Author’s response to reviews

Title: Validation and reproducibility of a new iodine specific food frequency questionnaire for assessing iodine intake in Norwegian pregnant women

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Author’s response to reviews:

Dear editor and reviewers,

Reference: Manuscript NUTJ-D-19-00218 entitled “Validation and reproducibility of a new iodine specific food frequency questionnaire for assessing iodine intake in Norwegian pregnant women”.

Thank you for allowing us to submit a revised version of our manuscript to Nutrition Journal, and thank you for all the valuable and constructive comments.

We have, as recommended, revised the manuscript along the lines suggested by the reviewers in the point-by-point response in the submission system and have highlighted (with yellow highlighted text) all substantive changes made in the revised manuscript.

All authors have read and approved the submission of the revised manuscript; the manuscript has not been published and is not being considered for publication elsewhere.
Reviewer 1

Reviewer 1: Please clarify in the abstract and background that this paper is describing methods of estimating dietary iodine content in a situation in which most iodine in the diet is from essentially intrinsic iodine, not iodine added through salt that is iodized. Thus, this method is only relevant for other countries where the primary sources of iodine are this type of food and supplements, not general addition of salt.

Author: Thank you for this valuable comment. We have inserted the following text in the introduction of the abstract, see line 22-24: “Iodized salt is not mandatory in Norway, and the permitted level of iodine in table salt is low (5 µg/g). Thus, milk and dairy products, fish and eggs are the main dietary sources of iodine in Norway.” Dietary sources of iodine have also already been described in the introduction, see lines 73-76. In the abstract and in the discussion, we have specified that that this method is only relevant in countries where the contribution of iodine from salt is negligible. Please see line 47-48 in the abstract and line 519-521 in the discussion.

Reviewer 1: Line 78: clarify the type of recommendation is being described; this appears to be the local 'estimated average requirement' (EAR) vs the recommended nutrient intake (RNI, if using FAO/WHO recommendations). The EAR is a different cutoff than the RNI, so should be specified, and why this is the cutoff being applied here.

Author: Thank you for highlighting this misunderstanding. The recommendation being described is the recommended amount of iodine in supplements, issued by the Norwegian government, and not the EAR or RNI. The following changes have been done in line 76-79: “Since 2018, women of childbearing age in Norway with a low intake of milk and fish have been advised by the Norwegian Directorate of Health to take iodine containing supplements in order to secure sufficient iodine intake (supplement of 150 µg/day for pregnant and lactating women and supplement of 100 µg/day for women in fertile age)”. 

Yours sincerely,

On behalf of all the authors

Corresponding author
Reviewer 1: Line 79: are you implying that the recommendation was instituted because of this study, or just happened to come for other reasons… and what is the implication of this recommendation relative to your findings?

Author: Several studies in Norway the recent years have shown insufficient iodine status in pregnant women, and the recommendation of supplements was initiated after this. The information has been included in order to update the reader of the current recommendations in Norway. The recommendation was given after the current study ended. Thus, this recommendation did not affect the results of this study.

Reviewer 1: Do you think that women who are getting sufficient iodine - based on I-FFQ could avoid taking iodine supplements?

Author: The Norwegian Health Authorities only recommends iodine containing supplements to pregnant women who:

- has a lower intake <6 dl milk/dairy products per day and eat fish regularly.
- has a lower intake <8 dl milk/dairy products per day and does not/rarely eat fish.

In this study, the I-FFQ was developed to collect scientific data of dietary intake in a population group of pregnant women, and not as a tool in the primary health care settings. If using the I-FFQ to recommend iodine supplementation, this should be further evaluated in a specific study.

Reviewer 1: Line 87: what other biomarkers? Are you referring to the TSH, etc that you included? Please either drop this sentence or make sense out of it.

Author: Thank you for pointing this out. We agree that this was unclear. WHO recommends using thyroglobulin (Tg) and thyroid stimulating hormone (TSH) as biomarkers for assessing iodine status (WHO Assessment of iodine deficiency disorders and monitoring their elimination - A guide for programme managers, Third edition. 2007.). We have now inserted the specific biomarkers of Tg and TSH in the text and inserted the WHO reference, see line 86-87.

Reviewer 1: Lines 90-95: you don't seem to take this into account at the end when you conclude to use I-FFQ… if dietary methods are so bad, why are you proposing them over biochemical? The reader is left not really getting to the salient point of why I-FFQ is preferred over diet diary or 24 hour or UIC or blood TSH…

Author: Thank you for this valuable comment. We agree that this may be confusing for the reader and have now inserted a paragraph arguing of why an I-FFQ can be a preferred...
method, over other dietary assessment tools and biomarkers. Please consider line 111-116 in the introduction: “An I-FFQ has the advantage to measure long-term dietary iodine intake in a simple, cost- and time-efficient manner, in a large sample size that is geographically widespread (16). It can also be useful in identifying the most important sources of iodine in the diet (23). Continuously monitoring of iodine intake in a population is important, especially in groups where deficiency already has been ascertained, such as pregnant women in Norway and in Europe.”

However, as an FFQ also has limitations and disadvantages, we also find it important to specify these, and that these sources of errors further are taken into account. We therefore find it relevant of still including line 90-95, as we have also specified the advantages of an I-FFQ later.

Reviewer 1: Correct the multiple mismatched plural vs singular verbs

Author: We have now corrected several errors throughout the manuscript. This is marked as yellow highlighting.

Reviewer 1: Lines 125 & 128: please reference how many diets are considered sufficient for validation studies (diet to diet vs diet to biomarker

Author: To our knowledge, there are current no methods that are considered the “gold standard” for assessing the validity of dietary methods (Cade et al. 2002). Another dietary method (e.g. 24-h recall, diet record, food diary) is most commonly used as a reference method when validating an FFQ. However, the use of several methods, including biomarkers, is considered a strength when performing validation studies (Lombard et al. 2015). Therefore, we did not follow any specific recommendations on how many methods that is required to assess validity, however, we decided to include all relevant data as this provides comprehensive insight into the validity of the I-FFQ.

Reviewer 1: Line 145: "the participants were asked to report"… how? Was this an online questionnaire, with an enumerator, on paper?...

Author: Thank you for making us aware of this. We have now added a sentence in line 156: “In the I-FFQ completed in gestational week 18-19”. In addition, in line 152 we have previous specified that the I-FFQ was an online questionnaire.

Reviewer 1: Lines 150-151: confusing for non-local readers. Why only spreads, and list all potential responses for each set of questions, perhaps in a table or annex?
Author: Thank you for this comment. We agree that this may be somewhat confusing for the reader. We have now edited the sentence. Please consider line 163-164. In addition, we have inserted a table in the additional files that explains the number of responses for each set of questions from the I-FFQ. Please see table S1 in appendix.

Reviewer 1: Somewhere in methods: clarify the overall number of foods in the I-FFQ vs in the food diary; are they the same categories? Perhaps a table comparing the two? This shows up slightly in discussion, but that is too late.

Author: We have now inserted a table in the additional files that explain the number of food items included in the I-FFQ and the food diary. Please see table S1.

Reviewer 1: Line 175+: clarify the order of the different collection methods: simultaneous, sequential, … inconsistent? Later you imply the 6 days of diary are the exact same as the 6 days of UI, but please make this clear.

Author: Thank you for pointing this out. We have now inserted this and reorganized this sentence to make this clear. Please consider line 188-191. In addition, we have made an overview of the methods used in the validation of the I-FFQ in a figure listed in additional file 1. Please consider figure S1.

Reviewer 1: Line 176: "handed out" is that all? No instructions on how to complete?

Author: In addition, instructions were given from the researchers. We have now reorganized this sentence to make this clear. Please consider line 188-191 as above.

Reviewer 1: Line 181: to make the pancakes and waffles more understandable, consider this shift: ; 19 questions regarding milk and dairy products, including foods made with milk, such as pancakes, waffles and others mixed dished with milk; ; and

Author: Thank you for this suggestion. The following has been inserted in line 195: “including foods made with milk, such as”

Reviewer 1: Line 200: mean daily iodine from supplements assumes the absorption of a bolus on one day is equal to daily smaller amounts, is that true of iodine? Please clarify why you felt it was okay to estimate this way.

Author: This is an interesting approach. To our knowledge, there are no concluding literature that the absorption of iodine varies from a bolus dose (daily supplement use) vs iodine from
foods in smaller amount during the day. Most of iodine is absorbed from the intestine with an absorption rate up to 90% from the stomach and upper small intestine (Nath et al 1992, Miller et al 1975). Thus, we do not have any literature on assessing this estimation in another way.

However, the absorption rate of iodine to the thyroid gland may be affected of the current iodine status. If adequate iodine supply, <10% of absorbed iodine is taken up by the thyroid gland. In contrast, if iodine deficiency is present the thyroid gland may increase its absorption rate up to 80% (Rohner at al. 2014.)

Reviewer 1: Line 245: what is meant by "compliance"? Compliance usually refers to a person's choice, but this appears to look at analyses of data. Perhaps choose another description

Author: Thank you for highlighting this. We have replaced the word “compliance” with “agreement” as seen in line 263.

Reviewer 1: Lines 296-297, please clarify which numbers are "similar", mean/ median/similar based on regression… I keep reading this statement in comparison to the numbers in Table 2 and wondering if the data descriptions are flipped.

The means of 134 and 202 (IFFQ, diet and diet+supplements) are closer to 135 and 220 (estimated by UIC) than the means of 116 and 171 (food diary) … Please explain this to the reader Table 3 (line 336+) food diary seems to be higher correlation, but actual values (table 2) seemed to be closer between FFQ and UIC estimates…

Author: We have now inserted the median of estimated iodine intake from UIC and from the food diary. Please see the highlighted text in line 298-300. We have also deleted some text, as proposed in the next comment.

In the comparison with the estimated intake from UIC, the relevant comparison must be performed with all participants (N= 117), as this includes both supplement- and non-supplement users (median: 166). This was lower than what is estimated from the diet and supplements from the I-FFQ (N= 124, median: 202), and similar to the estimated intake from diet and supplements from the food diary (N= 134, median: 171). Thus, the row of non-supplements users and supplement users of UIC and estimated iodine intake from UIC, were given to indicate the effect of supplement on the biomarker of UIC. We agree that this may are confusing for the reader. If this still is unclear we can delete the rows of non-supplements users and supplement users.

Reviewer 1: Much of what is in the text of the results is already in the tables… please reduce somewhat to just highlight the most important points. Pg 18 starts to be better because the text clarifies the figures, and provides some numbers that are not present in the figures.
Author: Thank you for highlighting this. We have now reduced some texts on page 14 to 17.

Reviewer 1: Line 412, authors bring up ranking, but seemingly as an after-thought. Is ranking important?

Author: FFQs are in general not considered appropriate for estimating individual true nutrient intake (Masson et al. 2003). However, within epidemiological research, as long as FFQs can rank individuals, one can explore possible negative health consequences of different iodine intakes. Therefore, obtaining the absolute true intake is not necessary, as long as those individuals with a low intake can be separated from those with a high intake (Biro et al. 2002).

Reviewer 1: The fact that both dietary methods only include certain high iodine foods makes it clear that these estimates are likely going to be underestimates, but the authors should emphasize why estimates and why ranking would be important or how these would actually be used in programs. There isn't enough emphasis on how much value these tools could be!, particularly for pregnant women to identify those who are potentially at risk of IDD.

Author: We included the most important sources of iodine in Norway, which are milk and dairy products, seafood, eggs and supplements (contributes with >80% of total iodine intake) (Carlsen et al. 2018, Brantsaeter et al. 2013, Dahl et al. 2004). In contrast to other countries, where iodized salt contributes with a significant amount in foods such as bread, pastries, ready-to-eat meals etc., this is not the case in Norway. Thus, we further believe that these potential underestimates are minor and of low impact. The estimated iodine intake from the food diary (mean: 171 ug/day) was also similar to the estimated iodine intake from UIC (mean: 166 ug/day), which further shows this.

We have also highlighted the use of an I-FFQ as a tool and why these estimates are important and inserted new paragraphs in the introduction and the discussion. Please see line 111-116 in the introduction as mentioned earlier and line 418-426 at the beginning of the discussion.

Reviewer 1: Line 432, can't find it, but it seems there was a comment in the intro saying that this was the first time this type of validation was done…

Author: There has only been performed one study in Australia validating an iodine-specific FFQ for pregnant women as specified in the discussion part, see line 413-415. However, there has been performed studies using a full FFQ in both pregnant women and other populations. When we refer to “other studies” in line 437-439 (previous line 432) we compare our results to other studies that have used a full FFQ (not iodine-specific), and also other populations than pregnant women (e.g. adults and young women).
Reviewer 1: Paragraph starting line 434, please try to reorganize this paragraph, wanders around and seems to repeat some things

Author: We have now reorganized this paragraph. Please consider line 440-455. New text is marked as yellow highlight.

Reviewer 1: Lines 455-456: it is obvious that inclusion of supplements would provide higher iodine estimates, instead what is important to bring up about the contribution of the supplements to the iodine intakes of these women?

Author: We agree that it is obvious that the inclusion of supplements provide higher iodine intake. However, we believe it is important to include as it shows the contribution of iodine from supplements, as iodine is present in few food sources. In this study, supplements contributed with approximately 30% of the total iodine intake, both from the I-FFQ and the food diary.

Reviewer 1: Line 481: what can you say about intra-individual variability across these 6 days? (results) … Is it likely another 4 days of data would have altered your findings?

Author: As iodine is present in few food sources the intra- and inter variability is considered high in UIC. However, 6 days were considered acceptable as it covered at least one weekend day and variation in food intake for almost one week. We also wanted to keep the participant burden as low as possible. The literature shows that 10 days of spot urine samples is considered the optimal amount for assessing individual iodine status König et al. 2011). Further, in this study we assessed iodine status (UIC) and iodine intake on a group level, and it would have been a greater issue if the aim was to assess individual iodine status and intake.

Reviewer 1: Line 486 says UIC and diary were collected same days, but this was not in the methods. Also, the authors said previously that UIC was not a good measure if only one time point, please clarify why you are now saying UIC would be a good comparison… actually this should be clarified previously - why you are taking one spot urine in the evening each day. You explain 6 days vs 10, but before that please explain why 6 days * 1 spot would be appropriate.

Author: Thank you for making us aware of this. We have now specified in the methods that the UIC and food diary were collected on the same days, see line 190-191.

One spot sample of UIC is not a good indicator of individual iodine status as status varies considerable within and between days. However, we used 6 spot urine samples homogenized into one pooled sample. Thus, the between day variation will be smaller as we included several days of samples. In addition, the intra- and interindividual variability are minimized when measuring iodine status and intake on a group level.
Reviewer 1: Line 489: "which gives a realistic intake of iodine" this is sort of thrown in there... what do you mean by "realistic" and there are also limitations to the dietary methods as well as the biomarkers. Further, UIC also gives a good estimate of iodine status at population level and could be much easier to collect (less training required, etc), so please choose a reason for this recommendation other than realistic intake. For example, would you be recommending practitioners send out these recommendations digitally to pregnant women, or with their first ANC visit or be administered during their visits,... ?

Author: Thank you for this input. We agree with this, and we have now moved this sentence to the beginning of the discussion, please see line 422-424 as mentioned earlier. We have also replaced the word “realistic” with “estimate”.

As mentioned earlier, we have also inserted why using an I-FFQ can be an advantage compared to UIC. See line 111-116 in the introduction and line 418-426 in the discussion. In addition, this FFQ was developed to collect scientific data of dietary intake in a population group, and not as a tool in the primary health care settings.

Reviewer 1: Line 497: if an association is not expected, why did you include the costly and invasive TSH etc tests? Please clarify, perhaps in methods, why this was included at all.

Author: This validation study is part of a larger study, where the thyroid function tests were included. As TSH, fT3, fT4 is found to be altered if excessive iodine deficiency is present, we found it interesting to include in this validation study as the data already were present. Even though a significant association was not excepted, we could also compare the direction and strength of the regression coefficients with other studies which further strength our results. We have specified in the methods section that more information about the study design are further described in another article (Markhus et al. 2018). In addition, using more than one approach to validate an FFQ gives further credibility to the results (Cade et al. 2002), as we have also stated in line 511-513.

Reviewer 1: Line 512: include above in methods how many interviews are considered adequate for validat ion, don't wait until discussion to add this.

Author: Thank you for this comment. We have now added this in the methods part. Please see line 135-136: “The sample size was considered adequate in according to validate an FFQ in a population group where of at least 50-100 subjects is recommended (20).”

Reviewer 1: Please consider organizing the strengths and weaknesses differently, either all strengths and all weaknesses, or each assessment method with its related strengths and weaknesses or another system to help the reader recognize when you are shifting between strength and weakness.
Author: We have now organized this paragraph and moved the specific limitations of the I-FFQ to line 455-462.

Reviewer 1: Lines 531-532, as above about 'estimate and rank'
Author: As above, where the importance of ranking is given.

Reviewer 1: Line 532: "association" please explain what you mean - use the full appropriate statistical terms.
Author: Thank you for this comment. We have now inserted the full appropriate statistical term. Please see line 525-526.

Reviewer 1: Line 536: "need for tools" tools are already available, explain more of what type of tools are needed that you believe you have identified. 'non-invasive', 'low-cost', 'self-administered' ...
Author: Thank you for this valuable comment. We agree with this, and have now inserted this in line 529-530 in the conclusion.

Reviewer 2

Reviewer 2: Abstract: line 29 - modify the statement on reference methods analyzed
Author: To validate the I-FFQ, we used the reference methods of a food diary, UIC and thyroid function tests. We did not quite understand the meaning of modify this sentence. Please let us know if you had any suggestion in mind.

Reviewer 2: line 79 - as stated, it recommended by the Govt of Norway (re-frame the sentence) and send the reference link of this statement in English language for correlation.
Author: Thank you for this comment. We have now inserted that the recommendation is from the Norwegian Directorate of Health, please see line 77. Unfortunately, this reference is not available in English, it is only published in Norwegian, so we do not have the opportunity to reference this link in English.
Reviewer 2: line 101-103 - what is the specificity between RCT and I-FFQ? Reframe the sentence since it shows difference in statement of the problem

Author: Thank you for making us aware of this. We have now inserted “for the RCT” in line 103, stating that the I-FFQ was developed specifically for this study.

Reviewer 2: line 117 & 121-122 - reframe the first sentence in terms of past tense.

Author: Corrected. See line 125 and 131.

Reviewer 2: line 125 - clarify the actual meaning of 124, 134 & 134 participants. Reframe as accordingly.

Author: As data collection were not complete for all participants the numbers of participants of completing the different data varied. This is specified in this sentence, where data from the I-FFQ were available from 124 participants, food diary 134 participants and UIC 134 participants. Please let us know if this was not clear or if you had any suggested revisions in mind.

Reviewer 2: line 209 - check for grammatically mistake.

Author: Corrected. See line 227 where “visits” is changed to “visit”. If you had any other suggestion in mind, please clarify.

Reviewer 2: include the procedure of sample collection by the authors from the study participants

Author: Further information about the study design, including enrolment, randomization, study procedure and ethics are described in detail in a protocol article by Markhus et al. 2018. This is specified in the methods section, see line 128-129. As this paper was a validation study, we decided to focus the methods section towards the aim and analyses of this current paper.

Reviewer 2: line 223 - why the serum samples were stored for 3 months and why it is not analyzed immediately? what is the difference between them?

Do your food diary has any impact on the thyroid marker?
Author: It was more convenient and practical to collect several samples and deliver them together to the external laboratory. However, the storage of 3 months does not influence the analyses of the thyroid hormones.

In this study we validated the I-FFQ, and therefore we decided not to include the regression models between the thyroid markers and the food diary. However, we have performed the analyses and we did not find any statistically significant association between the food diary and the thyroid markers. Except for fT3, the directions of association were similar as with the I-FFQ (adjusted coefficients (95% CI): TSH: 6.91 (-14.15, 27.98); fT3: 3.39 (-33.15, 39.92); fT4: -5.51 (-15.53, 5.52)).

Reviewer 2: line 483 - clarify whether bio-marker assessed everyday or after 3 month as mentioned in the line 223.

Author: It was only the serum samples that were stored for maximum three months. In the sentence of the line specified by the reviewer we explain limitations of UIC, as further elaborated by Rohner et al. 2014.

Reviewer 3

Reviewer 3: The Norwegian dietary habits are definitely different from the rest of the world and this should be mentioned as a limitation even in the abstract.

Author: Thank you for valuable input. We agree that the Norwegian dietary habits are different compared to low- and middle-income countries. However, we believe the Norwegian diet is comparable to the other Nordic countries, and, in addition, other European countries where milk and dairy products, and seafood is a part of the diet. We therefore believe this research can be useful in countries where similarly dietary patterns are present. We have also stated this in the discussion, please see line 520-521.