Challenges in conducting clinical trials on the association between sodium and health effects
Disclosures

Related to this presentation
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Unrelated to this presentation
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Notes
• All fees are paid to the George Institute for Global Health
• The George Institute for Global Health holds research contracts with multiple commercial and other entities
Key publications


Outline

Background and pilot work

The challenges

The Salt Substitute and Stroke Study (SSaSS)
Background

- Excess sodium clearly raises blood pressure
- High blood pressure clearly increases vascular risk
- Sodium intake inconsistently associated with vascular risk
- Reducing sodium intake clearly reduces blood pressure
- Lowering blood pressure clearly lowers vascular risk
- No adequately powered trial defining effects of lowering sodium on vascular risk
- Sodium reduction widely recommended but mostly not implemented
Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial

The China Salt Substitute Study Collaborative Group*

Objective Dietary sodium and potassium consumption is associated with blood pressure levels. The objective of this study was to define a practical and low-cost method for the control of blood pressure by modification of these dietary cations in rural Chinese.

Methods This study was a double-blind, randomized, controlled trial designed to establish the long-term effects of a reduced-sodium, high-potassium salt substitute (65% sodium chloride, 25% potassium chloride, 10% magnesium sulphate) compared to normal salt (100% sodium chloride) on blood pressure among high-risk individuals. Following a 4-week run-in period on salt substitute, participants were randomly assigned to replace their household salt with either the study salt substitute or normal salt for a 12-month period.


Keywords: blood pressure, cardiovascular disease, China, potassium, randomized controlled trial, salt, sodium

Correspondence to Bruce Neal, The George Institute for International Health, University of Sydney, PO Box M201, Camperdown, Sydney, NSW2050, Australia
Tel: +61 2 9993 4558; fax: +61 2 9993 4502; e-mail: bneal@george.org.au

or to Wu Yangfeng, The George Institute for International Health China, Room 1302, Tower B, Horizon Tower, No. 6 Zhichun Road, Haidian District, Beijing, 100088 PR China
Tel: +86 10 8280 0577; fax +86 10 8280 0177; e-mail: ywu@george.org.cn
RESEARCH ARTICLE

The Effects of a Community-Based Sodium Reduction Program in Rural China – A Cluster-Randomized Trial

Nicole Li¹, ², ³, 4+, Lijing L. Yan¹, ⁴‡, Wenyi Niu⁵, Chen Yao⁶, Xiangxian Feng⁷, Jianxin Zhang⁸, Jingpu Shi⁹, Yuhong Zhang¹⁰, Ruijuan Zhang¹¹, Zhixin Hao¹, Hongling Chu¹, ⁵, Jing Zhang¹, Xian Li¹, Jianhong Pan⁶, Zhifang Li⁷, Jixin Sun⁸, Bo Zhou⁹, Yi Zhao¹⁰, Yan Yu¹¹, Michael Engelgau¹², Darwin Labarthe⁶, Jixiang Ma¹³, Stephen MacMahon², ³, Paul Elliott¹⁴, Yangfeng Wu¹, ⁵, ⁶‡, ⁷, Bruce Nea², ³, ¹⁴, ¹⁵

¹ The George Institute for Global Health at Peking University Health Science Center, Beijing, China, ² The George Institute for Global Health, Sydney, Australia, ³ Sydney Medical School, the University of Sydney, Sydney, Australia, ⁴ Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States of America, ⁵ School of Public Health, Peking University Health Science Center, Beijing, China, ⁶ Peking University Clinical Research Institute, Beijing, China, ⁷ Changzhi Medical College, Changzhi, Shanxi, China, ⁸ Hebei Province Center for Disease Prevention and Control, Shijiazhuang, Hebei, China, ⁹ First Hospital of China Medical University, Shenyang, Liaoning, China, ¹⁰ Ningxia Medical University, Yinchuan, Ningxia, China, ¹¹ Xi’an Jiaotong University, Xi’an, Shaanxi, China, ¹² United States Centers for Disease Control and Prevention, Beijing, China, ¹³ Chinese Center for Disease Control and Prevention, Beijing, China, ¹⁴ Imperial College London, United Kingdom, ¹⁵ Royal Prince Alfred Hospital, Sydney
The Salt Substitute and Stroke Study (SSaSS)

Rationale, design, and baseline characteristics of the Salt Substitute and Stroke Study (SSaSS)—A large-scale cluster randomized controlled trial

Bruce Neal, PhD, a,b Maoyi Tian, PhD, a,c Nicole Li, PhD, a Paul Elliott, PhD, b Lijing L. Yan, PhD, c,d Darwin R. Labarthe, PhD, e Liping Huang, MPhil, f Xuejun Yin, MPH, g Zhixin Hao, MD, c Sandrine Stepien, MBiostat, a Jingpu Shi, MSc, f Xiangxian Feng, PhD, g Jianxin Zhang, PhD, h Yuhong Zhang, MSc, i Ruijuan Zhang, MPH, i and Yangfeng Wu, PhD c,k

Sydney, Australia; London, United Kingdom; Beijing, Kunshan, China; Chicago, IL; Shenyang, Changzhi, Shijiazhuang, Yinchuan, and Xi’an, China

Abstract  Lowering sodium intake with a reduced-sodium, added potassium salt substitute has been proved to lower blood pressure levels. Whether the same strategy will also reduce the risks of vascular outcomes is uncertain and controversial. The SSaSS has been designed to test whether sodium reduction achieved with a salt substitute can reduce the risk of vascular disease. The study is a large-scale, open, cluster-randomized controlled trial done in 600 villages across 5 provinces in China. Participants have either a history of stroke or an elevated risk of stroke based on age and blood pressure level at entry. Villages were randomized in a 1:1 ratio to intervention or continued usual care. Salt substitute is provided free of charge to participants in villages assigned to the intervention group. Follow-up is scheduled every 6 months for 5 years, and all potential endpoints
The optimal trial design

- International, randomised, double-blind trial
- Representative population samples
- Intervention based upon sodium reduced foods
- Major adverse cardiovascular event outcome
- Adjudicated endpoints
- High statistical power
- Quality of life, cost-effectiveness assessments
- Broad-based multidisciplinary collaboration
The challenges

• Statistical power
• Intervention
• Recruitment
• Follow-up
• Outcome choice
• Outcome ascertainment
• Translation into policy
• Funding
Funding

• Potential funding bodies
• Quantum
• Duration
Statistical power

Must provide good test of hypothesis

• Exposure difference between groups (drives magnitude of treatment effect)
• Event rate for primary outcome
Participants

Align with design and implementation plans
• Likely to have events of interest
• Identifiable
• Able to be followed
• Amenable to intervention
The intervention

Feasible, affordable, effective and actionable

• Education
• Low sodium food supply
• Salt substitution
Follow-up

Completeness essential
• Telephone
• Face-to-face
• Routinely collected data
• Combination

• Process measures
Outcome choice

Maximise potential for testing hypothesis and delivering a result that will have impact

• Sensitive to effects of sodium reduction
• Meaningful to users of the research
Outcome ascertainment

Assurance of diagnoses to maximise power and impact
• Sensitive
• Specific
• Adjudication committee
Translation into policy

Ensure trial result (positive or negative) will be used
• Design with translation in mind
• Involve potential users of the research
  – Industry
  – Government
  – Consumers
  – Civil society
The Salt Substitute and Stroke Study (SSaSS)
Aims

Primary
The primary objective is to evaluate amongst a high risk population group the effects of sodium reduction achieved through the use of salt substitute on the risk of fatal or non-fatal stroke

Secondary
To determine the effects on:
• Major vascular events (stroke, acute coronary syndrome or vascular death)
• Total mortality

Safety
• Hyperkalaemia
Design

The trial is an open, large-scale, cluster-randomized, controlled trial done in rural China with the village as the unit of randomisation.
Participants - inclusion

35 high risk individuals per village

• Prior stroke
AND/OR
• Age 60 years or over and with uncontrolled high blood pressure
  • SBP>=140mmHg if on blood pressure lowering medication, or
  • SBP>=160mmHg if not on blood pressure lowering medication
AND
• Ownership of a phone by the participant or a household member

The goal was to recruit as many individuals with a history of stroke as possible in each village.
Participants - exclusion

- Participant or family member is using a potassium-sparing diuretic
- Participant or family member is using a potassium supplement
- Participant or family member has known serious renal impairment
- Participant or family member has other reason for concern about use of salt substitute
- Participant is not expected to live longer than 6 months from the date of assessment as estimated by the village doctor
- Participant eats most meals outside the home
Randomisation

- Randomization done by computer through assignment of a random number with stratification by county and a 1:1 allocation of villages to the sodium reduction program or control.
- Randomisation done only after all participants in the villages had been recruited and the baseline survey has been completed.
Intervention and control

**Intervention**
- Provision of reduced-sodium salt substitute to replace salt use amongst the 35 high risk individuals in the intervention villages.
- Sufficient salt substitute to cover the household cooking and food preservation requirements
- Advice to try to reduce the total amount of salt substitute used compared to prior salt consumption
- Advice about potential benefits of using salt substitute instead of regular salt

**Control**
- Usual care
Safety

• The salt substitute is considered generally safe but may cause hyperkalaemia if consumed in a very large quantity (more than 50g/day), if serious renal impairment is present or if there is concurrent use of potassium-sparing or potassium-supplementing medicines.

• Hyperkalaemia is the primary safety outcome.
Follow-up

All participants every 6 months for study outcomes, all hospitalisations, other serious illnesses, safety
• Planned telephone +/- face-to-face
• Then all face-to-face
• Now routinely collected data +/- face-to-face

Random sample every 12 months for process measures
• Face-to-face
• 20 individuals from 60 villages
• Urine, blood pressure, use of salt substitute
Masked endpoint adjudication

All suspected strokes, deaths and non-fatal ACS

Additional data sought
• During follow-up visit (including verbal autopsy for deaths)
• From hospital records
• From rural health insurance scheme and mortality registry

Adjudication committee of Chinese physicians
Statistical power – primary outcome

80% power (with a two-sided alpha=0.05) to detect a 13% or greater relative risk reduction for stroke

- 600 clusters (300 intervention and 300 control)
- 35 individuals in each cluster
- 5 year mean follow-up
- 3.5%p.a. stroke rate
- 3mmHg SBP difference
- ICC of 0.04
Interim monitoring

Steering Committee will review
• Overall outcome event rates
• Unblinded differences between randomised groups for:
  • Urinary sodium
  • Urinary potassium
  • Blood pressure
  • Use of salt substitute

• No uncertainty about effects of salt substitute/salt on these intermediate markers
Independent data monitoring

Review un-blinded safety and efficacy data throughout the course of the trial. The IDMC will advise the SSaSS Steering Committee Chair if premature discontinuation of the study or any other change is recommended. IDMC meetings are held every 6 to 12 months depending upon the recommendation of the committee.

Membership and Charter agreed
Current status

- >99% complete follow-up for primary outcome at 24 months
- Blood pressure difference slightly greater than power assumption
- Suspected stroke event rate far above power assumption, but adjudicated event rate slightly below
Current challenges

- Funding
- Outcome event confirmation
- On track to meet objectives as planned
Challenges in conducting clinical trials on the association between sodium and health effects