

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic review of the effects of iodised salt and iodine supplements on prenatal and postnatal growth: Study protocol
AUTHORS	Farebrother, Jessica; Naude, Celeste; Nicol, Liesl; Sang, Zhongna; Yang, Zhenyu; Andersson, Maria; Jooste, Pieter; Zimmermann, Michael

VERSION 1 - REVIEW

REVIEWER	John Lazarus Cardiff University UK
REVIEW RETURNED	22-Dec-2014

GENERAL COMMENTS	This review is timely and important My only concern is that the authors have not chosen to include any IQ or neuropsychological assessments in their analysis. It would seem a pity to omit these in view of the very comprehensive analysis which is proposed
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REVIEWER	Ines Velasco Obstetrician, Maternal-Fetal Medicine Specialist. Obstetrics & Gynecology Unit Hospital de Riotinto Andalusian Health Service Spain
REVIEW RETURNED	27-Jan-2015

GENERAL COMMENTS	The article entitled "Systematic review of the effects of iodised salt and iodine supplements on prenatal and postnatal growth: Study protocol" shows an attempt to analyze the available evidence regarding the relationship between iodine nutrition status and growth from early stages of childhood to the end of adolescence. Although iodine deficiency has been classically identified as a hampering factor for an adequate growth and development in infant populations, the implications of iodine status on both prenatal and postnatal somatic growth have not properly analyzed in terms of clinical or epidemiological significance. This approach constitutes a very important novelty and is likely to provide some pieces of evidence for the prevention of iodine deficiency worldwide. The authors have supplied a very exhaustive proposal which describes in detail not only the main objectives and data collection procedure but also the analysis and assessment of obtained results. The exposition demonstrates the authors' knowledge on methodology for systematic reviews and the solvency for the achievement of this goal.
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	In my opinion, this manuscript clearly fulfills the requirements to be published.
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REVIEWER	Zulfiqar A Bhutta Centre for Global Child Health, Hospital for Sick Children, Toronto, Canada I have been involved extensively in evidence reviews for nutrition interventions including fortification strategies. Most published and one underway in collaboration with GAIN
REVIEW RETURNED	14-Feb-2015

GENERAL COMMENTS	<p>This is a standard protocol to evaluate the evidence related to iodized salt use and the use of iodine supplements on prenatal and postnatal growth. The methodology and criteria for selection of studies are pretty straightforward and the links to development are well established. However, the biological plausibility of a potential link of iodine fortification and growth is weakly argued and referenced. I am not sure that there is sufficient supportive evidence of an effect justifying the isolated review of impact of salt iodization on growth, especially if programs include multiple confounders.</p> <p>In so far as the current thinking on growth is concerned, a link with iodine deficiency and linear growth or indeed fetal growth is not established. I believe that the authors need to provide stronger evidence as to the link between iodine physiology and growth for this review to be credible and not a repeat of past or current reviews of the link between iodized salt use and health outcomes.</p> <p>I believe that the subject area of the link between iodized salt use and health and development outcomes is also part of a forthcoming Campbell review on the subject and has been covered recently by the World Health Organization http://www.who.int/nutrition/publications/micronutrients/effect_safety_saltiodization/en/</p>
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VERSION 1 – AUTHOR RESPONSE

Professor Lazarus: “This review is timely and important. My only concern is that the authors have not chosen to include any IQ or neuropsychological assessments in their analysis. It would seem a pity to omit these in view of the very comprehensive analysis which is proposed.”

Authors’ response: We thank Professor Lazarus for his consideration of our protocol manuscript and the forthcoming systematic review. Our scoping review identified six systematic reviews that have already addressed the question of the effects of iodine on mental development and cognitive function (references #16, 18, 20-23 of the revised manuscript). The research question that our systematic review aims to answer is specific to growth, since this question has not previously been systematically addressed.

Dr. Velasco: “The article entitled “Systematic review of the effects of iodised salt and iodine supplements on prenatal and postnatal growth: Study protocol” shows an attempt to analyze the available evidence regarding the relationship between iodine nutrition status and growth from early stages of childhood to the end of adolescence.

Although iodine deficiency has been classically identified as a hampering factor for an adequate growth and development in infant populations, the implications of iodine status on both prenatal and postnatal somatic growth have not properly analyzed in terms of clinical or epidemiological significance. This approach constitutes a very important novelty and is likely to provide some pieces of evidence for the prevention of iodine deficiency worldwide.

The authors have supplied a very exhaustive proposal which describes in detail not only the main objectives and data collection procedure but also the analysis and assessment of obtained results. The exposition demonstrates the authors' knowledge on methodology for systematic reviews and the solvency for the achievement of this goal.

In my opinion, this manuscript clearly fulfills the requirements to be published.”

Authors' response: We would like to thank Dr. Velasco for the consideration she has give to our protocol, and her encouraging comments for our review.

Professor Bhutta: “This is a standard protocol to evaluate the evidence related to iodized salt use and the use of iodine supplements on prenatal and postnatal growth. The methodology and criteria for selection of studies are pretty straightforward and the links to development are well established. However, the biological plausibility of a potential link of iodine fortification and growth is weakly argued and referenced. I am not sure that there is sufficient supportive evidence of an effect justifying the isolated review of impact of salt iodization on growth, especially if programs include multiple confounders.

In so far as the current thinking on growth is concerned, a link with iodine deficiency and linear growth or indeed fetal growth is not established. I believe that the authors need to provide stronger evidence as to the link between iodine physiology and growth for this review to be credible and not a repeat of past or current reviews of the link between iodized salt use and health outcomes.

I believe that the subject area of the link between iodized salt use and health and development outcomes is also part of a forthcoming Campbell review on the subject and has been covered recently by the World Health Organization

http://www.who.int/nutrition/publications/micronutrients/effect_safety_saltiodization/en/”

Authors' response: We thank Professor Butta for his comments and the careful consideration that he has given to our protocol.

In response to his concerns that there is limited evidence of the link between the effects of enhanced iodine nutrition on somatic growth (be it through fortified salt, supplements or otherwise), we believe that there is a considerable biological plausibility to this relationship, and have extended our manuscript to reflect this with the citation of more relevant data (references #7, 8, 10, 27-29 added). Furthermore, with respect to the risk of confounding evidence within such studies, we will attempt to use rigorous methods in the inclusion, analysis and interpretation of the data in order to account for confounding factors as far as possible, as described by the protocol.

The recent systematic review by Aburto et al. (2014) published by the World Health Organisation is discussed within the protocol on page 5 (at the point of submission the review was still unpublished; the reference has now been updated (#26)). This systematic review compared iodised salt with non-iodised salt in the prevention of iodine deficiency disorders. This review did not cover all forms of iodine supplementation, and did not look at growth outcomes.

The forthcoming Campbell review mentioned has been reviewed, and may indeed have a small overlap with our systematic review - as is naturally the case for the other reviews already cited. However, our review is different in a number of aspects. Firstly, in its scope. The Campbell review is asking a broad question and has a promising outlook, looking to answer many programmatic-related issues relating to single and/or multiple micronutrient fortification. Our systematic review is designed to answer a very specific question that considers only the relationship between iodine interventions and somatic growth. That said, our review question is also broader than the proposed Campbell review in terms of the intervention/exposure, in that we will review not only fortification, but also

supplementation programmes, both of which are different strategies for addressing correct iodine nutrition. Lastly, our review will focus specifically on growth and growth outcomes, as its primary outcome. In the Campbell review, growth (“stunting”) is listed as a secondary outcome, and no further growth-related outcomes are included.