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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Dear Dr. Lawrence and Mr. Dizon,

We thank the reviewer for her thoughtful suggestions and written revisions. Below, we outline each concern and note our further revisions. The sections rewritten by the reviewer were all incorporated. We believe the changes have improved the quality of the manuscript. All changes in the manuscript are highlighted in yellow.

Editor's comments:

The revisions that have been made to date are noted as having significantly strengthened the manuscript. A few further relatively minor but essential revisions are recommended as indicated as inserts in the following text taken from the paper

Discussion:
To our knowledge, this is the first representative survey to report prevalence estimates of anemia and depleted iron stores for Canadian Inuit women in ISR, Nunavut, and Nunatsiavut. Anemia was moderately prevalent according to the WHO classification system (20-39.9 % = moderate public health problem). Half of the anemia cases could be attributed to IDA based on SF and hemoglobin, although this is likely an overestimate as, functional ID was rare, even among premenopausal women (3.0 %). Low sTfR levels suggest that IDA is not the main cause of the anemia observed. (Why?) See: Suominen P, Punnonen K, Rajamaki A, Irjala K. Serum transferrin receptor and transferrin receptor-ferritin index identify healthy subjects with subclinical iron deficits. Blood. 1998;92(8):2934-2939.

According to Suominen et al (1998) the stage of iron deficiency anemia (3rd stage) is characterized by stfr>3.6 mg/L + ferritin <22 + hemoglobin <117 g/L. In our population, we see anemia + low ferritin but stfr is not elevated. Therefore it would appear
there must be other causes of the anemia observed.

The ID or IDA? present is more likely explained by the pervasiveness of H. pylori exposure and not inadequate iron intake. This is supported by the high prevalence of dietary iron intake and high proportion of heme iron in the diet. In fact, dietary recalls are known to underestimate intake, making iron intake even more likely to be adequate (ref for FFQ underestimation). This statement was changed to IDA. Reference 22 was added to support this statement.

H. Pylori is an inflammatory condition which may trigger overexpression of the iron regulatory protein hepcidin (you need a reference to support this). Reference 31 was added to support this statement.

Therefore, discordance between adequate iron intake and iron status in the population may be a result of inflammation-induced hepcidin expression, resulting in degradation of the iron exporter ferroportin and diminished dietary iron absorption [14, 15]. The mild anemia observed may be the result of chronic inflammation which can depress erythropoietin and hemoglobin synthesis [32], but does not appear to exacerbate severe IDA?.

Paragraph 2 is fine. We report that obesity is associated with a lower risk of iron depletion. This finding does not agree with several observations in Caucasians and other populations [14, 15, 31]. Higher traditional food intake and RBC? LC-PUFA status among obese Inuit could explain this contradictory relationship (Why?, How does intake compare to the populations in which obesity is associated with greater iron depletion? ). However, there was no significant difference between RBC? LCPUFA status among those with elevated body fat compared to those within the normal weight range after controlling for age, smoking status and inflammation (CRP) (Table 4). Geographical analyses within the population reveal higher n-3 PUFA status (related to sea mammal and fish intake) among coastal communities, particularly in the Baffin and Kivalliq regions of Nunavut [33]. Indeed, in our subset analysis (Table 4) there was a trend toward higher LC-PUFA status among the obese after excluding in-land communities and the more westernized region (ISR) from the model. Clearly, more research is needed to clarify the relationship between adiposity and iron status for Inuit.
Frequency of sea mammal consumption was the only dietary variable associated with SF. Sea mammals are rich sources of dietary iron, but notably the fat from these mammals are an important source of n3 LC-PUFA for Inuit [34]. Among food insecure women, we observed that higher RBC % LC-PUFA was associated with reduced risk of iron depletion. Lower rates of chronic disease among Inuit has been attributed to their higher intake of LC-PUFA, through the anti-inflammatory properties of n3-fatty acids, [16]. Therefore, consumption of n3-PUFA may support iron status through down regulation of inflammatory processes, including reduced hepcidin expression, and subsequently improved dietary iron absorption. This interaction demonstrates the importance of TF intake (specifically marine mammals and fish) for iron status, especially when quality market foods are not abundant. It is therefore prudent, for environmental and public health programs to support enhanced use of, sustainability( explain this ?), and education about the importance of TF throughout the Canadian Arctic. The current findings will enhance public health messaging about the value of TF in the contemporary Arctic diet and contribute to the global literature regarding the importance of TF for the health of Canadian Indigenous Peoples [35].

**Sustainable harvesting of TF – this statement was revised.**

Conclusions
The high prevalence of H. pylori exposure, together with dietary iron adequacy, suggest an inflammation-driven ID and mild anemia.

*The reference to obesity was removed from the conclusion.*

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

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