoplasms: 5.08
- Diseases of the Respiratory System: 11.86
- Endocrine, Nutritional & Metabolic Diseases: 3.43
- Injury & Poisoning: 1.01
- Other: 27.12

Rural

- Cerebrovascular Disease: 10.45
- Heart Disease: 21.73
- Malignant Neoplasms: 8.59
- Diseases of the Respiratory System: 16.88
- Endocrine, Nutritional & Metabolic Diseases: 1.79
- Injury & Poisoning: 1.06
- Other: 14.11

Australia | China | India | UK
Reducing sodium intake significantly reduced systolic and diastolic blood pressure in adults and children. The reduction in blood pressure was detected across a wide range of intake levels, and was independent of baseline sodium intake. Reducing sodium intake to <2 g/day was more beneficial for blood pressure than reducing sodium intake but still consuming >2 g/day. Reducing sodium intake had no significant adverse effect on blood lipids, catecholamine levels or renal function. Higher sodium intake was associated with higher risk of incident stroke, fatal stroke and fatal coronary heart disease. There was no association between sodium intake and all-cause mortality, incident cardiovascular disease and non-fatal coronary heart disease. However, the strong positive relationship between blood pressure and these outcomes provides indirect evidence that reducing sodium intake can improve these outcomes through a beneficial effect on blood pressure. Based on the entire body of evidence, WHO generated the following recommendations for sodium intake in adults and children.
WHO strongly recommends:

✧ Adults: a reduction to <2g/day sodium (<5g/day salt)
✧ Children: a reduction in Na intake (max. <2g/day relative to age)
✧ To reduce blood pressure, and potentially CVD.
Salt Consumption in China

### China: Urban, Rural Salt Intake

![Bar chart showing salt intake in China](chart1)

### China: Urban, Rural Na Intake

![Bar chart showing sodium intake in China](chart2)

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**Note:** Data from WASH website [http://www.worldactiononsalt.com](http://www.worldactiononsalt.com). WHO 2006《人群减少钠盐摄入的技术报告》. WHO 2010《建设减盐支持性环境技术报告》.
Five Priority Interventions to Fight NCDs in LMICs proposed by the Lancet

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Cost per person per year (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>China</td>
</tr>
<tr>
<td>1. Tobacco use</td>
<td>0.14</td>
</tr>
<tr>
<td>Accelerated implementation of the WHO Framework Convention on Tobacco Control⁵</td>
<td></td>
</tr>
<tr>
<td>2. Dietary salt</td>
<td>0.05</td>
</tr>
<tr>
<td>Mass-media campaigns and voluntary action by food industry to reduce consumption⁶</td>
<td></td>
</tr>
<tr>
<td>3. Obesity, unhealthy diet, and physical inactivity</td>
<td>0.43</td>
</tr>
<tr>
<td>Mass-media campaigns, food taxes, subsidies, labelling, and marketing restrictions¹⁶</td>
<td></td>
</tr>
<tr>
<td>4. Harmful alcohol intake</td>
<td>0.07</td>
</tr>
<tr>
<td>Tax increases, advertising bans, and restricted access¹⁵</td>
<td></td>
</tr>
<tr>
<td>5. Cardiovascular risk reduction</td>
<td>1.02</td>
</tr>
<tr>
<td>Combination of drugs for individuals at high risk of NCDs¹⁰</td>
<td></td>
</tr>
<tr>
<td>Total cost per person *</td>
<td>1.72</td>
</tr>
</tbody>
</table>

* Total cost per person is the sum of the costs of the five interventions.

Lancet 2011; 377: 1438–47
## Sources of Dietary Sodium in Rural China

*N=839 from INTERMAP study*

<table>
<thead>
<tr>
<th>Source</th>
<th>mg/d</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt added during cooking</td>
<td>3,025</td>
<td>77.5</td>
</tr>
<tr>
<td>Soy sauce</td>
<td>255</td>
<td>6.5</td>
</tr>
<tr>
<td>Vegetables (pickled)</td>
<td>191</td>
<td>4.9</td>
</tr>
<tr>
<td>Sodium bicarbonate (tenderiser)</td>
<td>98</td>
<td>2.5</td>
</tr>
<tr>
<td>Noodles</td>
<td>89</td>
<td>2.3</td>
</tr>
<tr>
<td>Bread</td>
<td>88</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3,746</td>
<td>96.9</td>
</tr>
</tbody>
</table>
What is a Salt Substitute?
How do Salt Substitutes Work?

✧ Decrease sodium chloride (100% to 65%)
✧ Increase Potassium chloride (0% to 25%)

Blood Pressure

Guideline:
Potassium intake for adults and children
Salt Substitutes Studies

- China Salt Substitute Study
- Pulse Wave Analysis
- Taste and Acceptability Study
- China Salt Substitute Study – Tibet
- Meta-analysis
Meta Analysis (N=11 trials)
Effect on Blood Pressure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Salt substitute</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geelenjse et al (1994)</td>
<td>-7</td>
<td>1.95</td>
<td>49</td>
<td>-1.6</td>
</tr>
<tr>
<td>Gilleran et al (1996)</td>
<td>-8.2</td>
<td>21.55</td>
<td>20</td>
<td>-1.6</td>
</tr>
<tr>
<td>Chang et al (2006)</td>
<td>-12.2</td>
<td>22.63</td>
<td>139</td>
<td>-4.5</td>
</tr>
<tr>
<td>CSSS (2007)</td>
<td>-3.34</td>
<td>21.51</td>
<td>306</td>
<td>2.24</td>
</tr>
<tr>
<td>Charlton et al (2008)</td>
<td>-6.4</td>
<td>15.7</td>
<td>40</td>
<td>-2.9</td>
</tr>
<tr>
<td>Zhou et al (2009)</td>
<td>-6.5</td>
<td>18.6</td>
<td>119</td>
<td>3.1</td>
</tr>
<tr>
<td>Mu et al (2009)</td>
<td>-5.9</td>
<td>12.08</td>
<td>101</td>
<td>1.3</td>
</tr>
<tr>
<td>Sarkkinen et al (2011)</td>
<td>-7.5</td>
<td>7.52</td>
<td>22</td>
<td>3.8</td>
</tr>
<tr>
<td>Wu et al (unpublished)</td>
<td>-19</td>
<td>14.41</td>
<td>110</td>
<td>-10.3</td>
</tr>
<tr>
<td>Zhao et al (unpublished)</td>
<td>-13.8</td>
<td>24.92</td>
<td>141</td>
<td>-6.6</td>
</tr>
<tr>
<td>Zhoubi et al (unpublished)</td>
<td>-18.1</td>
<td>24.22</td>
<td>224</td>
<td>-7.4</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>1271</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 2.28; Chi² = 17.23; df = 10 (P = 0.07); I² = 42%
Test for overall effect: Z = 4.67 (P < 0.000001)

Unpublished results; CONFIDENTIAL.

Overall effect on SBP
Overall effect on DBP
China Rural Health Initiative – Sodium Reduction Study: the effects of a community-based sodium reduction program on 24hr urinary sodium and blood pressure in rural China
Objective

To define the effects of a novel, low-cost, scalable and sustainable, community-based salt reduction strategy on salt consumption, as estimated from 24-hour urinary sodium excretion
Design

120 villages

Randomized

60 villages in intervention group

Randomized

30 villages without price subsidy

30 villages with price subsidy

60 villages in control group
Intervention and control

**Intervention**

- **Health education**
  - Health belief model
    - Awareness
    - Beliefs
    - Behavior
  - Key messages
  - Implementation Strategy

- **Access to salt substitute**
  - Salt Substitute
    - 65-75% NaCl
    - 15-25% KCl
    - 0-10% MgSO4
  - Double cost of usual salt
  - Promotion of sales

**Control: usual practice**
PHOTOS OF VILLAGE KICK-OFF MEETINGS
多吃盐不健康 少吃盐活得长

中国营养学会权威推荐
每人每天吃盐量应少于6克

低钠盐不减咸 血压降健康添

低钠盐不减咸 血压降健康添

- 和普通盐相比，低钠盐的钠含量较低。同时添加了钾，咸味不变。
- 嘴里有味道，不会改变味道，也能预防高血压和其他心脑血管疾病。
- 咸味关键在钠。低钠盐也不宜多吃，如果吃得过多，就失去减盐的意义。
- 患有严重肾病或在吃保钾利钠药的病人，请咨询医生是否适合吃低钠盐。
Outcomes

- **Primary**
  - 24h urinary sodium (90% power, 11 mmol/day difference)

- **Secondary**
  - 24-hour urinary potassium
  - Na/K ratio
  - Knowledge, attitude and practices
  - Systolic and diastolic blood pressure
  - Proportion with hypertension

- Questionnaire, examination and 24hr urine collection
Analysis

- Intention to treat, no imputation for missing value
- GEE model accounting for cluster effects
- Primary comparison of 60 intervention vs. 60 control villages
- Secondary comparison of 30 price subsidy vs. 30 no price subsidy villages
- Pre-defined subgroups – age, sex, education, BMI, smoking, alcohol
Survey data

- 60 intervention villages
  - 1,295 questionnaire and examination
  - 1,063 urine sample (82%)

- 59 control villages
  - 1,272 questionnaire and examination
  - 1,001 urine sample (77%)
Characteristics of survey participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Drinks alcohol (%)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Education &gt;9 years (%)</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>56</td>
<td>58</td>
</tr>
</tbody>
</table>
## Knowledge on Salt: Rural Chinese 2010

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Correct</th>
<th>Incorrect</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.8 Which of the following will reduce blood pressure? (read out one by one)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.8.1 Medicine</td>
<td>□ 1 Yes □ 0 No □ 9 Don’t know</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.8.2 Smoking</td>
<td>□ 1 Yes □ 0 No □ 9 Don’t know</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.8.3 Eat less salt</td>
<td>□ 1 Yes □ 0 No □ 9 Don’t know</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.8.4 Eat more food</td>
<td>□ 1 Yes □ 0 No □ 9 Don’t know</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Category</th>
<th>% Correct</th>
<th>Harm</th>
<th>Salt reduction</th>
<th>RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct</td>
<td>57</td>
<td>32</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Incorrect</td>
<td>14</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>29</td>
<td>60</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Strengths

- Robust large scale randomized design
- Excellent statistical power for primary outcome
- Gold standard 24 hour urine collections
- Simple, low-cost, scalable intervention

Weakness

- Limited power for secondary blood pressure and hypertension outcomes
Conclusions

- Anticipated effects on sodium excretion were achieved.
- Effects appear to have been driven primarily by use of the salt substitute (through provision of education and access).
- Subsidization of the price of salt substitute was important for uptake.
- Salt substitution may have significant potential to reduce the large burden of blood-pressure related disease in rural China.
Acknowledgments

Partial list:
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- Yangfeng Wu
- Xuejun Yin
- Jing Zhang

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- Zhifang Li
- Jingpu Shi
- Jixin Sun
- Yan Yu
- Jixin Zhang
- Ruijuan Zhang
- Yuhong Zhang
- Yi Zhao
- Bo Zhou

Major Sponsors:
- NHLBI, NIH, USA
- UnitedHealth Group
- US CDC
- Medtronic Foundation
- China MoH
- Local governments
Salt Substitute and Stroke Study: The SSaSSS Trial

Steering Committee: Bruce Neal (Chair), Paul Elliott, Darwin Labarthe, Nicole Li, Yangfeng Wu, Lijing L. Yan

Chair of IDMC (DSMB): Rory Collins

SCIENCE. 12 SEPTEMBER 2014 • VOL 345 ISSUE 6202; PAGES 1268-9.
Salt Reduction and Hard Outcomes

- Abundant (generally uncontroversial) evidence on the relationship between salt and blood pressure
- Controversies regarding the relationship between salt and hard outcomes (morbidity and mortality)
  - Observational studies generally shown lower salt associated with better outcomes
  - Meta-analyses on mortality using data from trials on blood pressure – inconclusive and controversial
  - No trial on salt and hard outcomes to date
Why we care about stroke:
High mortality rate in China

Figure from: Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. The Lancet Neurology, Volume 8, Issue 4, Pages 345-354
Why we care about stroke: High economic burden

Figure from: PLoS One. 2010; 5(9): e13041. Published online 2010 September 28. doi: 10.1371/journal.pone.0013041

GRP: Gross Regional Product

Rural median income = ￥11,401
Objectives

• Primary objective:
  Define the effects of salt substitutes (sodium reduction and potassium enrichment) on the risk of fatal and non-fatal stroke.

• Secondary objective:
  Determine the effects of salt substitutes on major vascular events and total mortality.
Methods

- **Study Design**: a large-scale cluster-randomised controlled trial (1:1 allocation of 600 villages)
- **Study Population**: stroke patients or at high risk (35/vil.)
- **Intervention**: free supply of salt substitutes to cover household cooking; duration 4-6 years.
- **Control**: continue to buy and use regular salt, health education on salt reduction at baseline.
- **Outcome Evaluation**: using telephone calls, every 6 months + home visits + adjudication com. (5 years)
Site selection

Liaoning
Hebei
Shanxi
Shaanxi
Ningxia

Staged Launches by Province from March 2014 to March 2015
Figure 1 – Study flow chart – site selection and randomization

- Each Province (Hebei, Liaoning, Ningxia, Shanxi, and Shaanxi)
  - Province 1 (Hebei)
    - 2 counties
      - 24 townships (12 per county)
        - 120 villages (9 per township)
          - Randomisation: 60 intervention villages, 60 control villages
  - Provinces 2-3 etc.
    - Counties
      - Townships
        - Villages
          - Randomisation: Int., Cont.

IN TOTAL
- 5 Provinces
- 10 counties
- 120 townships
- 600 villages
- Randomisation: 300 intervention villages, 300 control villages
- 4200 high risk individuals in each Province (35 per village)
- 21,000 high risk individuals in total
- 10,500 intervention
- 10,500 control
Figure 2 – Participants, surveillance and surveys

For 600 villages (intervention and control)

**PARTICIPANTS (total 21,000)**

- **35 high risk individuals identified in each village**
  - All people with history of prior stroke (on average 25 per village), or
  - History of high blood pressure (SBP>160mmHg) and age >60 years old (on average 100 per village)

**SURVEILLANCE (all 21,000)**

- Primary and secondary outcomes
  - Fatal and non-fatal strokes
  - Total major vascular events
  - All deaths

**SURVEYS of minimum 80 villages (40 intervention and 40 control) each year**

**Survey data collected**
- In at least 15 individuals from each selected village each year

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Year 1</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Year 2</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Year 3</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Year 4</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3000</strong></td>
<td><strong>3000</strong></td>
</tr>
</tbody>
</table>

**Process indicators**
- Sodium consumption and potassium consumption estimated from 24-hour urine collections
- Blood pressure
- Self-reported efforts to reduce salt consumption
- Self-reported use of salt substitute
Savoring ... 

• High salt intake: a major modifiable risk factor for NCDs
• Salt substitutes: potentially a cost-effective approach in LMICs
• RCTs demonstrated the effect of salt substitutes on blood pressure.
• CRHI evaluated the community-based sodium reduction intervention in rural China
• A new study to investigate SS and stroke (SSaSS)
Areas of collaborations

- Resource-limited disadvantaged population
- Cardio-metabolic diseases
- Primary and secondary prevention and rehabilitation
- System-oriented community-based policy-relevant implementation research
DKU Master of Science in Global Health

Who should apply?
- Recent graduates with an interest in global health
- Professionals with research experience and/or who wish to pursue a free standing MSc-GH
- Medical students and residents wishing to prepare for a medical career in global health

Structure
- 1.5 – 2 years
- 6 core courses and 5 electives
- Field research project >10 weeks
- Research-based thesis

Employment
- Medical schools and PhD programs
- NGOs and government
- MNCs

Features
- Expert, multidisciplinary faculty
- Funded fieldwork opportunities
- Focus on applied, relevant research and skills
- Small and diverse cohort of students
- Professional development and career advising
MSc-GH Field Projects Location

**USA**
- North Carolina
- California

**Latin America & Caribbean**
- Argentina
- Brazil
- Haiti
- Honduras
- Peru

**Africa**
- South Africa
- Ghana
- Tanzania
- Zimbabwe

**Asia**
- China
- India
- Singapore
- Sri Lanka
- Cambodia
- Laos
- Nepal

**Ethiopia**
- Rwanda
- Uganda
- Kenya
THANK YOU 😊

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