

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	He, Feng; Ma, Yuan; Feng, Xiangxian; Zhang, Wanqi; Lin, Laixiang; Guo, Xiaohui; Zhang, Jing; Niu, Wenyi; Wu, Yangfeng; MacGregor, Graham

VERSION 1 - REVIEW

REVIEWER	Professor Simon Capewell University of Liverpool. Department of Public Health & Policy, LIVERPOOL, United Kingdom I am a member of CASH (Consensus Action on Salt & Health)
REVIEW RETURNED	11-Mar-2016

GENERAL COMMENTS	<p>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</p> <p>This is an elegant and useful study. I have no major concerns.</p> <p>Minor Points</p> <p>Introduction: Basically fine. Needs half a paragraph on why iodine needs to be added to salt in Changzhi, and indeed elsewhere</p> <p>Methods: Basically fine. Please write EAR and UL in full when they are first mentioned.</p> <p>No adjustment for SocioEconomic Status? Please mention this in the Discussion as a Limitation.</p> <p>Results: Basically fine.</p> <p>Discussion: Basically fine.</p> <p>Two minor questions: 1. Why were salt & iodine baseline values consistently higher in</p>
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	<p>intervention adults & kids than in controls?</p> <p>2. Does it matter that 8-15% of children exceeded the Iodine Tolerable Upper Limit?</p> <p>Nil else.</p>
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REVIEWER	Rachael McLean University of Otago New Zealand
REVIEW RETURNED	08-Apr-2016

GENERAL COMMENTS	<p>This is an extremely interesting paper, which is very well written and presented. It is highly relevant to policy, and will be of considerable interest to researchers and practitioners in the field. It describes the effect of a randomized controlled trial of a salt reduction intervention on iodine status in a group of children and their families in northern China. It shows that in this setting a significant and clinically relevant reduction in salt intake as a result of the intervention was associated with a reduction in iodine intake, but not to the extent that it compromised iodine status.</p> <p>There are a number of features of the setting that mean the findings of this study may not be generalizable to populations in other countries, including the universal iodisation of salt (including table salt and salt in processed foods), and the high contribution of discretionary salt to total salt intake in some Chinese populations. The fact that an education programme in schools could have such an effect on the salt intake of children and their families is extremely impressive, but unlikely to be generalizable to many populations outside China. I think some comment on these issues would make the paper more useful to an international audience, particularly for informing policy in this context.</p>
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REVIEWER	Aryelly Rodriguez (ECTU) Edinburgh Clinical Trials Unit The Usher Institute of Population Health Sciences and Informatics The University of Edinburgh Medical School United Kingdom
REVIEW RETURNED	30-May-2016

GENERAL COMMENTS	Review Checklist	
	Introduction	I did enjoy reviewing this paper as the topic is very interesting and relevant for the current standards of living in urban areas not only in China but in the whole world.
	1. Is the research question or study objective clearly defined?	No, because I thought that the "Iodine excretion" was the original trial, only by going into the text and references I realised this is a sub-study. It should be clear on the title

		and the abstract
	2. Is the abstract accurate, balanced and complete?	No. (see above 1 and 14 below). Please rewrite it so "iodine Intake" takes a starring role for this publication (ie iodine result should not be mentioned after salt results)
	8. Are the references up-to-date and appropriate?	The paper is missing a reference to the results for the Edu-Salt sub-study IODINE in the following publication. http://middleeast.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)00615-7.pdf
	10. Are they presented clearly?	This paper could have more impact by actually being shorter and concentrating in the new results, this would provide a sharper focus on the new research question about iodine intake.
	14. To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)?	The reviewed paper heavily borrows from the parent paper (http://www.bmj.com/content/350/bmj.h770).
	Statistics	
	1. Does this paper require specialist statistical review?	Yes and I have performed this review

	GENERAL COMMENTS	<p>*Please keep the reporting of units consistent (ug vs µg or g/d vs g/day)</p> <p>*Was the data collected in a CRF or eCRF, is currently in a secure database?</p> <p>*Question: have you explored as a post-hoc sensitivity analysis what would have happened if salt intake stayed the same for the control group but decreased for the intervention. Also, in the original paper you explained: “During our study, the control group showed an increase in salt intake. This is probably because of seasonal influence as our baseline assessments were carried out in summer and the follow-up was in winter. Salt intake in northern China is usually higher in winter because people eat more pickles because of reduced availability of fresh vegetables.”. This is reasonable, but I would also re-analyse the results by swapping follow up with baseline in the control to reverse the seasonality</p>
	“we report a prespecified sub-study”	Please add a reference of where it was pre-specified as it is not present in the original study protocol. It would be interesting to know if the iodine was tested at the same time that the sodium content was measured or it was detected from frozen urine samples after the end of the study. Also, as a reader, I would like to know which institute/authority approved the pre-specified study
	“As urinary iodine was not normally distributed, we used median and interquartile range (IQR) to assess the iodine status.”	Instead of “assess” I would use “summarise” the iodine status
	“Three urine samples with iodine >5000 ug/24h were outliers and excluded from the analysis.”	In which group they lied (all in control or all in intervention or 2 vs 1 or 1 vs 2)

	<p>We included group (intervention, control), time (baseline, end trial), and time*group interaction, with the time*group interaction term indicating the mean effect.</p>	<p>If you cut the redundant text there would be space for a more explicit statistical model in the form of: Outcome= covariate + parameter + interaction1+... + error This would set it apart from the original paper</p>	
	<p>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.</p>	<p>If you going to talk about this, please specify ML or REML. Also use an appropriate quote.</p> <p>From the SAS website (https://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm#statug_mixed_sect025.htm)“ In many situations, the best approach is to use likelihood-based methods, exploiting the assumption that Y and e are normally distributed (Hartley and Rao 1967; Patterson and Thompson 1971; Harville 1977; Laird and Ware 1982; Jennrich and Schluchter 1986). PROC MIXED implements two likelihood-based methods: maximum likelihood (ML) and restricted/residual maximum likelihood (REML). A favorable theoretical property of ML and REML is that they accommodate data that are missing at random (Rubin 1976; Little 1995)”</p>	
	<p>The baseline characteristics of the participants were well balanced between the intervention and the control group (Table 1).</p>	<p>This table 1 has already been published at: Results for Edu-Salt http://www.bmj.com/content/350/bmj.h770 I would remove and quote original paper, if you want to keep it put it in the supplement and again quote original paper</p>	
	<p>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.</p>	<p>Agree, but please consider to remove the salt results from the abstract</p>	

	In China, since the introduction of universal salt iodisation in 1995	Is there not regulation to quote?
	Currently many countries have started salt reduction initiatives and also implemented salt iodisation programmes	Quote or give example of countries
	Table 2	Call Iodine results first then salt. Also add a footnote to explain that salt results are from a previous paper
	Supplement Table 3 and Table 4.	These tables could be merge into 1 table

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Professor Simon Capewell

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

This is an elegant and useful study.

I have no major concerns.

Minor Points

Introduction:

Basically fine.

Needs half a paragraph on why iodine needs to be added to salt in Changzhi, and indeed elsewhere

Answer: We have added the following paragraph to the beginning of the 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. China was one of the countries that had serious epidemic of iodine deficiency disorders. In 1993, the WHO (World Health Organisation) and UNICEF (United Nations Children’s Fund) recommended universal salt iodization to prevent and control iodine deficiency. China launched a universal salt iodisation programme in 1995. Since then a significant progress has been made in reducing iodine deficiency disorders. 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.”

Methods:

Basically fine.

Please write EAR and UL in full when they are first mentioned.

Answer: Done.

No adjustment for SocioEconomic Status?

Please mention this in the Discussion as a Limitation.

Answer: To address this point, we have performed additional analyses by adjusting for adults’ education level (1=no school education; 2=primary school; 3= junior high school; 4= senior high school or college; 5=university). The results were essentially unchanged as shown in the table below.

Comparison of the mean effect for salt and iodine with vs without adjustment for adults' education level

	Mean effect	95%CI		P value
		lower	upper	
Adults - Iodine				
Without adjustment for education level	11.3602%	1.4680%	20.2592%	0.025568
Adjusted for education level	11.3637%	1.4855%	20.2513%	0.025329
Adults - Salt (g/d)				
Without adjustment for education level	-2.9225	-3.6908	-2.1541	<0.0001
Adjusted for education level	-2.9261	-3.6948	-2.1575	<0.0001
Children - Iodine				
Without adjustment for education level	19.28%	7.75%	29.37%	0.00177
Adjusted for female adults' education level	18.58%	6.85%	28.83%	0.00289
Adjusted for male adults' education level	19.10%	7.50%	29.24%	0.00204
Children – Salt (g/d)				
Without adjustment for education level	-1.9455	-2.585	-1.306	<0.0001
Adjusted for female adults' education level	-1.9724	-2.6325	-1.3123	<0.0001
Adjusted for male adults' education level	-1.9578	-2.5965	-1.3191	<0.0001

*Results:
Basically fine.*

*Discussion:
Basically fine.*

Two minor questions:

1. Why were salt & iodine baseline values consistently higher in intervention adults & kids than in controls?

Answer: We were also surprised by this finding. One possible explanation is that the study did not randomise individual participants, but randomised schools instead, due to the nature of the design (i.e. cluster randomised trial). It is of note that the randomisation was stratified by the location of schools (i.e. urban or suburban) and the size of the class.

In relation to the consistency between salt and iodine, i.e. both were higher in the intervention group, this is because over 80% of iodine in the diet came from salt and therefore the imbalance in baseline

iodine is most likely due to the imbalance in salt between the two groups. Nevertheless, these baseline imbalances have been taken into account at the data analysis stage for both salt and iodine.

2. Does it matter that 8-15% of children exceeded the Iodine Tolerable Upper Limit?

Answer: The Tolerable Upper Limit (UL) is the level that should not be exceeded on a chronic basis. In terms of salt and iodine intake, it is well known that there is a large day-to-day variation in salt intake and thereby iodine consumption. Although 24h urine collection is considered as the gold standard for assessing salt and iodine intake, one or two 24h urine collections do not reflect an individual's usual intake. Indeed, carefully controlled studies have shown that, to get a reasonably accurate estimate of salt intake in one individual, 6 to 11 24h urine collections need to be made (Reference: Liu et al. Assessment of the association between habitual salt intake and high blood pressure: methodological problems. *Am J Epidemiol* 1979;110:219-26).

Our study collected two consecutive 24h urines at baseline and another two consecutive 24h urines at the end of the trial (i.e. about 3.5 months after the baseline collections). Such data would provide reliable data for both salt and iodine at the study population level. However, any interpretation on individual participant level data should be cautious.

Reviewer: 2

Reviewer Name: Rachael McLean

This is an extremely interesting paper, which is very well written and presented. It is highly relevant to policy, and will be of considerable interest to researchers and practitioners in the field. It describes the effect of a randomized controlled trial of a salt reduction intervention on iodine status in a group of children and their families in northern China. It shows that in this setting a significant and clinically relevant reduction in salt intake as a result of the intervention was associated with a reduction in iodine intake, but not to the extent that it compromised iodine status.

There are a number of features of the setting that mean the findings of this study may not be generalizable to populations in other countries, including the universal iodisation of salt (including table salt and salt in processed foods), and the high contribution of discretionary salt to total salt intake in some Chinese populations. The fact that an education programme in schools could have such an effect on the salt intake of children and their families is extremely impressive, but unlikely to be generalizable to many populations outside China. I think some comment on these issues would make the paper more useful to an international audience, particularly for informing policy in this context.

Answer: We agree that these are very good points. On page 16, following the discussion that our results could be broadly applicable to most parts of China, we have added a sentence - "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."

Reviewer: 3 (Dr. Aryelly Rodriguez)

Review Checklist	
<i>Introduction</i>	<i>I did enjoy reviewing this paper as the topic is very interesting and relevant for the current standards of living in urban areas not only in China but in the whole world.</i>
1. Is the research question or study objective clearly defined?	<i>No, because I thought that the "Iodine excretion" was the original trial, only by going into the text and references I realised this is a sub-study. It should be clear on the title and the abstract</i> Answer: We have added "a sub-study" to the title and the abstract.
2. Is the abstract accurate, balanced and complete?	<i>No. (see above 1 and 14 below). Please rewrite it so "iodine Intake" takes a starring role for this publication (ie iodine result should not be mentioned after salt results)</i> Answer: The changes in iodine were due to the changes in salt intake. It would be strange to report iodine first and salt later. We therefore did not make this change. However, if the editors and the reviewers think this change is necessary, we would be happy to do so.
8. Are the references up-to-date and appropriate?	<i>The paper is missing a reference to the results for the Edu-Salt sub-study IODINE in the following publication.</i> http://middleeast.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)00615-7.pdf Answer: We have added this reference.
10. Are they presented clearly?	<i>This paper could have more impact by actually being shorter and concentrating in the new results, this would provide a sharper focus on the new research question about iodine intake.</i> Answer: We have shortened the manuscript considerably.
14. To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)?	<i>The reviewed paper heavily borrows from the parent paper (http://www.bmj.com/content/350/bmj.h770).</i> Answer: We have shortened the manuscript and, in particular, we have deleted several paragraphs in the method section and referred to the parent paper.
Statistics	
1. Does this paper require specialist statistical review?	<i>Yes and I have performed this review</i>

GENERAL COMMENTS	<p><i>*Please keep the reporting of units consistent (ug vs µg or g/d vs g/day)</i></p> <p>Answer: Corrected.</p> <p><i>*Was the data collected in a CRF or eCRF, is currently in a secure database?</i></p> <p>Answer: The data were collected in CRFs and the original printed files of all the questionnaires were stored in the safe archives that can only be accessed by the authorised research team members. The electronic database is locked after removing personal identifiable information and is used in secure environment as per GCP guidelines.</p> <p><i>*Question: have you explored as a post-hoc sensitivity analysis what would have happened if salt intake stayed the same for the control group but decreased for the intervention. Also, in the original paper you explained: "During our study, the control group showed an increase in salt intake. This is probably because of seasonal influence as our baseline assessments were carried out in summer and the follow-up was in winter. Salt intake in northern China is usually higher in winter because people eat more pickles because of reduced availability of fresh vegetables." This is reasonable, but I would also re-analyse the results by swapping follow up with baseline in the control to reverse the seasonality</i></p> <p>Answer: We didn't perform this post-hoc analysis as we were not aware of this method. We thank the reviewer for providing us with this valuable information. However, to our understanding, the natural factors including seasonal variation should have the same effect on both the intervention group and the concurrent control group. Therefore, the net effect of the intervention should have been clearly presented using the traditional method by comparing the intervention with the control.</p>
"we report a prespecified sub-study"	<p><i>Please add a reference of where it was pre-specified as it is not present in the original study protocol. It would be interesting to know if the iodine was tested at the same time that the sodium content was measured or it was detected from frozen urine samples after the end of the study. Also, as a reader, I would like to know which institute/authority approved the pre-specified study</i></p> <p>Answer: A similar point has also been raised by the Editors. Please see the answer to the Editorial Request for detail.</p>
"As urinary iodine was not normally distributed, we used median and interquartile range (IQR) to assess the iodine status."	<p><i>Instead of "assess" I would use "summarise" the iodine status</i></p> <p>Answer: Amended.</p>
"Three urine samples with iodine >5000 ug/24h were outliers and excluded from the analysis."	<p><i>In which group they lied (all in control or all in intervention or 2 vs 1 or 1 vs 2)</i></p> <p>Answer: All the three samples came from two participants in the intervention group, i.e. two samples were from the same person.</p>

<p>We included group (intervention, control), time (baseline, end trial), and time*group interaction, with the time*group interaction term indicating the mean effect.</p>	<p>If you cut the redundant text there would be space for a more explicit statistical model in the form of: $Outcome = covariate + parameter + interaction_1 + \dots + error$ This would set it apart from the original paper</p> <p>Answer: We have shortened the statistical analysis method and used the formula as follows.</p> <p>The statistical model was in the form: $Outcome = Group + Time + Interaction(time \times group) + Stratification\ variables\ at\ randomisation\ (school\ location\ and\ class\ size) + Confounding\ variables\ (age,\ sex,\ body\ mass\ index,\ indoor\ and\ outdoor\ temperature).$</p>
<p>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.</p>	<p>If you going to talk about this, please specify ML or REML. Also use an appropriate quote. From the SAS website (https://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm#statug_mixed_sect025.htm) In many situations, the best approach is to use likelihood-based methods, exploiting the assumption that Y and e are normally distributed (Hartley and Rao 1967; Patterson and Thompson 1971; Harville 1977; Laird and Ware 1982; Jennrich and Schluchter 1986). PROC MIXED implements two likelihood-based methods: maximum likelihood (ML) and restricted/residual maximum likelihood (REML). A favorable theoretical property of ML and REML is that they accommodate data that are missing at random (Rubin 1976; Little 1995)”</p> <p>Answer: In the mixed models, we used the REML method for the analysis on iodine and we have specified it in the text accordingly.</p> <p>As suggested, we have also added the following reference. Carpenter, J.R. and M.G. Kenward, Missing data in randomised controlled trials-a practical guide. London School of Hygiene, 2007.</p>
<p>The baseline characteristics of the participants were well balanced between the intervention and the control group (Table 1).</p>	<p>This table 1 has already been published at: Results for Edu-Salt http://www.bmj.com/content/350/bmj.h770 I would remove and quote original paper, if you want to keep it put it in the supplement and again quote original paper</p> <p>Answer: We have moved table 1 to the supplement.</p>
<p>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.</p>	<p>Agree, but please consider to remove the salt results from the abstract</p> <p>Answer: Please see answer to this point on the abstract.</p>
<p>In China, since the introduction of universal salt iodisation in 1995</p>	<p>Is there not regulation to quote?</p> <p>Answer: A reference has been added.</p>
<p>Currently many countries have started salt reduction initiatives and also implemented salt iodisation programmes</p>	<p>Quote or give example of countries</p> <p>Answer: A reference has been added.</p>
<p>Table 2</p>	<p>Call Iodine results first then salt. Also add a footnote to explain that salt results are from a previous paper</p> <p>Answer: We have added a footnote to explain that the results for salt were taken from the previous paper (He et al. BMJ 2015;350:h770).</p>
<p>Supplement Table 3 and Table 4.</p>	<p>These tables could be merge into 1 table</p> <p>Answer: Amended as suggested.</p>

VERSION 2 – REVIEW

REVIEWER	Aryelly Rodriguez University of Edinburgh, UK
REVIEW RETURNED	12-Jul-2016

GENERAL COMMENTS	Minor comments (please bear in mind that manuscript is acceptable as it is) 1.- after "Sandell-Kolthoff reaction was used for urinary iodine measurement with quality control 17" it is the perfect spot to mention something about "frozen samples at the end of sutdy" 2.-"Three urine samples with iodine >5000 ug/24h were outliers and excluded from the analysis" please indicate that all samples are from the intervention group. 3.- "The number of 24h urine samples included and excluded in each analysis was shown in supplement figure" which figure, please be specific?
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VERSION 2 – AUTHOR RESPONSE

Reviewer 3: Aryelly Rodriguez

Minor comments (please bear in mind that manuscript is acceptable as it is)

1.- after "Sandell-Kolthoff reaction was used for urinary iodine measurement with quality control 17" it is the perfect spot to mention something about "frozen samples at the end of sutdy"

Answer: Added.

2.-"Three urine samples with iodine >5000 ug/24h were outliers and excluded from the analysis" please indicate that all samples are from the intervention group.

Answer: Added.

3.- "The number of 24h urine samples included and excluded in each analysis was shown in supplement figure" which figure, please be specific?

Answer: We have specified this as Supplement Figure 1.