Prevalence of unexplained anaemia in Inuit men and Inuit post-menopausal women in Northern Labrador: International Polar Year Inuit Health Survey

Jennifer A. Jamieson, PhD,¹ Hope A. Weiler, PhD,² Harriet V. Kuhnlein, PhD,^{2,3} Grace M. Egeland, PhD⁴

ABSTRACT

OBJECTIVE: To identify correlates of hemoglobin (Hb) and anaemia unexplained by iron deficiency (UA) in Canadian Inuit adults.

METHODS: A cross-sectional survey assessed diet, demographic information, anthropometry, fasting Hb, ferritin, soluble transferrin receptor (on a subset), high-sensitivity C-reactive protein (hs-CRP) in serum, red blood cell (RBC) fatty acid composition, blood lead, and antibodies to *Helicobacter pylori* in non-pregnant, Inuit adults ($n = 2550$), ≥ 18 years of age from randomly selected households in 36 Inuit communities in Inuvialuit Settlement Region, Nunavut Territory and Nunatsiavut of Northern Labrador, Canada.

RESULTS: Hb concentrations were lower and UA prevalence higher in Inuit men after 50 years of age. Rate of anaemia was constant among Inuit women but changed from primarily iron deficiency anaemia pre-menopause, to primarily UA in post-menopause. Low education levels and hs-CRP were associated with increased risk of UA. For Inuit men, % RBC eicosapentaenoic acid (EPA) and elevated blood lead were also associated with increased risk of UA. Frequency of traditional food intake was positively associated with Hb.

CONCLUSION: Age patterns and regional variation of anaemia suggest that ethnicity-related physiological differences cannot explain anaemia prevalence for Inuit. High RBC EPA status, inflammation and infections, and lower education levels may contribute to the prevalence of anaemia in this population, which is not related to iron status. Thus, traditional lifestyle may protect Inuit from nutritional anaemia but contribute to lower Hb through environmental exposures. The clinical significance of UA for older Inuit adults requires further investigation, as the prevalence represents a moderate public health problem.

KEY WORDS: Hemoglobin; anaemia; indigenous health; inflammation; nutrition

La traduction du résumé se trouve à la fin de l'article.

Can J Public Health 2016;107(1):e81–e87
doi: 10.17269/CJPH.107.5173

Anaemia, a disorder commonly observed in tropical nations with grain-based diets, has long been a concern in the Arctic, despite a traditional diet rich in animal-source foods. The 2007–2008 Inuit Health Survey reported 24.9% and 30.3% anaemia prevalence rates among women and men over 50 years of age, according to WHO (World Health Organization) cut-offs.¹ In adults 18–50 years, 20.2% of women and 9.3% of men were anaemic, with iron deficiency anaemia (IDA) observed in 14.1% of women and 3.1% of men. IDA was observed in only 3.9% and 1.1% of women and men over 50 years of age^{2,3} respectively, indicating that iron status did not explain the prevalence of anaemia in this age group.

According to nationally representative US survey data, women are typically disproportionately affected by anaemia until 75 years of age, when the prevalence becomes 5% higher among men.⁴ Therefore, the comparable rates of anaemia among Inuit men and women and higher prevalence among those >50 years of age may suggest an environmental or pathological etiology. Potential causes or contributing factors to anaemia for Inuit include micronutrient deficiencies, poverty, inflammation, *Helicobacter pylori* infection, lead exposure, chronic blood loss, and impaired iron absorption and/or utilization.⁵ Centers for Disease Control studies of Alaska, a similar geographical and cultural region, found no parasitic or

genetic cause of anaemia in the Indigenous Peoples of Alaska.^{6–9} It has been hypothesized that Inuit may have physiologically lower hemoglobin (Hb) concentrations.^{10,11} However, this hypothesis has yet to be experimentally tested and does not concur with the lower prevalence rate of anaemia in younger Inuit adults.

The available literature on the etiology of anaemia among Inuit Peoples, defined as “the Inupiat (Alaska), Yupik (Alaska), Inuit,

Author Affiliations

1. Department of Human Nutrition, St. Francis Xavier University, Antigonish, NS
2. School of Dietetics and Human Nutrition, McGill University, Montreal, QC
3. Centre for Indigenous Peoples' Nutrition and Environment, McGill University, Montreal, QC
4. Department of Global Public Health and Primary Care, University of Bergen & Norwegian Institute of Public Health, Bergen, Norway

Correspondence: Jennifer Jamieson, PhD, Department of Human Nutrition, St. Francis Xavier University, PO Box 5000, Antigonish, NS B2G 2W5, Tel: 902-867-5568, E-mail: jjamieso@stfx.ca

Acknowledgements: Sources of funding included: Canadian Federal Program for International Polar Year, Health Canada, Canadian Institutes of Health Research, Indian and Northern Affairs Canada, Government of Nunavut Health and Social Services, ArcticNet. JJ was supported by a CIHR Doctoral Research Award. GE and HW were both in receipt of Canada Research Chair salary awards. We acknowledge the guidance throughout this project of the regional steering committees of Inuvialuit Settlement Region, Nunavut and Nunatsiavut for the Inuit Health Survey, and the entire survey team, especially CINE and McGill University support staff and our many collaborators. Finally, all participating communities and participants are warmly acknowledged and thanked.

Conflict of Interest: None to declare.

Inuvialuit (Canada), Kalaallit (Greenland), and Yupik (Russia)" in the charter of the Inuit Circumpolar Conference, is limited. Previous surveys assessed iron status by serum ferritin without accounting for the confounding effect of inflammation.^{7,10,11} There has also been inadequate information regarding the many socio-environmental conditions important in understanding the context of anaemia in a population experiencing rapid social, cultural and dietary transition. Further losses of traditional lifestyle, dietary patterns¹² and pervasive food insecurity¹³ may place Inuit at increased risk of anaemia. A deeper understanding of the factors related to anaemia in Inuit is therefore needed to inform health policy. The objectives of this study were to identify correlates of Hb and anaemia unexplained by iron deficiency (UA) in Inuit adults of Inuvialuit Settlement Region (ISR), Nunavut Territory and Nunatsiavut Canada.

METHODS

Study population and assessment

This research is part of the Inuit Health Survey conducted in 36 Arctic communities within ISR, Nunavut and Nunatsiavut. Details of the study design and methods were previously described.¹⁴ Briefly, sampling was stratified by community with randomization of households within communities. The household response rate was 68% overall and included 2,550 eligible adults ≥ 18 years of age (60.9% female). Individual informed consent was obtained, as well as ethical approval through the McGill University Faculty of Medicine Institutional Review Board in 2007, with ongoing renewals through 2015. The laboratory and clinical measures used in this study, including cut-offs used, are reported in Supplementary Table 1 (see ARTICLE TOOLS section on journal website). In the development of the International Polar Year Inuit Health Survey, pre-existing Statistics Canada and other survey instruments capturing socio-demographic, health and household characteristics were

utilized.¹⁴ Education level was assessed by number of school grades completed and dichotomized into $\leq$ elementary school (grade 6) or $>$ elementary school. Dietary assessment was conducted with a single 24-hour recall using a four-stage, multi-pass approach and a semi-quantitative food frequency questionnaire (FFQ) with 37 traditional food (TF) items and 5 market foods. The FFQ assessed frequency of intake over the past year according to seasonal availability, as previously described.^{2,14} TF was defined as animal and plant species culturally identified as food and harvested from the local environment, whereas market food was that shipped from the South and purchased in stores¹². Recall data were entered into CANDAT software (Godin London) and nutrient analyses obtained from the 2007b Canadian Nutrient File and supplemental databases, as previously described.^{2,3,14}

Statistical analysis

Smoking-adjusted (# cigarettes/day) mean Hb concentrations by age decile were analyzed by one-way ANOVA and reported in Figure 1. Weighted prevalence estimates of IDWA (iron deficiency without anaemia), IDA and UA are presented in Figure 2. Sampling weights reflected the proportion of participating adults using Statistics Canada's Census data of age-appropriate Inuit by community. Independent determinants of Hb were assessed in a multivariate linear model using a priori selection of variables known or suspected to be related to Hb (Table 1). Independent determinants of UA vs. non-anaemic were assessed in a multivariable logistic model with region and community included as a random effect intercept in a mixed model, after exclusion of all IDWA and IDA participants (Table 2). Age- and sex-adjusted correlates of Hb and UA were compared across regions in Table 3, using linear regression. All analyses were performed in STATA (version 11; StataCorp LP, College Station, TX). *P*-values were all two-sided and significance was set at $p \leq 0.05$, with the exception of interaction terms ($p \leq 0.1$).

Table 1. Multiple linear regression coefficients for hemoglobin* based upon non-dietary and dietary determinants as independent variables among Inuit men: International Polar Year Inuit Health Survey, 2007–2008†‡

	Multivariate coefficient	SE	<i>p</i> -value
Constant	116.891	2.055	<0.001
Age-group (1 = ≥ 51 years, 0 = ≤ 50 years)	-1.227	1.805	0.497
Sex (1 = male, 0 = female)	18.395	0.885	<0.001
Adiposity (%)	0.296	0.040	<0.001
hs-CRP (mg/L)	-0.173	0.222	0.435
hs-CRP $\times$ age-group interaction	-0.760	0.356	0.032
Serum ferritin (μ g/L)	0.026	0.005	<0.001
RBC EPA (%)	1.138	0.378	0.003
RBA EPA (%) $\times$ sex interaction	-2.861	0.497	<0.001
Elevated blood lead (1 = yes, 0 = no)	3.301	2.383	0.166
Elevated blood lead $\times$ sex interaction	-4.575	3.209	0.154
TF, daily frequency (FFQ)	0.756	0.373	0.043
≥ 1 seropositive tests (1 = yes, 0 = no)	0.149	0.978	0.879
Age-group $\times$ ≥ 1 seropositive tests interaction	-4.720	1.938	0.015
$\leq$ Elementary school education (1 = yes, 0 = no)	-2.702	0.940	0.004

* Analyses conducted on $n = 1653$.

† The regional and community variance components for the model were 3.96 and 3.30 respectively. The intraclass correlation was $\rho = 0.023$ (region) and $\rho = 0.019$ (community).

‡ All variables presented were evaluated together in one model. Missing values are due to lack of blood sample collection ($n = 329$), clinical assessment ($n = 378$) or dietary assessment ($n = 469$).

hs-CRP = high sensitivity C-reactive protein; RBC = red blood cell; EPA = eicosapentaenoic acid; TF = traditional food.

Figure 1. Mean hemoglobin* (95% CI) by age among men ($n = 846$) and women ($n = 1286$)[†]: International Polar Inuit Health Survey, 2007–2008. *Superscripts with different letters are significantly different. [†]Missing values are due to the lack of a hemoglobin ($n = 374$) or C-reactive protein (CRP) ($n = 344$) determination.

Figure 2. Weighted prevalence of iron depletion, iron deficiency anaemia and unexplained anaemia among men and women: International Polar Inuit Health Survey, 2007–2008*. *Analyses on a subsample ($n = 1092$) with venous blood sampling for hemoglobin (Hb) determination where anaemia = Hb <120 g/L (women) or Hb <130 g/L (men). Iron deficiency without anaemia (IDWA) was defined as normal hemoglobin + serum ferritin <15 µg/L or ferritin 15–50 µg/L if hs-CRP >10 mg/L; IDA was defined as anaemia + serum ferritin <15 µg/L or ferritin 15–50 µg/L + hs-CRP >10 mg/L; and unexplained anaemia (UA) defined as anaemia + serum ferritin ≥15 µg/L.

RESULTS

Study population

Mean age ± SD of the study population was 42 ± 15 years (range: 18–90), with 28% of participants overweight and 36% obese by

WHO criteria. Underweight was almost non-existent (0.8%). Seventy percent of the sample currently smoked, with a median of 10 cigarettes/day (IQR: 6–13). High blood pressure, diabetes mellitus and high cholesterol were self-reported in 26%, 7% and 11% respectively, and a low hs-CRP (high-sensitivity C-reactive protein) concentration (<3 mg/L) was observed in 73% of the sample. Five percent of participants reported taking a daily dose (80–325 mg) of acetylsalicylic acid (ASA) and a further 4% reported regular use of other non-steroidal anti-inflammatory drugs (NSAID). However, these participants did not differ in Hb concentrations from age-adjusted non-ASA or NSAID users and were therefore included in analyses.

Anaemia prevalence

Hb concentrations were lower and rates of anaemia higher in men after approximately 50 years of age, but both remained relatively stable among women across age groups (Figures 1 and 2). For men, iron depletion was associated with only 18% of anaemia cases while 82% of cases were unexplained by iron stores. Over one third of men with UA (37%) had elevated hs-CRP. Among premenopausal women, iron depletion (ID) was associated with most cases of anaemia, although this is likely an overestimate of IDA based on a one-parameter model for classifying ID.³ Nonetheless, ID among premenopausal women with and without accompanying anaemia was pervasive. For women with UA, 17% of cases also had an elevated hs-CRP. Among men, 96% of all anaemia cases were mild (Hb 100–129 g/L) and none were severe (Hb <70 g/L). For women, 87.5% of all anaemia cases were mild (Hb 100–119 g/L) and none severe (Hb <70 g/L). In a subset analysis of men and women with anaemia, who also had sTfR (soluble transferrin receptor) and SF (serum ferritin) measured ($n = 211$), 94% of men and 89% of women were categorized with anaemia of inflammation (AOI) (sTfR index <1.5). Using the total body iron calculation on the subset sample, 1.6% of men (95% CI: 0.7–3.6%) and 6.1% of women (95% CI: 4.1–8.7) had no body iron stores (<0 mg iron/kg).

Anaemia, other causes

Lead exposure was investigated as a potential cause of anaemia and was negatively associated with Hb in men after multivariate adjustment (Table 1). Median blood lead concentration was higher among men than women. Elevated blood lead (EBL) may have contributed to low Hb in 16 men and 13 women but concentrations were only moderately elevated (100–250 µg/L) in these cases. No participants had evidence of overt lead toxicity. No women of child-bearing age ($n = 232$) were found to have inadequate or low folate stores that would be associated with macrocytic anaemia. No individual relationships between anaemia and parasitic infections including *Toxoplasmosis*, *Trichinella*, *Toxocara*, *Echinococcus* and *H. pylori*, were evident. Antibody response to *H. pylori* did not vary ($p = 0.189$) among anaemic (71% positive) or non-anaemic (74% positive) participants. However, as a composite variable, the number of seropositive test results was related to Hb concentration (Table 1). Low vitamin D status was observed in 80.3% of those 18–30 years of age, 50.3% of those 31–50 years of age and 11.9% of those 51+ years of age. No relationship was evident between UA and low serum 25(OH) vitamin D or number of seropositive test results.

Table 2. Logistic regression coefficients, odds ratios (OR and 95% CI) with unexplained anaemia* as the dependent variable among Inuit adults: International Polar Year Inuit Health Survey, 2007–2008†‡

	Multivariate OR	95% CI	P
Age-group (1 = ≥51 years, 0 = ≤50 years)	1.562	0.682–3.577	0.291
Sex (1 = men, 0 = women)	0.520	0.344–0.786	0.002
Adiposity, %	0.949	0.931–0.967	<0.001
hs-CRP, mg/L	1.099	1.020–1.183	0.013
RBC EPA, % of total fatty acids	0.879	0.737–1.048	0.151
EPA × sex interaction	1.282	1.040–1.582	0.020
Elevated blood lead (1 = yes, 0 = no)	0.298	0.080–1.103	0.070
Sex × elevated blood lead interaction	4.761	1.035–21.91	0.045
Traditional food, n/day	0.905	0.761–1.077	0.261
≥1 seropositive tests (1 = yes, 0 = no)	0.905	0.536–1.528	0.709
Age-group × ≥1 seropositive tests interaction	2.153	0.895–5.177	0.087
≤Elementary school education (1 = yes, 0 = no)	1.683	1.138–2.477	0.009

* The regional and community variance components were 0.12 and 0.05 respectively. The intraclass correlation was $\rho = 0.034$ (region) and $\rho = 0.015$ (community). All variables were evaluated together in the same logistic mixed model.

† For highly prevalent outcomes, the odds ratio will tend to exaggerate the true relative risk.

‡ Participants with iron depletion or iron deficiency anaemia were excluded from the model ($n = 1337$).

Table 3. Regional comparisons in correlates of unexplained anaemia among Inuit adults, adjusted for age and sex: International Polar Year Inuit Health Survey, 2007–2008*

	n	Nunavut (74%)	ISR (14%)	Nunatsiavut (12%)	P
Hemoglobin, g/L					
Male	846	139 ± 1	147 ± 1	146 ± 1	<0.0001
Female	1286	126 ± 1	131 ± 1	128 ± 1	<0.0001
RBC EPA, % of total fatty acids	2159	1.26 (1.22–1.31)	0.54 (0.49–0.59)	0.98 (0.89–1.07)	<0.0001
RBC DHA, % of total fatty acids	2159	1.87 (1.78–1.97)	0.55 (0.49–0.62)	3.41 (3.01–3.85)	<0.0001
Serum 25(OH) vitamin D, µmol/L	2207	49.4 (48.2–50.6)	49.9 (47.1–52.9)	52.4 (49.3–55.6)	0.2088
Adiposity, %	2128	27.2 (26.7–27.6)	31.5 (30.2–32.8)	30.4 (29.2–31.7)	<0.0001
Serum hs-CRP, mg/L	2164	1.31 (1.23–1.39)	1.37 (1.18–1.59)	1.52 (1.30–1.77)	0.2145
Blood lead, µg/L	2132	21.8 (20.7–23.1)	4.3 (3.8–5.0)	3.1 (2.7–3.6)	<0.0001
Traditional food, n/day	2037	0.74 (0.70–0.78)	0.57 (0.50–0.65)	0.67 (0.58–0.76)	0.0016
Marine mammals, n/day	2037	0.13 (0.12–0.15)	0.09 (0.07–0.11)	0.04 (0.03–0.05)	<0.0001
Game, n/day	2037	0.23 (0.22–0.25)	0.21 (0.17–0.25)	0.19 (0.16–0.23)	0.1270
Fish, n/day	2037	0.10 (0.09–0.11)	0.12 (0.10–0.14)	0.16 (0.13–0.20)	<0.0001
Birds, n/day	2037	0.02 (0.02–0.02)	0.03 (0.02–0.03)	0.06 (0.05–0.06)	<0.0001
Bird eggs, n/day	2037	<0.01 (<0.01–0.01)	0.01 (<0.01–0.01)	0.02 (0.01–0.02)	<0.0001
Seafood, n/day	2037	<0.01 (<0.01–0.01)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.0742
Seropositive tests, n	1964	1.35 (1.32–1.37)	1.03 (0.98–1.08)	1.05 (0.99–1.11)	<0.0001

* Values are geometric means, adjusted for age and sex for all variables except hemoglobin (adjusted for age).

ISR = Inuvialuit Settlement Region; DHA = docosahexaenoic acid.

Dietary intake

Median dietary intakes were analyzed for men and women, using 24-hour recall derived nutrient intakes, considered relevant to anaemia. Median intakes of men and women exceeded both the estimated average requirement (EAR) and recommended daily allowance (RDA) for vitamin B₁₂ (4.9 and 3.6 µg/day respectively) and riboflavin (2.5 and 1.9 mg/day respectively). Median intakes of folate (318 and 275 mg DFE/day), however, were less than the EAR for both men and women respectively. Median iron, vitamin C and calcium intakes as well as macronutrient distributions were reported elsewhere,^{2,3} with insufficient micronutrient intakes observed (median < EAR) for vitamin C, vitamin A and calcium, but not iron (2.3% of men and <1% of post-menopausal women consumed < EAR after statistical adjustment of the one-day recall.^{2,3}

Correlates of hemoglobin and unexplained anaemia

In a multivariate-adjusted linear model (adjusted $R^2 = 0.30$), SF, % adiposity, and frequency of TF intake were positively associated with Hb, while having an elementary school education or less was associated with lower Hb levels (Table 1). For participants over

50 years of age, hs-CRP and one or more seropositive tests were also negatively associated with Hb. For men, % eicosapentaenoic acid (EPA) and EBL were negatively associated with Hb. An analysis of missing values revealed that participants with missing data were 3.4 years older ($p = 0.001$) than included participants, but did not differ in sex, body mass index, % adiposity, food security status, or current smoking status. In a multivariate-adjusted logistic model (Pseudo $R^2 = 0.09$), % adiposity was independently associated with reduced risk while higher hs-CRP and having an elementary school education or less was associated with increased risk of UA (Table 2). For men, % red blood cell (RBC) EPA and EBL were also associated with increased risk of UA. Having one or more seropositive tests was marginally associated with higher risk among those over 50 years of age.

Regional variations in unexplained anaemia and correlates

Regionally, the prevalence of anaemia differed, with the highest rate observed in Nunavut (26.7%), followed by Nunatsiavut (21.1%) and ISR (13.4%). This paralleled RBC EPA, TF intake, and

blood lead concentrations (Table 3). Despite similar concentrations of hs-CRP and serum 25(OH) vitamin D across regions, Nunavut participants had a higher number of seropositive test results than the other regions. In Nunavut, the higher RBC EPA corresponded to greater marine mammal intake frequencies. In Nunatsiavut, high RBC docosahexaenoic acid (DHA) and intermediate EPA were reflected by higher fish but less marine mammal consumption.

DISCUSSION

Anaemia has been observed among Inuit adults for decades but the etiology was never fully explained. While ID can explain much of the anaemia observed in pre-menopausal women (Figure 2), men >50 years of age and post-menopausal women have moderate rates of anaemia, according to World Health Organization guidelines,¹ despite adequate iron stores. This population is unique in that anaemia disproportionately affects men instead of women⁴ before 75 years of age. Consequently, this is not simply an anaemia of aging, as most cases were observed between 51 and 70 years of age and Hb was lower, specifically in men, after 50 years of age (Figure 1). Although the definitive cause of the UA could not be defined, our study provides important clues that can direct further investigation. Our data suggest that there is regional variation in anaemia and that multiple factors may contribute to anaemia among older Inuit, including inflammation, infections and low socio-economic status (SES), as well as RBC EPA status and elevated blood lead in men. Thus, the nutrient-rich traditional diet and lifestyle may protect Inuit from nutritional anaemias (e.g., iron, folate, vitamin B₁₂), but contribute to lower Hb values through environmental exposures.

In our sample, the highest rates of anaemia were observed in the more traditional region of Nunavut and an intermediary rate in Nunatsiavut, which corresponded to regional differences in RBC EPA % and blood lead levels (Table 3). Similarly, anaemia prevalence was highest in a more traditional Alaskan region compared to other regions among both Indigenous and non-Indigenous children of Alaska, suggesting an environmental determinant might be involved⁹. Prevalence of anaemia for Inuit, therefore, appears to be highest in more traditional regions, which may be related to many factors, including dietary patterns, health care access, infectious disease exposure, and/or lower SES. Indeed, a low level of education was independently associated with lower Hb and increased risk of UA, after multivariate adjustment in the current study. AOI is not easily measured due to the lack of a single unequivocal marker of inflammation and non-specificity of the indicators. Thus, AOI may include anaemias of various pathophysiological causes. Although *H. pylori* seropositivity on its own was not related to anaemia risk, the associations of hs-CRP and the composite index of seropositive tests with risk of UA, as well as the low sTfR:SF index in this population, supports a role for inflammation in the UA cases. Similarly, AOI was reported to explain 42% of the anaemia among post-menopausal Nunavik women in 2004, with 14% due to IDA and 44% remaining unexplained.¹⁵

Iron intake and iron stores did not contribute to anaemia among older adults. Vitamin B₁₂ intake appeared adequate and is supported by observations of adequate serum B₁₂ in Nunavik women.¹⁵ Folate intakes were low but RBC folate levels, at least among young women, were not in a range associated with

macrocytic anaemia. Given the current consumption of (fortified) wheat flour bread and other market foods,¹⁶ severe folate deficiency would not be suspected. Vitamin A intakes < EAR were common, although reliable estimates of vitamin A intake require many days of dietary recalls. A 1998–1999 dietary survey of Canadian Inuit observed low probability of vitamin A inadequacy among Inuit >40 years of age and high probability of inadequacy among those ≤40 years of age, reflecting the ongoing nutrition transition.¹⁷ Therefore it is unlikely that low vitamin A status could explain the UA among older adults. Similarly, 25(OH) (25-hydroxy) vitamin D increased with age so that few adults with UA also had low vitamin D status. Thus, although low vitamin D status may be associated with increased risk of infections and a pro-inflammatory state,¹⁸ it does not appear to be a contributing factor to UA for Inuit. It should be noted, however, that the cross-sectional nature of the study may have limited these assessments.

The primary source of lead for Inuit is thought to be through bird and game tissues contaminated with lead shot,^{19,20} though age may be the most important predictor.²¹ In general, blood lead levels have declined among Inuit over time in accordance with national regulations, yet concentrations are still higher for Inuit than among general population comparison groups.²¹ Although there are toxic effects of lead on several enzymes involved in heme synthesis at concentrations as low as 50–100 µg/L,²² overt anaemia occurs only with acute toxicity (≥600 µg/L). Therefore, given the moderate blood concentrations in this population, lead is not likely an important cause of anaemia. It is difficult to separate the effects of TF components in a cross-sectional survey, given that markers of TF use were correlated with blood lead levels and TF is a source of both micronutrients and contaminants. The use of nutrient-rich TF must be balanced with potential exposure to environmental contaminants.

It is interesting that % RBC EPA, but not % DHA, was associated with lower Hb and increased risk of UA, despite positive associations between long-chain polyunsaturated fatty acid (LC-PUFA) and SF.²³ There is biological plausibility for this effect, including increased RBC oxidative stress, accelerated RBC turnover, and increased RBC vitamin E requirement with a highly unsaturated fish oil-rich diet.²³ Although not measured in the current study, vitamin E intakes were previously a concern for adequacy among Inuit adults.²⁰ It is possible that vitamin E status is insufficient to maintain RBC stability at higher EPA proportions and should be further investigated. Despite the negative association between % RBC EPA and Hb, daily frequency of TF intake was positively associated with Hb concentrations after multivariate adjustment. While frequency of consumption of marine mammals (rich sources of EPA and DHA²⁴) alone is negatively associated with Hb, the overall index (sea mammals, game, fish, birds, bird eggs, and seafood) remained positive. Inuit TF are mainly animal source foods, rich in micronutrients. On days when TF is consumed, Inuit have been shown to consume more protein, iron, zinc, copper, vitamins A, B₆, E and riboflavin,¹² all nutrients necessary for erythropoiesis.

Inuit in a healthy adiposity category appear to be at increased risk for UA compared to Inuit in an “at-risk” adiposity category, even after controlling for age and hs-CRP. In contrast, higher BMI categories were associated with anaemia in post-menopausal US women.²⁵ The chronic inflammation of obesity is associated with

higher hepcidin levels and lower iron status, resulting in an anaemia with characteristics of both IDA and AOI.²⁶ Although Inuit are not immune from the metabolic consequences of obesity,²⁷ it is likely that obese Inuit differ from obese Americans, especially in terms of dietary patterns. Overweight and obese Inuit adults have been shown to consume higher % energy as TF than those in the healthy BMI category and TF consumption has been associated with higher micronutrient intakes.¹² Higher LC-PUFA status with greater TF use may also attenuate the relationship between adiposity and inflammation.

Limitations

There are several important limitations to this analysis. Inflammation status was defined by hs-CRP alone and may have underestimated chronic inflammation in the population. Dietary assessment is problematic and logistical constraints limited dietary assessment to a single 24-hour recall and to a traditional FFQ, thus additional caution should be used in interpreting dietary adequacy. Field-based measurements necessitated the use of a portable hemoglobinometer, rather than an automated complete blood count, which would have aided in anaemia classification. However, WHO anaemia assessment methodology was followed. Missing data were more prevalent among older than among younger participants, which may have introduced a source of selection bias for the older participants included in the multivariable models. Linguistic challenges existed, but were minimized through local dialect translations, trained bilingual interviewers, pictures of subsistence species, and food portion size model kits. Finally, renal disease/function data were not available, but would be rare and not expected to modify results.

CONCLUSION

Anaemia unexplained by iron deficiency among Inuit men and women over 50 years of age, and iron deficiency anaemia among pre-menopausal women, are moderate public health concerns. Although a definitive cause of anaemia among older adults could not be established, our study identifies factors that may contribute to UA for elder Inuit including inflammation, infections and low SES, as well as higher % RBC EPA and EBL in men. Despite the negative association between % EPA in RBC and Hb, TF intake overall remained positively associated with Hb, likely due to the micronutrient-rich content of these foods, which may protect Inuit from nutritional anaemias. Given the associated morbidity and mortality of anaemia in older adults, and the uncertainty around appropriate age- and ethnicity-based anaemia cut-offs, determining the clinical significance of this mild but prevalent anaemia is important for the health and well-being of older Inuit adults. Future research is needed to evaluate the determinants and consequences of UA.

REFERENCES

- World Health Organization. Focusing on Anaemia: Towards an Integrated Approach for Effective Anaemia Control. Joint Statement of the World Health Organization and the United Nations Children's Fund. Geneva: WHO, 2004. Available at: http://www.who.int/nutrition/publications/micronutrients/WHOandUNICEF_statement_anaemia/en/ (Accessed June 17, 2014).
- Jamieson J, Weiler H, Kuhnlein H, Egeland GM. Traditional food intake is correlated with iron stores in Canadian Inuit men. *J Nutr* 2012;142:764–70. PMID: 22378332. doi: 10.3945/jn.111.140475.
- Jamieson J, Kuhnlein H, Weiler H, Egeland GM. Higher n3-fatty acid status is associated with lower risk of iron depletion among food insecure Canadian

- Inuit women. *BMC Public Health* 2013;13:289–97. PMID: 23547888. doi: 10.1186/1471-2458-13-289.
- Guralnik J, Ershler W, Schrier S, Picozzi V. Anemia in the elderly: A public health crisis in hematology. *Hematology. Am Soc Hematol Educ Program* 2005; 528–32. PMID: 16304431. doi: 10.1182/asheducation-2005.1.528.
- Jamieson J, Kuhnlein H. The paradox of anemia with high meat intake: A review of the multifactorial etiology of anemia in the Inuit of North America. *Nutr Rev* 2008; 66(5):256–71. PMID: 18454812. doi: 10.1111/j.1753-4887.2008.00030.x.
- Scott E, Wright R, Hanan B. Anemia in Alaskan Eskimos. *J Nutr* 1955;55:137–49. PMID: 13234001.
- Petersen KM, Parkinson AJ, Nobmann ED, Bulkow L, Yip R, Mockdad A. Iron deficiency anemia among Alaska Natives may be due to fecal loss rather than inadequate intake. *J Nutr* 1996;126(11):2774–83. PMID: 8914948.
- Hitchcock DJ. Parasitological study on the Eskimos in the Bethel area of Alaska. *J Parasitol* 1950;36(3):232–34. PMID: 15422459. doi: 10.2307/3273150.
- Gessner B. Geographic and racial patterns of anemia prevalence among low-income Alaskan children and pregnant or postpartum women limit potential etiologies. *J Pediatr Gastroenterol Nutr* 2009;48(4):475–81. PMID: 19322058. doi: 10.1097/MPG.0b013e31818888fac.
- Milman N, Nyg K, Mulvad G, Pedersen H, Bjerregard P. Haemoglobin concentrations appear to be lower in indigenous Greenlanders than in Danes: Assessment of haemoglobin in 234 Greenlanders and in 2804 Danes. *Eur J Haematol* 2001;67(1):23–29. PMID: 11553263. doi: 10.1034/j.1600-0609.2001.067001023.x.
- Valberg L, Birkett N, Haist J, Zamecnik J, Pelletier O. Evaluation of the body iron status of native Canadians. *Can Med Assoc J* 1979;120:285–89. PMID: 427665.
- Kuhnlein HV, Receveur O, Soueida R, Egeland GM. Arctic Indigenous Peoples experience the nutrition transition with changing dietary patterns and obesity. *J Nutr* 2004;134:1447–53. PMID: 15173410.
- Egeland G, Pacey A, Cao Z, Sobol I. Food insecurity among Inuit preschoolers: Nunavut Inuit Child Health Survey, 2007–2008. *Can Med Assoc J* 2010; 182(3):243–48. PMID: 20100848. doi: 10.1503/cmaj.091297.
- Saudny H, Leggee D, Egeland G. Design and methods of the adult Inuit health survey 2007–2008. *Int J Circumpolar Health* 2012;71:19752. PMID: 23166895.
- Plante C, Blanchet C, Rochette L, O'Brien H. Prevalence of anemia among Inuit women in Nunavik, Canada. *Int J Circumpolar Health* 2011; 70(2):154–65. PMID: 21524361. doi: 10.3402/ijch.v70i2.17811.
- Kuhnlein H, Receveur O, Soueida R, Berti P. Unique patterns of dietary adequacy in three cultures of Canadian Arctic indigenous peoples. *Public Health Nutr* 2008; 11(4): 349–60. PMID: 17610753. doi: 10.1017/S1368980007000353.
- Egeland G, Berti P, Soueida R, Arbour L, Receveur O, Kuhnlein HV. Age differences in vitamin A intake among Canadian Inuit. *Can J Public Health* 2004; 95(6):465–69. PMID: 15622799. doi: 10.3109/13697137.2010.514366.
- Mason R. Vitamin D: A hormone for all seasons. *Climacteric* 2011;14(2):197–203. PMID: 20964549.
- Bjerregaard P, Johansen P, Mulvad G, Pedersen HS, Hansen J. Lead sources in human diet in Greenland. *Environ Health Perspect* 2004;112(15):1496–98. PMID: 15531433. doi: 10.1016/S0269-7491(98)00083-9.
- Scheuhammer A, Perrault J, Routhier E, Braune B, Campbell G. Elevated lead concentrations in edible portions of game birds harvested with lead shot. *Environ Pollution* 1998;102:251–57. doi: 10.1186/1476-069X-7-25.
- Fontaine J, Dewailly E, Benedetti J, Pereg D, Ayotte P, Dery S. Re-evaluation of blood mercury, lead and cadmium concentrations in the Inuit population of Nunavik (Québec): A cross-sectional study. *Environ Health* 2008;7:25–38. PMID: 18518986.
- Papanikolaou N, Hatzidaki E, Belivanis S, Tzanakakis G, Tsatsakis A. Lead toxicity update. A brief review. *Med Sci Monit* 2005;11(10):RA329–36. PMID: 16192916.
- Miret S, Saiz MP, Mitjavila MT. Effects of fish oil- and olive oil-rich diets on iron metabolism and oxidative stress in the rat. *Br J Nutr* 2003;89(1): 11–18. PMID: 12568660. doi: 10.1079/BJN2002737.
- Innis S, Kuhnlein HV. The fatty acid composition of Northern-Canadian marine and terrestrial mammals. *Acta Med Scand* 1987;222(2):105–9. PMID: 2890267.
- Thomson C, Stanaway J, Neuhauser M, Snetselaar L, Stefanick M, Arendell L, Chen Z. Nutrient intake and anemia risk in the women's health initiative observational study. *J Am Diet Assoc* 2011;111(4): 532–41. PMID: 21443985. doi: 10.1016/j.jada.2011.01.017.
- Tussing-Humphreys L, Braunschweig C. Anemia in postmenopausal women: Dietary inadequacy or nondietary factors? *J Am Diet Assoc* 2011; 111(4):528–31. PMID: 21443984. doi: 10.1016/j.jada.2011.01.006.
- Egeland G, Cao Z, Young T. Hypertriglyceridemic-waist phenotype and glucose intolerance among Canadian Inuit: The International Polar Year Inuit Health Survey for Adults 2007–2008. *Can Med Assoc J* 2011;183:E553–58. PMID: 21555386. doi: 10.1503/cmaj.101801.
- Nestel P. *Adjusting Hemoglobin Values in Program Surveys*. Washington, DC: International Nutritional Anemia Consultative Group (INACG), 2002. Available at: http://pdf.usaid.gov/pdf_docs/PNACQ927.pdf (Accessed June 17, 2014).

29. Centers for Disease Control and Prevention. Adult Blood Lead Epidemiology and Surveillance – United States, 1998–2001. In: *Surveillance Summaries*, M.a.M.W. Atlanta, GA: CDC, 2002; p. 1–10. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5111a1.htm> (Accessed June 17, 2014).
30. El Hayek J, Egeland G, Weiler H. Older age and lower adiposity predict better 25-hydroxy vitamin D concentration in Inuit adults: International Polar Year Inuit Health Survey, 2007–2008. *Arch Osteoporosis* 2011;6(1-2):167–77. PMID: 22886103. doi: 10.1007/s11657-011-0062-z.
31. Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press, 2000. Available at: <http://www.nap.edu/topic/287/food-and-nutrition> (Accessed June 17, 2014).
32. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic: Report on a WHO Consultation*, Geneva: WHO, 2000. Available at: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/ (Accessed June 17, 2014).
33. Cook J, Boy E, Flowers C, Daroca M. The quantitative assessment of body iron. *Blood* 2003;101(9): 3359–63. PMID: 12521995. doi: 10.1182/blood-2002-10-3071.
34. Flowers C, Skikne B, Covell A, Cook J. The clinical measurement of serum transferrin receptor. *J Lab Clin Med* 1989;114:368–77. PMID: 2677198.

Received: June 17, 2015

Accepted: November 19, 2015

RÉSUMÉ

OBJECTIF : Déterminer les corrélats de l'hémoglobine (Hb) et de l'anémie non expliquée par une carence en fer (anémie inexpliquée) chez les Inuits adultes du Canada.

MÉTHODE : Une enquête transversale a permis d'évaluer le régime, le profil démographique, l'anthropométrie, l'Hb à jeun, la ferritine, le récepteur soluble de la transferrine (sur un sous-ensemble), la protéine C-réactive ultrasensible (hsCRP) sérique, la composition des acides gras

érythrocytaires, le taux de plomb dans le sang, et les anticorps à *Helicobacter pylori* chez les Inuits adultes à l'exception des femmes enceintes ($n = 2\,550$), âgés de ≥ 18 ans provenant de ménages sélectionnés au hasard dans 36 communautés inuites dans la région désignée des Inuvialuits, au Nunavut et au Nunatsiavut dans le Nordlabrador, au Canada.

RÉSULTATS : Les concentrations en Hb étaient inférieures et la prévalence de l'anémie inexpliquée était supérieure chez les hommes inuits après l'âge de 50 ans. Le taux d'anémie était constant chez les femmes inuites, mais alors qu'avant la ménopause il s'agissait principalement d'anémie ferriprive, après la ménopause, il s'agissait principalement d'anémie inexpliquée. Les faibles niveaux d'instruction et l'hsCRP étaient associés à un risque accru d'anémie inexpliquée. Chez les hommes inuits, les taux élevés d'acide eicosapentanoïque (AEP) érythrocytaire et de plomb dans le sang étaient également associés à un risque accru d'anémie inexpliquée. La fréquence de l'alimentation traditionnelle présentait une association positive avec l'Hb.

CONCLUSION : La répartition par âge et les écarts régionaux de l'anémie indiquent que les différences physiologiques liées à l'ethnicité ne peuvent expliquer la prévalence de l'anémie chez les Inuits. L'AEP érythrocytaire, l'inflammation et les infections élevées, ainsi que les faibles niveaux d'instruction, peuvent contribuer à la prévalence de l'anémie dans cette population, prévalence qui n'est pas liée au bilan en fer. Ainsi, le mode de vie traditionnel peut protéger les Inuits contre l'anémie nutritionnelle, mais contribuer à réduire l'Hb par les expositions environnementales. La signification clinique de l'anémie inexpliquée chez les Inuits adultes plus âgés exige une enquête plus poussée, car sa prévalence représente un problème de santé publique modéré.

MOTS CLÉS : hémoglobine; anémie; santé autochtone; inflammation; nutrition