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Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a cluster randomised controlled trial

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Abstract

Objective To study the effect of salt reduction on iodine status and to determine whether iodine consumption was still adequate after salt intake was reduced in a population where universal salt iodisation is mandatory.

Design Cluster randomised controlled trial, with schools randomly assigned to either the intervention or control group.

Setting 28 primary schools in urban Changzhi, northern China.

Participants 279 children in grade 5 of primary school (mean age: 10.1); 553 adults (age: 43.8).

Intervention Children were educated about the harmful effects of salt and how to reduce salt intake using the schools' usual health education lessons. Children then delivered the message to their families. The duration was one school term (≈3.5 months).

Main outcome measure Difference between the intervention and control group in the change of iodine intake as measured by repeat 24h urinary iodine from baseline to the end of the trial.

Results At baseline, the mean salt intake was 7.0±2.5g/d in children and 11.7±4.4g/d in adults and the median iodine intake was 165.1 μg/d (IQR: 122.6-216.7) and 280.7 μg/d (IQR: 205.1-380.9) in children and adults respectively. At the end of the study, both salt and iodine decreased in the intervention compared with control group. The mean effect on salt for intervention vs control was -1.9g/d (95% CI: -2.6 to -1.3) in children and -2.9g/d (95% CI: -3.7 to -2.2) in adults. The mean effect on iodine was -19.3% (95%CI: -29.4% to -7.7%) in children and -11.4% (95%CI: -20.3% to -1.5%) in adults.

Conclusions With ≈25% reduction in salt intake, there was a significant reduction in iodine consumption in northern China where salt is iodised. Despite this, iodine intake was

still adequate, and well above the estimated average requirement. Our findings indicate that reducing salt to the WHO's target─30% reduction by 2025, will not compromise iodine status.

Trial registration ClinicalTrials.gov NCT01821144.

Strengths and limitations of this study

- 24h urinary iodine excretion is the most reliable biochemical marker for assessing iodine status. However, almost all previous surveys on iodine have used spot urine due to the apparent logistic challenges and costs in collecting 24h urine. Our study is the first to have assessed iodine status by repeat 24h urine collections in a large number of primary school children and their adult family members in northern China where universal salt iodisation is mandatory.
- Our study, for the first time, has assessed the effect of a modest reduction in salt intake, as currently recommended, on iodine status using a well-controlled randomised trial. The findings provide strong support for the WHO's recommendations to reduce population salt intake to prevent cardiovascular disease, and to improve iodine intake by fortifying salt with iodine to prevent iodine deficiency.
- Despite all 24h urine collections followed stringent protocol with careful supervision, there might still be under collections in some participants. However, the consistent findings from various sensitivity analyses indicate that this is unlikely to alter the primary outcome.

Introduction

A reduction in salt intake is one of the most cost-effective public health policies to prevent hypertension and cardiovascular disease.[1-3] The WHO recommends a 30% reduction in salt intake by 2025 for all countries around the world with an eventual target of 5 g/d.[4] At the same time, salt has been used as a vehicle for iodine fortification to prevent iodine deficiency in many countries. It is therefore important to monitor iodine status to ensure that iodine consumption is still adequate when salt intake is reduced.

More than 90% of iodine consumed is excreted in the urine within 24-48 hours.[5 6] Therefore, 24h urinary iodine excretion is a good marker of recent dietary iodine intake and is the ideal biochemical indicator for assessing iodine status.[7] We measured 24h urinary iodine excretion in individuals who took part in School-EduSalt (**School**-based **Edu**cation Programme to Reduce **Salt**),[8 9] a cluster randomised controlled trial in Changzhi, northern China where universal salt iodisation is mandatory. The primary aim of the School-EduSalt trial was to determine whether an education programme targeted at primary school children could lower salt intake in children and their families. The study collected two consecutive 24h urines at baseline and at the end of the trial using a standardised protocol with careful supervision. The results showed that the education led to a significant reduction in salt intake by approximately 25% in both children and adults compared with the controls. In this paper, we report a pre-specified sub-study, the aim of which was to assess iodine status by repeat 24h urinary iodine excretion and to study the effect of salt reduction on iodine status, and in particular to determine whether iodine consumption was still adequate after the participants had been on a reduced salt intake for a few months.

Methods

Study design and participants

A detailed description of the methods of the School-EduSalt study has been published elsewhere[8 9] and only methods relevant to the current study are reported in brief here.

The study was a cluster randomised controlled trial. We recruited 28 primary schools in urban Changzhi. From each school, we selected one class in Grade 5 (age ≈10 years). From each class we randomly selected 10 children for assessment and the inclusion criteria were eating home-made meals for at least 3 days a week and children's home not too far from the school (less than 3 km). From each child's family we also enrolled two adults who shared the same meals with the child.

Randomisation

Schools (clusters) were randomly assigned (1:1) to either the intervention or the control group with stratification by the location of schools (i.e. urban or suburban) and the size of the class. The randomisation was carried out using computer generated random number system by an independent statistician who was blinded to the identity of the schools. The randomisation took place after written consents had been obtained and the baseline assessments had completed. Therefore, the participants, the school teachers and the local investigators who undertook participant recruitment and data collection, were unaware of the allocation until the point prior to the commencement of the intervention.

Intervention

Children in the intervention group were educated about the harmful effects of salt on health and how to reduce salt intake using the schools' usual health education lessons, i.e. one 40 min lesson every two weeks.[8 9] The salt reduction education was delivered to the whole class in spite of only 10 children being selected for assessment. Children were asked to deliver the salt reduction message to the families, particularly children needed to persuade the persons

who did the cooking to reduce the amount of salt used during food preparation at home. The duration of the intervention was one school term (≈3.5 months).

Children in the control group carried on with their usual health education lessons as in the curriculum and these lessons did not contain information on salt.

Outcome measures

The primary outcome of the School-EduSalt trial was the difference between the intervention and the control group in the change of salt intake as measured by 24h urinary sodium excretion from baseline to the end of the trial. The primary outcome of the present sub-study was the difference between the intervention and the control group in the change of iodine intake as measured by 24h urinary iodine excretion from baseline to the end of the trial.

Two consecutive 24h urine collections were made at baseline and at the end of the trial. Participants were carefully instructed on how to accurately collect 24h urine and the collections were supervised by trained research staff.[8 9] In the event that the participant reported to have missed one or more urine voids or spilt with an estimated spillage >10% of the total 24h urine volume, this 24h urine collection was discarded and the participant was asked to do a further 24h urine collection .

Ion-selective electrode method was used for urinary sodium analysis (AC9102 Electrolyte Analyzer, Audicom Medical Technology Co., LTD) and Jaffe method for creatinine (Hitachi 7080 automatic biochemical analyzer, Japan). Urinary iodine was measured by the Key Laboratory of Hormone and Development (Ministry of Health, China), that participated in the US Centers for Disease Control and Prevention EQUIP (Ensuring the Quality of Urinary Iodine Procedures) programme.[10] Ammonium persulfate digestion with spectrophotometric detection of the Sandell-Kolthoff reaction was used for urinary iodine measurement with quality control.[11] For each batch of samples, we ran four levels of certified reference

material—lyophilized human urine (lot nos. GBW09108l, GBW09110n, GBW09111a and GBW09112a; National Reference Laboratory for iodine deficiency disorder, Beijing) with mean certified iodine concentrations of 67.9 μg/L (95%CI: 58.9 to 76.9), 195μg/L (95%CI: 185 to 205), 558 μg/L (95%CI: 541 to 575) and 885 μg/L (95%CI: 857 to 913), respectively.

The biochemists who performed the urinary electrolyte and iodine measurements were not aware which group the participant was allocated. The average of the two 24h urinary measurements at each time point was used in the analysis.

Project timeline

The baseline assessments were carried out between late May and early July 2013, i.e. before the schools' summer holiday. Randomisation took place during the summer holiday in August. The intervention programme was carried out during the school term from September to December. The follow-up assessments were carried out between late November and December 2013.

Statistical analyses

As urinary iodine was not normally distributed, we used median and interquartile range (IQR) to assess the iodine status. Three urine samples with iodine >5000 ug/24h were outliers and excluded from the analysis. We used the cut-off points (EAR, estimated average requirement and UL, tolerable upper limit) as recommended by the Chinese Nutrition Society[12] to define iodine intake as insufficient if urinary iodine was less than EAR, i.e. <65 ug/24h in children aged ≈10 or <85 ug/24h in adults; adequate if iodine was between EAR and UL, i.e. 65-300 ug/24h in children or 85-600 ug/24h in adults; excessive if urinary iodine was more than UL, i.e. >300 in children or >600 ug/24h in adults. For the purpose of comparison with other surveys, we also reported 24h urinary iodine concentration and iodine status based on urinary

iodine concentration according the WHO's criteria (i.e. iodine deficient <100 ug/L; adequate 100-199 ug/L, above requirement 200-299 ug/L; excessive ≥300 ug/L).

Our main analysis was based on intention-to-treat. The mean effects of intervention on outcomes including both salt and iodine were tested using linear mixed models with participants nested within family units and families nested within school units. Logarithmic transformed iodine was used, and as such, the mean effect on iodine was presented as percentage change. We included group (intervention, control), time (baseline, end trial), and time×group interaction, with the time×group interaction term indicating the mean effect. To account for missing data on continuous outcomes, we used the likelihood-based random effects model that uses all available data and provides valid estimates of the intervention effects when data are missing at random. We adjusted for the stratification variables at randomisation (school location and class size) and potential confounding variables including age (continuous variable in children, categorical variable in adults ≤40 years=1; 41-60 years=2; >60 years=3), sex (male=0; female=1), body mass index (BMI), indoor and outdoor temperature.

We carried out various sensitivity analyses to examine the robustness of the conclusions of the primary analysis: (1) An analysis based on intention-to-treat approach, but excluding possibly incomplete 24h urine collections defined as, in adults, urine volume was <500 mL/24h, or creatinine <4.0 mmol/24h for women or <6.0 mmol/24h for men[13] and for children, urine volume was <300 mL/24h[14] or creatinine less than 5th percentile, i.e. <2.5 mmol/24h for girls and <2.9 mmol/24h for boys. (2) An analysis including only participants who completed both baseline and end trial assessments (named as "completers"); (3) A per-protocol analysis which included completers with complete 24h urine collections (i.e. excluding possibly incomplete 24h urine collections). The number of 24h urine samples

included and excluded in each analysis was shown in Supplement Figure. If one of the two 24h urine collections was incomplete, only one was used in the sensitivity analysis.

We used SAS (version 9.4) for the analyses. Results are reported as mean, SD and 95% CI or median and IQR where appropriate. All analyses were 2-sided and P values of <0.05 were considered statistically significant.

Results

The School-EduSalt trial enrolled 279 children and 553 adults, all of whom were included in the current report. The baseline characteristics of the participants were well balanced between the intervention and the control group (Table 1). The mean age was 10.1±0.5 years for children and 43.8±12.2 years for adults.

The result on salt has been published previously.[9] We report it again in this paper explicitly for the purpose of allowing the readers to compare the salt and iodine levels. At baseline, the mean salt intake as calculated from 24h urinary sodium excretion was 7.0±2.5 g/d in children and 11.7±4.4 g/d in adults. The median iodine consumption as measured by 24h urinary iodine was 165.1 μg/d (IQR: 122.6-216.7, 95% CI: 156.9 to 172.9) and 280.7 μg/d (IQR: 205.1-380.9, 95% CI: 270.3 to 293.8) in children and adults respectively.

Table 2 shows the salt and iodine intake by group, as well as their changes during the study. From baseline to the end of the trial, both salt and iodine intake decreased in the intervention group and increased in the control group. The mean effect size on salt for intervention vs control was -1.9 g/d (95% CI: -2.6 to -1.3, P<0.0001) in children and -2.9 g/d (95% CI: -3.7 to -2.2, P<0.0001) in adults. The mean effect size on iodine was -19.3% (95% CI: -29.4% to -7.7%, P=0.002) in children and -11.4% (95% CI: -20.3% to -1.5%, P=0.03) in adults.

Table 3 shows iodine status according to the Chinese Nutrition Society's guidelines.[12] In the intervention group, there was an increase in the proportion of individuals with iodine intake

below EAR from baseline to the end of the trial. Despite this, there were only less than 5% children and less than 3% adults who had iodine intake below EAR after salt intake was reduced.

The results from sensitivity analyses are shown in Supplement Table 1. The first analysis excluded possibly incomplete 24 urine collections. As expected, the absolute levels of salt and iodine intake were higher compared with those when all 24h urine collections were included. However, the primary outcome, i.e. the difference between the two groups in the change of salt and iodine intake was very similar to that from the main analysis. The results for completers and per-protocol analyses were very close to those from the corresponding analyses with all participants included.

Supplement Table 2 shows the iodine status based on 24h urinary iodine concentration using the WHO's criteria, as well as the median 24h urinary iodine concentration and the median 24h urinary iodine excretion for each category. In both children and adults, the median 24h urinary iodine excretions in the group classified as iodine deficient according to the WHO's criteria (i.e. <100 μg/L) were well above EAR across the study.

Discussion

Our study produced two important findings. First, the study for the first time has measured iodine intake using repeat 24h urine collections in a large number of primary school children and their families in northern China. A conservative estimate showed that the median baseline iodine intake was 165 μg/d in children and 281 μg/d in adults. These intakes are adequate. According to the Chinese Nutrition Society's guideline, EAR (i.e. daily intake meeting the requirement of one-half of the population) is 65 μg/d in children aged 7-10 years and 85 μg/d in adults, and RNI (recommended nutrient intake, i.e. intake meeting the requirement of 97-98% of the population) is 90 μg/d in children aged 7-10 and 120 μg/d in

adults.[12] The median iodine intakes in our study were 254% and 331% of EAR, and 183% and 234% of RNI for children and adults respectively. Additionally, the median iodine intakes were far below the tolerable upper limit of 300 µg/d in children and 600 µg/d in adults (Figure).

Second, our study is the first to have studied the effect of salt reduction, as currently recommended, on iodine status in a population where salt is universally iodised. The mean effect was a reduction in salt intake of 1.9 g/d in children and 2.9 g/d in adults which led to a decrease in iodine intake of 19.3% and 11.4% in children and adults respectively. These mean effects represent the differences between the intervention and control group in the changes in salt and iodine from baseline to the end of the trial. As shown in table 2, during the study, both salt and iodine intake decreased in the intervention group and increased in the control group. If applying the mean reduction in iodine level (19.3% in children and 11.4% in adults) to all participants irrespective of their group allocation, the average iodine intake would be 133 µg/d in children and 249 µg/d in adults after salt reduction. These iodine levels are still adequate, and 205% and 293% of EAR and 148% and 208% of RNI for children and adults respectively.

In our study, all 24h urine collections were carefully supervised with both the start and finish time recorded by trained research staff. It is certain that there was no over-collection. However, it is difficult to know whether there was any under-collection. Although the participants who admitted to having missed urine voids, were asked to re-do 24h urine collections, it is still possible that some participants did not report missing urine collection. Excluding potential incomplete 24h urine collections, as expected, led to a slightly higher salt and iodine intake for both baseline and end trial, and for both the intervention and the control group. It is therefore likely that our main results have under-estimated the average salt and

iodine intake of the study population. However, this is unlikely to alter the primary outcome, i.e. the difference between the intervention and control group. Indeed, various sensitivity analyses have shown consistent findings (Supplement Table 1).

In Changzhi where our study was carried out, the iodine content in salt varied from 18 to 33 mg/kg in 2013 (data was provided by the local salt manufacturer). Based on the iodine content in salt and the 24h urinary sodium and iodine excretion, we estimated that approximately 80% of iodine in the diet was from iodised salt. The changes in 24h urinary iodine observed in our study is consistent with that predicted from the changes in salt intake (Supplement Table 3 and 4). Therefore any potential influence from other dietary sources would be small.

Despite 24h urinary iodine is the most reliable biochemical marker for assessing iodine status, almost all previous surveys on iodine have used spot urine due to the apparent logistic challenges and costs in collecting 24h urine. The WHO also endorsed the use of spot urine and provided cut-offs of median spot urinary iodine concentration to categorise population's iodine status.[7] However, this has been inappropriately used by previous surveys to define the number of individuals who were iodine deficient.[15] Our study demonstrates that, in the group of individuals classified as iodine deficient according to the WHO's criteria based on urinary iodine concentration, the median 24h urinary iodine levels were well above EAR. These findings clearly illustrate the inappropriateness of spot urine in monitoring iodine status and, as a result, previous surveys would have over-estimated the prevalence of iodine deficiency. It is worth noting that our study did not collect spot urine, however, 24h urinary iodine concentration is a better index than any of the spot urine iodine concentration (e.g. casual, first morning void). Additionally, our study shows that it is entirely feasible to collect 24h urine not only in adults but also in primary school children. The WHO has recommended 24h

urine collections for determining and monitoring population salt intake.[16] It will be more efficient and highly cost-effective if the iodine intake is monitored in the same population surveys using the same methods.

In China, since the introduction of universal salt iodisation in 1995, regular surveys using casual spot urine have been carried out to monitor the population's iodine status and adjust the iodine content in salt accordingly. The surveys were largely conducted in primary schoolchildren aged 8-10 because these children are readily accessible in schools and they have been assumed to have iodine intakes characteristic of general populations. At country level, the median spot urinary iodine in schoolchildren aged 8-10 increased from 165 μg/L in 1995 to over 300 μg/L by 1999 and declined to 241 μg/L and 246 μg/L in 2002 and 2005, respectively.[17] This was in parallel with the changes of iodine content in salt which increased from 16.2 mg/kg in 1995, to 42.3 mg/kg in 1999, then declined to 30.8 mg/kg in 2005 and has remained at this level.[17] These changes reflect the alterations of the standard for 'qualified' iodised salt set by the Chinese Ministry of Health.[17] Initially the regulation for iodine content was ⩾20 mg/kg in 1995. As there was no upper limit, most salt producers tended to iodise salt with iodine over 40 mg/kg. In 1997, an upper limit of 60 mg/kg was set. National iodine survey at the time indicated an excessive population iodine intake and such data led to a reduction in the upper limit from 60 to 50 mg/kg in 2002. The standard of 35±15 (or 20-50) mg/kg had remained till 2012 when provinces were allowed to choose from the three standards, i.e. 20 (14-26), 25 (18-33) and 30 (21-39) mg/kg, depending on local diet and spot urinary iodine concentration.[18]

In our study site—Changzhi, the changes in urinary iodine followed a similar pattern to that occurred nationally although some of the surveys showed a higher iodine level. The most recent survey in Changzhi was carried out in 2010 and showed that the median spot urinary

iodine was 241, 284 and 310 μg/L in schoolchildren aged 8, 9 and 10 respectively.[19] In our study which was done in 2013, the median baseline 24h urinary iodine concentration was 215.8 μg/L for schoolchildren aged ≈10 years. The lower iodine level observed in our study could be largely due to the decrease in iodine content in salt following the change in the standard for iodised salt (i.e. from 20-50 mg/kg to 18-33 mg/kg) in 2012.

Despite our study was carried out in Changzhi and included individuals who mainly ate home-made meals, the results could be broadly applicable to most parts of China for the following reasons: (1) Universal salt iodisation is mandatory in China, and the food manufacturers and restaurants also use iodised salt; (2) The iodine content in salt (18-33 mg/kg) in Changzhi is similar to the national level (14-39 mg/kg)[18]; (3) Salt is the major source of iodine in the diet across China. Although there is a variation in iodine level from natural sources such as water and foods, iodised salt contributes to 60-80% of total iodine intake in most parts of China.[20 21] In Changzhi where our study was carried out, iodised salt accounts for ≈80% of iodine intake (i.e. at the higher end of the range in China). The iodine intake in our study population was still adequate after an approximate 25% reduction in salt intake for 3.5 months, it is therefore most likely that the same reduction in salt if achieved across China would not compromise iodine status.

Conclusions

Our study demonstrates that in northern China where universal salt iodisation is mandatory, a reduction in salt intake by ≈25% which is close to the WHO's target of 30% reduction by 2025 does not compromise iodine status as measured by repeat 24h urinary iodine excretion in both children and adults. These findings provide strong support for the WHO's recommendations to reduce population salt intake to prevent hypertension and cardiovascular

disease, and to improve iodine intake by fortifying salt with iodine to prevent iodine deficiency.

Currently many countries have started salt reduction initiatives and also implemented salt iodisation programmes. However, there is a lack of coordination between the two. To maximise the benefits, there is an urgent need for close coordination and collaboration, particularly in disseminating consistent messages and monitoring population salt and iodine intake using the same methods which will provide valuable data required for appropriate adjustment of the iodine level in salt after population salt intake is reduced. This will be the most cost-effective way in implementing the two important public health policies.

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Trial Steering Committee: Peter Sever (chair), Francesco Cappuccio, Kiang Liu, Dong Zhao, Feng He, Yangfeng Wu, and Graham MacGregor.

Contributors: FJH, YW and GAM designed the School-EduSalt trial. WZ developed the protocol for urinary iodine measurement and interpreted the iodine results. WZ, LL and XG organised urinary iodine measurement. JZ and YM performed quality control for iodine measurement. XF, JZ and YM contributed to data collection. FJH and YM developed the analysis plan, performed statistical analyses and took responsibility for the integrity of the data and the accuracy of the data analysis. FH wrote the manuscript. All authors contributed to the revision and approved the final manuscript. FJH is guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH, WASH and Action on Sugar (AoS). BPUK, CASH, WASH and AoS are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. YM was sponsored by the China Scholarship Council while she was carrying out statistical analysis for this study at the Wolfson Institute of Preventive Medicine, Queen Mary University of London. Other authors declare that they have no conflicts of interest.

Ethical approval: The study protocol was approved by Queen Mary (University of London) Research Ethics Committee (QMREC2012/81) and Peking University Health Science Centre IRB (IRB00001052-12072). Permissions were obtained from the local education authority (i.e. Changzhi Education Bureau) and head-teachers of the schools. All participants who took part in the assessments gave written informed consent. For children, participant assent and parental written consent were obtained.

Data sharing: No additional data available.

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Legend to figure. Mean salt, median iodine intake and their 95% confidence intervals in children (A) and adults (B). EAR: Estimated average requirement; RNI: Recommended nutrient intake; UL: Tolerable upper limit.

Table 1. Baseline characteristics of the participants*

Parameters	Control	Intervention	All
Children			
Number of schools	14	14	28
Number of children	138	141	279
Boys, N (%)	67 (48.6)	67 (47.5)	134 (48.0)
Age (year)	10.2 (0.5)	10.0 (0.5)	10.1 (0.5)
Weight (kg)	33.3 (7.2)	33.4 (7.8)	33.3 (7.5)
Height (cm)	140.7 (6.6)	139.2 (6.2)	140.0 (6.5)
Body mass index (kg/m^2)	16.7 (2.7)	17.1 (3.2)	16.9 (3.0)
Adults			
Number of adults	275	278	553
Men, N (%)	133 (48.4)	135 (48.6)	268 (48.5)
Parents, N (%)	208 (75.6)	203 (73.0)	411 (74.3)
Grandparents, N (%)	67 (24.4)	75 (27.0)	142 (25.7)
Age (year)	43.6 (11.8)	43.9 (12.5)	43.8 (12.2)
Weight (kg)	66.2 (12.9)	66.1 (11.6)	66.2 (12.3)
Height (cm)	162.8 (8.7)	162.4 (8.0)	162.6 (8.4)
Body mass index (kg/m^2)	24.9 (3.6)	25.0 (3.4)	24.9 (3.5)

*Data are means (SD) unless otherwise specified.

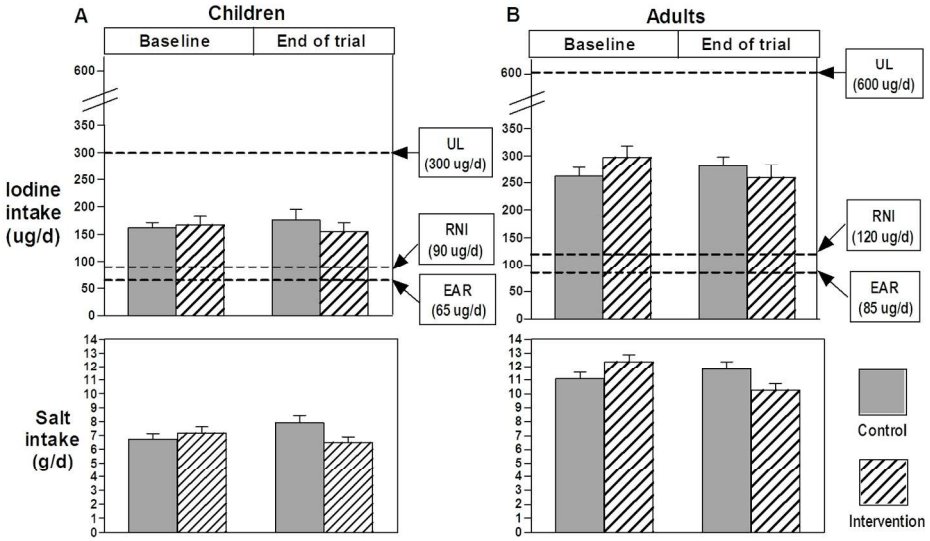
Table 2. Salt and iodine intake as calculated from 24h urinary sodium and iodine excretion based on intention-to-treat analysis

Outcome	Control			Intervention			Mean effect† (intervention vs control)	P value
	Baseline*	End of trial*	Change from baseline*	Baseline*	End of trial*	Change from baseline*		
Children								
Salt, mean (95%CI) (g/d)	6.8 (6.2─7.4)	8.0 (7.4─8.6)	1.2 (0.7─1.7)	7.3 (6.7─7.9)	6.6 (6.0─7.2)	-0.7 (-1.2─ -0.2)	-1.9 (-2.6─ -1.3)	<0.0001
Iodine								
Geometric mean (95%CI) (µg/d)	162.8 (146.7─180.5)	187.5 (168.9─208.0)	115.2% (104.7%─126.7%)	173.7 (156.7─192.4)	163.2 (147.2─180.9)	94.0% (85.6%─103.2%)	-19.3% (-29.4%─ -7.7%)	0.002
Median (IQR) (µg/d)	161.7 (117.7─209.5)	176.0 (136.5─237.2)	27.4 (-18.3─76.7)	167.0 (128.9─217.7)	154.8 (118.6─234.1)	-13.1 (-54.5─37.8)		
Adults								
Salt, mean (95%CI) (g/d)	11.3 (10.5─12.1)	12.1 (11.3─12.9)	0.8 (0.2─1.3)	12.6 (11.8─13.3)	10.4 (9.7─11.2)	-2.1 (-2.7─ -1.6)	-2.9 (-3.7─ -2.2)	<0.0001
Iodine								
Geometric mean (95%CI) (µg/d)	271.2 (245.1─300.1)	284.6 (256.9─315.2)	104.9% (97.2%─113.3%)	291.2 (263.3─322.1)	271.9 (245.7─301.0)	93.4% (86.6%─100.7%)	-11.4% (-20.3%─ -1.5%)	0.030
Median (IQR) (µg/d)	262.1 (197.8─357.5)	281.3 (207.9─387.6)	10.7 (-72.8─105.3)	297.4 (213.2─390.8)	258.5 (199.8─350.0)	-36.5 (-128.4─88.9)		

* Mean and geometric mean were adjusted for stratification variables at randomisation (school location and class size). †Adjusted for age, sex, body mass index, stratification variables at randomisation (school location and class size), and indoor and outdoor temperature.

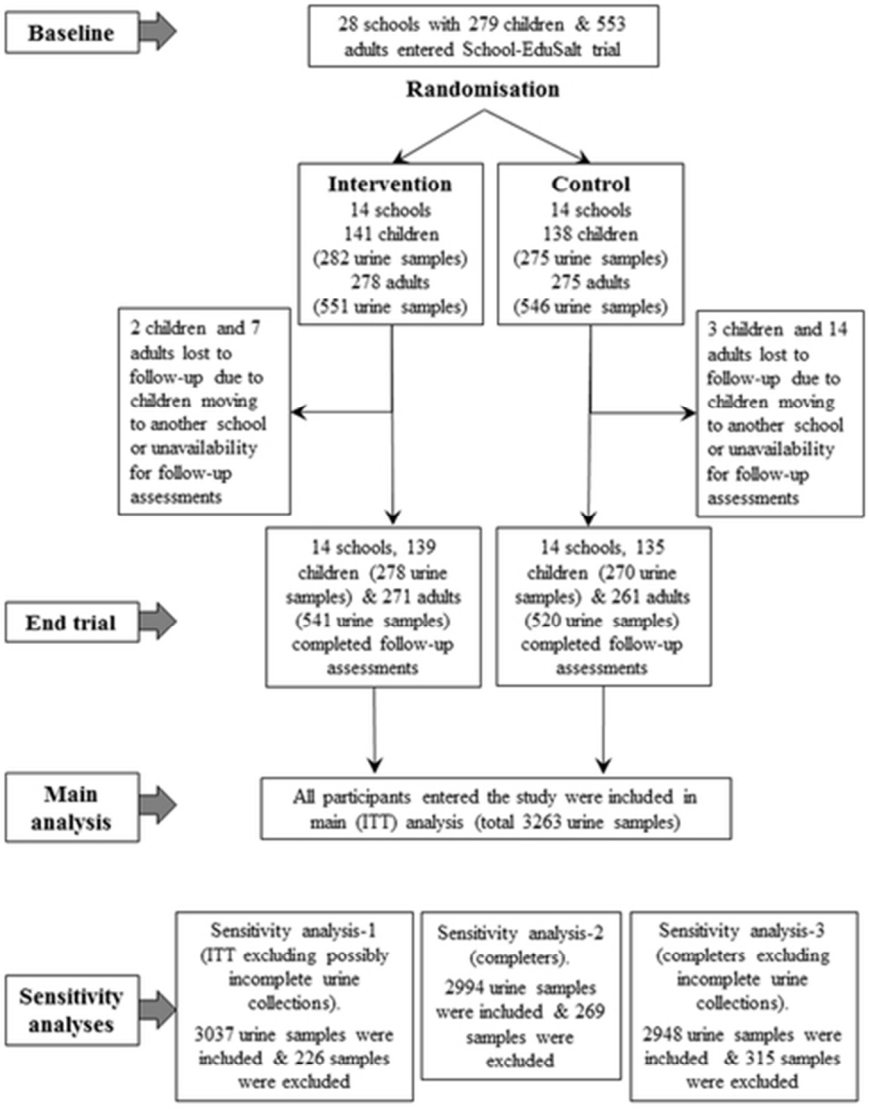
Table 3. Iodine status assessed by 24h urinary iodine excretion

Category	Control		Intervention	
	Baseline N (%)	End of trial N (%)	Baseline N (%)	End of trial N (%)
Children				
<65 (µg/24h) (Estimated average requirement)	5 (3.62)	1 (0.74)	1 (0.71)	6 (4.32)
65-300 (µg/24h)	123 (89.13)	114 (84.44)	128 (90.78)	119 (85.61)
>300 (µg/24h) (Tolerable upper limit)	10 (7.25)	20 (14.81)	12 (8.51)	14 (10.07)
Adults				
<85 (µg/24h) (Estimated average requirement)	3 (1.09)	4 (1.53)	2 (0.72)	7 (2.58)
85-600 (µg/24h)	260 (94.55)	243 (93.10)	263 (94.95)	243 (89.67)
>600 (µg/24h) (Tolerable upper limit)	12 (4.36)	14 (5.36)	12 (4.33)	21 (7.75)



Mean salt, median iodine intake and their 95% confidence intervals in children (A) and adults (B). EAR: Estimated average requirement; RNI: Recommended nutrient intake; UL: Tolerable upper limit.

154x93mm (300 x 300 DPI)



Trial profile

20x26mm (600 x 600 DPI)

ONLINE SUPPLEMENT

Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a cluster randomised controlled trial

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Supplement Table 1. Sensitivity analysis for salt and iodine intake as calculated from 24h urinary sodium and iodine excretion

Outcome	Number of participant Control /Intervention	Control		Intervention		Adjusted difference‖ (intervention vs control)	P value
		Baseline‡	Change from baseline‡	Baseline‡	Change from baseline‡		
Population excluding possibly incomplete 24h urine							
Children							
Salt (mean, 95%CI) (g/d)	138/140	7.0 (6.4─7.6)	1.2 (0.7─1.6)	7.5 (6.9─8.1)	-0.7 (-1.1 ─ -0.2)	-1.9 (-2.6─ -1.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	138/140	170.8 (155.0─188.2)	112.9% (102.7%─124.2%)	180.0 (163.6─198.1)	95.4% (86.9%─104.8%)	-16.5% (-26.9%─ -4.6%)	0.008
Iodine (median, IQR) (μg/d)	138/140	166.5 (119.0─220.4)	27.3 (-20.6─79.0)	175.4 (131.3─228.7)	-9.3 (-52.4─39.0)		
Adults							
Salt (mean, 95%CI) (g/d)	273/275	11.6 (10.8─12.3)	0.8 (0.3─1.4)	12.8 (12.1─13.6)	-2.1 (-2.6─-1.6)	-3.0 (-3.7─ -2.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	273/275	280.7 (255.0─308.9)	104.6% (97.1%─112.7%)	298.0 (270.9─327.7)	95.6% 88.8%─102.9%)	-9.5% (-18.3%─0.2%)	0.055
Iodine (median, IQR) (μg/d)	273/275	275.7 (201.9─360.1)	15.1 (-78.3─105.3)	300.5 (219.2─392.5)	-30.2 (-117.7─ 90.2)		
Completers*							
Children							
Salt (mean, 95%CI) (g/d)	135/139	6.8 (6.2─7.4)	1.2 (0.8─1.7)	7.2 (6.6─7.9)	-0.7 (-1.2─ -0.2)	-1.9 (-2.6─ -1.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	135/139	162.0 (146.0─180.0)	115.4% (104.9%─126.9%)	173.5 (156.4─192.4)	94.0% (85.6%─103.2%)	-19.3% (-29.4%─ -7.8%)	0.002

Iodine (median, IQR) (μg/d)	135/139	160.9 (117.7—208.1)	27.4 (-18.3—76.7)	169.6 (128.5—221.6)	-13.1 (-54.5—37.8)		
Adults							
Salt (mean, 95%CI) (g/d)	261/271	11.4 (10.6—12.1)	0.8 (0.2—1.3)	12.7 (11.9—13.5)	-2.2 (-2.7— -1.6)	-3.0 (-3.7— -2.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	261/270	272.1 (245.3—301.7)	104.7% (96.9%—113.1%)	292.6 (264.1—324.3)	93.1% (86.3%—100.4%)	-11.1% (-20.1%— -1.1%)	0.030
Iodine (median, IQR) (μg/d)	261/270	261.8 (197.8—348.8)	10.7 (-72.8—105.3)	297.7 (213.2—391.8)	-36.5 (-128.4— 88.9)		
Per protocol population†							
Children							
Salt (mean, 95%CI) (g/d)	132/137	7.0 (6.4—7.6)	1.2 (0.7—1.7)	7.5 (6.9—8.1)	-0.7 (-1.1— -0.2)	-1.9 (-2.6— -1.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	132/137	169.5 (154.1—186.4)	114.1% (103.7%—125.5%)	179.6 (163.5—197.2)	95.9% (87.3%—105.3%)	-16.8% (-27.2%— -4.9%)	0.007
Iodine (median, IQR) (μg/d)	132/137	166.5 (120.3—216.8)	27.3 (-20.6—79.0)	178.8 (131.3—228.7)	-9.3 (-52.4—39.0)		
Adults							
Salt (mean, 95%CI) (g/d)	249/256	11.6 (10.8—12.3)	0.9 (0.3—1.4)	12.9 (12.2—13.7)	-2.1 (-2.6— -1.6)	-3.0 (-3.7— -2.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	249/255	282.4 (256.5—311.0)	104.3% (96.7%—112.5%)	296.3 (269.3—326.0)	96.1% (89.2%—103.6%)	-8.3% (-17.3%—1.7%)	0.102
Iodine (median, IQR) (μg/d)	249/255	275.8 (203.1—360.1)	15.1 (-78.3—105.3)	300.1 (218.3—391.8)	-30.2 (-117.7— 90.2)		

* Completers refer to the participants who had 24h urine collections both at baseline and the end of the trial. † Per protocol population refers to completers with complete 24h urine collections. ‡ Mean and geometric mean were adjusted for stratification variables at randomisation (school location and class size). ‖Adjusted for age, sex, body mass index, stratification variables at randomisation (school location and class size), and indoor and outdoor temperature.

Supplement Table 2. Iodine status assessed by 24h urinary iodine concentration using WHO's criteria, and median 24h urinary iodine concentration and 24h urinary iodine excretion for each category

Urinary iodine (µg/L)	Control						Intervention					
	Baseline			End of trial			Baseline			End of trial		
	N (%)	Iodine (median)		N (%)	Iodine (median)		N (%)	Iodine (median)		N (%)	Iodine (median)	
		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)
Children												
<100 (Iodine deficient)	10 (7.25)	85.07	94.93	10 (7.41)	84.26	114.51	5 (3.55)	86.17	89.84	11 (7.91)	86.65	113.78
100-199 (Adequate)	55 (39.86)	155.60	139.77	40 (29.63)	152.39	143.31	54 (38.30)	156.60	152.99	48 (34.53)	153.87	125.17
200-299 (Above requirement)	48 (34.78)	235.92	172.93	52 (38.52)	243.06	184.82	43 (30.50)	248.98	173.10	41 (29.5)	238.24	165.24
300 (Excessive)	25 (18.12)	430.84	249.11	33 (24.44)	371.52	279.42	39 (27.66)	357.28	236.15	39 (28.06)	411.03	260.88
ALL	138	204.60	161.70	135	222.50	176.0	141	225.30	167.00	139	217.10	154.80
Adults												
<100 (Iodine deficient)	32 (11.64)	81.31	137.25	38 (14.56)	72.84	149.13	31 (11.19)	79.49	140.35	48 (17.71)	74.71	164.03
100-199 (Adequate)	121 (44.00)	152.37	240.44	108 (41.38)	147.78	246.58	103 (37.18)	150.95	281.83	116 (42.80)	142.55	250.69
200-299 (Above requirement)	68 (24.73)	239.54	280.75	72 (27.59)	243.17	353.36	79 (28.52)	246.73	326.61	56 (20.66)	240.86	293.21
≥300 (Excessive)	54 (19.64)	372.08	420.86	43 (16.48)	351.76	460.61	64 (23.10)	372.21	423.84	51 (18.82)	364.22	535.18
ALL	275	188.80	262.10	261	183.60	281.3	277	209.4	297.40	271	176.20	258.5

Supplement Table 3. Comparison of iodine levels observed from 24h urinary iodine with that predicted from salt intake and iodine content in salt

	Control		Intervention	
	Baseline	**End of trial**	**Baseline**	**End of trial**
Children				
Observed from 24h urinary measurements				
Mean salt (g/d)	6.8	8.0	7.3	6.6
Median iodine (µg/d)	161.7	176.0	167.0	154.8
Predicted iodine based on salt intake and iodine content in salt using the minimum level of 18 mg/kg				
Predicted iodine (µg/d)	122.4	144.0	131.4	118.8
Ratio (predicted/observed)	0.8	0.8	0.8	0.8
Adults				
Observed from 24h urinary measurements				
Mean salt (g/d)	11.3	12.1	12.6	10.4
Median iodine (µg/d)	262.1	281.3	297.4	258.5
Predicted iodine based on salt intake and iodine content in salt using the minimum level of 18 mg/kg				
Predicted iodine (µg/d)	203.4	217.8	226.8	187.2
Ratio (predicted/observed)	0.8	0.8	0.8	0.7

Supplement Table 4. Salt and iodine intake, and iodine/salt ratio as calculated from 24h urinary sodium and iodine excretion

	Control		Intervention	
	Baseline	**End of trial**	**Baseline**	**End of trial**
Children				
Salt, mean (g/d)*	6.8	8.0	7.3	6.6
Iodine, median (µg/d)	161.7	176.0	167.0	154.8
Iodine/salt ratio, median (µg/g)	23.8	24.4	25.0	24.9
Adults				
Salt, mean (g/d)*	11.3	12.1	12.6	10.4
Iodine, median (µg/d)	262.1	281.3	297.4	258.5
Iodine/salt ratio, median (µg/g)	24.8	24.8	24.6	26.7

*adjusted for stratification variables at randomisation (school location and class size).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Not applicable
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9-10 & Supplement Figure
	13b	For each group, losses and exclusions after randomisation, together with reasons	9-10 & Supplement Figure
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 1 & 3, Supplement Figure
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2 & 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Supplement Table 1 & 2
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12-13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-16
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	6 & Reference 8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a sub-study of a cluster randomised controlled trial

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Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a sub-study of a cluster randomised controlled trial

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Running Title: Effect of salt reduction on iodine status

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Abstract

Objective To study the effect of salt reduction on iodine status and to determine whether iodine consumption was still adequate after salt intake was reduced in a population where universal salt iodisation is mandatory.

Design A sub-study of a cluster randomised controlled trial, where schools randomly assigned to either the intervention or control group.

Setting 28 primary schools in urban Changzhi, northern China.

Participants 279 children in grade 5 of primary school (mean age: 10.1); 553 adults (age: 43.8).

Intervention Children were educated about the harmful effects of salt and how to reduce salt intake using the schools' usual health education lessons. Children then delivered the message to their families. The duration was one school term (≈3.5 months).

Main outcome measure Difference between the intervention and control group in the change of iodine intake as measured by repeat 24h urinary iodine from baseline to the end of the trial.

Results At baseline, the mean salt intake was 7.0±2.5g/d in children and 11.7±4.4g/d in adults and the median iodine intake was 165.1 μg/d (IQR: 122.6-216.7) and 280.7 μg/d (IQR: 205.1-380.9) in children and adults respectively. At the end of the study, both salt and iodine decreased in the intervention compared with control group. The mean effect on salt for intervention vs control was -1.9g/d (95% CI: -2.6 to -1.3) in children and -2.9g/d (95% CI: -3.7 to -2.2) in adults. The mean effect on iodine was -19.3% (95%CI: -29.4% to -7.7%) in children and -11.4% (95%CI: -20.3% to -1.5%) in adults.

Conclusions With ≈25% reduction in salt intake, there was a significant reduction in iodine consumption in northern China where salt is iodised. Despite this, iodine intake was

still adequate, and well above the estimated average requirement. Our findings indicate that reducing salt to the WHO's target─30% reduction by 2025, will not compromise iodine status.

Trial registration ClinicalTrials.gov NCT01821144.

Strengths and limitations of this study

- 24h urinary iodine excretion is the most reliable biochemical marker for assessing iodine status.
- Our study is the first to have assessed iodine status by repeat 24h urine collections in a large number of primary school children and their adult family members in northern China where universal salt iodisation is mandatory.
- Our study, for the first time, has assessed the effect of a modest reduction in salt intake on iodine status using a well-controlled randomised trial.
- The results demonstrate that ≈25% reduction in salt intake which is close to the WHO's target, does not compromise iodine status.
- Despite all 24h urine collections followed stringent protocol with careful supervision, there might still be under collections in some participants. However, the consistent findings from various sensitivity analyses indicate that this is unlikely to alter the primary outcome.

Introduction

Iodine deficiency disorder is a global public health problem with approximately 1.88 billion people including 241 million school-age children having insufficient intake of iodine worldwide.[1] China was one of the countries that had serious epidemic of iodine deficiency disorders.[2] In 1993, the WHO (World Health Organisation) and UNICEF (United Nations Children's Fund) recommended universal salt iodization to prevent and control iodine deficiency.[1] China launched a universal salt iodisation programme in 1995.[3] Since then a significant progress has been made in reducing iodine deficiency disorders.[3 4] In recent years there has been debate about the optimal levels of iodine fortification in salt, particularly as salt intake is very high in China and iodine excess could also lead to thyroid diseases.[3 5 6]

A reduction in salt intake is one of the most cost-effective public health policies to prevent hypertension and cardiovascular disease.[7-9] The WHO recommends a 30% reduction in salt intake by 2025 for all countries around the world with an eventual target of 5 g/d.[10] As salt has been used as a vehicle for iodine fortification in many countries, it is important to monitor iodine status to ensure that iodine consumption is still adequate when salt intake is reduced.

More than 90% of iodine consumed is excreted in the urine within 24-48 hours.[11 12] Therefore, 24h urinary iodine excretion is a good marker of recent dietary iodine intake and is the ideal biochemical indicator for assessing iodine status.[1] We measured 24h urinary iodine excretion in individuals who took part in School-EduSalt (**School**-based **Edu**cation Programme to Reduce **Salt**),[13 14] a cluster randomised controlled trial in Changzhi, northern China where universal salt iodisation is mandatory. The primary aim of the School-EduSalt trial was to determine whether an education programme targeted at primary school children could lower salt intake in children and their families. The study collected two consecutive 24h urines at baseline and at the end of the trial using a standardised protocol with careful

supervision. The results showed that the education led to a significant reduction in salt intake by approximately 25% in both children and adults compared with the controls. In this paper, we report a pre-specified sub-study,[15] the aim of which was to assess iodine status by repeat 24h urinary iodine excretion and to study the effect of salt reduction on iodine status, and in particular to determine whether iodine consumption was still adequate after the participants had been on a reduced salt intake for a few months.

Methods

A detailed description of the methods of the School-EduSalt study has been published elsewhere[13 14] and the abridged methods are reported here. The study was a cluster randomised controlled trial in 28 primary schools in urban Changzhi, Northern China. From each school, we selected one class in Grade 5 (age ≈10 years). From each class we randomly selected 10 children who met the inclusion criteria.[14] From each child's family we also enrolled two adults. Schools were randomly assigned to either the intervention or the control group with stratification by the location of schools and the size of the class.

Children in the intervention group were educated about the harmful effects of salt on health and how to reduce salt intake using the schools' usual health education lessons, i.e. one 40 min lesson every two weeks.[13 14] The salt reduction education was delivered to the whole class in spite of only 10 children being selected for assessment. Children were asked to deliver the salt reduction message to the families, particularly children needed to persuade the persons who did the cooking to reduce the amount of salt used during food preparation at home. The duration of the intervention was one school term (≈3.5 months). Children in the control group carried on with their usual health education lessons as in the curriculum.

The primary outcome of this sub-study was the difference between the intervention and the control group in the change of iodine intake as measured by 24h urinary iodine excretion from baseline to the end of the trial.

Urinary iodine was measured by the Key Laboratory of Hormone and Development (Ministry of Health, China), that participated in the US Centers for Disease Control and Prevention EQUIP (Ensuring the Quality of Urinary Iodine Procedures) programme.[16] Ammonium persulfate digestion with spectrophotometric detection of the Sandell-Kolthoff reaction was used for urinary iodine measurement with quality control.[17] For each batch of samples, we ran four levels of certified reference material—lyophilized human urine (lot nos. GBW09108l, GBW09110n, GBW09111a and GBW09112a; National Reference Laboratory for iodine deficiency disorder, Beijing) with mean certified iodine concentrations of 67.9 μg/L (95%CI: 58.9 to 76.9), 195μg/L (95%CI: 185 to 205), 558 μg/L (95%CI: 541 to 575) and 885 μg/L (95%CI: 857 to 913), respectively. The biochemists who performed the urinary iodine measurements were not aware which group the participant was allocated.

Statistical analyses

As urinary iodine was not normally distributed, we used median and interquartile range (IQR) to summarise the iodine status. Three urine samples with iodine >5000 μg/24h were outliers and excluded from the analysis. We used the cut-off points (EAR, Estimated Average Requirement and UL, Tolerable Upper Limit) as recommended by the Chinese Nutrition Society[18] to define iodine intake as insufficient if urinary iodine was less than EAR, i.e. <65 μg/24h in children aged ≈10 or <85 μg/24h in adults; adequate if iodine was between EAR and UL, i.e. 65-300 μg/24h in children or 85-600 μg/24h in adults; excessive if urinary iodine was more than UL, i.e. >300 μg/24h in children or >600 μg/24h in adults. For the purpose of comparison with other surveys, we also reported 24h urinary iodine concentration and iodine status based on urinary iodine concentration according the WHO's criteria (i.e. iodine deficient <100 μg/L; adequate 100-199 μg/L, above requirement 200-299 μg/L; excessive ≥300 μg/L).

Our main analysis was based on intention-to-treat using linear mixed models as reported previously.[14 19] Logarithmic transformed iodine was used, and as such, the mean effect on iodine was presented as percentage change. The statistical model was in the form: Outcome= Group+Time+Interaction (time×group)+Stratification variables at randomisation (school location and class size)+Confounding variables (age, sex, body mass index, indoor and outdoor temperature). To examine the robustness of the conclusions of the primary analysis we carried out various sensitivity analyses as specified previously.[14] The number of 24h urine samples included and excluded in each analysis was shown in Supplement Figure.

We used SAS (version 9.4) for the analyses. Results are reported as mean, SD and 95% CI or median and IQR where appropriate. All analyses were 2-sided and P values of <0.05 were considered statistically significant.

Results

The School-EduSalt trial enrolled 279 children and 553 adults, all of whom were included in the current report. The baseline characteristics of the participants were well balanced between the intervention and the control group (Supplement Table 1). The mean age was 10.1±0.5 years for children and 43.8±12.2 years for adults.

The result on salt has been published previously.[14] We report it again in this paper explicitly for the purpose of allowing the readers to compare the salt and iodine levels. At baseline, the mean salt intake as calculated from 24h urinary sodium excretion was 7.0±2.5 g/d in children and 11.7±4.4 g/d in adults. The median iodine consumption as measured by 24h urinary iodine was 165.1 μg/d (IQR: 122.6-216.7, 95% CI: 156.9 to 172.9) and 280.7 μg/d (IQR: 205.1-380.9, 95% CI: 270.3 to 293.8) in children and adults respectively.

Table 1 shows the salt and iodine intake by group, as well as their changes during the study. From baseline to the end of the trial, both salt and iodine intake decreased in the intervention

group and increased in the control group. The mean effect size on salt for intervention vs control was -1.9 g/d (95% CI: -2.6 to -1.3, P<0.0001) in children and -2.9 g/d (95% CI: -3.7 to -2.2, P<0.0001) in adults. The mean effect size on iodine was -19.3% (95% CI: -29.4% to -7.7%, P=0.002) in children and -11.4% (95% CI: -20.3% to -1.5%, P=0.03) in adults.

Table 2 shows iodine status according to the Chinese Nutrition Society's guidelines.[18] In the intervention group, there was an increase in the proportion of individuals with iodine intake below EAR from baseline to the end of the trial. Despite this, there were only less than 5% children and less than 3% adults who had iodine intake below EAR after salt intake was reduced.

The results from sensitivity analyses are shown in Supplement Table 2. The first analysis excluded possibly incomplete 24 urine collections. As expected, the absolute levels of salt and iodine intake were higher compared with those when all 24h urine collections were included. However, the primary outcome, i.e. the difference between the two groups in the change of salt and iodine intake was very similar to that from the main analysis. The results for completers (i.e. the participants who had 24h urine collections both at baseline and end of the trial) and per-protocol analyses (including completers with complete 24h urine collections) were very close to those from the corresponding analyses with all participants included.

Supplement Table 3 shows the iodine status based on 24h urinary iodine concentration using the WHO's criteria, as well as the median 24h urinary iodine concentration and the median 24h urinary iodine excretion for each category. In both children and adults, the median 24h urinary iodine excretions in the group classified as iodine deficient according to the WHO's criteria (i.e. <100 μg/L) were well above EAR across the study.

Discussion

Our study produced two important findings. First, the study for the first time has measured iodine intake using repeat 24h urine collections in a large number of primary school children and their families in northern China. A conservative estimate showed that the median baseline iodine intake was 165 μg/d in children and 281 μg/d in adults. These intakes are adequate. According to the Chinese Nutrition Society's guideline, EAR (i.e. daily intake meeting the requirement of one-half of the population) is 65 μg/d in children aged 7-10 years and 85 μg/d in adults, and RNI (recommended nutrient intake, i.e. intake meeting the requirement of 97-98% of the population) is 90 μg/d in children aged 7-10 and 120 μg/d in adults.[18] The median iodine intakes in our study were 254% and 331% of EAR, and 183% and 234% of RNI for children and adults respectively. Additionally, the median iodine intakes were far below the tolerable upper limit of 300 μg/d in children and 600 μg/d in adults (Figure).

Second, our study is the first to have studied the effect of salt reduction, as currently recommended, on iodine status in a population where salt is universally iodised. The mean effect was a reduction in salt intake of 1.9 g/d in children and 2.9 g/d in adults which led to a decrease in iodine intake of 19.3% and 11.4% in children and adults respectively. These mean effects represent the differences between the intervention and control group in the changes in salt and iodine from baseline to the end of the trial. As shown in table 1, during the study, both salt and iodine intake decreased in the intervention group and increased in the control group. If applying the mean reduction in iodine level (19.3% in children and 11.4% in adults) to all participants irrespective of their group allocation, the average iodine intake would be 133 μg/d in children and 249 μg/d in adults after salt reduction. These iodine levels are still adequate, and 205% and 293% of EAR and 148% and 208% of RNI for children and adults respectively.

In our study, all 24h urine collections were carefully supervised with both the start and finish time recorded by trained research staff. It is certain that there was no over-collection. However, it is difficult to know whether there was any under-collection. Although the participants who admitted to having missed urine voids, were asked to re-do 24h urine collections, it is still possible that some participants did not report missing urine collection. Excluding potential incomplete 24h urine collections, as expected, led to a slightly higher salt and iodine intake for both baseline and end trial, and for both the intervention and the control group. It is therefore likely that our main results have under-estimated the average salt and iodine intake of the study population. However, this is unlikely to alter the primary outcome, i.e. the difference between the intervention and control group. Indeed, various sensitivity analyses have shown consistent findings (Supplement Table 2).

In Changzhi where our study was carried out, the iodine content in salt varied from 18 to 33 mg/kg in 2013 (data was provided by the local salt manufacturer). Based on the iodine content in salt and the 24h urinary sodium and iodine excretion, we estimated that ≈80% of iodine in the diet was from iodised salt. The changes in 24h urinary iodine observed in our study is consistent with that predicted from the changes in salt intake (Supplement Table 4). Therefore any potential influence from other dietary sources would be small.

Despite 24h urinary iodine is the most reliable biochemical marker for assessing iodine status, almost all previous surveys on iodine have used spot urine due to the apparent logistic challenges and costs in collecting 24h urine. The WHO also endorsed the use of spot urine and provided cut-offs of median spot urinary iodine concentration to categorise population's iodine status.[1] However, this has been inappropriately used by previous surveys to define the number of individuals who were iodine deficient.[20] Our study demonstrates that, in the group of individuals classified as iodine deficient according to the WHO's criteria based on urinary iodine concentration, the median 24h urinary iodine levels were well above EAR. These

findings clearly illustrate the inappropriateness of spot urine in monitoring iodine status and, as a result, previous surveys would have over-estimated the prevalence of iodine deficiency. It is worth noting that our study did not collect spot urine, however, 24h urinary iodine concentration is a better index than any of the spot urine iodine concentration (e.g. casual, first morning void). Additionally, our study shows that it is entirely feasible to collect 24h urine not only in adults but also in primary school children. The WHO has recommended 24h urine collections for determining and monitoring population salt intake.[21] It will be more efficient and highly cost-effective if the iodine intake is monitored in the same population surveys using the same methods.

In China, since the introduction of universal salt iodisation in 1995, regular surveys using casual spot urine have been carried out to monitor the population's iodine status and adjust the iodine content in salt accordingly.[3] The surveys were largely conducted in primary schoolchildren aged 8-10 because these children are readily accessible in schools and they have been assumed to have iodine intakes characteristic of general populations. At country level, the median spot urinary iodine in schoolchildren aged 8-10 increased from 165 μg/L in 1995 to over 300 μg/L by 1999 and declined to 241 μg/L and 246 μg/L in 2002 and 2005, respectively.[3] This was in parallel with the changes of iodine content in salt which increased from 16.2 mg/kg in 1995, to 42.3 mg/kg in 1999, then declined to 30.8 mg/kg in 2005 and has remained at this level.[3] These changes reflect the alterations of the standard for 'qualified' iodised salt set by the Chinese Ministry of Health.[3] Initially the regulation for iodine content was ⩾20 mg/kg in 1995. As there was no upper limit, most salt producers tended to iodise salt with iodine over 40 mg/kg. In 1997, an upper limit of 60 mg/kg was set. National iodine survey at the time indicated an excessive population iodine intake and such data led to a reduction in the upper limit from 60 to 50 mg/kg in 2002. The standard of 35±15 (or 20-50) mg/kg had remained till 2012 when provinces were allowed to choose from the

three standards, i.e. 20 (14-26), 25 (18-33) and 30 (21-39) mg/kg, depending on local diet and spot urinary iodine concentration.[22]

In our study site—Changzhi, the changes in urinary iodine followed a similar pattern to that occurred nationally although some of the surveys showed a higher iodine level. The most recent survey in Changzhi was carried out in 2010 and showed that the median spot urinary iodine was 241, 284 and 310 μg/L in schoolchildren aged 8, 9 and 10 respectively.[23] In our study which was done in 2013, the median baseline 24h urinary iodine concentration was 215.8 μg/L for schoolchildren aged ≈10 years. The lower iodine level observed in our study could be largely due to the decrease in iodine content in salt following the change in the standard for iodised salt (i.e. from 20-50 mg/kg to 18-33 mg/kg) in 2012.

Despite our study was carried out in Changzhi and included individuals who mainly ate home-made meals, the results could be broadly applicable to most parts of China for the following reasons: (1) Universal salt iodisation is mandatory in China, and the food manufacturers and restaurants also use iodised salt; (2) The iodine content in salt (18-33 mg/kg) in Changzhi is similar to the national level (14-39 mg/kg)[22]; (3) Salt is the major source of iodine in the diet across China. Although there is a variation in iodine level from natural sources such as water and foods, iodised salt contributes to 60-80% of total iodine intake in most parts of China.[24 25] In Changzhi where our study was carried out, iodised salt accounts for ≈80% of iodine intake (i.e. at the higher end of the range in China). The iodine intake in our study population was still adequate after an approximate 25% reduction in salt intake for 3.5 months, it is therefore most likely that the same reduction in salt if achieved across China would not compromise iodine status. The findings of our study, however, may not be generalisable to populations in other countries due to a number of features in the setting, such as universal salt iodisation and high contribution of discretionary salt to total salt intake in the Chinese diet.

Conclusions

Our study demonstrates that in northern China where universal salt iodisation is mandatory, a reduction in salt intake by ≈25% which is close to the WHO's target of 30% reduction by 2025 does not compromise iodine status as measured by repeat 24h urinary iodine excretion in both children and adults. These findings provide strong support for the WHO's recommendations to reduce population salt intake to prevent hypertension and cardiovascular disease, and to improve iodine intake by fortifying salt with iodine to prevent iodine deficiency.

Currently many countries have started salt reduction initiatives and also implemented salt iodisation programmes.[26] However, there is a lack of coordination between the two. To maximise the benefits, there is an urgent need for close coordination and collaboration, particularly in disseminating consistent messages and monitoring population salt and iodine intake using the same methods which will provide valuable data required for appropriate adjustment of the iodine level in salt after population salt intake is reduced. This will be the most cost-effective way in implementing the two important public health policies.

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Trial Steering Committee: Peter Sever (chair), Francesco Cappuccio, Kiang Liu, Dong Zhao, Feng He, Yangfeng Wu, and Graham MacGregor.

Contributors: FJH, YW and GAM designed the School-EduSalt trial. WZ developed the protocol for urinary iodine measurement and interpreted the iodine results. WZ, LL and XG organised urinary iodine measurement. JZ and YM performed quality control for iodine measurement. XF, JZ and YM contributed to data collection. FJH and YM developed the analysis plan, performed statistical analyses and took responsibility for the integrity of the data and the accuracy of the data analysis. FH wrote the manuscript. All authors contributed to the revision and approved the final manuscript. FJH is guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH, WASH and Action on Sugar (AoS). BPUK, CASH, WASH and AoS are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. YM was sponsored by the China Scholarship Council while she was carrying out statistical analysis for this study at the Wolfson Institute of Preventive Medicine, Queen Mary University of London. Other authors declare that they have no conflicts of interest.

Ethical approval: The study protocol was approved by Queen Mary (University of London) Research Ethics Committee (QMREC2012/81) and Peking University Health Science Centre IRB (IRB00001052-12072). Permissions were obtained from the local education authority (i.e. Changzhi Education Bureau) and head-teachers of the schools. All participants who took part in the assessments gave written informed consent. For children, participant assent and parental written consent were obtained.

Data sharing: No additional data available.

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Legend to figure. Mean salt, median iodine intake and their 95% confidence intervals in children (A) and adults (B). EAR: Estimated average requirement; RNI: Recommended nutrient intake; UL: Tolerable upper limit.

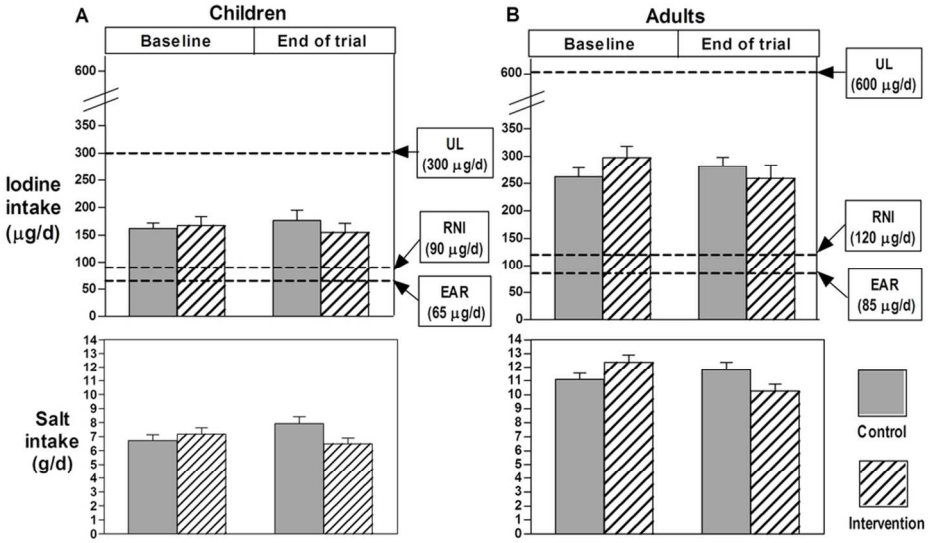
Table 1. Salt and iodine intake as calculated from 24h urinary sodium and iodine excretion based on intention-to-treat analysis

Outcome	Control			Intervention			Mean effect† (intervention vs control)	P value
	Baseline*	End of trial*	Change from baseline*	Baseline*	End of trial*	Change from baseline*		
Children								
Salt, mean‡ (95%CI) (g/d)	6.8 (6.2─7.4)	8.0 (7.4─8.6)	1.2 (0.7─1.7)	7.3 (6.7─7.9)	6.6 (6.0─7.2)	-0.7 (-1.2─ -0.2)	-1.9 (-2.6─ -1.3)	<0.0001
Iodine								
Geometric mean (95%CI) (µg/d)	162.8 (146.7─180.5)	187.5 (168.9─208.0)	115.2% (104.7%─126.7%)	173.7 (156.7─192.4)	163.2 (147.2─180.9)	94.0% (85.6%─103.2%)	-19.3% (-29.4%─ -7.7%)	0.002
Median (IQR) (µg/d)	161.7 (117.7─209.5)	176.0 (136.5─237.2)	27.4 (-18.3─76.7)	167.0 (128.9─217.7)	154.8 (118.6─234.1)	-13.1 (-54.5─37.8)		
Adults								
Salt, mean (95%CI) (g/d)	11.3 (10.5─12.1)	12.1 (11.3─12.9)	0.8 (0.2─1.3)	12.6 (11.8─13.3)	10.4 (9.7─11.2)	-2.1 (-2.7─ -1.6)	-2.9 (-3.7─ -2.2)	<0.0001
Iodine								
Geometric mean (95%CI) (µg/d)	271.2 (245.1─300.1)	284.6 (256.9─315.2)	104.9% (97.2%─113.3%)	291.2 (263.3─322.1)	271.9 (245.7─301.0)	93.4% (86.6%─100.7%)	-11.4% (-20.3%─ -1.5%)	0.030
Median (IQR) (µg/d)	262.1 (197.8─357.5)	281.3 (207.9─387.6)	10.7 (-72.8─105.3)	297.4 (213.2─390.8)	258.5 (199.8─350.0)	-36.5 (-128.4─88.9)		

* Mean and geometric mean were adjusted for stratification variables at randomisation (school location and class size). †Adjusted for age, sex, body mass index, stratification variables at randomisation (school location and class size), and indoor and outdoor temperature. ‡The results for salt were taken from previous report.[14]

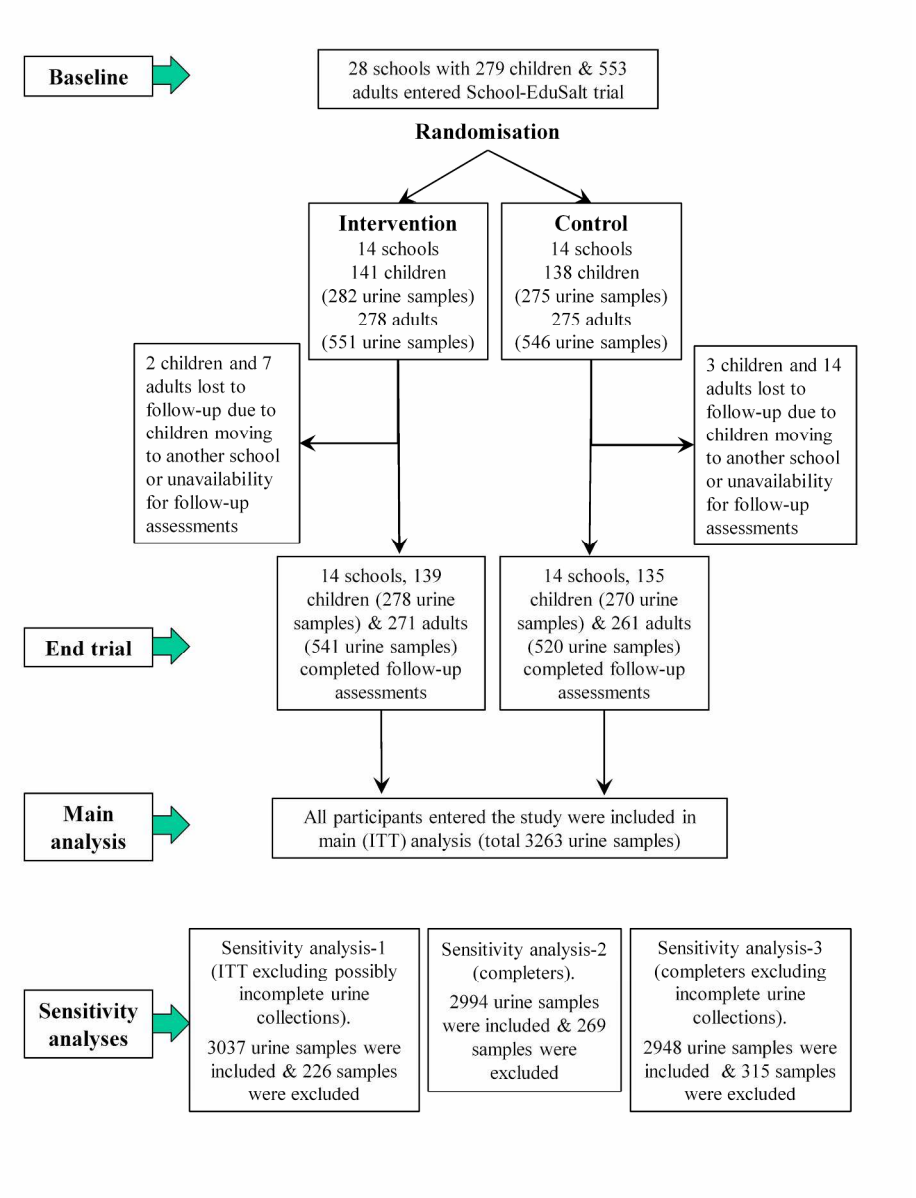
Table 2. Iodine status assessed by 24h urinary iodine excretion

Category	Control		Intervention	
	Baseline N (%)	End of trial N (%)	Baseline N (%)	End of trial N (%)
Children				
<65 (µg/d) (Estimated average requirement)	5 (3.62)	1 (0.74)	1 (0.71)	6 (4.32)
65-300 (µg/d)	123 (89.13)	114 (84.44)	128 (90.78)	119 (85.61)
>300 (µg/d) (Tolerable upper limit)	10 (7.25)	20 (14.81)	12 (8.51)	14 (10.07)
Adults				
<85 (µg/d) (Estimated average requirement)	3 (1.09)	4 (1.53)	2 (0.72)	7 (2.58)
85-600 (µg/d)	260 (94.55)	243 (93.10)	263 (94.95)	243 (89.67)
>600 (µg/d) (Tolerable upper limit)	12 (4.36)	14 (5.36)	12 (4.33)	21 (7.75)



Mean salt, median iodine intake and their 95% confidence intervals in children (A) and adults (B). EAR: Estimated average requirement; RNI: Recommended nutrient intake; UL: Tolerable upper limit.

93x57mm (300 x 300 DPI)



Trial profile

233x307mm (300 x 300 DPI)

ONLINE SUPPLEMENT

Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a sub-study of a cluster randomised controlled trial

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Supplement Table 1. Baseline characteristics of the participants*

Parameters	Control	Intervention	All
Children			
Number of schools	14	14	28
Number of children	138	141	279
Boys, N (%)	67 (48.6)	67 (47.5)	134 (48.0)
Age (year)	10.2 (0.5)	10.0 (0.5)	10.1 (0.5)
Weight (kg)	33.3 (7.2)	33.4 (7.8)	33.3 (7.5)
Height (cm)	140.7 (6.6)	139.2 (6.2)	140.0 (6.5)
Body mass index (kg/m^2)	16.7 (2.7)	17.1 (3.2)	16.9 (3.0)
Adults			
Number of adults	275	278	553
Men, N (%)	133 (48.4)	135 (48.6)	268 (48.5)
Parents, N (%)	208 (75.6)	203 (73.0)	411 (74.3)
Grandparents, N (%)	67 (24.4)	75 (27.0)	142 (25.7)
Age (year)	43.6 (11.8)	43.9 (12.5)	43.8 (12.2)
Weight (kg)	66.2 (12.9)	66.1 (11.6)	66.2 (12.3)
Height (cm)	162.8 (8.7)	162.4 (8.0)	162.6 (8.4)
Body mass index (kg/m^2)	24.9 (3.6)	25.0 (3.4)	24.9 (3.5)

*Data are means (SD) unless otherwise specified.

Supplement Table 2. Sensitivity analysis for salt and iodine intake as calculated from 24h urinary sodium and iodine excretion

Outcome	Number of participant Control /Intervention	Control		Intervention		Adjusted difference‖ (intervention vs control)	P value
		Baseline‡	Change from baseline‡	Baseline‡	Change from baseline‡		
Population excluding possibly incomplete 24h urine							
Children							
Salt (mean, 95%CI) (g/d)	138/140	7.0 (6.4—7.6)	1.2 (0.7—1.6)	7.5 (6.9—8.1)	-0.7 (-1.1 — -0.2)	-1.9 (-2.6— -1.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	138/140	170.8 (155.0—188.2)	112.9% (102.7%—124.2%)	180.0 (163.6—198.1)	95.4% (86.9%—104.8%)	-16.5% (-26.9%— -4.6%)	0.008
Iodine (median, IQR) (μg/d)	138/140	166.5 (119.0—220.4)	27.3 (-20.6—79.0)	175.4 (131.3—228.7)	-9.3 (-52.4—39.0)		
Adults							
Salt (mean, 95%CI) (g/d)	273/275	11.6 (10.8—12.3)	0.8 (0.3—1.4)	12.8 (12.1—13.6)	-2.1 (-2.6—-1.6)	-3.0 (-3.7— -2.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	273/275	280.7 (255.0—308.9)	104.6% (97.1%—112.7%)	298.0 (270.9—327.7)	95.6% 88.8%—102.9%)	-9.5% (-18.3%—0.2%)	0.055
Iodine (median, IQR) (μg/d)	273/275	275.7 (201.9—360.1)	15.1 (-78.3—105.3)	300.5 (219.2—392.5)	-30.2 (-117.7— 90.2)		
Completers*							
Children							
Salt (mean, 95%CI) (g/d)	135/139	6.8 (6.2—7.4)	1.2 (0.8—1.7)	7.2 (6.6—7.9)	-0.7 (-1.2— -0.2)	-1.9 (-2.6— -1.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	135/139	162.0 (146.0—180.0)	115.4% (104.9%—126.9%)	173.5 (156.4—192.4)	94.0% (85.6%—103.2%)	-19.3% (-29.4%— -7.8%)	0.002

Iodine (median, IQR) (μg/d)	135/139	160.9 (117.7—208.1)	27.4 (-18.3—76.7)	169.6 (128.5—221.6)	-13.1 (-54.5—37.8)		
Adults							
Salt (mean, 95%CI) (g/d)	261/271	11.4 (10.6—12.1)	0.8 (0.2—1.3)	12.7 (11.9—13.5)	-2.2 (-2.7— -1.6)	-3.0 (-3.7— -2.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	261/270	272.1 (245.3—301.7)	104.7% (96.9%—113.1%)	292.6 (264.1—324.3)	93.1% (86.3%—100.4%)	-11.1% (-20.1%— -1.1%)	0.030
Iodine (median, IQR) (μg/d)	261/270	261.8 (197.8—348.8)	10.7 (-72.8—105.3)	297.7 (213.2—391.8)	-36.5 (-128.4— 88.9)		
Per protocol population†							
Children							
Salt (mean, 95%CI) (g/d)	132/137	7.0 (6.4—7.6)	1.2 (0.7—1.7)	7.5 (6.9—8.1)	-0.7 (-1.1— -0.2)	-1.9 (-2.6— -1.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	132/137	169.5 (154.1—186.4)	114.1% (103.7%—125.5%)	179.6 (163.5—197.2)	95.9% (87.3%—105.3%)	-16.8% (-27.2%— -4.9%)	0.007
Iodine (median, IQR) (μg/d)	132/137	166.5 (120.3—216.8)	27.3 (-20.6—79.0)	178.8 (131.3—228.7)	-9.3 (-52.4—39.0)		
Adults							
Salt (mean, 95%CI) (g/d)	249/256	11.6 (10.8—12.3)	0.9 (0.3—1.4)	12.9 (12.2—13.7)	-2.1 (-2.6— -1.6)	-3.0 (-3.7— -2.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	249/255	282.4 (256.5—311.0)	104.3% (96.7%—112.5%)	296.3 (269.3—326.0)	96.1% (89.2%—103.6%)	-8.3% (-17.3%—1.7%)	0.102
Iodine (median, IQR) (μg/d)	249/255	275.8 (203.1—360.1)	15.1 (-78.3—105.3)	300.1 (218.3—391.8)	-30.2 (-117.7— 90.2)		

* Completers refer to the participants who had 24h urine collections both at baseline and end of the trial. † Per protocol population refers to completers with complete 24h urine collections. ‡ Mean and geometric mean were adjusted for stratification variables at randomisation (school location and class size). ‖Adjusted for age, sex, body mass index, stratification variables at randomisation (school location and class size), and indoor and outdoor temperature.

Supplement Table 3. Iodine status assessed by 24h urinary iodine concentration using WHO's criteria, and median 24h urinary iodine concentration and 24h urinary iodine excretion for each category

Urinary iodine (µg/L)	Control						Intervention					
	Baseline			End of trial			Baseline			End of trial		
	N (%)	Iodine (median)		N (%)	Iodine (median)		N (%)	Iodine (median)		N (%)	Iodine (median)	
		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)
Children												
<100 (Iodine deficient)	10 (7.25)	85.07	94.93	10 (7.41)	84.26	114.51	5 (3.55)	86.17	89.84	11 (7.91)	86.65	113.78
100-199 (Adequate)	55 (39.86)	155.60	139.77	40 (29.63)	152.39	143.31	54 (38.30)	156.60	152.99	48 (34.53)	153.87	125.17
200-299 (Above requirement)	48 (34.78)	235.92	172.93	52 (38.52)	243.06	184.82	43 (30.50)	248.98	173.10	41 (29.5)	238.24	165.24
300 (Excessive)	25 (18.12)	430.84	249.11	33 (24.44)	371.52	279.42	39 (27.66)	357.28	236.15	39 (28.06)	411.03	260.88
ALL	138	204.60	161.70	135	222.50	176.0	141	225.30	167.00	139	217.10	154.80
Adults												
<100 (Iodine deficient)	32 (11.64)	81.31	137.25	38 (14.56)	72.84	149.13	31 (11.19)	79.49	140.35	48 (17.71)	74.71	164.03
100-199 (Adequate)	121 (44.00)	152.37	240.44	108 (41.38)	147.78	246.58	103 (37.18)	150.95	281.83	116 (42.80)	142.55	250.69
200-299 (Above requirement)	68 (24.73)	239.54	280.75	72 (27.59)	243.17	353.36	79 (28.52)	246.73	326.61	56 (20.66)	240.86	293.21
≥300 (Excessive)	54 (19.64)	372.08	420.86	43 (16.48)	351.76	460.61	64 (23.10)	372.21	423.84	51 (18.82)	364.22	535.18
ALL	275	188.80	262.10	261	183.60	281.3	277	209.4	297.40	271	176.20	258.5

Supplement Table 4. Comparison of iodine levels observed from 24h urinary iodine with that predicted from salt intake and iodine content in salt

	Control		Intervention	
	Baseline*	End of trial*	Baseline*	End of trial*
Children				
Observed from 24h urinary measurements				
Mean salt (g/d)	6.8	8.0	7.3	6.6
Median iodine (µg/d)	161.7	176.0	167.0	154.8
Iodine/salt ratio, median (µg/g)	23.8	24.4	25.0	24.9
Predicted iodine based on salt intake and iodine content in salt using the minimum level of 18 mg/kg				
Predicted iodine (µg/d)	122.4	144.0	131.4	118.8
Ratio (predicted/observed)	0.8	0.8	0.8	0.8
Adults				
Observed from 24h urinary measurements				
Mean salt (g/d)	11.3	12.1	12.6	10.4
Median iodine (µg/d)	262.1	281.3	297.4	258.5
Iodine/salt ratio, median (µg/g)	24.8	24.8	24.6	26.7
Predicted iodine based on salt intake and iodine content in salt using the minimum level of 18 mg/kg				
Predicted iodine (µg/d)	203.4	217.8	226.8	187.2
Ratio (predicted/observed)	0.8	0.8	0.8	0.7

*adjusted for stratification variables at randomisation (school location and class size).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	6 & Reference 13 &14
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7 & Reference 13 &14
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Not applicable
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Reference 13 &14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Reference 13 &14

mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Reference 13 &14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8 & Supplement Figure
	13b	For each group, losses and exclusions after randomisation, together with reasons	8 & Supplement Figure
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Reference 13 &14
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Supplement Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Supplement Table 1, Table 3, & Supplement Figure
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Supplement Table 2 & 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10-11

Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Submitted as supplement file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a sub-study of a cluster randomised controlled trial

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Keywords:	Salt reduction, Iodine status, 24h urine collections, Cluster randomised trial

Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a sub-study of a cluster randomised controlled trial

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Running Title: Effect of salt reduction on iodine status

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Abstract

Objective To study the effect of salt reduction on iodine status and to determine whether iodine consumption was still adequate after salt reduction in a population where universal salt iodisation is mandatory.

Design A sub-study of a cluster randomised controlled trial, with schools randomly assigned to either the intervention or control group.

Setting 28 primary schools in Changzhi, northern China.

Participants 279 children in grade 5 of primary school (mean age: 10.1); 553 adults (age: 43.8).

Intervention Children were educated about the harmful effects of salt and how to reduce salt intake using the schools' usual health education lessons. Children then delivered the message to their families. The duration was one school term (≈3.5 months).

Main outcome measure Difference between the intervention and control group in the change of iodine intake as measured by repeat 24h urinary iodine from baseline to the end of the trial.

Results At baseline, the mean salt intake was 7.0±2.5g/d in children and 11.7±4.4g/d in adults and the median iodine intake was 165.1μg/d (IQR: 122.6-216.7) and 280.7μg/d (IQR: 205.1-380.9) in children and adults respectively. At the end of the study, both salt and iodine decreased in the intervention compared with control group. The mean effect on salt for intervention vs control was -1.9g/d (95% CI: -2.6 to -1.3) in children and -2.9g/d (95% CI: -3.7 to -2.2) in adults. The mean effect on iodine was -19.3% (95%CI: -29.4% to -7.7%) in children and -11.4% (95%CI: -20.3% to -1.5%) in adults.

Conclusions With ≈25% reduction in salt intake, there was a significant reduction in iodine consumption in northern China where salt is iodised. Despite this, iodine intake was

still adequate, and well above the estimated average requirement. Our findings indicate that reducing salt to the WHO's target─30% reduction by 2025, will not compromise iodine status.

Trial registration ClinicalTrials.gov NCT01821144.

Strengths and limitations of this study

- 24h urinary iodine excretion is the most reliable biochemical marker for assessing iodine status.
- Our study is the first to have assessed iodine status by repeat 24h urine collections in a large number of primary school children and their adult family members in northern China where universal salt iodisation is mandatory.
- Our study, for the first time, has assessed the effect of a modest reduction in salt intake on iodine status using a well-controlled randomised trial.
- The results demonstrate that ≈25% reduction in salt intake which is close to the WHO's target, does not compromise iodine status.
- Despite all 24h urine collections followed stringent protocol with careful supervision, there might still be under collections in some participants. However, the consistent findings from various sensitivity analyses indicate that this is unlikely to alter the primary outcome.

Introduction

Iodine deficiency disorder is a global public health problem with approximately 1.88 billion people including 241 million school-age children having insufficient intake of iodine worldwide.[1] China was one of the countries that had a serious epidemic of iodine deficiency disorders.[2] In 1993, the WHO (World Health Organisation) and UNICEF (United Nations Children's Fund) recommended universal salt iodization to prevent and control iodine deficiency.[1] China launched a universal salt iodisation programme in 1995.[3] Since then significant progress has been made in reducing iodine deficiency disorders.[3 4] In recent years there has been debate about the optimal levels of iodine fortification in salt, particularly as salt intake is very high in China and iodine excess could also lead to thyroid diseases.[3 5 6]

A reduction in salt intake is one of the most cost-effective public health policies to prevent hypertension and cardiovascular disease.[7-9] The WHO recommends a 30% reduction in salt intake by 2025 for all countries around the world with an eventual target of 5 g/d.[10] As salt has been used as a vehicle for iodine fortification in many countries, it is important to monitor iodine status to ensure that iodine consumption is still adequate when salt intake is reduced.

More than 90% of iodine consumed is excreted in the urine within 24-48 hours.[11 12] Therefore, 24h urinary iodine excretion is a good marker of recent dietary iodine intake and is the ideal biochemical indicator for assessing iodine status.[1] We measured 24h urinary iodine excretion in individuals who took part in School-EduSalt (**School**-based **Edu**cation Programme to Reduce **Salt**),[13 14] a cluster randomised controlled trial in Changzhi, northern China where universal salt iodisation is mandatory. The primary aim of the School-EduSalt trial was to determine whether an education programme targeted at primary school children could lower salt intake in children and their families. The study collected two consecutive 24h urines at baseline and at the end of the trial using a standardised protocol with careful

supervision. The results showed that the education led to a significant reduction in salt intake by approximately 25% in both children and adults compared with the controls. In this paper, we report a pre-specified sub-study,[15] the aim of which was to assess iodine status by repeat 24h urinary iodine excretion and to study the effect of salt reduction on iodine status, and in particular to determine whether iodine consumption was still adequate after the participants had been on a reduced salt intake for a few months.

Methods

A detailed description of the methods of the School-EduSalt study has been published elsewhere[13 14] and the abridged methods are reported here. The study was a cluster randomised controlled trial in 28 primary schools in urban Changzhi, Northern China. From each school, we selected one class in Grade 5 (age ≈10 years). From each class we randomly selected 10 children who met the inclusion criteria.[14] From each child's family we also enrolled two adults. Schools were randomly assigned to either the intervention or the control group with stratification by the location of schools and the size of the class.

Children in the intervention group were educated about the harmful effects of salt on health and how to reduce salt intake using the schools' usual health education lessons, i.e. one 40 min lesson every two weeks.[13 14] The salt reduction education was delivered to the whole class in spite of only 10 children being selected for assessment. Children were asked to deliver the salt reduction message to the families, particularly children needed to persuade the persons who did the cooking to reduce the amount of salt used during food preparation at home. The duration of the intervention was one school term (≈3.5 months). Children in the control group carried on with their usual health education lessons as in the curriculum.

The primary outcome of this sub-study was the difference between the intervention and the control group in the change of iodine intake as measured by 24h urinary iodine excretion from baseline to the end of the trial.

Urinary iodine was measured by the Key Laboratory of Hormone and Development (Ministry of Health, China), that participated in the US Centers for Disease Control and Prevention EQUIP (Ensuring the Quality of Urinary Iodine Procedures) programme.[16] Ammonium persulfate digestion with spectrophotometric detection of the Sandell-Kolthoff reaction was used for urinary iodine measurement with quality control,[17] using the samples collected during the study with the storage condition of -80^{0}C. For each batch of samples, we ran four levels of certified reference material—lyophilized human urine (lot nos. GBW09108l, GBW09110n, GBW09111a and GBW09112a; National Reference Laboratory for iodine deficiency disorder, Beijing) with mean certified iodine concentrations of 67.9 μg/L (95%CI: 58.9 to 76.9), 195μg/L (95%CI: 185 to 205), 558 μg/L (95%CI: 541 to 575) and 885 μg/L (95%CI: 857 to 913), respectively. The biochemists who performed the urinary iodine measurements were not aware which group the participant was allocated.

Statistical analyses

As urinary iodine was not normally distributed, we used median and interquartile range (IQR) to summarise the iodine status. Three urine samples with iodine >5000 μg/24h were outliers and excluded from the analysis. All three were from the intervention group. We used the cut-off points (EAR, Estimated Average Requirement and UL, Tolerable Upper Limit) as recommended by the Chinese Nutrition Society[18] to define iodine intake as insufficient if urinary iodine was less than EAR, i.e. <65 μg/24h in children aged ≈10 or <85 μg/24h in adults; adequate if iodine was between EAR and UL, i.e. 65-300 μg/24h in children or 85-600 μg/24h in adults; excessive if urinary iodine was more than UL, i.e. >300 μg/24h in children or >600 μg/24h in adults. For the purpose of comparison with other surveys, we also reported 24h urinary iodine concentration and iodine status based on urinary iodine concentration according the WHO's criteria (i.e. iodine deficient <100 μg/L; adequate 100-199 μg/L, above requirement 200-299 μg/L; excessive ≥300 μg/L).

Our main analysis was based on intention-to-treat using linear mixed models as reported previously.[14 19] Logarithmic transformed iodine was used, and as such, the mean effect on iodine was presented as percentage change. The statistical model was in the form: Outcome= Group+Time+Interaction (time×group)+Stratification variables at randomisation (school location and class size)+Confounding variables (age, sex, body mass index, indoor and outdoor temperature). To examine the robustness of the conclusions of the primary analysis we carried out various sensitivity analyses as specified previously.[14] The number of 24h urine samples included and excluded in each analysis was shown in Supplement Figure 1.

We used SAS (version 9.4) for the analyses. Results are reported as mean, SD and 95% CI or median and IQR where appropriate. All analyses were 2-sided and P values of <0.05 were considered statistically significant.

Results

The School-EduSalt trial enrolled 279 children and 553 adults, all of whom were included in the current report. The baseline characteristics of the participants were well balanced between the intervention and the control group (Supplement Table 1). The mean age was 10.1±0.5 years for children and 43.8±12.2 years for adults.

The result on salt has been published previously.[14] We report it again in this paper explicitly for the purpose of allowing the readers to compare the salt and iodine levels. At baseline, the mean salt intake as calculated from 24h urinary sodium excretion was 7.0±2.5 g/d in children and 11.7±4.4 g/d in adults. The median iodine consumption as measured by 24h urinary iodine was 165.1 μg/d (IQR: 122.6-216.7, 95% CI: 156.9 to 172.9) and 280.7 μg/d (IQR: 205.1-380.9, 95% CI: 270.3 to 293.8) in children and adults respectively.

Table 1 shows the salt and iodine intake by group, as well as their changes during the study. From baseline to the end of the trial, both salt and iodine intake decreased in the intervention

group and increased in the control group. The mean effect size on salt for intervention vs control was -1.9 g/d (95% CI: -2.6 to -1.3, P<0.0001) in children and -2.9 g/d (95% CI: -3.7 to -2.2, P<0.0001) in adults. The mean effect size on iodine was -19.3% (95% CI: -29.4% to -7.7%, P=0.002) in children and -11.4% (95% CI: -20.3% to -1.5%, P=0.03) in adults.

Table 2 shows iodine status according to the Chinese Nutrition Society's guidelines.[18] In the intervention group, there was an increase in the proportion of individuals with iodine intake below EAR from baseline to the end of the trial. Despite this, there were only less than 5% children and less than 3% adults who had iodine intake below EAR after salt intake was reduced.

The results from sensitivity analyses are shown in Supplement Table 2. The first analysis excluded possibly incomplete 24 urine collections. As expected, the absolute levels of salt and iodine intake were higher compared with those when all 24h urine collections were included. However, the primary outcome, i.e. the difference between the two groups in the change of salt and iodine intake was very similar to that from the main analysis. The results for completers (i.e. the participants who had 24h urine collections both at baseline and end of the trial) and per-protocol analyses (including completers with complete 24h urine collections) were very close to those from the corresponding analyses with all participants included.

Supplement Table 3 shows the iodine status based on 24h urinary iodine concentration using the WHO's criteria, as well as the median 24h urinary iodine concentration and the median 24h urinary iodine excretion for each category. In both children and adults, the median 24h urinary iodine excretions in the group classified as iodine deficient according to the WHO's criteria (i.e. <100 μg/L) were well above EAR across the study.

Discussion

Our study produced two important findings. First, the study for the first time has measured iodine intake using repeat 24h urine collections in a large number of primary school children and their families in northern China. A conservative estimate showed that the median baseline iodine intake was 165 μg/d in children and 281 μg/d in adults. These intakes are adequate. According to the Chinese Nutrition Society's guideline, EAR (i.e. daily intake meeting the requirement of one-half of the population) is 65 μg/d in children aged 7-10 years and 85 μg/d in adults, and RNI (recommended nutrient intake, i.e. intake meeting the requirement of 97-98% of the population) is 90 μg/d in children aged 7-10 and 120 μg/d in adults.[18] The median iodine intakes in our study were 254% and 331% of EAR, and 183% and 234% of RNI for children and adults respectively. Additionally, the median iodine intakes were far below the tolerable upper limit of 300 μg/d in children and 600 μg/d in adults (Figure 1).

Second, our study is the first to have studied the effect of salt reduction, as currently recommended, on iodine status in a population where salt is universally iodised. The mean effect was a reduction in salt intake of 1.9 g/d in children and 2.9 g/d in adults which led to a decrease in iodine intake of 19.3% and 11.4% in children and adults respectively. These mean effects represent the differences between the intervention and control group in the changes in salt and iodine from baseline to the end of the trial. As shown in table 1, during the study, both salt and iodine intake decreased in the intervention group and increased in the control group. If applying the mean reduction in iodine level (19.3% in children and 11.4% in adults) to all participants irrespective of their group allocation, the average iodine intake would be 133 μg/d in children and 249 μg/d in adults after salt reduction. These iodine levels are still adequate, and 205% and 293% of EAR and 148% and 208% of RNI for children and adults respectively.

In our study, all 24h urine collections were carefully supervised with both the start and finish time recorded by trained research staff. It is certain that there was no over-collection. However, it is difficult to know whether there was any under-collection. Although the participants who admitted to having missed urine voids, were asked to re-do 24h urine collections, it is still possible that some participants did not report missing urine collection. Excluding potential incomplete 24h urine collections, as expected, led to a slightly higher salt and iodine intake for both baseline and end trial, and for both the intervention and the control group. It is therefore likely that our main results have under-estimated the average salt and iodine intake of the study population. However, this is unlikely to alter the primary outcome, i.e. the difference between the intervention and control group. Indeed, various sensitivity analyses have shown consistent findings (Supplement Table 2).

In Changzhi where our study was carried out, the iodine content in salt varied from 18 to 33 mg/kg in 2013 (data was provided by the local salt manufacturer). Based on the iodine content in salt and the 24h urinary sodium and iodine excretion, we estimated that ≈80% of iodine in the diet was from iodised salt. The changes in 24h urinary iodine observed in our study is consistent with that predicted from the changes in salt intake (Supplement Table 4). Therefore any potential influence from other dietary sources would be small.

Despite 24h urinary iodine is the most reliable biochemical marker for assessing iodine status, almost all previous surveys on iodine have used spot urine due to the apparent logistic challenges and costs in collecting 24h urine. The WHO also endorsed the use of spot urine and provided cut-offs of median spot urinary iodine concentration to categorise population's iodine status.[1] However, this has been inappropriately used by previous surveys to define the number of individuals who were iodine deficient.[20] Our study demonstrates that, in the group of individuals classified as iodine deficient according to the WHO's criteria based on urinary iodine concentration, the median 24h urinary iodine levels were well above EAR. These

findings clearly illustrate the inappropriateness of spot urine in monitoring iodine status and, as a result, previous surveys would have over-estimated the prevalence of iodine deficiency. It is worth noting that our study did not collect spot urine, however, 24h urinary iodine concentration is a better index than any of the spot urine iodine concentration (e.g. casual, first morning void). Additionally, our study shows that it is entirely feasible to collect 24h urine not only in adults but also in primary school children. The WHO has recommended 24h urine collections for determining and monitoring population salt intake.[21] It will be more efficient and highly cost-effective if the iodine intake is monitored in the same population surveys using the same methods.

In China, since the introduction of universal salt iodisation in 1995, regular surveys using casual spot urine have been carried out to monitor the population's iodine status and adjust the iodine content in salt accordingly.[3] The surveys were largely conducted in primary schoolchildren aged 8-10 because these children are readily accessible in schools and they have been assumed to have iodine intakes characteristic of general populations. At country level, the median spot urinary iodine in schoolchildren aged 8-10 increased from 165 μg/L in 1995 to over 300 μg/L by 1999 and declined to 241 μg/L and 246 μg/L in 2002 and 2005, respectively.[3] This was in parallel with the changes of iodine content in salt which increased from 16.2 mg/kg in 1995, to 42.3 mg/kg in 1999, then declined to 30.8 mg/kg in 2005 and has remained at this level.[3] These changes reflect the alterations of the standard for 'qualified' iodised salt set by the Chinese Ministry of Health.[3] Initially the regulation for iodine content was ⩾20 mg/kg in 1995. As there was no upper limit, most salt producers tended to iodise salt with iodine over 40 mg/kg. In 1997, an upper limit of 60 mg/kg was set. National iodine survey at the time indicated an excessive population iodine intake and such data led to a reduction in the upper limit from 60 to 50 mg/kg in 2002. The standard of 35±15 (or 20-50) mg/kg had remained till 2012 when provinces were allowed to choose from the

three standards, i.e. 20 (14-26), 25 (18-33) and 30 (21-39) mg/kg, depending on local diet and spot urinary iodine concentration.[22]

In our study site—Changzhi, the changes in urinary iodine followed a similar pattern to that occurred nationally although some of the surveys showed a higher iodine level. The most recent survey in Changzhi was carried out in 2010 and showed that the median spot urinary iodine was 241, 284 and 310 μg/L in schoolchildren aged 8, 9 and 10 respectively.[23] In our study which was done in 2013, the median baseline 24h urinary iodine concentration was 215.8 μg/L for schoolchildren aged ≈10 years. The lower iodine level observed in our study could be largely due to the decrease in iodine content in salt following the change in the standard for iodised salt (i.e. from 20-50 mg/kg to 18-33 mg/kg) in 2012.

Despite our study was carried out in Changzhi and included individuals who mainly ate home-made meals, the results could be broadly applicable to most parts of China for the following reasons: (1) Universal salt iodisation is mandatory in China, and the food manufacturers and restaurants also use iodised salt; (2) The iodine content in salt (18-33 mg/kg) in Changzhi is similar to the national level (14-39 mg/kg)[22]; (3) Salt is the major source of iodine in the diet across China. Although there is a variation in iodine level from natural sources such as water and foods, iodised salt contributes to 60-80% of total iodine intake in most parts of China.[24 25] In Changzhi where our study was carried out, iodised salt accounts for ≈80% of iodine intake (i.e. at the higher end of the range in China). The iodine intake in our study population was still adequate after an approximate 25% reduction in salt intake for 3.5 months, it is therefore most likely that the same reduction in salt if achieved across China would not compromise iodine status. The findings of our study, however, may not be generalisable to populations in other countries due to a number of features in the setting, such as universal salt iodisation and high contribution of discretionary salt to total salt intake in the Chinese diet.

Conclusions

Our study demonstrates that in northern China where universal salt iodisation is mandatory, a reduction in salt intake by ≈25% which is close to the WHO's target of 30% reduction by 2025 does not compromise iodine status as measured by repeat 24h urinary iodine excretion in both children and adults. These findings provide strong support for the WHO's recommendations to reduce population salt intake to prevent hypertension and cardiovascular disease, and to improve iodine intake by fortifying salt with iodine to prevent iodine deficiency.

Currently many countries have started salt reduction initiatives and also implemented salt iodisation programmes.[26] However, there is a lack of coordination between the two. To maximise the benefits, there is an urgent need for close coordination and collaboration, particularly in disseminating consistent messages and monitoring population salt and iodine intake using the same methods which will provide valuable data required for appropriate adjustment of the iodine level in salt after population salt intake is reduced. This will be the most cost-effective way in implementing the two important public health policies.

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Trial Steering Committee: Peter Sever (chair), Francesco Cappuccio, Kiang Liu, Dong Zhao, Feng He, Yangfeng Wu, and Graham MacGregor.

Contributors: FJH, YW and GAM designed the School-EduSalt trial. WZ developed the protocol for urinary iodine measurement and interpreted the iodine results. WZ, LL and XG organised urinary iodine measurement. JZ and YM performed quality control for iodine measurement. XF, JZ and YM contributed to data collection. FJH and YM developed the analysis plan, performed statistical analyses and took responsibility for the integrity of the data and the accuracy of the data analysis. FH wrote the manuscript. All authors contributed to the revision and approved the final manuscript. FJH is guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. FJH is a member of Consensus Action on Salt & Health (CASH) and World Action on Salt & Health (WASH). Both CASH and WASH are non-profit charitable organisations and FJH does not receive any financial support from CASH or WASH. GAM is Chairman of Blood Pressure UK (BPUK), Chairman of CASH, WASH and Action on Sugar (AoS). BPUK, CASH, WASH and AoS are non-profit charitable organisations. GAM does not receive any financial support from any of these organisations. YM was sponsored by the China Scholarship Council while she was carrying out statistical analysis for this study at the Wolfson Institute of Preventive Medicine, Queen Mary University of London. Other authors declare that they have no conflicts of interest.

Ethical approval: The study protocol was approved by Queen Mary (University of London) Research Ethics Committee (QMREC2012/81) and Peking University Health Science Centre IRB (IRB00001052-12072). Permissions were obtained from the local education authority (i.e. Changzhi Education Bureau) and head-teachers of the schools. All participants who took part in the assessments gave written informed consent. For children, participant assent and parental written consent were obtained.

Data sharing: No additional data available.

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Legend to figures.

Figure 1. Mean salt, median iodine intake and their 95% confidence intervals in children (A) and adults (B). EAR: Estimated average requirement; RNI: Recommended nutrient intake; UL: Tolerable upper limit.

Supplement Figure 1. Trial profile. ITT: Intention-to-treat.

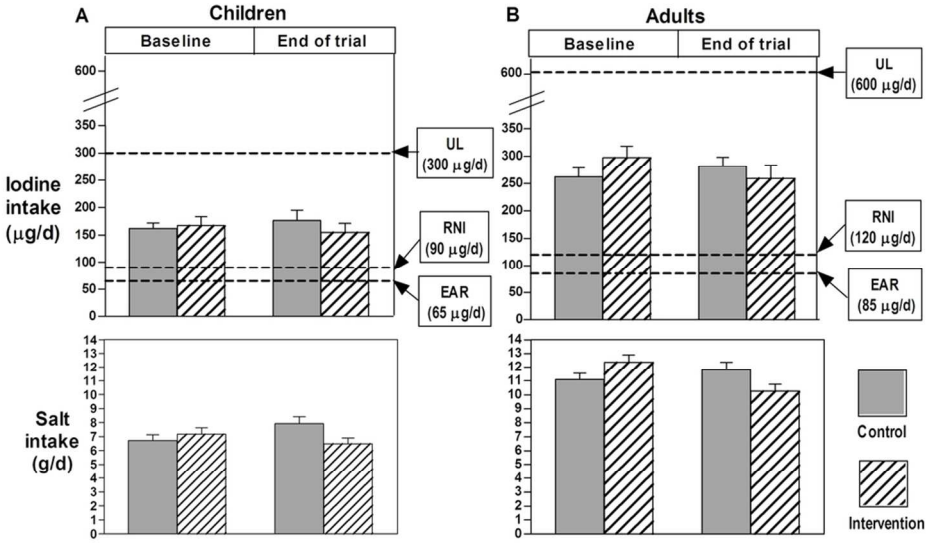
Table 1. Salt and iodine intake as calculated from 24h urinary sodium and iodine excretion based on intention-to-treat analysis

Outcome	Control			Intervention			Mean effect† (intervention vs control)	P value
	Baseline*	End of trial*	Change from baseline*	Baseline*	End of trial*	Change from baseline*		
Children								
Salt, mean‡ (95%CI) (g/d)	6.8 (6.2─7.4)	8.0 (7.4─8.6)	1.2 (0.7─1.7)	7.3 (6.7─7.9)	6.6 (6.0─7.2)	-0.7 (-1.2─ -0.2)	-1.9 (-2.6─ -1.3)	<0.0001
Iodine								
Geometric mean (95%CI) (µg/d)	162.8 (146.7─180.5)	187.5 (168.9─208.0)	115.2% (104.7%─126.7%)	173.7 (156.7─192.4)	163.2 (147.2─180.9)	94.0% (85.6%─103.2%)	-19.3% (-29.4%─ -7.7%)	0.002
Median (IQR) (µg/d)	161.7 (117.7─209.5)	176.0 (136.5─237.2)	27.4 (-18.3─76.7)	167.0 (128.9─217.7)	154.8 (118.6─234.1)	-13.1 (-54.5─37.8)		
Adults								
Salt, mean (95%CI) (g/d)	11.3 (10.5─12.1)	12.1 (11.3─12.9)	0.8 (0.2─1.3)	12.6 (11.8─13.3)	10.4 (9.7─11.2)	-2.1 (-2.7─ -1.6)	-2.9 (-3.7─ -2.2)	<0.0001
Iodine								
Geometric mean (95%CI) (µg/d)	271.2 (245.1─300.1)	284.6 (256.9─315.2)	104.9% (97.2%─113.3%)	291.2 (263.3─322.1)	271.9 (245.7─301.0)	93.4% (86.6%─100.7%)	-11.4% (-20.3%─ -1.5%)	0.030
Median (IQR) (µg/d)	262.1 (197.8─357.5)	281.3 (207.9─387.6)	10.7 (-72.8─105.3)	297.4 (213.2─390.8)	258.5 (199.8─350.0)	-36.5 (-128.4─88.9)		

* Mean and geometric mean were adjusted for stratification variables at randomisation (school location and class size). †Adjusted for age, sex, body mass index, stratification variables at randomisation (school location and class size), and indoor and outdoor temperature. ‡The results for salt were taken from previous report.[14]

Table 2. Iodine status assessed by 24h urinary iodine excretion

Category	Control		Intervention	
	Baseline N (%)	End of trial N (%)	Baseline N (%)	End of trial N (%)
Children				
<65 (µg/d) (Estimated average requirement)	5 (3.62)	1 (0.74)	1 (0.71)	6 (4.32)
65-300 (µg/d)	123 (89.13)	114 (84.44)	128 (90.78)	119 (85.61)
>300 (µg/d) (Tolerable upper limit)	10 (7.25)	20 (14.81)	12 (8.51)	14 (10.07)
Adults				
<85 (µg/d) (Estimated average requirement)	3 (1.09)	4 (1.53)	2 (0.72)	7 (2.58)
85-600 (µg/d)	260 (94.55)	243 (93.10)	263 (94.95)	243 (89.67)
>600 (µg/d) (Tolerable upper limit)	12 (4.36)	14 (5.36)	12 (4.33)	21 (7.75)



Mean salt, median iodine intake and their 95% confidence intervals in children (A) and adults (B). EAR: Estimated average requirement; RNI: Recommended nutrient intake; UL: Tolerable upper limit.

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ONLINE SUPPLEMENT

Effect of salt reduction on iodine status assessed by 24h urinary iodine excretion in children and their families in northern China: a sub-study of a cluster randomised controlled trial

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Supplement Table 1. Baseline characteristics of the participants*

Parameters	Control	Intervention	All
Children			
Number of schools	14	14	28
Number of children	138	141	279
Boys, N (%)	67 (48.6)	67 (47.5)	134 (48.0)
Age (year)	10.2 (0.5)	10.0 (0.5)	10.1 (0.5)
Weight (kg)	33.3 (7.2)	33.4 (7.8)	33.3 (7.5)
Height (cm)	140.7 (6.6)	139.2 (6.2)	140.0 (6.5)
Body mass index (kg/m^2)	16.7 (2.7)	17.1 (3.2)	16.9 (3.0)
Adults			
Number of adults	275	278	553
Men, N (%)	133 (48.4)	135 (48.6)	268 (48.5)
Parents, N (%)	208 (75.6)	203 (73.0)	411 (74.3)
Grandparents, N (%)	67 (24.4)	75 (27.0)	142 (25.7)
Age (year)	43.6 (11.8)	43.9 (12.5)	43.8 (12.2)
Weight (kg)	66.2 (12.9)	66.1 (11.6)	66.2 (12.3)
Height (cm)	162.8 (8.7)	162.4 (8.0)	162.6 (8.4)
Body mass index (kg/m^2)	24.9 (3.6)	25.0 (3.4)	24.9 (3.5)

*Data are means (SD) unless otherwise specified.

Supplement Table 2. Sensitivity analysis for salt and iodine intake as calculated from 24h urinary sodium and iodine excretion

Outcome	Number of participant Control /Intervention	Control		Intervention		Adjusted difference‖ (intervention vs control)	P value
		Baseline‡	Change from baseline‡	Baseline‡	Change from baseline‡		
Population excluding possibly incomplete 24h urine							
Children							
Salt (mean, 95%CI) (g/d)	138/140	7.0 (6.4—7.6)	1.2 (0.7—1.6)	7.5 (6.9—8.1)	-0.7 (-1.1 — -0.2)	-1.9 (-2.6— -1.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	138/140	170.8 (155.0—188.2)	112.9% (102.7%—124.2%)	180.0 (163.6—198.1)	95.4% (86.9%—104.8%)	-16.5% (-26.9%— -4.6%)	0.008
Iodine (median, IQR) (μg/d)	138/140	166.5 (119.0—220.4)	27.3 (-20.6—79.0)	175.4 (131.3—228.7)	-9.3 (-52.4—39.0)		
Adults							
Salt (mean, 95%CI) (g/d)	273/275	11.6 (10.8—12.3)	0.8 (0.3—1.4)	12.8 (12.1—13.6)	-2.1 (-2.6—-1.6)	-3.0 (-3.7— -2.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	273/275	280.7 (255.0—308.9)	104.6% (97.1%—112.7%)	298.0 (270.9—327.7)	95.6% 88.8%—102.9%)	-9.5% (-18.3%—0.2%)	0.055
Iodine (median, IQR) (μg/d)	273/275	275.7 (201.9—360.1)	15.1 (-78.3—105.3)	300.5 (219.2—392.5)	-30.2 (-117.7— 90.2)		
Completers*							
Children							
Salt (mean, 95%CI) (g/d)	135/139	6.8 (6.2—7.4)	1.2 (0.8—1.7)	7.2 (6.6—7.9)	-0.7 (-1.2— -0.2)	-1.9 (-2.6— -1.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	135/139	162.0 (146.0—180.0)	115.4% (104.9%—126.9%)	173.5 (156.4—192.4)	94.0% (85.6%—103.2%)	-19.3% (-29.4%— -7.8%)	0.002

Iodine (median, IQR) (μg/d)	135/139	160.9 (117.7─208.1)	27.4 (-18.3─76.7)	169.6 (128.5─221.6)	-13.1 (-54.5─37.8)		
Adults							
Salt (mean, 95%CI) (g/d)	261/271	11.4 (10.6─12.1)	0.8 (0.2─1.3)	12.7 (11.9─13.5)	-2.2 (-2.7─ -1.6)	-3.0 (-3.7─ -2.2)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	261/270	272.1 (245.3─301.7)	104.7% (96.9%─113.1%)	292.6 (264.1─324.3)	93.1% (86.3%─100.4%)	-11.1% (-20.1%─ -1.1%)	0.030
Iodine (median, IQR) (μg/d)	261/270	261.8 (197.8─348.8)	10.7 (-72.8─105.3)	297.7 (213.2─391.8)	-36.5 (-128.4─ 88.9)		
Per protocol population†							
Children							
Salt (mean, 95%CI) (g/d)	132/137	7.0 (6.4─7.6)	1.2 (0.7─1.7)	7.5 (6.9─8.1)	-0.7 (-1.1─ -0.2)	-1.9 (-2.6─ -1.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	132/137	169.5 (154.1─186.4)	114.1% (103.7%─125.5%)	179.6 (163.5─197.2)	95.9% (87.3%─105.3%)	-16.8% (-27.2%─ -4.9%)	0.007
Iodine (median, IQR) (μg/d)	132/137	166.5 (120.3─216.8)	27.3 (-20.6─79.0)	178.8 (131.3─228.7)	-9.3 (-52.4─39.0)		
Adults							
Salt (mean, 95%CI) (g/d)	249/256	11.6 (10.8─12.3)	0.9 (0.3─1.4)	12.9 (12.2─13.7)	-2.1 (-2.6─ -1.6)	-3.0 (-3.7─ -2.3)	<0.0001
Iodine (geometric mean, 95%CI) (μg/d)	249/255	282.4 (256.5─311.0)	104.3% (96.7%─112.5%)	296.3 (269.3─326.0)	96.1% (89.2%─103.6%)	-8.3% (-17.3%─1.7%)	0.102
Iodine (median, IQR) (μg/d)	249/255	275.8 (203.1─360.1)	15.1 (-78.3─105.3)	300.1 (218.3─391.8)	-30.2 (-117.7─ 90.2)		

* Completers refer to the participants who had 24h urine collections both at baseline and end of the trial. † Per protocol population refers to completers with complete 24h urine collections. ‡ Mean and geometric mean were adjusted for stratification variables at randomisation (school location and class size). ‖Adjusted for age, sex, body mass index, stratification variables at randomisation (school location and class size), and indoor and outdoor temperature.

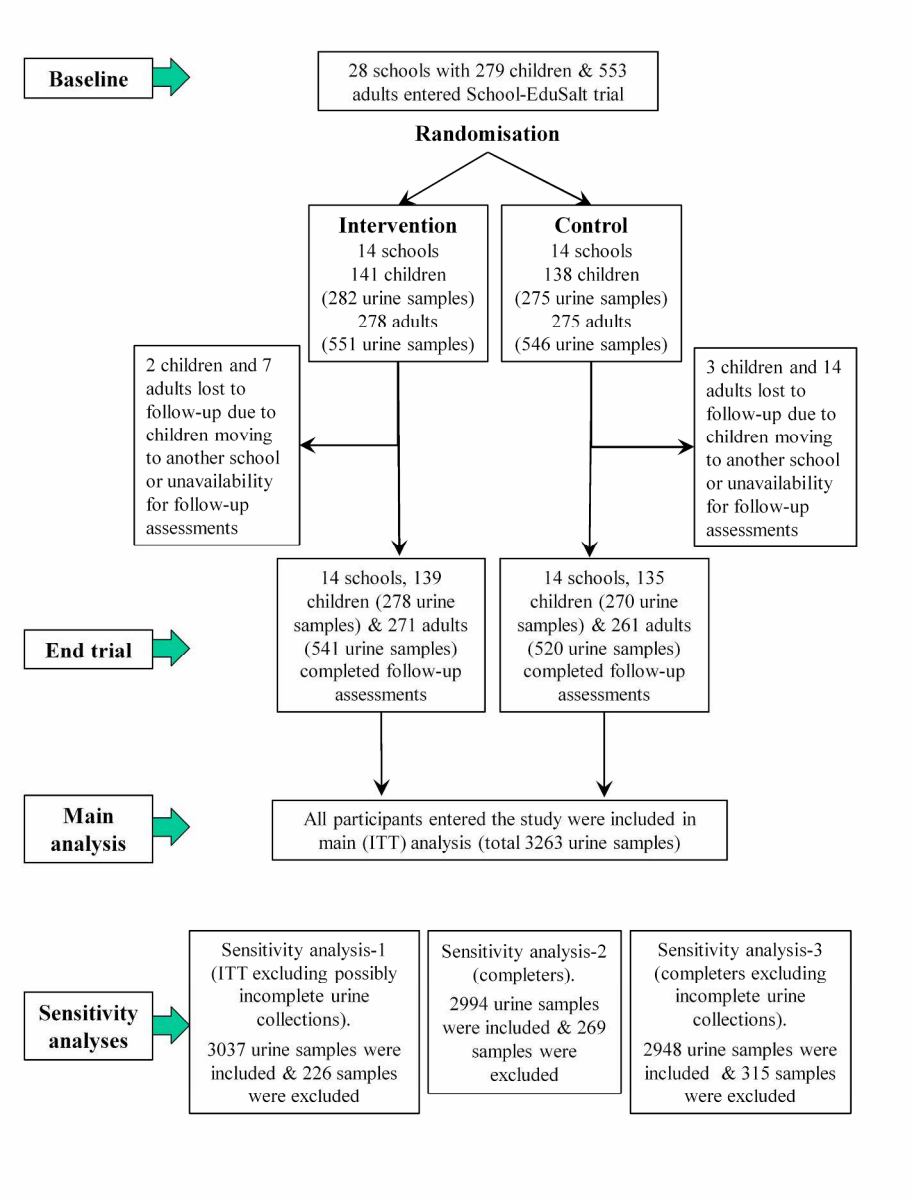
Supplement Table 3. Iodine status assessed by 24h urinary iodine concentration using WHO's criteria, and median 24h urinary iodine concentration and 24h urinary iodine excretion for each category

Urinary iodine (µg/L)	Control						Intervention					
	Baseline			End of trial			Baseline			End of trial		
	N (%)	Iodine (median)		N (%)	Iodine (median)		N (%)	Iodine (median)		N (%)	Iodine (median)	
		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)		(µg/L)	(µg/24h)
Children												
<100 (Iodine deficient)	10 (7.25)	85.07	94.93	10 (7.41)	84.26	114.51	5 (3.55)	86.17	89.84	11 (7.91)	86.65	113.78
100-199 (Adequate)	55 (39.86)	155.60	139.77	40 (29.63)	152.39	143.31	54 (38.30)	156.60	152.99	48 (34.53)	153.87	125.17
200-299 (Above requirement)	48 (34.78)	235.92	172.93	52 (38.52)	243.06	184.82	43 (30.50)	248.98	173.10	41 (29.5)	238.24	165.24
300 (Excessive)	25 (18.12)	430.84	249.11	33 (24.44)	371.52	279.42	39 (27.66)	357.28	236.15	39 (28.06)	411.03	260.88
ALL	138	204.60	161.70	135	222.50	176.0	141	225.30	167.00	139	217.10	154.80
Adults												
<100 (Iodine deficient)	32 (11.64)	81.31	137.25	38 (14.56)	72.84	149.13	31 (11.19)	79.49	140.35	48 (17.71)	74.71	164.03
100-199 (Adequate)	121 (44.00)	152.37	240.44	108 (41.38)	147.78	246.58	103 (37.18)	150.95	281.83	116 (42.80)	142.55	250.69
200-299 (Above requirement)	68 (24.73)	239.54	280.75	72 (27.59)	243.17	353.36	79 (28.52)	246.73	326.61	56 (20.66)	240.86	293.21
≥300 (Excessive)	54 (19.64)	372.08	420.86	43 (16.48)	351.76	460.61	64 (23.10)	372.21	423.84	51 (18.82)	364.22	535.18
ALL	275	188.80	262.10	261	183.60	281.3	277	209.4	297.40	271	176.20	258.5

Supplement Table 4. Comparison of iodine levels observed from 24h urinary iodine with that predicted from salt intake and iodine content in salt

	Control		Intervention	
	Baseline	End of trial	Baseline	End of trial
Children				
Observed from 24h urinary measurements				
Mean salt (g/d)*	6.8	8.0	7.3	6.6
Median iodine (µg/d)	161.7	176.0	167.0	154.8
Iodine/salt ratio, median (µg/g)	23.8	24.4	25.0	24.9
Predicted iodine based on salt intake and iodine content in salt using the minimum level of 18 mg/kg				
Predicted iodine (µg/d)	122.4	144.0	131.4	118.8
Ratio (predicted/observed)	0.8	0.8	0.8	0.8
Adults				
Observed from 24h urinary measurements				
Mean salt (g/d)*	11.3	12.1	12.6	10.4
Median iodine (µg/d)	262.1	281.3	297.4	258.5
Iodine/salt ratio, median (µg/g)	24.8	24.8	24.6	26.7
Predicted iodine based on salt intake and iodine content in salt using the minimum level of 18 mg/kg				
Predicted iodine (µg/d)	203.4	217.8	226.8	187.2
Ratio (predicted/observed)	0.8	0.8	0.8	0.7

*adjusted for stratification variables at randomisation (school location and class size).



Trial profile

233x307mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	6 & Reference 13 &14
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7 & Reference 13 &14
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Not applicable
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Reference 13 &14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Reference 13 &14

mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Reference 13 &14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8 & Supplement Figure
	13b	For each group, losses and exclusions after randomisation, together with reasons	8 & Supplement Figure
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Reference 13 &14
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Supplement Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Supplement Table 1, Table 3, & Supplement Figure
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Supplement Table 2 & 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10-11

Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Submitted as supplement file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.