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Community-driven research in the canadian arctic: dietary exposure to methylmercury and gastric health outcomes

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ABSTRACT

Indigenous Arctic Canadians have a higher prevalence of gastric neoplasms relative to North Americans of European ancestry. We investigated the hypothesis that low-dose methylmercury exposure from eating fish/whale increases the risk of gastric cancer in Arctic communities. We used intermediate endpoints from an established model of gastric carcinogenesis: intestinal metaplasia, atrophy, and severe chronic gastritis. During 2008–2012, we obtained gastric biopsies from participants of community-driven projects in 3 communities. In 2016, we collected hair samples to measure methylmercury levels and interviewed them about diet. In cross-sectional analysis, logistic regression estimated odds ratios for the estimated effect of hair-methylmercury concentration on the prevalence of each pathology outcome stratified by selenium intake. Among 80 participants, prevalence of intestinal metaplasia, atrophy and severe chronic gastritis was 17, 29 and 38%, respectively. Adjusted Odds of severe chronic gastritis and atrophy were highest at hair-methylmercury concentrations ≥1μg/g when estimated selenium intake was 0, and approached 0 for all methylmercury levels as estimated selenium intake increased. Gastric pathology increased with methylmercury exposure when selenium intake was low. Though limited by small numbers, these findings suggest selenium ingested by eating fish/whale may counter harmful effects of methylmercury exposure in Arctic populations.

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Introduction

Community-driven projects conducted by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group have demonstrated higher prevalence of severe gastritis in *Hp*-positive residents of Indigenous communities in Arctic Canada compared to *Hp*-positive members of a southern Canadian urban population[1]. While the causes of this increased prevalence of severe gastritis are not clear, exposure to exogenous chemicals is a major concern in northern communities, due to awareness of the vulnerability of Arctic ecosystems to contaminants. In semi-structured interviews with key-informants from participating communities, most informants expressed concern that environmental contaminants, and mercury (Hg) in particular, adversely affect digestive health. Informants explained that residents of Arctic communities follow a subsistence lifestyle, and this makes them vulnerable to being harmed by contaminants in local water sources, and in the aquatic and land animals they rely on for food.

As a pathological diagnosis, gastritis is characterised by inflammation of the gastric mucosa, triggered by injury to gastric epithelial cells [2,3]. Gastritis may be acute or chronic, depending on the specific causes of injury and the duration of exposure to these factors [2–4]. Gastric mucosal inflammation has a severity spectrum from mild to severe; the determinants of severity, however, are poorly understood. Chronic gastritis increases the risk of serious digestive diseases, including peptic ulcer disease and gastric cancer [5–7]. In a widely accepted model of gastric carcinogenesis, lesions that follow chronic gastritis and indicate increased risk of carcinoma include gastric atrophy (deterioration of gastric glands) [4,8–11] and gastric intestinal metaplasia (a continuum of changes characterised by replacement of atrophied gastric glands with phenotypically intestinal epithelium) [3,4,8–11].

Causes of gastric mucosal cell injury leading to gastritis include biological agents, exogenous and endogenous chemicals, hypoxia and ischaemia, physical factors, and genetic abnormalities [2–4]. The most common known cause of chronic gastritis is *Helicobacter pylori* (*Hp*), bacteria that colonise the stomach and/or duodenum [2–4],

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causing an infection that often persists indefinitely. *Hp* infects people around the globe, though the prevalence varies widely across regions [12–15]. Community-driven projects conducted by the Canadian North *Helicobacter pylori* (CAN*Help*) Working Group have demonstrated high prevalence of severe gastritis in *Hp*-positive residents of Indigenous communities in Arctic Canada relative to *Hp*-positive patients at an urban hospital in southern Canada [1]. The causes of this increased prevalence of severe gastritis are not clear.

Mercury-induced toxicity does not result from action on a single cellular target, and can lead to a wide range of toxic effects on tissues throughout the body [16–23]. The highly reactive nature of MeHg results in a series of complex effects that initiate processes eventually leading to apoptosis [16–23]. Potential mechanisms through which mercury can induce damage to cells, genes and tissues include: interruption of intracellular calcium homoeostasis [16,18,24,25]; oxidative stress [16–21,26,27]; alteration of glutamate homoeostasis [16,17,27]; disruption of membrane potential [18]; alteration of protein synthesis [18,20]; disruption of excitatory pathways of the central nervous system [21,24–28]; and inhibition of protein synthesis [18,21]. Oxidative stress is considered one of the most common pathways through which mercury-induced cytotoxicity occurs [16–21,26,27]. Mercury-induced oxidative stress is characterised by modifications to DNA bases [20], mitochondrial damage [17,18,25] and lipid peroxidation [16–18,21,27,28]. The production of hydroxyl radicals exacerbates an imbalance in the ratio of reactive oxygen species (ROS) to antioxidants by depleting glutathione and selenium stores and inhibiting glutathione synthetase [20].

Review of the available scientific literature suggests regular exposure to methylmercury may lead to chronic gastritis and subsequent serious digestive disease through oxidative stress [2,29–31]. Proposed pathways through which ROS contribute to gastric mucosal injury include membrane damage through lipid peroxidation, protein dysfunction resulting from protein oxidation and disruption of DNA repair resulting from the oxidisation of nucleic acids [29,30]. Interruption of repair mechanisms may result in apoptosis or mutagenic changes [29,30]. Therefore, while direct assessment of the potential for mercury to induce gastric mucosal injury has not been a focus of scientific studies on mercury toxicity, review of toxicokinetic and toxicodynamic properties of methylmercury and mechanisms through which gastric cells become injured make it reasonable to hypothesise that mercury could play a role in the pathogenesis of gastritis among individuals who consume large quantities of fish containing mercury concentrated in tissues.

The literature on Hg contamination in the Arctic, Hg toxicity and mechanisms of gastric mucosal injury substantiate the concerns of Arctic community members [2,29,30,32–35]. However, little epidemiologic investigation of the effect of chronic Hg exposure on gastric disease has been reported. Here, we investigate the hypothesis that chronic ingestion of low doses of Hg through consumption of aquatic species influences the severity of chronic gastritis and the occurrence of pre-cancerous gastric lesions among residents of Canadian Arctic communities.

Methods

Study Design. This research constituted an environmental health component of community-driven projects led by the CAN*Help* Working Group at the request of community leaders in western Canadian Arctic communities [36,37]. We used a cross-sectional observational study to test the hypothesis that MeHg increases the severity of pre-cancerous gastric lesions and thereby causes them to progress towards gastric cancer, according to a widely accepted model of gastric carcinogenesis [8]. While causal effects cannot be demonstrated by any individual epidemiologic study, any epidemiologic study can constitute a test of a causal hypothesis, with the rigour of the test depending on study strengths and limitations. While cross-sectional studies do not observe changes in disease status over time, associations with disease progression can be inferred from associations with chronic disease outcomes known to be more or less advanced along a hypothesised causal pathway. Cross-sectional studies can be limited by an inability to determine whether the exposure was caused by the outcome rather than causing it; in this study, however, it does not seem likely that gastric histopathology status influenced exposure to MeHg. For these reasons, this design constitutes an informative test of our study hypothesis.

Here, we report a cross-sectional analysis of data collected at baseline in 3 CAN*Help* Working Group projects. Project initiation occurred in Aklavik, NT in 2007 (2006 census population = 590; 92% identifying as Inuvialuit or Gwich'in) [38,39], in Old Crow, YT in 2010 (2011 census population = 245; ~85% identifying as Gwich'in) [40,41], and in Fort McPherson, NT in 2012 (2011 census population = 844; ~90% identifying as Gwich'in) [42]. Each community project was guided by a local planning committee comprising community residents. This research received ethics approval from the University of Alberta Health Research Ethics Board. Fieldwork for this research was conducted in the Northwest Territories and Yukon, requiring two

territorial research licences from the Aurora Institute and a Yukon Tourism and Culture "Scientist and Explorers License". In accordance with ethical and legal standards, we outlined the research process to each participant through an information sheet that was approved by the research ethics board. Once the participant reviewed the sheet, had the opportunity to ask questions and indicated they understood the information they had been given, they completed a consent form. For individuals under the age of 18, parental consent was obtained.

Outcome Ascertainment. We offered participants aged ≥15 years (and younger participants at parents' request) upper gastrointestinal endoscopy with gastric biopsy, regardless of *Hp* status or history of dyspeptic symptoms, in Aklavik in February 2008, Old Crow in January 2012 and Fort McPherson in March 2013. A gastroenterology team from the University of Alberta performed trans-nasal (Aklavik) and trans-oral (Old Crow and Fort McPherson) gastroscopies on participants in community health centres, taking 7 biopsies from each participant (5 for histopathology and 2 for microbiology), with pre-determined biopsy sites based on the Updated Sydney Protocol [43,44]. Visible lesions were also biopsied. A single pathologist specialising in gastric pathology graded the severity of acute gastritis, chronic gastritis, atrophy and intestinal metaplasia in each biopsy using the updated Sydney System, with scores corresponding to ordinal categories of none, mild, moderate and severe [44]. Since acute gastritis has a shorter average duration, it was not included in the present analysis [44]. We used the highest level of severity among each participant's biopsies to classify pathological outcome severity (Table 1). The low prevalence of chronic gastritis graded as absent or mild required the creation of a dichotomous chronic gastritis outcome variable comparing severe to none/mild/moderate. Similarly, the low prevalence of gastric atrophy and intestinal metaplasia graded as mild, moderate or severe led to dichotomous variables comparing presence to absence for each of these pathology outcomes (Table 1).

Exposure Ascertainment. Measurement of Hg exposure was not within the initial design of the community projects and, therefore, we did not collect Hg exposure data at the time of endoscopy. We ascertained Hg exposure in 2 ways: from average mercury concentrations in consumed seafood, which we use as a shorthand for whale and fish (whether ocean or freshwater), and individual mercury concentration in hair samples. We collected seafood consumption data and hair samples in September–November 2016 as a proxy for exposure during the aetiologically relevant timeperiod. Much evidence shows that Hg concentrations are higher in people who fish regularly [16–22,45]. For this reason, ascertainment of human exposure to Hg often involves characterising fish consumption patterns [16–22,45]. We developed a food-frequency questionnaire (FFQ) focused on long-term average seafood intake to obtain more detailed data than we collected using a more general FFQ at baseline. The seafood FFQ measured consumption frequencies as average number of meals of each species per week. We did not collect data on portion size, because validation studies have shown that portion size does not substantially improve diet characterisation due to poor recall [46]. We asked participants to specify the time of year in which they typically harvested each species, to account for seasonal variation. Previously, we assessed the validity of the data on fish/whale consumption collected by the developed questionnaire by comparing reported frequencies to biochemical measurements of methylmercury (MeHg), and observed a reasonable level of agreement. [47]

We collected hair samples for laboratory measurement of Hg concentration, using procedures for collection and transportation of these samples outlined by the U.S Centers for Disease Control for use in the National Health and Nutrition Examination Survey [48]. The form of Hg we selected for analysis was MeHg, which bioaccumulates in the tissues of aquatic species [17,18,32,33,49]. Hair samples were analysed by the University of Alberta Biogeochemical Analytical Service Laboratory using gas chromatography inductively

Table 1. Severity distribution of gastric pathology outcomes among participants included in this analysis (n = 80) and among all participants with gastric biopsies evaluated from all 3 community projects (n = 289).

	Participants Included in this Analysis n (%)			All Participants with Biopsies Evaluated n (%)		
Severity	Severe Chronic Gastritis	Gastric Atrophy	Intestinal Metaplasia	Severe Chronic Gastritis	Gastric Atrophy	Intestinal Metaplasia
None	8 (10)	57 (71)	66 (83)	73 (25)	204 (71)	251 (87)
Mild	7 (9)	18 (23)	10 (12)	26 (9)	60 (21)	26 (9)
Moderate	35 (44)	4 (5)	4 (5)	92 (32)	22 (8)	9 (3)
Severe	30 (38)	1 (1)	0 (0)	98 (34)	3 (1)	3 (1)

coupled plasma-mass spectrometry [50,51]. Repeated measurements taken for selected samples had a -median percent change in concentration values of 14.67% (IQR:10.75%) [36]. We inspected the mean percent change between measurements across outcome categories and used a t-test to assess whether exposure misclassification was non-differential.

We did not have hair samples from all participants with outcome data. To estimate MeHg exposure in participants without hair samples, we constructed a predictive multivariable random-effects linear regression model using data from 101 participants who provided detailed fish consumption data and hair samples for biochemical measurement of MeHg concentration. To assess the predictive power of the model, which included sex, hair length, use of permanent hair treatments, and total fish consumption in summer as predictors, we conducted a 10-fold cross-validation analysis (data not shown) [36].

Estimated Intake of Selenium and Mercury. Selenium (Se) is an antioxidant essential nutrient. Se intake modifies Hg toxicity by bonding competitively with Hg compounds and rendering them inert [16,17,-17,52–56]. Much research has described the complex relationship between Se and MeHg to accurately estimate risks from regularly consuming fish/seafood [16,17,52–56]. This evidence suggests that Se may be a confounder, effect-measure modifier and mediator of the toxic effects of MeHg on various endpoints [16,17,-17,52–56]. Because resource constraints prevented biochemical measurement of Se in participants, we approximated Se intake using FFQ data and Se concentration estimates from published Canadian Arctic research [57–61]for the fish/whale species consumed by participants. We calculated weighted mean concentrations (µg/g) of estimates for the same species measured in multiple studies (Table 2) [57–61]. According to the Canadian Food Guide, one serving of cooked fish is approximately 75 g [62]. We multiplied species-specific Se concentrations (µg/g) by 75 g to estimate the per-meal Se intake and by the reported number of servings/week of each species in each season. We combined total Se intake from all species in each season to estimate an overall average µg/week intake of Se.

Lacking anthropometric data, we standardised Se dose for weight using average sex – and age-specific body weights reported for Canadian Arctic populations [63]. We divided estimated weekly Se µg/week by estimated body weight (bw), yielding an estimated dose in units of µg/kg bw/week. In case the estimated average 75 g meal size was not accurate, we also estimated Se intake for average meal sizes of 100 g and 150 g (Table 3).

To control for the influence of Se on MeHg toxicity, experts recommend using the molar ratio of Se:MeHg rather than absolute Se intake, because the formation of MeHg-Se complexes in fish/whale tissues eliminate the bioavailability of the sequestered MeHg [52–55]. We estimated the molar ratio of Se:MeHg intake in nmol/kg bw/week by converting estimated mean concentrations (µg/g) of Hg and Se obtained from the literature to nmol/g (Table 2), and applying the formula proposed by Ganther (1972) [55]: estimated ratios >1 indicate reduced MeHg toxicity and increased health benefits from excess Se [55]. We also generated the Se Health Benefit Value (HBV) based on nmol/kg bw/week intake of Se and MeHg, using the formula proposed by Kaneko and Ralston (2007) [54]: HBV = [Se*(Se/MeHg)]–[MeHg*(MeHg/Se)]: estimates >0 indicate increased health benefits [54].

Assessment of Consistency in Diet Over Time. To assess consistency in dietary intake between data collection periods, we collected repeat frequencies of food items ascertained at baseline of relevance to gastric health outcomes and/or MeHg metabolism: fruit; vegetables; milk; yoghurt; carbonated drinks; coffee; and tea [16,17,64,65]. We also ascertained the frequency of dietary supplements.

We estimated correlations between weekly consumption frequencies derived from baseline FFQs and those derived from FFQs administered when we ascertained MeHg exposure in 2016[46]. We used weekly food frequencies averaged across four seasons for each FFQ item, scaled as continuous variables. We estimated Pearson's correlation coefficients for the total study population, and by community, gastritis severity category, atrophy status, and intestinal metaplasia status. Reproducibility studies of dietary intake yield correlation coefficients for repeated measurements of nutrient intake for periods spanning 1 to 10 years with a typical range of 0.5–0.7, while coefficients for repeated measurements of whole food items over long time periods typically range from 0.34 to 0.7[46]. These correlations are comparable to those observed for other biological indicators shown to predict health outcomes in observational studies with reasonable accuracy [46].

Statistical Analysis. Given that our study hypothesis concerns disease aetiology, our statistical approach centres on effect estimation [66,67]. The statistical analyses estimated the association between measured or predicted hair-MeHg concentration and the prevalence of each pathological outcome. We fit a separate model for each outcome, to estimate prevalence odds ratios (OR) and 95% confidence intervals (CI) for the estimated effect of hair-MeHg concentration on the prevalence of the outcome. We also used generalised ordinal logistic regression to estimate

Table 2. *Estimated concentrations of selenium and total mercury in the fish/whale species consumed by participants in studies reported in the literature* [57–61].

Author (Date)	n	Selenium		Mercury		Molar Ratios	
		Mean µg/g	Mean [a] nmol/g	Mean µg/g	Mean[b] nmol/g	Sample Specific	Weighted Average
Burbot (*L. lota*)							
Evans *et al*. (2005)	14	0.19	2.41	0.13	0.65	3.71	
	14	0.75	9.50	0.06	0.30	31.76	
Reyes *et al*. (2016)	6	0.14	1.79	0.32	1.58	1.13	14.80
Arctic Char (*S. aplinus*)							
Evans *et al*. (2005)	5	0.17	2.15	1.30	6.48	0.33	
	5	0.66	8.36	0.21	1.05	7.98	
	4	0.73	9.25	0.55	2.74	3.37	
	14	0.37	4.69	0.20	1.00	4.70	
	18	0.68	8.61	0.16	0.80	10.80	
	10	0.71	8.99	0.14	0.70	12.88	
	8	0.67	8.49	0.29	1.45	5.87	7.67
Beluga Whale (*D. Leucas*)							
Lemire *et al*. (2015)	16	4.35	55.09	0.46	2.29	24.02	
	16	3.52	44.58	0.38	1.89	23.53	
	17	0.73	9.25	1.07	5.33	1.73	
	9	1.26	15.96	4.01	19.99	0.80	
	15	6.25	79.15	10.14	50.55	1.57	11.25
Inconnu (*S. nelma*)							
Evans *et al*. (2005)	3	0.31	3.93	0.19	0.95	4.14	
	3	0.88	11.14	0.17	0.85	13.15	8.65
Arctic Cisco (*C. autumnalis*)							
Evans *et al*. (2005)	10	0.29	3.67	0.03	0.15	24.56	
Reyes *et al*. (2016)	10	0.17	2.20	0.057	0.28	7.75	16.16
Lake Whitefish (*C. clupeaformis*)							
Reyes *et al*. (2016)	15	0.17	2.19	0.07	0.36	6.02	6.02
Broad Whitefish (*C. nasus*)							
Evans *et al*. (2005)	ND [c]	0.17	2.15	0.05	0.25	8.64	
		0.79	10.01	0.08	0.40	25.09	
		0.08	1.01	0.04	0.20	5.08	
		0.16	2.03	0.25	1.25	1.63	
		0.1	1.27	0.08	0.40	3.18	
		0.11	1.39	0.1	0.50	2.79	
		0.37	4.69	0.17	0.85	5.53	
		0.22	2.79	0.13	0.65	4.30	
		0.23	2.91	0.08	0.40	7.30	
		0.38	4.81	0.09	0.45	10.73	
		0.16	2.03	0.16	0.80	2.54	
		0.35	4.43	0.35	1.74	2.54	
		0.11	1.39	0.15	0.75	1.86	
		0.15	1.90	0.15	0.75	2.54	
		0.25	3.17	0.07	0.35	9.07	
		0.06	0.76	0.08	0.40	1.91	
		0.07	0.89	0.11	0.55	1.62	5.67
Sockeye Salmon (*O. nerka*)							
Kelly *et al*. (2008)	11	0.14	1.77	0.05	0.26	6.84	
Burger *et al*. (2012)	15	0.25	3.17	0.04	0.20	15.88	12.05
Chinook Salmon (*O. tshawytscha*)							
Kelly *et al*. (2008)	10	0.17	2.15	0.09	0.44	4.85	
	11	0.16	2.03	0.07	0.36	5.65	5.27
Chum Salmon (*O. keta*)							
Kelly *et al*. (2008)	12	0.27	3.42	0.02	0.10	34.30	34.30
Pink Salmon (*O. gorbuscha*)							
Kelly *et al*. (2008)	10	0.17	2.15	0.013	0.06	33.22	33.22
Coho Salmon (*O. kisutch*)							
Kelly *et al*. (2008)	10	0.16	2.03	0.04	0.20	10.16	
	12	0.13	1.65	0.05	0.26	6.23	
	13	0.17	2.15	0.06	0.28	7.71	7.90
Dolly Varden (*S. malma*)							
Burger *et al*. (2012)	75	0.35	4.43	0.11	0.55	8.08	8.08

[a]Converted using a molecular weight of 78.96; [b] Converted using a molecular weight of 200.59; [c] ND = No data – The combined mean values are not weighted

Table 3. *Estimated concentrations of selenium and total mercury in fish/whale by serving size* [57–61].

		Serving Size		
Fish/Whale Species [a]	µg/g	µg/75 g Serving	µg/100 g Serving	µg/150 g Serving
Estimated Amount of Selenium				
Coho Salmon (*O. kisutch*)	0.153	11.5	15.3	23.0
Chinook Salmon (*O. tshawytscha*)	0.165	12.4	16.5	24.7
Pink Salmon (*O. gorbuscha*)	0.170	12.8	17.0	25.5
Lake Whitefish (*C. clupeaformis*)	0.173	13.0	17.3	26.0
Sockeye Salmon (*O. nerka*)	0.203	15.3	20.4	30.5
Broad Whitefish (*C. nasus*)	0.221	16.6	22.1	33.2
Burbot (*L. lota*)	0.223	16.7	22.3	33.5
Arctic Cisco (*C. autumnalis*)	0.232	17.4	23.2	34.8
Chum Salmon (*O. keta*)	0.270	20.3	27.0	40.5
Dolly Varden (*S. malma*)	0.350	26.3	35.0	52.5
Arctic Char (*S. aplinus*)	0.577	43.3	57.7	86.6
Inconnu (*S. nelma*)	0.595	44.6	59.5	89.3
Beluga Whale (*D. Leucas*)	0.994	74.5	99.4	149.1
Estimated Amount of Total Mercury				
Pink Salmon (*O. gorbuscha*)	0.013	1.0	1.3	2.0
Chum Salmon (*O. keta*)	0.020	1.5	2.0	3.0
Sockeye Salmon (*O. nerka*)	0.045	3.4	4.5	6.8
Coho Salmon (*O. kisutch*)	0.050	3.8	5.0	7.6
Arctic Cisco (*C. autumnalis*)	0.050	3.8	5.0	7.6
Lake Whitefish (*C. clupeaformis*)	0.073	5.5	7.3	11.0
Chinook Salmon (*O. tshawytscha*)	0.080	6.0	8.0	12.0
Dolly Varden (*S. malma*)	0.110	8.3	11.0	16.5
Broad Whitefish (*C. nasus*)	0.126	9.4	12.6	18.9
Inconnu (*S. nelma*)	0.180	13.5	18.0	27
Burbot (*L. lota*)	0.277	20.8	27.7	41.5
Arctic Char (*S. aplinus*)	0.299	22.4	29.9	44.9
Beluga Whale (*D. Leucas*)	1.649	123.8	165.0	247.5

[a] Species ordered according to the concentration of each compound (lowest to highest)

ORs and 95% CIs for the estimated effect of hair-MeHg concentration on gastric lesions with increasing severity, with progression inferred from the severity of prevalent lesions according to current knowledge of gastric carcinogenesis. For this analysis, the outcome status of each participant was the most advanced pathology graded in their biopsies. We tested the parallel regression assumption using the Brant test [68].

We used purposeful selection, as proposed by Hosmer and Lemeshow (2000), to select adjustment variables for estimating prevalence odds ratios in multivariable models [69]. Variables considered were: age, sex, ethnicity, education level, *H.pylori* infection status, alcohol consumption, cigarette smoking, and fruit and vegetable intake. According to Willet, strengths and weaknesses of estimating effects of consuming compounds contained in food and of whole foods warrant combining these exposure classifications in modelling exposure effects [46]. Therefore, we included fish/whale consumption frequency in each model along with hair-MeHg concentrations, which may also mitigate confounding by other nutrients or chemicals in fish [46]. We used the likelihood-ratio (LR) test to assess interactions between hair-MeHg concentration and selected variables. We further analysed interactions using a post-estimation analysis to generate the adjusted predicted marginal effect of hair-MeHg level on gastric pathology outcomes across levels of an effect-measure modifier; this post-estimation analysis generated the log odds adjusted for variables included in the multivariable model; we transformed these adjusted log odds to odds for interpretability.

Because data on residents of the same community may violate the assumption of independent disease odds, we used the LR test to compare the fit of models with and without a random effect determine whether the magnitude of unexplained clustering in communities was large enough to require including a random effect in the model. We also assessed whether modelling community as a fixed effect achieved a better model fit [69]. If inclusion of community as a fixed or random effect did not improve model fit and did not alter effect estimates of selected covariates, we excluded them from the model and estimated robust standard errors (SE) to improve the accuracy of SEs when outcomes clustered [69].

Results

Of the 101 participants who provided hair samples for measurement of MeHg concentration, 64 had gastric pathology outcomes; 16 additional participants who had pathology data provided 2016 data on diet and hair characteristics but did not provide a hair sample for

measurement of MeHg concentration. In total, 80 participants had measured or predicted MeHg concentration and gastric pathology data.

Participant Characteristics. Table 4 shows the distributions of participant characteristics. Mean age was 53.2 years (SD:14.7; Range:20–85 years) in 2016 and 45.9 years (SD:15.9; Range:11–82 years) at baseline. Females were over-represented (64%; 51/80). Participants were predominately residents of Aklavik, NT (64%; 51/80). The prevalence of *Hp* infection by urea breath test was 93% (74/80). The prevalence of histopathology outcomes was 38% (30/80) for severe gastritis; 29% (23/80) for gastric atrophy; and 18% (14/80) for intestinal metaplasia, with severity distributions shown in Table 1.

MeHg Concentration. Mean MeHg concentration was 0.565 µg/g (SD:0.440; Range:0.063–2.07 µg/g) in hair samples from 64 participants with pathology data and hair samples and 0.695 µg/g (SD:0.226; Range:0.371–1.08 µg/g) based on predicted values for 16 participants with data on diet and hair attributes. The combined mean MeHg concentration was 0.591 µg/g (SD:0.409; Range:0.063–2.07 µg/g). Table 5 shows mean percent change in MeHg concentration µg/g for duplicate measurements by outcome status. T-tests comparing mean values across outcome categories indicated that variability of duplicate measurements was random with respect to outcome status.

Estimated Intake of Selenium and Mercury. Assuming a serving size of 75 g, the estimated mean intake of Se was 0.73 ± 1.01 µg/kg bw/week, and the mean intake of Hg was 0.51 ± 0.83 µg/kg bw/week. Among 55 participants who reported regularly consuming fish, the mean molar Se:MeHg ratio was 7.21 (SD:7.44; range:1.53–41.86) [55]. Participants who did not report consuming fish regularly were assigned a molar ratio value of 1. All participants who regularly consumed fish had ratios greater than 1 (excess Se intake relative to Hg intake). The HBV was consistent with the molar ratio, with a mean of 210.68 (SD: 426.17).

Consistency in Diet Over Time. Of the 80 participants in this analysis, 75 had complete data on gastric pathology outcomes, baseline diet, and 2016 diet (49 from Aklavik; 14 from Old Crow; and 12 from Fort McPherson). Table 6 shows correlation coefficients comparing baseline and 2016 diet. These correlations were predominantly within the expected range, based on reproducibility studies of whole food frequencies [46]. The lowest correlation coefficients in the total study population were for milk and yoghurt. Estimated correlations between repeated measurements of fruit and milk intake were particularly low among Fort McPherson, though the small number of participants in this group should be noted [46]. Community-specific estimates do not reveal a clear pattern relating magnitude of correlation

Table 4. Socio-demographic characteristics of the subset of participants included in this analysis, all participants who underwent upper endoscopy with gastric biopsy and all participants of the Aklavik, Old Crow, and Fort McPherson community projects (2008–2016).

	Total Sample Included in this Analysis (n = 80)		All Participants who Underwent Endoscopy (n = 289) [a]		All Participants of Community Projects (n = 675)[b]	
Socio-Demographic Characteristics	n	%	n	%	n	%
Community	51	64	191	66	329	49
Aklavik, NT	13	16	52	18	211	31
Fort McPherson, NT	16	20	46	16	135	20
Old Crow, YT						
Age	7	9	73	25	234	35
Less than 30 years	7	9	41	14	88	13
30–39 years	15	19	58	20	113	17
40–49 years	24	30	62	21	117	17
50–59 years	16	20	34	12	73	11
60–69 years	11	14	21	7	50	4
70 + years						
Sex	29	36	130	45	305	45
Male	51	64	159	55	370	55
Female						
Ethnicity	3	4	22	8	64	9
Non-Indigenous	33	41	116	40	194	29
Inuvialuit	38	48	136	47	379	56
Gwich'in	6	8	15	5	38	6
Other Indigenous						
Education Level Completed	43	54	179	62	429	64
Less than High School	37	46	110	38	246	36
High School [c]						

[a] Participants who underwent endoscopy and had complete data on socio-demographic characteristics
[b] All participants of the Aklavik, Fort McPherson and Old Crow *H. pylori* Projects with complete data on socio-demographic characteristics
[c]Completion of high school corresponds to completion of grade 12

Table 5. Mean percent change in methylmercury concentration (ug/g) values across repeated measurements by outcome status among 23 participants with methylmercury measurements on divided * hair samples and data on gastric health outcomes, 2016.

	% Change in Repeated Measurements of MeHg			
Outcome Status	n	Mean	SD	p-value
Chronic Gastritis				
None/Mild/Moderate	15	16.54	11.25	0.88
Severe	8	17.27	9.35	
Gastric Atrophy				
Absent	18	17.08	11.53	0.81
Present	5	15.77	5.43	
Intestinal Metaplasia				
Absent	17	16.48	11.14	
Present	6	17.68	8.88	0.82

10 participants had samples divided in two by investigators and submitted to lab as unique individuals; 22 participants had samples divided in two by lab personnel, including 4 samples that were duplicates; 4 participants had 3 measurements and their percent change was based on the highest and lowest of the 3 values

Table 6. Pearson's correlation coefficients and p-values comparing measurements obtained during the original data collection period and repeated in fall 2016 among 75 participants with complete data.

	All Participants (n = 75)	
Food Item	Correlation Coefficient	p-value
Fruit	0.53	<0.00
Vegetables	0.49	<0.00
Milk	0.20	0.08
Yoghurt	0.25	0.03
Pop	0.39	<0.00
Coffee	0.70	<0.00
Tea	0.82	<0.00
Total Fish	0.32	0.01

coefficients to time between data collection points. Table 7 shows correlation coefficients stratified by gastric pathology outcome status. The largest absolute differences in correlation coefficients were between participants with and without intestinal metaplasia. Assessment of correlations between repeated measurements of diet does not yield conclusive inferences about the dependence of diet measurement error on community or outcome status, given the small number of participants in each stratum [46].

Hair-MeHg Concentration & Gastric Pathology Outcomes. Table 8 shows the distribution of each gastric pathology outcome across participant characteristics. The addition of either a random or fixed effect to account for clustering in communities did not improve the fit of any regression model or alter effect estimates for other covariates; accordingly, community was not included as an adjustment variable in any model and robust SEs were estimated for each. Hair-MeHg concentrations were categorised so there was less than a 2-fold increase in concentration within each category: <0.25 (low); 0.25–0.49 (medium low); 0.50–-0.99 (medium high); ≥1 (high). Variable selection criteria selected sex, total fish/whale consumption and selenium intake for all 3 outcome models, with age added to models for gastric atrophy and intestinal metaplasia. Table 9 shows unadjusted and adjusted ORs and 95% CIs for severe chronic gastritis and gastric atrophy, contrasting each of the 3 higher MeHg levels with the low level. In multivariable models, participants with high or medium high MeHg levels had reduced odds of severe chronic gastritis and gastric atrophy relative to participants with low MeHg levels (Table 9). Data were insufficient for accurate estimation of the effect of hair-MeHg on intestinal metaplasia in a multivariable model (Table 9).

Model building procedures did not yield evidence of a statistical interaction between Se intake and hair-MeHg concentration, possibly due to insufficient statistical power to detect this relationship [66]. Despite insufficient data for precise estimation of effect-measure modification, a product term for estimated Se intake and MeHg concentration was added to each multivariable model. Results of the post-estimation analysis aimed at further describing this interaction appear in Table 10 with odds of severe chronic gastritis and gastric atrophy, for each MeHg level at specified values of Se intake, adjusted for variables included in the multivariable model presented in Table 9. This analysis yielded evidence of variation in the effect of hair-MeHg level on gastric pathology outcomes by Se intake.

As depicted graphically in Figure 1, this analysis indicates that when Se intake is 0, the highest MeHg concentrations are associated with higher odds of severe chronic gastritis and gastric atrophy relative to the lowest MeHg concentrations, and the odds decline as Se intake increases.

Table 11 shows adjusted ORs and 95%CIs for the estimated effect of each covariate on each increasingly advanced gastric pathologies. Of 80 participants with complete data, 7 had no diagnosis of chronic gastritis, atrophy or intestinal metaplasia. Among 73 participants diagnosed with gastric pathology, the most advanced lesion was chronic gastritis (mild, moderate or severe) in 60% (44/73), gastric atrophy in 21% (15/73), and intestinal metaplasia in 19% (14/73). The parallel regression assumption was not violated for any selected covariate (overall p-value = 0.43). The ordinal logistic regression model results were consistent with those from logistic regression models fit for each outcome separately.

Table 7. Pearson's correlation coefficients comparing measurements obtained during the original data collection period and repeated in fall 2016 stratified by outcome status, among 75 participants with complete data.

	Chronic Gastritis Severity				Gastric Atrophy				Intestinal Metaplasia			
	Severe (n = 28)		Not Severe (n = 47)		Present (n = 20)		Absent (n = 55)		Present (n = 12)		Absent (n = 63)	
Food Item	Correlation Coefficient	p-value	Correlation Coefficient	p-value	Correlation Coefficient	p-value	Correlation Coefficient	p-value	Correlation Coefficient	p-value	Correlation Coefficient	p-value
Fruit	0.44	0.02	0.57	<0.00	0.49	0.03	0.54	<0.00	0.91	<0.00	0.36	<0.00
Vegetables	0.48	0.01	0.52	<0.00	0.65	<0.00	0.40	<0.00	0.87	<0.00	0.41	<0.00
Milk	0.21	0.28	0.20	0.18	0.44	0.06	0.12	0.39	−0.07	0.82	0.28	0.03
Yoghurt	0.07	0.73	0.32	0.03	0.62	<0.00	0.15	0.27	0.67	0.02	0.17	0.17
Pop	0.22	0.25	0.41	0.01	0.15	0.54	0.42	<0.00	0.79	<0.00	0.32	0.01
Coffee	0.74	<0.00	0.70	<0.00	0.68	<0.00	0.70	<0.00	0.91	<0.00	0.57	<0.00
Tea	0.87	<0.00	0.78	<0.00	0.89	<0.00	0.76	<0.00	0.33	0.30	0.84	<0.00
Total Fish	0.43	0.02	0.25	0.09	0.48	0.03	0.26	0.05	0.37	0.24	0.32	0.01

Table 8. Prevalence of each of the gastric pathology outcomes stratified by participant characteristics included in the multivariable logistic regression models among 80 participants from 3 western Canadian arctic communities, 2016.

		Prevalence of Gastric Pathology Outcomes		
Participant Characteristics	n	Severe Chronic Gastritis (n = 30)	Gastric Atrophy (n = 23)	Intestinal Metaplasia (n = 14)
Sex	29	57	57	50
Male	51	43	43	50
Female				
Age	7	14	14	14
Less than 30 years	7	57	29	0
30–39 years	15	40	13	13
40–49 years	24	38	21	13
50–59 years	16	44	50	19
60–69 years	11	27	45	45
70 + years				
Total Fish Consumption in the	29	45	21	17
Summer	13	31	38	15
<1 meals/week	14	43	36	0
1–2 meals/week	24	29	29	29
3–4 meals/week				
≥ 5 meals/week				
MeHg in Hair	27	30	22	14
<0.25 µg/g	31	37	35	29
0.25–0.49 µg/g	39	23	22	36
0.5–0.99 µg/g	20	10	22	21
≥1 µg/g				
Selenium Intake from Fish	44	48	32	16
<0.5 µg/kg bw [a]/week	15	40	27	13
0.5–0.99 µg/kg bw/week	20	15	20	20
1–2 µg/kg bw/week	0	0	0	0
3–4 µg/kg bw/week	1	0	100	100
≥ 5 µg/kg bw/week				

[a] bw = body weight

Discussion

This investigation of the effect of MeHg, as a dietary contaminant in Arctic communities, on the prevalence of three gastric pathology outcomes provides evidence of interaction between MeHg and Se ingested by eating aquatic species. The adjusted odds of severe chronic gastritis and gastric atrophy were highest among participants with hair-MeHg ≥1 µg/g, relative to those with lower MeHg concentrations when estimated Se intake from fish was 0. As Se intake increased, odds of both gastric pathology outcomes decreased for participants in most categories of hair-MeHg concentration (µg/g). All participants who regularly ate fish/whale had estimated Se:Hg ratios >1 (and estimated HBVs for all fish-eating members of the study population were >0). These findings suggest that most Hg ingested by eating fish/whale was sequestered by Se and rendered toxicologically inert [52,53]. Assuming the values used to estimate these ratios accurately represent the true exposure pattern among participants, residual toxic effects could be related to insufficient Se resulting from MeHg exposure [52,53]. Since MeHg bonds competitively with Se molecules, the supply of Se would be depleted by MeHg, leaving those exposed susceptible to the toxic effects of other compounds that would otherwise be sequestered by Se [52,53].

Adjusted ORs for the estimated effects of each higher category of MeHg concentration, compared to the lowest category, on prevalence of each gastric pathology outcome, indicated reduced pathology as MeHg concentration increased. The estimated protective effect is inconsistent with the literature on toxicological consequences of MeHg exposure [53,70,71]. However, decreasing toxicological effects with increasing MeHg exposure have been observed in epidemiological studies investigating effects of MeHg on other health outcomes [53,70,71]. A proposed explanation for these contradictory findings is suboptimal statistical modelling of the complex relationship between Se and Hg [52]. Se is an essential nutrient that confers health benefits up to a critical dose, after which it induces toxic effects [46,52–55]. When Se intake exceeds toxic thresholds, MeHg may confer protection by sequestering excess Se and eliminating its toxic effects [52,53]. Health Canada has defined this

Table 9. Odds ratios for the effects of participant characteristics on prevalence of gastric pathology outcomes among 80 participants from 3 western Canadian arctic communities, 2016.

	Unadjusted		Adjusted [a]	
	OR	95%CI	OR	95%CI
Severe Chronic Gastritis				
Sex	*Reference*	0.51, 1.11	*Reference*	0.14, 0.96
Male	0.75		0.36	
Female				
Total Fish/Whale Consumption	0.83	0.64, 1.08	1.03	0.60, 1.76
Per unit increase (meals/week)				
Molar Ratio Se:Hg	0.98	0.97, 1.00	0.98	0.95, 1.02
Per 1.0 increase				
MeHg in Hair *(µg/g)*	*Reference*	0.69, 1.51	*Reference*	0.80, 1.65
<0.25 (Low)	1.02	0.40, 0.42	1.15	0.27, 0.44
0.25–0.49 (Medium low)	0.41	0.06, 2.49	0.35	0.02, 2.50
0.50–0.99 (Medium high)	0.37		0.22	
≥1 (High)				
Gastric Atrophy				
Sex	*Reference*	0.50, 0.56	*Reference*	0.31, 0.66
Male	0.53		0.45	
Female				
Age	1.02	1.01, 1.03	1.03	1.01, 1.04
Per one-year increase				
Total Fish/Whale Consumption	1.12	0.65, 1.92	1.24	0.76, 2.02
Per unit increase (meals/week)				
Molar Ratio Se:Hg*Per 1.0 increase*	0.99	0.92, 1.06	1.00	0.99, 1.02
MeHg in Hair *(µg/g)*	*Reference*	0.75, 2.15	*Reference*	0.65, 2.95
<0.25 (Low)	1.27	0.20, 2.05	1.39	0.11, 1.18
0.25–0.49 (Medium low)	0.63	0.20, 9.90	0.36	0.12, 5.52
0.50–0.99 (Medium high)	1.42		0.80	
≥1 (High)				
Intestinal Metaplasia				
Sex	*Reference*	0.12, 1.87		
Male	0.47			
Female				
Age	1.05	1.00, 1.10		
Per one-year increase				
Total Fish/Whale Consumption	1.10	1.07, 1.12		
Per unit increase (meals/week)				
Molar Ratio Se:Hg*Per 1.0 increase*	0.98	0.89, 1.09		
MeHg in Hair *(µg/g)*	*Reference*	0.37, 8.16		
<0.25 (Low)	1.73	0.25, 15.23		
0.25–0.49 (Medium low)	1.96	0.23, 31.20		
0.50–0.99 (Medium high)	2.65			
≥1 (High)				

[a] Adjusted for all model covariates
[b] bw = Body Weight
Note: Models do not contain a product term for the interaction between MeHg and Se

threshold at 350 µg/g/week [72]. The estimated mean body weights used for this analysis were 76 kg for males and 70 kg for females [63]. Using these values, the estimated Se intake threshold for this population would be 4.6 µg/week for males and 5 µg/week for females. Based on estimated intake from fish alone only 1 participant had estimated intake exceeding these thresholds. However, dietary Se intake is not exclusively from fish/whale, so the values estimated for this analysis do not capture total Se intake [46,52].

This study was limited by insufficient data for precise estimation of exposure effects and interaction between hair-MeHg concentration and estimated Se intake. It also lacked biochemically measured Se levels. Accuracy of Se intake values estimated from FFQ data and published Se concentrations in the species that participants consume rests on the accuracy of the food frequencies reported by participants and the assumption that Se concentrations in these species remains approximately constant [46]. Se concentrations in food items such as farm-raised meats and vegetables have been shown to fluctuate widely due to variation in Se concentrations in soil across geographic regions [46]. Thus, approximation of Se intake from such food items is not considered reliable. For this reason, we did not use Se intake from foods other than fish/whale [46]. To the extent that Se intake from other food sources is not proportional to Se intake from fish/whale, results of our analysis may be biased by residual confounding of MeHg effects by Se. To the extent that biochemical interactions between Se and

Table 10. Odds of severe chronic gastritis and gastric atrophy for methylmercury levels in hair at specified values of estimated selenium intake, adjusted for sex and total fish consumption frequency among 80 participants from 3 arctic communities, 2016 [a].

	Estimated Se Intake from Fish/Whale			
MeHg in Hair	0 (µg/kg bw/week)	2 (µg/kg bw/week)	4 (µg/kg bw/week)	6 (µg/kg bw/week)
Severe Chronic Gastritis				
<0.25 (µg/g)				
Adjusted Odds				
95%CI	0.65	0.51	0.50	0.50
	0.64, 0.67	0.50, 0.51	0.50, 0.50	0.50, 0.50
0.25–0.49 (µg/g)				
Adjusted Odds				
1	0.64	0.57	0.52	0.51
	0.63, 0.65	0.51, 0.62	0.47, 0.57	0.48, 0.53
0.5–0.99 (µg/g)				
Adjusted Odds				
95%CI	0.61	0.53	0.51	0.50
	0.52, 0.70	0.50, 0.57	0.49, 0.53	0.50, 0.51
≥1 (µg/g)				
Adjusted Odds				
95%CI	0.71	0.50	0.50	0.50
	0.67, 0.75	0.50, 0.50	0.50, 0.50	0.50, 0.50
Gastric Atrophy				
<0.25 (µg/g)				
Adjusted Odds				
95%CI	0.61	0.50	-0.50	0.50
	0.55, 0.67	0.50, 0.50	0.50, 0.50	0.50, 0.50
0.25–0.49 (µg/g)				
Adjusted Odds				
95%CI	0.60	0.55	0.52	0.51
	0.57, 0.63	0.45, 0.65	0.42, 0.62	0.45, 0.57
0.5–0.99 (µg/g)				
Adjusted Odds				
95%CI	0.53	0.56	0.59	0.63
	0.50, 0.57	0.53, 0.59	0.56, 0.63	0.57, 0.70
≥1 (µg/g)				
Adjusted Odds				
95%CI	0.67	0.57	0.51	0.50
	0.63, 0.71	0.49, 0.64	0.49, 0.53	0.50, 0.50

[a]These values are plotted in Figure 1

Table 11. Odds ratios for the effects of participant characteristics on each more advanced gastric pathologies among 73 participants from 3 western canadian arctic communities, 2016.

	Unadjusted		Adjusted [a]	
	OR	95%CI	OR	95%CI
Sex	*Reference*	0.34, 0.79	m	0.13, 1.13
Male	0.52		*Reference*	
Female			0.38	
Age	1.03	1.00, 1.06	1.04	1.00, 1.08
Per one-year increase				
Total Fish Consumption	1.08	0.96, 1.20	1.20	0.91, 1.59
Per unit increase (meals/week)				
Molar Ratio Se:Hg *Per 1.0 increase*	1.16	0.75, 1.80	0.79	0.25, 1.45
MeHg in Hair *(µg/g)*	*Reference*	0.45, 3.71	*Reference*	0.39, 4.21
<0.25	1.29	0.23, 2.02	1.27	0.11, 1.86
0.25–0.49	0.68	0.21, 3.37	0.44	0.10, 4.62
0.5–0.99	0.84		0.69	
≥1				

[a] Adjusted for all model covariates

MeHg extend beyond their simultaneous intake through fish/whale, our statistical models may not accurately reflect the influence of Se intake on the relationship between MeHg exposure and gastric pathology outcomes. Additionally, this analysis was not able to assess the extent to which participants consumed Se at toxic levels.

For most food items, correlation coefficients comparing the baseline serving frequencies to the 2016 serving frequencies were in the expected range for this type of

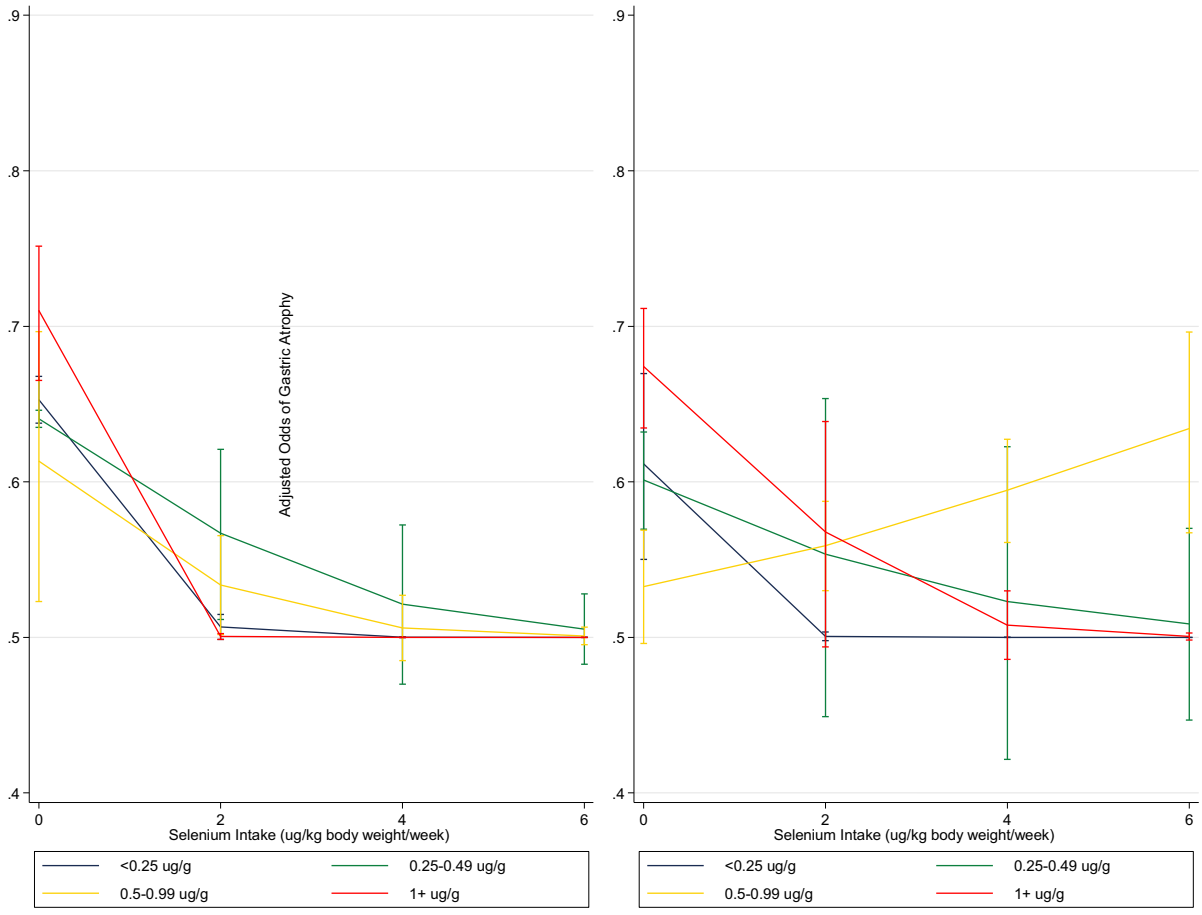

Figure 1. Odds of severe chronic gastritis and gastric atrophy for methylmercury concentration levels in hair at specified values of estimated selenium intake, adjusted for sex and total fish consumption frequency among 80 participants from 3 arctic communities, 2016.

data [46]. However, given the 4-8-year time interval between the two data collection points, differences in responses likely reflect a combination of measurement error and true changes in diet [46]. It should be noted that correlations between time points could reflect correlated errors in food frequency reporting by participants [46]. We did not have sufficient data to accurately assess whether variations in reported food frequencies over time differed by gastric pathology outcome status.

Community-driven epidemiologic studies that collect data on diet along with hair samples for measuring MeHg are exceedingly rare, particularly in Arctic populations, due to inherent challenges. This study, therefore, contributes information of value, though given acknowledged limitations, it would be prudent to view its value as a test of the study hypothesis to that of hypothesis screening. While our measure of Se intake from eating fish/whale was an approximation with inherent limitations, the observed relationship between Se intake and other variables in our analysis showed expected patterns, providing qualitative evidence that our classification of Se status was sufficiently accurate for our analysis goals [46]. For example, our models estimated substantially decreasing prevalence odds of both severe chronic gastritis and gastric atrophy with increasing Se intake, consistent with evidence of health benefits from Se intake [46]. Unadjusted estimates indicated that total fish/whale consumption did not influence prevalence odds of severe chronic gastritis or gastric atrophy. Adjusting for Se intake, however, prevalence odds of each gastric pathology outcome increased with increasing fish/whale consumption, consistent with evidence that various contaminants that accumulate in fish tissue may injure the gastric mucosa [73]. While adjustment for Se intake did not eliminate inverse associations between hair-MeHg concentration and gastric pathology outcomes, among those with no Se intake from fish, adjusted odds of severe chronic

gastritis and gastric atrophy were higher among those with higher MeHg concentrations.

To better understand the relationship between MeHg exposure and gastric health outcomes, studies following a prospective design that measure internal dose of MeHg and pathologically assess gastric health outcomes would be particularly informative. In studies aiming to measure internal dose of Hg, biochemical measurement of Hg exposure in human tissues should be accompanied by concurrent measurements of Se exposure. The choice of tissue for measurements of Se concentration should be selected based on the toxicokinetic properties of Se; as well Se measurements should correspond to a similar time window captured in the tissue selected for Hg measurements. Internal dose of Hg, and in particular MeHg, should be measured in hair. Investigators using hair to measure chemical concentrations should consider including individuals with chemically treated hair to build a larger body of evidence on the influence these treatments have on the reliability of measurements so as to avoid selection bias in epidemiologic studies that rely on measuring biomarkers in hair, given that hair treatments are common in adult populations.

Conclusions

This research provides evidence of a potential relationship between higher MeHg exposure and gastric pathology outcomes, modified and mediated by Se intake, in Indigenous Arctic communities in western Canada. Though statistical precision was limited and biochemical measurements of Se intake were lacking, we believe this to be the first population-based epidemiological analysis investigating effects of MeHg exposure on gastric health outcomes. These findings, therefore, contribute new evidence to the literature on health outcomes related to MeHg exposure, suggesting, in particular, for Arctic populations where freshwater fish or seafood are key food sources, that selenium contained in aquatic food sources may counter harmful effects of MeHg contamination of Arctic environments. However, larger epidemiologic studies are needed to gain a better understanding of the role of MeHg in the pathogenesis of gastric disease. Such evidence is crucial in a time of environmental degradation on a global scale.

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Data Sharing

All data collected and created in partnership with Indigenous communities is considered confidential, sensitive and vulnerable to misappropriation. Data cannot be shared without the expressed permission of the communities who participated in the research. Researchers who are interested in the data can send a proposal to the corresponding author for consideration by community planning committees.

Disclosure statement

The authors have no conflicts of interest to declare

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