Author's response to reviews

Title: Higher n3-fatty acid status is associated with lower risk of iron depletion among food insecure Canadian Inuit women

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Author's response to reviews: see over
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Response to Reviewers

Re: n3-fatty acid status as a marker of traditional food intake is associated with lower risk of iron depletion among food insecure Canadian Inuit women.

Dear Dr. Lawrence and Mr. Dizon,

We thank the reviewers for their thoughtful suggestions. Below, we outline each concern and note our revisions. We believe the revisions have improved the quality of the manuscript.

Revised title:

Higher n3-fatty acid status is associated with lower risk of iron depletion among food insecure Canadian Inuit women

Reviewer 1

This paper provides important information regarding iron status in an understudied population. The data collection methodology is sound but the statistical methods could be improved. The authors need to do a much better review of the obesity/iron literature to get a better sense of the physiologic changes that may be determining iron status in their very obese/overweight population. This reviewer’s comments are detailed below.

Abstract Line 35: either hyphenate or don’t hyphenate post-menopausal

Changed to “postmenopausal” throughout the manuscript.

Abstract Line 38: Need to define PUFA

Defined, as requested (line 36-37).

Abstract Line 39: Delete: a marker of traditional food intake. It isn’t a marker of traditional food intake. You could say (which would be associated with a more traditional food pattern)

This was rephrased: “which reflects a more traditional food pattern” (line 37).

Abstract Line 39: State in your methods that you are looking at food insecurity OR, is this what you are referring to as a correlate?

Added: “food security status” (line 30)
Abstract Line 41: Please put a comma after positively.
Comma added.

Abstract Line 44: change to adequate total dietary intake from primarily heme sources.
Changed as requested (line 40).

Abstract Line 45: delete “the” before childbearing
The abstract conclusion was re-written.

Abstract Line 46: You state iron intake is adequate, so why would an intervention be necessary to ensure adequate iron status? What type of intervention are you suggesting? Given your observation that elevated CRP is associated with ID what do the author’s think is driving the iron depletion observed in your population? Given PUFAs, which are associated with decreased inflammation, were associated with better iron status, isn’t this the Big Take home from your findings?
This section was rewritten to reflect the new, revised discussion addressing the impact of obesity and inflammation.

Background:
Line 66: Delete “and overall nutritional”
This section was rewritten.

Line 68-71: Change to: “Although adequacy of dietary iron intake has been observed among Arctic Indigenous peoples [2-4], moderate to high rates of both ID (22-39 %) and anemia (10-42 %) are observed for Canadian Inuit [4-6] and Alaska Native [3] women
Delete text referring to child populations. The message you are trying to convey is that although dietary intake is adequate, ID and IDA are prevalent.
Your first paragraph talks about iron being adequate in the diet, then the second paragraph talks about diet possibly being inadequate in younger persons, try to make it clearer to the reader who the top group represents and how younger people may present with different dietary patterns based on moving away from less traditional foods.
The first two paragraphs from the original manuscript were re-written to focus on Inuit women and the effect of the dietary transition.

Are the Westernized Inuit more overweight/obese? I highly encourage you to look at the obesity/iron deficiency literature to more clearly understand what may be happening physiologically with your population which would result in ID/IDA. Also, how LCPUFA might be an important factor to improving iron absorption in this population.
Authors hint to the issue of inflammation/infection on iron status. Given your population and prevalence of H. Pylori and Obesity this reviewer strongly
suggests reframing the paper to focus on how this could impact iron status (i.e. hepcidin)

Why are you discussing Inuit men? Remove all text related to men throughout the entire paper. Iron status is vastly different in younger men and women.

The paper was reframed as suggested to address the impact of obesity and inflammation. Please note that morbid obesity was not present in this population.

Methods:

Would advise looking also looking at BMI and not just %BF. Would also advise looking at BMI and CRP in both a categorical and continuous fashion with log SF in the linear and logistic modeling. Would also look at a multivariable linear model predicting log sTfr. Also try predicting IDA (using hemoglobin) using your selected correlates. Was the population in which sTfr was measured, similar to the larger population?

We did run the models with BMI, waist circumference, and % BF (continuous and categorical) and found very similar results. % BF was the strongest predictor of the 3 so we chose to use it. We also explored using either dichotomous or continuous variables in the modeling.

We did try to model log10 stfr and there were a few statistically significant predictors but the explanatory power of the model was too low to have confidence in it (adjusted R2=0.05). A model using IDA instead of depleted iron stores produced similar results as reported in Table 4 (the revised Table 3).

Given that most women failed to report supplement use, wouldn’t authors presume that iron intake is even higher in the studied population? This again begs for the authors to move away from dietary adequacy/quality and at least discuss the implications of central adiposity, inflammation, hepcidin, and iron regulation within this paper given the population studied.

Yes, the implications of iron intake vs physiology are now discussed as requested. Participants brought their medications and supplements to the nurse during the survey to ensure accurate reporting and previous surveys have found low prevalence of supplement use in the Canadian Arctic.

The authors need to adjust the significance level to account for multiple comparisons.

Changed as requested (footnote of Table 2).

Results:

Please state where in the methods you discuss evaluating dietary factors that enhance or inhibit iron absorption, otherwise please state this.

Added to line 149-150.
Lines 256-260 can be condensed. Don’t repeat everything in the tables within the text.

**This was condensed to one line (line 227-8). All median intakes were <EAR.**

Line 260-262; Delete: Daily frequency of consumption of TF species was highest for game, followed by fish, sea mammals, birds and liver (all species) (Table 2). This is not important to the paper since you go on to describe the top sources of iron for the two groups.

**This line was deleted.**

Lines 264 please describe what constitutes a “market food” meat in the methods.

**Market food (and traditional food) is now defined in line 153.**

Lines 270-274. The correlations provide little insight given the authors did not adjust for multiple comparisons. Delete Table 2 and supporting text. Or keep and just report variable correlated with SF after adjustments were made. How do table 3 and 4 differ? What is the purpose of both multivariable models? Aren’t the predicting the same thing?

**Table 2 was changed as requested. Multivariate associations of key dietary variables are now shown and adjusted for multiple comparisons. Table 3 was redundant and therefore removed.**

How did the authors code depleted iron stores?

**See line 125 in the methods.**

Depleted iron stores was defined by SF<15 µg/L or SF=15-50 µg/L in the presence of acute inflammation (hs-CRP ≥10 mg/L).

Discussion

Why do the authors think sTfR was not elevated? It is rare that sTfR would be normal when IDA is present. Please provide an explanation.

**The discussion was rewritten, addressing this question (first paragraph).**

Line 309. Remove the comment about maternal and child health. It is unnecessary within this paper since you have a mixed population and comes across as an afterthought.

**These comments were removed, as requested.**

Line 313. What type of multifactorial anemia are the authors suggesting? Depletion of storage iron would not necessary increase sTfR but, IDA would.

**The discussion was rewritten, as suggested to reflect an inflammatory-driven iron depletion.**

Line 314. Drop all comparison to men. Instead compare younger and older women. Why might iron values differ? How does the discussion of the correlation analysis related to line 314-17. Drop the discussion on the correlation as no adjustment was made for multiple comparisons (Lines 317-332).
Comparisons to men and unadjusted correlations were removed from the discussion.

Line 337. Why is menopause associated with lower iron requirement and increased SF? This is well documented in the literature and should be cited. **This relationship is now explained in the discussion (line 267-270).**

Line 339-42 The authors state: Therefore, higher SF and lower rates of iron depletion are not surprising among participants with at-risk % body fat. Further investigation is needed to determine whether this relationship reflects analogous changes in these biomarkers or true differences in iron stores during obesity. So are you suggesting that the ferritin levels don’t reflect true iron status? Wouldn’t this suggest your population is even more deficient? This reviewer strongly suggests doing a thorough review of the obesity, inflammation, and iron literature. This is VERY important to your paper. The findings by the authors are discrepant with the existing literature. Obesity (particularly morbid obesity) is associated with depleted iron status and not adequate iron stores. **These issues were reinterpreted as requested throughout the manuscript.**

Lines 344-346 No references cited: In addition, low-grade inflammation (hs-CRP= 3-10 mg/L) and oral contraceptives, which decrease menstrual losses, were both associated with higher SF and less risk of iron depletion after multivariate adjustment. **This section was rewritten in light of the revised framing of the discussion and interpretation.**

Lines 349-356 Drop the discussion regarding men. Why might LCPUFA be associated with lower risk of iron depletion? This is an important finding and needs to be discussed not within the framework of food insecurity but instead as an anti-inflammatory agent. **This section was rewritten in light of the revised framing of the discussion and interpretation (see third paragraph of discussion).**

Lines 357-372. The authors need to discuss hepcidin. Shorten the discussion of dietary factors associated with enhanced iron absorption or chelation. **Rewritten as requested. Hepcidin is introduced in the introduction and further discussed in the discussion (first paragraph).**

Lines 373-378: Delete, not important to the paper. **Rewritten as requested.** Limitations also include lack of information regarding hepcidin. **This is now included in the limitations.**

Conclusion
This reviewer will review the conclusion after major methodologic items have been addressed and the discussion substantially improved.
The conclusion was rewritten to reflect the new focus of the manuscript.

Reviewer 2

Minor Essential Revisions
This is manuscript represents an important contribution to nutrition and food security literature, and contributes novel insights into the relationship between iron depletion, traditional foods, and food security among Inuit women of childbearing age.
Co-authors of this manuscript represent a unique cross-disciplinary collaboration, which enriches both the methodological rigor of the study as well as the interpretation of findings within indigenous nutrition and environmental sciences. The research question posed by authors was well defined. The nutritional methodology employed in this study is robust, elegantly described and offers a strong analytic platform from which to examine study objectives. The large sample size is noteworthy, enhancing the precision of inferential statistical. Description of methods and results are thorough.
Authors could consider implications of findings for Inuit populations with concurrent infectious diseases including HIV and HCV infection, which have shown to be elevated in northern Aboriginal populations and associated with adverse iron status.
The prevalence of HIV and HCV is considered to be low in the Canadian Artic. We are aware of one study in Baker Lake (one of our communities) in which HCV was identified for 2 out of 720 (0.3%) of individuals tested (Minuk et al., Can J Infect Disease 1991), and a recent publication of Greenlandic Inuit in which 0 of 441 Inuit tested were positive for HCV (Rex et al., Scan J Gastroenterol 2012). As we don’t have data regarding the HIV or HCV status of our study participants, and given concerns regarding manuscript length, we decided not to include a discussion on this topic.

Authors should consider elaborating on whether association between iron deficiency and food insecurity is due to food insufficiency or poor dietary quality, by drawing on available qualitative and quantitative literature. This would provide a more comprehensive context for discussion around the role of traditional foods in this population.
We expanded the interpretation and added details regarding the dietary context (paragraph 3 of discussion).

Discussion is lacking reflection about relevance of study findings for regional public health programming and policies. It would be beneficial for authors to expand on how existing public health, environmental nutritional supports to this community could enhance ongoing use, sustainability and education about the importance of traditional foods in this population.
Related to this, it authors may also consider making linkages between this research and similar research performed among indigenous populations internationally.

A discussion of public health implications has been included (lines 287-292).

Thank you for your time and consideration.
Sincerely,
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On behalf of all authors.

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