Official title of the study: SalT Reduction InterVEntion: Examination of the metabolic, behavioral and health consequences of reducing salt intake. A randomized controlled trial in a real life setting.

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English summary of the *Danish Scientific Ethical Committee protocol*

PROTOCOL SalT Reduction InterVEntion (STRIVE)

Project Title

English Title: SalT Reduction InterVEntion (STRIVE): Examination of the Metabolic, Behavioral and Health Consequences of Reducing Salt Intake. A Randomized Controlled Trial in a Real-Life Setting.

Danish title: "Brød og Sundhed: Undersøgelse af de stofskifte-, adfærds- og helbredsmæssige konsekvenser af at reducere saltindtaget? Et randomiseret kontrolleret forsøg "

Sponsor/ Collaborators

Principal Investigator: Ulla Toft
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Affiliation: Bispebjerg Hospital

Collaboration:

The project is based on collaboration between several relevant partners:

- Center for Clinical Research and Prevention (CCRP), Frederiksberg/Glostrup, Denmark (Ulla Toft, Kirsten Schroll Bjørnsbo and Allan Linneberg)
- DTU Food; National Food Institute, Søborg, Denmark (Anne Dahl Lassen, Nanna Louise Riis and Ellen Trolle)
- Danish Veterinary and Food Administration, Ministry of Environment and Food of Denmark (Hanne Høberg Hansen and Else Molander)
- Clinical Physiology/Nuclear Medicine Section, Glostrup Hospital, Denmark (Niklas Rye Jørgensen)
- Wolfson Institute of Preventive Medicine, London, UK (Graham MacGregor)
- Lantmännen Cerealia A/S (Jan H. Poulsen).

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Study aim

This controlled randomized trial deals with 14+ weeks of intervention with a) bread with gradually reduced salt content, b) combination of salt-reduced bread and dietary counseling in comparison with a control group (bread with standard salt content). Participants will be recruited as families living in the local area of the production bakery in the southwestern part of the Capital Region of Denmark. The study aims to elucidate the metabolic, behavioral and health consequences of reducing salt intake and to explore the effect of different salt reduction strategies among families.

Motivation for Salt intervention

Excess dietary sodium has a major role in the pathogenesis of hypertension, a leading risk factor for premature death in the world [1,2]. The dietary salt intake in most countries worldwide, including

Denmark, is far beyond the recommended level (<5-6 gram/day) [3] and population-based salt reduction has been rated to be one of the most cost-effective strategies to prevent cardiovascular disease (CVD)[4,5]. A lower salt diet, if continued, may lessen the subsequent rise in blood pressure (BP) with age, which would have major public health implications in terms of preventing the development of hypertension and CVD later in life. In a report developed for the Danish Ministry of Food, Agriculture and Fisheries, we have estimated that a reduction in the mean salt intake of 3 gram/day in the Danish population would reduce fatal and non-fatal cases of CVD by 1,700-2,800 annually and reduce health care costs by up to two billion DKK per year [6]. Much less studies in this area are done among children. However, there is good evidence that salt intake plays an important role in regulating BP in children too [7]. Although the magnitude of the association between salt reduction and blood pressure in children is relatively modest, blood pressure follows a tracking pattern from childhood into adulthood; therefore, the public health benefits of shifting the distribution of population levels is important. Additional consequences of excess salt intake during early life include increased risk of obesity and the development of taste preferences for saltier foods [8].
Several countries including Denmark have initiated national programs to decrease salt intake in the population [9,10]. However, some recent studies have shown a U-shaped association between sodium intake and cardiovascular disease and currently the effect of salt reduction on morbidity and mortality in the population is heavily discussed [9,11,12,13].
In addition to a better understanding of the health effects of a reduced salt intake, there is a need for better evidence regarding effective strategies to reduce salt intake in Denmark and other similar countries. National programs to reduce salt intake on a population-based level relies mainly on food product reformulation as up to 80% of the salt intake in most countries comes from salt added to processed foods [14]. The biggest contributor of dietary sodium intake in Denmark is bread. Therefore, reducing the sodium content in bread could be a relevant part of an effective strategy to reduce the sodium intake of the Danish population. Because sudden large reduction of salt can make foods unacceptable to consumers [15], a gradual reduction of the salt content in small steps is generally recommended [3,16].
To meet the national goal of lowering salt intake by 3 g/d, reformulation of a single food cannot stand alone. Dietary counseling is another possible strategy to reduce salt intake.
All in all, there is a need for high quality studies carried out in "real life settings" over a longer period.

Objectives
The overall aim of this study is to investigate the metabolic, behavioral and health consequences of reducing salt intake and to explore the effect of different salt reduction strategies among families. More specifically the objectives are:

- to examine the effects of two different salt reduction interventions (A. gradually lowering salt content in bread; A+B. intervention combining salt reduced bread and dietary counseling) on the overall dietary intake (including salt), salt-taste sensitivity and preferences

- to examine the (potential adverse) effects of different levels of salt reduction on selected cardiovascular risk factors (blood pressure, blood lipids, renin, aldosterone, noradrenaline, adrenaline, plasma glucose, Hb1AC, anthropometry)

- to explore the mechanisms in the possible association between salt intake, sugar-sweetened soft drink consumption and obesity.

Methods

The project will be carried out at the Center for Clinical Research and Prevention (CCRP), formerly known as *Research Center for Prevention and Health (RCPH), 'The Population Surveys in Glostrup'*, which has more than 50 years of experience in conducting population surveys. Data collecton is scheduled to be completed during the period 1 January 2018 to August 2018 and it is expected that 450 children and adults divided into 120 families will participate.

At baseline and endpoint participants will be examined about salt intake (24 hr urine collection, 7-day dietary record), salt preferences and salt sensitivity, blood pressure, anthropometry, blood lipids, sugar metabolism and hormones. The intervention will last 14+ weeks.

Study Design

STRIVE (SalT Reduction InterVEntion) is a single blinded, cluster randomized controlled trial, with children and adults recruited as families and randomly assigned to three parallel intervention arms (A: salt reduced bread; A+B: Salt reduced bread and dietary counseling; C: Bread with standard salt content).
Children and parents are targeted as families, to reflect the real life setting that salt is consumed in and because interventions that target the whole family, rather than single participants, are more effective for achieving dietary goals.
For a period of 14+ weeks, bread (rye bread, wheat bread and buns) will be delivered twice a week to the families, either as bread with gradually reduced salt or with a standard salt content.
All families start with a run-in period of bread with standard salt content, which is gradually lowered in intervention group A and A+B during the first month. The bread intervention begins after the baseline health examination (including urine collection and dietary record) has been completed and runs until data from the endpoint study has been collected.

Questionnaire

Information on socio-economic background, general health, smoking habits, physical activity, salt intake and knowledge on diet will be obtained through a short questionnaire. Questions are developed, tested and applied for use in Danish National Surveys

Health examination

Families are invited to attend a health examination at the research center at baseline and at endpoint. At both visits all participants will have a general health examination including measurement of blood pressure, weight, height, and waist circumference as well as semi-fasting blood samples. (No children < 10 years, but children 10 – 17 can volunteer for a blood sample, blood test is compulsory in adults).
Each donor delivers a maximum of 50 milliliters of blood, which corresponds to 1/10 of a normal blood donor loss.
For the testing of microalbuminuria all participant will make a spot urine sample during the health examination day.
Participants (> 10 years) will participate in a salt preference and sensitivity test. Participants are asked to order bread of varying salt content according to their preference. They will also indicate in a line of different salt solutions when they can taste, that the solution is different from water.

Furthermore, participants will collect 24-hour urine 3 days (children only one day) and register their dietary intake during the following 7 days (web-based, estimated portion sizes dietary record) within the week after the health examination both at baseline and at endpoint.
Repeated 24-hour urine collections and 7 days dietary records are chosen, because these methods are the most valid methods to estimate salt intake and the overall dietary intake on an individual level. To verify the completeness of the 24-hour urine collections the PABA (Para-aminobenzoic acid) method is applied in adults.

Urine Collection
Participants will receive materials for three 24hr urine collection; a brown bottle (3 L), a smaller 'visiting bottle' (0.5L), a safety pin for attachment to a suitable place as a reminder. Each family will receive a large backup bottle (5L) as a backup, a funnel and a urinary hat for the toilet, to aid urine collection. Adults are given three urine monovettes per day and children two for collection of urine aliquots after the completion of each 24 hr collection period. A pen to mark containers and monovettes with name, day and volume.
For validation adults are given 3*3 80mg PABA tablets (Glostrup Hospital Pharmacy).
Participants will also receive a form to register beginning and ending of the collection periods, PABA administration and exceptions to the protocol (ie estimation of urine loss, medicine).
Adults will be instructed to collect 24 h urine for three consecutive days (1 weekend day, 2 working days) and children for 1 day (weekend day).

Seven-day web-based dietary record
All participants must record their dietary intake for seven days at baseline and at endpoint using a web-based dietary record system. Each of the seven days participants will be guided through the meals of the days and asked to indicate the food consumed as well as the portion size based on images. Participants will receive verbal and written instructions in the use of the web-based system as well as a link to a video instruction. Parents will assist the registration of their children. Reminders will be send, if the record hasn't been completed the day before.

Biochemical analyses
In the blood samples, biomarkers are determined for fat metabolism (total cholesterol, HDL, LDL, triglycerides), sugar metabolism (plasma glucose, and HbA1C), hormones (aldosterone, renin, adrenaline and noradrenaline).
Urine samples will be analyzed for creatinine, sodium, potassium and in spot urine albumin will also be determined. These biomarkers are continuously analyzed at the Clinical Biochemistry Department at Rigshospitalet, Glostrup.
In addition to the above, biological material (urine, serum / plasma and whole blood) is stored for later research. The biological material is stored for up to 50 years (31 December 2068) after which the material is destroyed.
The purpose of the research biobank is to secure biological material for future research. The material will be unique as it represents representative samples of the population. This ensures a preparedness for public health research in the future. Participants provide informed written consent for the storage of biological material in research biobank. When a future research project wishes to use the biobank for purposes not covered by this protocol, the investigators shall ensure the retrieval of informed consent or seek exemption from this requirement by the Scientific Ethics Committee.

Dietary counselling
Participants in intervention group B will receive dietary counselling on top of salt reduced bread, to further reduce dietary salt and increase potassium. The group-based tuition will include official guidelines on salt and healthy diet (especially fruit and vegetables rich in potassium). Hereafter families will be invited to an individual meeting setting goals for reducing sodium and increasing potassium. To reinforce compliance families will receive weekly newsletters and two telephone calls.

Participants and Recruitment procedures
In January – February 2018 families will be recruited through digital and paper advertisements posted in social media, schools, kindergartens and companies sited in five municipalities (Albertslund, Ballerup, Egedal, Glostrup and Rødovre) in the southwestern part of the Capital Region of Denmark. The area is selected to be close to either Smørum Konditori, the baker that produces the intervention bread, or the research center (Center for Clinical Research and Prevention, Glostrup Hospital), where the health examinations will take place.
Families are defined as minimum one child and one parent living together. Children, who lives fifty percent of their time with each of their divorced parents, will be able to participate if both parents join the study. Participants will be screened to identify participants living with children between 3 and 17 years and with a daily intake of both white and/ or brown bread (> 175 gram of bread/day. Exclusion criteria are: antihypertensive and lipid-lowering treatment, pregnancy, diabetes, coronary heart disease, urine albumin greater than 300 mg/day.
At the end of the baseline health examination families will be systematically randomized by a computer into one of the three groups. In divorced families, both parents (and their families) will follow the randomization of the parent first examined.

Publication of experimental results
Both "negative" and "positive" as well as inconclusive results will be published in scientific journals under the Vancouver rules.

References
1. Campbell N, Correa-Rotter R, Neal B, Cappuccio F. New evidence to the health impact of reducing salt intake. Nutr Metab Cardiovasc Dis 2011; 21(9):617-619.

2. Aburto NJ, Ziolkovska A, Hooper L, Elliot P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 2013; 346, 1-20

3. World Health Organization. Report of the Formal Meeting of Member States to conclude the work on the comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases. Report, 1-6, Geneva, Switzerland: WHO Press, Worlds Health Organization; 2012.

4. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Advisory Report to the Secretary of Health and Human Services and Secretary of Agriculture. Feb. 2015.

5. Cobiac L, Vos T, Veerman J. Cost-effectiveness of interventions to reduce dietary salt intake. Heart 2010; 96(23):1920-192.

6. Cerqueira C, Jørgensen T, Andreasen AH, Siganos G, Toft U: Konsekvensberegninger for reduktion af danskernes saltindtag. Forskningscenter for Forebyggelse og Sund. Rapport udarbejdet for Fødevarestyrelsen, februar 2012.

7. Brown I, Tzoulaki I, Candeias V, Elliot P. Salt intakes around the world: implications for public health. Int J Epidemiol 2009; 38(3):791-813.

8. Grimes CA, Boothe A, Khokhar D et al. The Development of a Web-Based Program to Reduce Dietary Salt Intake in Schoolchildren: Study Protocol. JMIR Res Protoc. 2017 May; 6(5): e103

9. Smith-Spangler C, Juusole J, Enns E, Owens D, Garber A. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. Ann Intern Med 2010; 152(8):481-483.

10. He FJ, Pombo-Rodrigues S, MacGregor GA: Salt reduction in England from 2003 to 2011:its relationship to blood pressure, stroke and ischaemic heart diseae mortality. BMJ Open 2014; 4: e004549. Doi: 10.1136/bmjopen-2013-00454.

11. IOM (Institute of Medicine). Sodium Intake in Populations: Assessment of Evidence. Washington, DC: The National Academies Press, 2013.

12. Graudal N, Hubeck-Graudal T, Jurgens G et al. The significance of duration and amount of sodium reduction intervention in normotensive and hypertensive individuals: a meta-analysis. Advances in Nutrition. 6(2):169-77, 2015 Mar.

13. Cobb LK, Anerson CAM, Elliot P, Hu FB, Liu K, Neaton JD, Whelton PK, Woodward M, Appel LJ. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: A science advisory form the American Heart Association. Circulation. 2014; 129: 00-00.

14. He F, Macgregor G. Reducing population salt intake worldwide: from evidence to implementation. Prog Cardiovasc Dis 2010; 52(5):363-382.

15. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive sodium diets are associated with increased mortality: A meta-analysis. American Journal of Hypertension 2014. Doi: 10.1093/ajh/hpu028.

16. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride (Cochrane Review). Am J Hypertens 2012; 25(1):1-15.