PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Maternal urinary iodine concentration in pregnancy and children's cognition: Results from a population-based birth cohort in an iodine-sufficient area
AUTHORS	Ghassabian, Akhgar; Steenweg - de Graaff, Jolien; Peeters, Robin; Alec Ross, H.; Jaddoe, Vincent; Hofman, Albert; Verhulst, Frank; White, Tonya; Tiemeier, Henning

VERSION 1 - REVIEW

REVIEWER	Michael Zimmermann ETH Zurich, Switzerland
REVIEW RETURNED	08-May-2014

GENERAL COMMENTS	Page 3, line 27: substitute 'univariate correlation' for 'association' Page 3, Lines 25-26, please give the number of women with UICs < and > 150 and give the median UICs in these two groups. Page 3, Lines 33-34: Please give more detail here, the statement 'Similar results emerged in the analysis of language comprehension at six years.' is inadequate. Page 3, Line 42: The statement 'This may result from the Dutch iodine supplementation policy.' needs to be clarified. Do you mean Dutch iodized salt is supplying adequate intakes to pregnant women? Throughout, I would substitute the word 'fortification' for 'supplementation' when talking about the Dutch iodine program. p.6 line 32: which 'demographic' variables? p.8, line 10-11. How was maternal IQ assessed? p.8, line 54: In the Generation R study, thyroid function in the mothers was measured, and TSH andor fT4/TT4 should perhaps be used as a covariate in the third model. p.14, lines 41-44: Explain in more detail the findings of reference 14, and how they compare (and differ from) the results presented here. p.15, lines 13-14: Please elaborate on the Dutch iodine fortification policy here. Why are the mothers intakes adequate?

REVIEWER	Elizabeth N. Pearce Boston University School of Medicine USA
REVIEW RETURNED	10-May-2014

GENERAL COMMENTS	This is an analysis of associations between maternal urinary iodine concentrations at <18 weeks gestation and child cognition assessed at age 6 in the Generation R cohort. Strengths of the study include the large sample size and wealth of covariates. The conclusions are justified and thoughtfully discussed. My comments are relatively minor. 1. Reference 2 could be updated to the 2013 report Pearce EN, Andersson M, Zimmermann MB. Global iodine nutrition: Where do we stand in 2013? Thyroid. 2013;23(5):523-8. 2. Introduction, page 5: it would be helpful to describe the urinary iodine thresholds used in the Bath and Hynes studies. 3. Introduction, page 5, "... Hynes et al. found a relation between maternal mild iodine deficiency and spelling errors in children.": this might be better worded as "... Hynes et al. found a relation between maternal mild iodine deficiency and standardized academic test scores in children" since differences were also found in parameters other than spelling. 4. Introduction, page 6, "Adjustment of UIC for creatinine levels decreases the intra-individual variability in iodine excretion, and provides a accurate estimate of iodine status in individuals.": This would be more accurately stated as "Adjustment of UIC for creatinine levels decreases the intra-individual variability in iodine excretion, and provides a more accurate estimate of iodine status in individuals."Even with creatinine adjustment, single spot urinary iodine concentrations are not particularly reliable individual biomarkers (see, e.g., König F, Andersson M, Hotz K, Aeberli I, Zimmermann MB. Ten repeat collections for urinary iodine from spot samples or 24-hour samples are needed to reliably estimate individual iodine status in women. J Nutr. 2011;141:2049-54) 5. Page 7: typo: "150-49" should be "150-249" 6. Discussion, page 15: it is noted that the lack of clear association between child cognition and maternal urinary iodine likely reflects successful iodine supplementation in the Netherlands. Either here or in the Introduction, it would be helpful to describe these national iodine supplementation policies.

REVIEWER	John H Lazarus Professor Cardiff University UK
REVIEW RETURNED	12-May-2014

GENERAL COMMENTS	Another aspect to be considered in the discussion is that the current evidence for the effectiveness of iodine supplementation in MILD iodine deficient areas is incomplete with regard to an improvement in

	neurocognition. (As opposed to clear evidence in areas of severe I deficiency). The authors might consider mentioning this aspect. While I am not a statistical expert I am sure the statistics are ok but it would be good if an independent professional reviewed the tests. The authors are to be complimented on this study which adds evidence for iodine fortification in Europe where many countries are currently characterised as having iodine deficiency in pregnancy.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Michael Zimmermann
Institution and Country ETH Zurich, Switzerland
Please state any competing interests or state 'None declared': None
1. Page 3, line 27: substitute 'univariate correlation' for 'association'
We followed the suggestion of the reviewer and changed the abstract as following:
"There was a univariate association between maternal low UIC and children's suboptimum nonverbal IQ (unadjusted OR=1.44, 95%CI: 1.02-2.02)."
2. Page 3, Lines 25-26, please give the number of women with UICs < and > 150 and give the median UICs in these two groups.
The abstract is adapted and the exact number of women in two groups of UIC < and > 150, as well as the median UIC in each group are given.
"In total, 188 (12.3%) pregnant women had UIC<150 µg/g creatinine, with a median UIC equals to 119.3 µg/g creatinine. The median UIC in the group with UIC>150 µg/g creatinine was 322.9 µg/g and in the whole sample 296.5 µg/g creatinine."
3. Page 3, Lines 33-34: Please give more detail here, the statement 'Similar results emerged in the analysis of language comprehension at six years.' is inadequate.
The sentence is changed as following to avoid any ambiguity:
"There was no relation between maternal UIC in early pregnancy and children's language comprehension at six years."
4. Page 3, Line 42: The statement 'This may result from the Dutch iodine supplementation policy.' needs to be clarified. Do you mean Dutch iodized salt is supplying adequate intakes to pregnant women?
We agree with the reviewer that the Dutch government's policy on iodine in the population should be clearly described. Therefore, we briefly explain the Dutch government's policy for iodine fortification and population monitoring in the abstract. In addition, we elaborate on this point in the discussion.
Abstract:
"This may result from the Dutch iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population."
Discussion, page 15:
"The infrequent occurrence of maternal low UIC during pregnancy and the lack of a clear association with children's cognitive abilities likely reflect the Dutch government's iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population. In case of non-optimal intake at the population level, governmental measures are taken to boost the supply of iodine in the population.[1] This suggests that iodine fortification programmes can prevent adverse neurodevelopmental outcomes in children."
5. Throughout, I would substitute the word 'fortification' for 'supplementation' when talking about the Dutch iodine program.
We would like to thank the reviewer for the useful suggestion. The text has been adapted and the word 'fortification' is used in place of 'supplementation'.
6. p.6 line 32: which 'demographic' variables?
In the current version of the manuscript, we give some examples of the demographic, and maternal

and child characteristics, which were compared between the study population and non-respondents.
Methods, page 6:
“There was no difference in maternal iodine levels between mother-child pairs included in the analyses and those excluded because of missing data on child cognitive measures. Likewise, demographic characteristics including maternal age and education, household income, or child’s characteristics such as gestational age at birth or ethnic background did not differ between these two groups.”
7. p.8, line 10-11. How was maternal IQ assessed?
The information on assessment of maternal IQ is added to the text now.
Methods, page 8:
“Maternal nonverbal IQ was assessed during the child’s visit to the research center, using a computerized version of the Ravens Advanced Progressive Matrices Test, set I.[2]”
8. p.8, line 54: In the Generation R study, thyroid function in the mothers was measured, and TSH and/or fT4/TT4 should perhaps be used as a covariate in the third model.
We did not adjust the analyses for maternal thyroid parameters (despite the fact the data was available in the Generation Study), because maternal thyroid function could be a potential mediator in the relation between maternal iodine levels and child neurocognitive development. In the current version of the manuscript, we present the results of the analyses additionally adjusted for maternal thyroid parameters for the interested readers. The results remained unchanged.
Methods, page 8:
“In early pregnancy, maternal thyroid parameters [Thyroid Stimulating Hormone (TSH) and thyroxine] were measured in the blood.[3]”
Methods, page 9:
“We additionally adjusted the models for maternal thyroid parameters.”
Results, page 12:
“Additional adjustment of the models for maternal thyroid parameters did not change the results (B additionally adjusted for maternal TSH=-0.87, 95%CI: -3.32, 1.45; B additionally adjusted for maternal free thyroxine=-0.86, 95%CI: -3.19, 1.47).”
9. p.14, lines 41-44: Explain in more detail the findings of reference 14, and how they compare (and differ from) the results presented here.
We have adapted the manuscript and compared the findings of the present study with previous publication of Generation R on this topic.
Discussion, page 14:
“In the Generation R Study, we previously showed that low maternal UIC was related to poor working memory in children, but to not planning/organization.[4] The absence of any relation between maternal low iodine and cognitive aspects of executive function, in particular planning/organization, is in line with the findings of the present study. The mechanisms through which mild iodine insufficiency influences other aspects of child neurodevelopment, such as working memory, are not clear.”
10. p.15, lines 13-14: Please elaborate on the Dutch iodine fortification policy here. Why are the mothers intakes adequate?
In the discussion, we discussed our observation in the Generation R Study and compare it with the British and Australian samples. In our sample, the majority of pregnant women had urinary iodine levels in the optimal range. In the current version, we also discuss the Dutch government’s policy on iodine fortification; because the optimal iodine intake at the population level is simply a reflection of the Dutch government’s iodine fortification policy which allows adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population. Please see the answer to comment number 4.

Reviewer Name Elizabeth N. Pearce
Institution and Country Boston University School of Medicine, USA
Please state any competing interests or state ‘None declared’: None declared
1. Reference 2 could be updated to the 2013 report Pearce EN, Andersson M, Zimmermann MB.

Global iodine nutrition: Where do we stand in 2013? Thyroid. 2013;23(5):523-8.
We thank the reviewer for the remark. The reference has been updated in the current version of the manuscript.
2. Introduction, page 5: it would be helpful to describe the urinary iodine thresholds used in the Bath and Hynes studies.
We followed the suggestion of the reviewer and described the urinary iodine threshold used in studies by Bath et al. and Hynes et al.
Introduction, page 5:
“In this study, mild-to-moderate iodine deficiency was defined as having urinary iodine concentration (UIC) lower than 150 µg/g of creatinine on the basis of World Health Organization criteria.[5] Similarly, in 228 mother-child pairs in Australia, Hynes et al. found a relation between maternal mild iodine deficiency (UIC<150 µg/L) and standardized academic test score, e.g. spelling errors, in children.[6]”
3. Introduction, page 5, "... Hynes et al. found a relation between maternal mild iodine deficiency and spelling errors in children.": this might be better worded as "... Hynes et al. found a relation between maternal mild iodine deficiency and standardized academic test scores in children" since differences were also found in parameters other than spelling.
We changed the manuscript according to the suggestion of the reviewer.
Introduction, page 5:
“Similarly, in 228 mother-child pairs in Australia, Hynes et al. found a relation between maternal mild iodine deficiency (UIC<150 µg/L) and standardized academic test score, e.g. spelling errors, in children.”
4. Introduction, page 6, "Adjustment of UIC for creatinine levels decreases the intra-individual variability in iodine excretion, and provides a accurate estimate of iodine status in individuals.": This would be more accurately stated as "Adjustment of UIC for creatinine levels decreases the intra-individual variability in iodine excretion, and provides a more accurate estimate of iodine status in individuals. "Even with creatinine adjustment, single spot urinary iodine concentrations are not particularly reliable individual biomarkers (see, e.g., König F, Andersson M, Hotz K, Aeberli I, Zimmermann MB. Ten repeat collections for urinary iodine from spot samples or 24-hour samples are needed to reliably estimate individual iodine status in women. J Nutr. 2011;141:2049-54)
We acknowledge that the method used in the present study (adjusted urinary iodine for creatinine levels) was an attempt to optimize the estimate of urinary iodine in pregnant women. While ten repeat collections for urinary iodine from spot samples or 24-hour samples can provide a reliable estimate of individual iodine status. Therefore, the manuscript is changed as suggested by the reviewer to reflect this point.
Introduction, page 6:
“Adjustment of UIC for creatinine levels decreases the intra-individual variability in iodine excretion, and provides a more accurate estimate of iodine status in individuals compared to crude values.[7]”
5. Page 7: typo: "150-49" should be "150-249"
The typo is corrected.
6. Discussion, page 15: it is noted that the lack of clear association between child cognition and maternal urinary iodine likely reflects successful iodine supplementation in the Netherlands. Either here or in the Introduction, it would be helpful to describe these national iodine supplementation policies.
We thank the reviewer for the useful suggestion. We discuss the iodine fortification policy in the Netherlands in the manuscript. Please see the answers to comments 4 and 10 by the reviewer 1.
Discussion, page 15:
“The infrequent occurrence of maternal low UIC during pregnancy and the lack of a clear association with children’s cognitive abilities likely reflect the Dutch government’s iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population. In case of non-optimal intake at the population level, governmental measures are taken to boost the supply of iodine in the population.[1] This suggests that iodine fortification programmes can prevent adverse neurodevelopmental outcomes in children.”

Reviewer Name John H Lazarus
Institution and Country Professor Cardiff University, UK
Please state any competing interests or state 'None declared': None declared
1. Another aspect to be considered in the discussion is that the current evidence for the effectiveness of iodine supplementation in MILD iodine deficient areas is incomplete with regard to an improvement in neurocognition. (As opposed to clear evidence in areas of severe I deficiency). The authors might consider mentioning this aspect.
We thank the reviewer for the useful suggestion. This is added to the current version of the manuscript (Discussion).
Discussion, page 14:
"Convincing evidence from randomized controlled trials in severe iodine deficient countries has shown the effectiveness of iodine fortification policies or supplementation in pregnant women. However, the existing evidence on the effectiveness of intervention in mild-to-moderate iodine deficient areas is very limited with regard to an improvement in neurocognitive outcomes in children.[8]"
The authors are to be complimented on this study which adds evidence for iodine fortification in Europe where many countries are currently characterised as having iodine deficiency in pregnancy.
We thank the reviewers for their careful appraisal of the manuscript and their useful comments.
References
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8. Taylor PN, Okosieme OE, Dayan CM, Lazarus JH. Therapy of endocrine disease: Impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. Eur J Endocrinol;170(1):R1-R15.