Exposure to perfluoroalkyl substances (PFAS) and associations with thyroid parameters in First Nation children and youth from Quebec

Élyse Caron-Beaudoin⁎, Pierre Ayotteb,c,d, Elhadji Anassour Laouan Sidib, Community of Lac Simon, Community of Winneway – Long Point First Nation, CSSS Tshukuminu Kanani of Nutashkuan, Community of Unamen Shipu, Nancy Gros-Louis McHugh1, Mélanie Lemireb,c

a Université de Montreal School of Public Health, Department of Environmental and Occupational Health, QC, Montreal, Canada
b Axe santé des populations et pratiques optimales en santé, Centre de recherche du CHU de Québec – Université Laval, Canada
c Département de médecine sociale et préventive, Université Laval, Québec, Canada
d Institut national de santé publique du Québec, QC, Québec, Canada
e First Nations of Quebec and Labrador Health and Social Services Commission, Wendake, QC, Canada

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ABSTRACT
Background: Perfluoroalkyl substances (PFASs) are found in several consumer goods. Exposure to PFASs in children has been associated with alteration in thyroid hormones, which have critical roles in brain function.
Objective: In 2015, 198 children and youth (3–19y) were recruited as part of the pilot project Jeunes, Environnement et Santé/Youth, Environment and Health (JES!-YEH!), realized in collaboration with four First Nation communities in Quebec. We aimed to evaluate serum concentrations of PFASs in relation to concentrations of thyroid-stimulating hormone (TSH), free thyroxine (T4) and thyroglobulin while adjusting for relevant confounders.
Methods: PFASs (PFOS, PFOA, PFHxS, PFNA), 2,2′,4,4′-Tetrabromodiphenylether (PBDE-47) thyroid parameters (TSH, free T4, and thyroglobulin) were measured in serum samples of 186 participants. Iodine, creatinine, and cotinine were measured in urine samples. Serum levels of PFASs were compared to those measured in the general Canadian population and elsewhere. Multivariate regression analyses were performed to determine associations between PFASs and TSH, free T4 and thyroglobulin.
Results: PFOS, PFOA, and PFHxS serum concentrations were low. However, PFNA concentrations among participants aged 12 to 19 years old from Anishinabe communities were three times higher than those measured in the Canadian Health Measures Survey (2009–2011) for the same age group (Geometric Means: 3.01μg/L and 0.71μg/L, respectively) and were particularly higher in the Anishinabe participants aged 6 to 11 years old (GM: 9.44 μg/L). Few participants had levels of TSH, free T4, and thyroglobulin outside age-specific paediatric ranges. When adjusted for relevant covariates and other contaminants, PFNA serum concentrations were positively associated with free T4 levels (Adjusted β = 0.36; p = 0.0014), but not with TSH and thyroglobulin levels. No association was observed between the other PFAS and thyroid hormones parameters.
Conclusion: This pilot project reveals among the highest exposure to PFNA in children reported until today, and suggests effects of PFNA as an endocrine disruptor, highlighting the importance of investigating the sources and effects of disproportionate exposure to emerging contaminants in some indigenous communities and ban all PFAS at the international scale.

1. Introduction
Perfluoroalkyl substances (PFASs) have been produced since the 1950s and represent a large class of synthetic compounds that are highly stable and heat resistant (Lehmler, 2005). PFASs have various industrial applications and are found in food packaging, non-stick pan coatings, fire-fighting foams, paper and textile coatings, and personal care products (Houde et al., 2006). PFAS congeners with a longer carbon chain like perfluorooctanesulfonate (PFOS) were first released on the market, and once regulated, progressively replaced by...
perfluorooctanoate (PFOA) and perfluorohexanesulfonate (PFHxS), and later by perfluorononanoic acid (PFNA). In the early 2000s, the manufacture and import of PFOS and PFOA have also been eliminated in North America (Government of Canada, 2018; Paul et al., 2009). However, even if China restricted the production and use of PFOS, other PFASs are still being widely used and found in consumer goods from Asia (P. Wang et al., 2016).

Some PFASs are persistent and tend to bioaccumulate in the environment. In humans, PFASs half-lives in serum may vary greatly. PFOA and PFOS (8-carbon compounds) have a half-life of 3.5 and 4.8 years, respectively, whereas PFHxS, a 6-carbon compound, takes 7.3 years to be half-eliminated (Olsen et al., 2007). PFNA, a 9-carbon compound, has an estimated half-life of 2.5 years (Zhang et al., 2013). These PFASs are ubiquitous and have been detected also in the oceans (Wei et al., 2007; Yamashita et al., 2005), as well as surface and drinking waters (Mak et al., 2009; Quinte et al., 2009; Skutlarek et al., 2006). Thus, human exposure to PFASs can occur through different and multiple pathways, including food, drinking water (Tittlemier et al., 2007; Trudel et al., 2008) and indoor dust from other consumer goods (Haug et al., 2011; Kubwabo et al., 2005; Mitro et al., 2016; Shoeib et al., 2011; Strynar and Lindstrom, 2008). As a consequence, PFASs have been detected in adults and children from various countries, including in Canada (AMAP, 2015, 2017; Health Canada, 2012).

Several recent studies highlighted the effects of PFASs on thyroid hormones levels imbalance in adults, although the associations between PFASs exposure and thyroid parameters have shown mixed results that seem to be compound, age and sex-dependent (Ballesteros et al., 2017; Blake et al., 2018; Ji et al., 2012; Lewis et al., 2015; Melzer et al., 2010; Shrestha et al., 2015; Wen et al., 2013; Winquist and Steenland, 2014). Conversely, few studies are available in children. Lin et al. (2013) reported a positive association between PFNA and free thyroxine (T4), but no association with thyroid-stimulating hormone (TSH) in teenagers and young adults aged 12–30 years from Taiwan. Similarly, in children aged between 1 and 17 years old and living near a petrochemical plant in Ohio, United States, mild but positive associations between concentrations of PFNA and PFOS, and total T4 were found (Lopez-Espinosa et al., 2012). Considering the large number of recent studies in adults suggesting thyroid disruption by PFASs, studying their potential endocrine effects in children is of uttermost importance as they are in development and rely on a well-functioning thyroid system (Dussault and Ruel, 1987; Koibuchi and Chin, 2006; Porterfield, 1994).

Indigenous Peoples are considered among the most vulnerable to environmental contamination because of their close connection to the land for cultural, traditional and/or subsistence activities (Hoover et al., 2012). In Canada, they may also be more vulnerable due to poorer diet and/or water quality as well as poor housing conditions (Government of Canada, 2011). Children and youth may be more exposed to environmental contaminants than adults, as they often play on the floor where there is more dust, and absorb more contaminants via air, water or foods (Government of Canada, 2011). Children and teenagers are also more sensitive to contaminants since their bodies and brains are developing (Lanphear, 2015). Thus, Indigenous children and youth are particularly vulnerable to contaminants that may be present in their environment.

The First Nations Youth, Environment and Health Pilot Study – JES!-YEH! – is a biomonitoring initiative of environmental contaminants, nutritional status and other health determinants that was conducted in 2015 and involved Indigenous children and youth from four First Nations communities in the Quebec Province, Canada. This pilot project was undertaken since few data are available for Indigenous children and youth in Canada. The Canadian Health Measures Survey (CHMS) (Health Canada, 2012) does not include Indigenous Peoples living on reserve and the 2011 First Nations Biomonitoring Initiative (FNBI) recruited only adults (Assembly of First Nations, 2013). In the present study, we compared serum PFOS, PFOA, PFHxS and PFNA concentrations in JES!-YEH! to those reported in the second cycle of CHMS and elsewhere in the world. We also investigated the associations between exposure to these compounds and serum levels of thyroid parameters (TSH, free T4, and thyroglobulin).

2. Materials and methods

2.1. Study design and recruitment

The JES!-YEH! pilot project is a cross-sectional study realized in 2015 and in collaboration with two Innu and two Anishinabe First Nations communities that involved 198 participants aged 3 to 19 years old. The aim of the JES!-YEH! pilot study was to document exposure to environmental contaminants, nutritional and health status, and other health determinants in First Nation children and young adults. The two First Nations targeted for the study were selected in collaboration with study partners at the First Nations of Quebec and Labrador Health and Social Services Commission, primarily to represent two distinct ecological regions of the Quebec Province (Fig. 1). The Abitibi-Témiscamingue is an inland region with multiple lakes in Northwest Quebec. It is the natural habitat of several wildlife species such as freshwater fish, moose, beaver and black bears, and a region characterized by several mining, forestry and agricultural activities. The Minganie and Lower-North-Shore comprise a large coastal region in Northeast Quebec where fisheries are the central community and economic activities. All Anishinabe and Innu communities from these two regions with > 500 children and youth were invited to participate. The four communities participating in the project were involved primarily based on their interest in the pilot study. Field research periods (May and June 2015 for Anishinabe communities and September and October 2015 for Innu communities) were selected with community partners to not interfere with main hunting and fishing seasons as well as other important local events.

A total of 177 participants were randomly selected out of 279 candidates contacted from the lists of potential participants aged 3 to 19 years old and provided by the four community partners. These were recruited according to the underlying population distribution in each of the four communities (3–5 y, 6–11 y and 12–19 y for both sexes) based on the 2014 Statistics Canada Census (Government of Canada, 2014). To reach our recruitment target, 21 additional participants were recruited on a voluntary basis but in accordance with recruitment targets by age and sex groups. Overall, out of the 198 participants recruited, 95% of participants (n = 106/111) from the two Anishinabe communities and 82% of participants (n = 71/87) from the two Innu communities were selected on a random basis. Each parent or legal guardian of potential participant aged 3 to 17 years old and participant aged 18 and 19 years old were contacted directly by the local recruiter (phone, Facebook messenger or in person), who explained the research project and gave an appointment (morning, afternoon, evening or weekend) at their convenience. Pregnant teenagers and young women were excluded from the initial lists or at recruitment. To facilitate recruitment at different times of the day while minimizing the research impact on school attendance, children and teenagers were not required to be in fasting conditions. On the site of study and sample collection (health center, family house or daycare), participants, parents and/or guardian received additional information on the research project and had the opportunity to ask questions. If agreeing to be part of the study (including a verbal consent from participants aged 3 to 17 years old), a consent form was signed by the parent/guardian or the participant aged 18 or 19 years old. Participants aged 14 to 17 years old were also asked to sign the consent form but were accompanied by their parent or guardian for the whole data collection.

The research was approved by ethics review committees from the CHU de Québec – Université Laval (no. C14-08-2105) and Health Canada (no. 2014-0043). Community project leaders signed a community research agreement for their respective communities, inspired by the research protocol of First Nations of Quebec and Labrador and...
respecting the OCAP® (ownership, control, access, and possession) principles. Community partners and representatives of the First Nations of Quebec and Labrador Health and Social Services Commission were involved at all steps of the study (design, data collection, analyses, interpretation and presentation of results) in the communities and at the regional level. Participants’ results for contaminants with known sources of exposure (ex. mercury and lead) and for the nutritional status (ex. anemia) were returned in person to the parents or legal guardian, and local clinical interventions were undertaken when relevant. Aggregated data for emerging contaminants concentrations such as PFASs were shared and discussed with community members, in order to work together to identify local or regional sources and eventually implement preventive actions.

2.2. Data collection

A registered nurse collected anthropometric measures (height, weight, waist circumference) and biological samples (blood and urine samples) from the participants. Medical history and socio-demographic information were collected using interviewer-administered questionnaires with the parent, guardian or participant aged 18 and 19 years old. Consent forms and questionnaires were completed in French and English according to the parent, guardian or participant’s preference. Local staff provided simultaneous translation in Anishinabe or Innu language if needed. A $50 food voucher was given to the parent, guardian or participant as compensation for their time.

Blood specimens for PFASs, PBDE and total lipids analyses were collected by venipuncture in a 10mL serum determination tube (Red cap silicone-coated interior tube with a clot activator), while blood samples for thyroid parameters analyses were collected in a 3.5mL SST™ serum separation Tube. Blood tubes were then kept at room temperature for a minimum of 30 min and a maximum of an hour, before being centrifuged at 6000 rpm for 15 min at room temperature. Serum samples were then aliquoted into separated 2mL Sarstedt vials for serum PFAS and thyroid parameters analyses as well as into a 4mL glass vial (organochlorine free) for serum PBDE and total lipid analyses, and readily stored at −20°C. Urine spot samples were collected in 60mL container and aliquoted into 3.5mL samples in Sarstedt tubes for iodine and cotinine analyses, and stored at −20°C. All samples were transported frozen to the different laboratory facilities for further analyses.

Fig. 1. Map of the Quebec province. The Abitibi-Témiscamingue (left) and Minganie and Lower-North-Shore (right) regions where the study took place are indicated by red rectangles. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
2.3. Laboratory analyses

Environmental contaminants, serum total lipids, urinary iodine and urinary cotinine were analyzed at the Centre de toxicologie du Québec (CTQ) of the Institut national de santé publique du Québec (INSPQ).

The analyses for a total of 4 PFASs (perfluorooctanoic acid (PFOA), perfluorooctanoic acid (PFNA), perfluorohexane sulfonate (PFHxS) and perfluorooctane sulfonate (PFOS)) were performed as follows: serum samples (100 μL) were enriched with labeled internal standards (PFOA-13C4, PFNA-13C9, PFHxS-13C3, and PFOS-13C4) and were acidified with a 50% formic acid solution. Thereafter, the samples were extracted using a solid phase extraction (SPE) with a Strata-X AW 96 well plate 30 mg (33 μm) (Phenomenex; Torrance, CA, USA). The 96 well plate was washed first with NH4OH 5% in methanol to remove contaminants and conditioned with methanol and water prior to process the samples. The resin was washed with a 2% formic acid solution and methanol and analytes were eluted by 980 μL of NH4OH 5% in methanol. The extracts were evaporated to dryness and dissolved in 900 μL of ammonium acetate 5 mM in methanol 40%.

The samples were analyzed by Ultra Performance Liquid Chromatography (UPLC Waters Acquity) with a tandem mass spectrometer (MS/MS Waters Xevo TQ-S) (Waters, Milford, MA, USA) in the MRM mode with an electrospray ion source in the negative ion mode. The mobile phase consisted of a gradient of (30:70) methanol: H2O with ammonium acetate 5mM to 100% methanol in 14.6 min with a flow rate of 0.5 mL/min. The LODs for PFOS, PFOA, PFHxS, and PFNA were 0.03, 0.2, 0.04 and 0.07 μg/L, respectively. The intra-day precision varied between 3.3 and 8.1 and the inter-day precision varied between 4.2 and 13% depending on the analytes. The calibration curve was made in bovine serum and was linear with a weighting of 1/x between 0.15 and 50 μg/L for PFNA, PFOA, PFHxS and between 0.6 and 200 μg/L for PFOS.

The internal reference materials used to control the quality of the analyses were the certified reference material SRM-1958 from the National Institute of Standards and Technology (NIST; Gaithersburg, MD) and some in-house quality controls (QCs) for PFASs. The overall quality and accuracy for the analytical method was monitored by the participation in the interlaboratory program as the AMAP External Quality Assessment Scheme (CTQ, INSPQ, Quebec, Canada) for the analytes PFOA, PFNA, PFHxS and PFOS as well as the German External Quality Assessment Scheme (G-EQUAS; Erlangen, Germany) for the analytes PFOA and PFOS. It is to note that contaminants concentrations measured in serum are perfectly comparable to those measured in plasma samples, as in CHMS Cycle 1 to 4 (Leblanc, personal communication).

PBDEs (PBDE-47, PBDE-99, PBDE-100, PBDE-153, and PBDE-209) were measured in serum samples by GC–MS using the INSPQ E-446 method previously published. For PBDE-47, the limit of detection in serum was 0.03 μg/L (Fisher et al., 2016). For other PBDEs, the limit of detection in serum was 0.02 μg/L (Fisher et al., 2016). Total serum lipids were analyzed at the CTQ by gas chromatography following the method published by Fisher et al. (2016).

Urinary iodine was analyzed by inductively-coupled plasma mass spectrometry (ICP-MS) using a Perkin Elmer NexION 300S single-quadrupole ICP-MS (Shelton, CT, USA) operated in standard mode. Samples were diluted 20-fold in a diluent containing 0.5% (v/v) HNO3. The external calibration curve was prepared by diluting 20-fold the corresponding volume of human urine (from healthy volunteers) with the same diluent and then spiking with different volumes of iodide standard solution (Alfa Aesar, Iodide Specpure®, 1000 μg/mL, #42567). The internal standard for 127I was 150Pt in both calibration curve and samples analyses. The LOD for the iodine was 1.27 μg/L.

Free cotinine was extracted from urine using an automated mixed-mode solid phase extraction (SPE) with a 96-well plate Oasis MCK 30 mg (Waters; Milford, MA, USA) on a Janus robotic station (Perkin Elmer; Waltham, MA, USA). Extracts were then analyzed by UPLC-MS/MS with an Ultra Performance Liquid Chromatography (UPLC Waters Acquity) coupled with a tandem mass spectrometer Quattro Premier XE (Waters; Milford, MA, USA) in MRM mode with an electrospray ion source in the positive mode. The analytical column used was an Acquity UPLC BEH C18, 50 mm × 2.1 mm, 1.7 μm (Waters; Milford, MA, USA). The LOD for the cotinine was 1.1 μg/L.

Free T4, TSH, anti-TPO, thyroglobulin and anti-thyroglobulin analyses were performed in serum samples at the Laboratoire Multidisciplinaire of the Centre Hospitalier de l'Université Laval (Quebec, Canada) by chemiluminescence immunoassay using the Beckman Coulter Unicel Dxi 800 system and by electrochemiluminescence using the Roche Modular E170 Analyzer kits (Mississauga, ON, Canada).

2.4. Statistical analyses

Descriptive analyses and non-parametric Wilcoxon Each Pair, as well as χ² and Fisher exact tests, were used to investigate differences in thyroid parameters and contaminant concentrations (PFOS, PFOA, PFHxS, PFNA, ΣPFASs) by nation, age groups, sex, iodine and cotinine categories. For PBDEs, PBDE-47 was the only one detected in >40% of the samples and therefore included in descriptive analyses and later in the statistical models as a confounder. PFASs concentrations were compared between JESI-YEH! and CHMS using 95% CIs overlap. Associations between chemicals (PFOS, PFOA, PFHxS, PFNA, and PBDE-47) and BMI z-score, urinary cotinine and serum lipids were tested using Spearman’s rank correlation test.

2.4.1. Confounders

For multiple regression models, potential confounders were chosen a priori based on previous literature and included age, sex, studied nation, urinary iodine, urinary cotinine, parent’s education and BMI z-score (Lopez-Espinosa et al., 2012; Okada et al., 2012; Wu et al., 2015). A backward procedure was performed to exclude unnecessary confounders (Sauer et al., 2013; Wang et al., 2014). To do so, potential confounders were selected based on preliminary univariate analysis: to be included in the model, a p-value lower than 0.20 for each thyroid parameter (free T4, TSH, thyroglobulin) and PFASs serum concentrations was necessary. This backward procedure was performed for each model separately. The selected confounders are described for each model in the Results section.

2.4.2. Multiple regression models and sensitivity analyses

Thyroid parameters and PFOS, PFOA, PFHxS, and PFNA serum concentrations were log-transformed to improve the distribution of the variables. To account for potential curvilinear effects of age on PFASs and thyroid parameters levels, age-squared was tested in the models. Age and age-squared were centered. Adjusted models including other endocrine disruptor chemicals potentially acting on thyroid functions (other PFASs and PBDE-47) and BMI z-score were performed. Statistical interactions with age, nation, and sex were tested. Multiple regressions were also stratified by nation and by sex.

Sensitivity analyses were done by conducting additional multiple regression models: (i) excluding individuals with anti-TPO levels over 34 kU/l; (ii) excluding individuals with TSH, free T4 and thyroglobulin levels outside the age-specific paediatric ranges; (iii) including total lipids levels in serum, since some of these contaminants may accumulate in lipids (Conder et al., 2008; Law et al., 2003; Wu et al., 2007); and (iv) excluding BMI z-score in the models using this confounder as there is some inconsistency in the literature with regards to the influence of BMI on health outcomes and environmental exposure (Corbin and Timpson, 2016; Y. Wang et al., 2016). For multiple regression models, the linear relationship between the outcome (thyroid parameters) and the predictors, the normal distribution of the residuals of the regression model, the multicollinearity as well as the
variance inflation factor (VIF) were verified.

To further explore the shape of the relationship between thyroid parameters, PFASs concentrations and other covariables in statistically significant multiple regression models, non-linear relationships were investigated using a restricted cubic spline function from the Desquilbet and Mariotti (2010) SAS macro with 3 knots at 5th, 50th, and 95th percentiles.

Statistical significance was established at $p$-value < 0.05, and analyses were performed using JMP 13.0.0 and SAS software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participants’ characteristics

From the 198 participants recruited in the JES!-YEH! study, data on PFASs exposure and thyroid parameters levels were available for 186 of them, among which 106 and 80 participants were recruited in Anishinabe and Innu communities, respectively. The study population is presented in Table 1. The mean age was 10 years old and 47.8% were females. Age and sex distribution were not statistically different between studied nations ($p = 0.2$). The percentage of smokers was significantly higher among Innu participants (22.5% versus 6.7%, $p = 0.002$). Several participants (40.6%) have insufficient iodine levels, from mild to severe deficiency (47.5% in Innu participants versus 35.0% in Anishinabe participants, $p = 0.10$). Up to 66.3% of the JES!-YEH! participants were considered overweight or obese (82.1% in Innu participants compared to 54.7% in Anishinabeg, $p = 0.0002$).

3.2. Serum concentrations of PFASs

Serum concentrations of PFOS, PFOA, PFHxS, and PFNA are presented in Table 2. Serum PFNA concentrations among participants aged 12 to 19 years old from Anishinabe communities in 2015 were three times higher than those measured in the CHMS study during Cycle 2 (2007–2009) for the same age group (data not available in CHMS for those aged 3 to 11 years old and PFASs were not measured in Cycles 3 and 4). Conversely, PFNA concentrations among 12–19 years old Innu participants were lower than comparable values for CHMS cycle 2 participants. Contrary to PFNA, serum concentrations of PFOS, PFOA, and PFHxS were all lower than those reported for aged 12 to 19 in CHMS Cycle 2.

Surprisingly, PFNA exposure was markedly different between studied nations: serum PFNA concentrations among Anishinabe participants were overall more than eight times higher ($p < 0.0001$) and much more variable (range: 0.42 and 29.00 μg/L) compared to those among Innu participants. Moreover, PFNA concentrations were particularly elevated among Anishinabe participants aged 6 to 11 years old ($p < 0.0001$) (Table 2). In both studied nations, PFNA concentrations were not statistically different between sex ($p = 0.52$ and 0.25 for Anishinabe and Innu communities, respectively), not significantly correlated with BMI z-score (Anishinabe: $p = -0.02$, $p = 0.86$; Innu: $p = -0.007$, $p = 0.95$) and serum total lipids (Anishinabe: $p = 0.06$, $p = 0.11$; Innu: $p = -0.1$, $p = 0.38$). PFNA concentrations were negatively correlated with urinary cotinine among Innu participants ($p = -0.3$, $p = 0.007$), but not in Anishinabe participants ($p = -0.12$, $p = 0.24$).

Serum concentrations of PFOS and PFOA were not different between studied nations but significantly higher in participants aged 6 to 11 years old in both nations ($p = 0.02$ and < 0.0001). Serum concentrations of PFHxS were higher in Anishinabe participants across all age groups ($p < 0.0001$) (Table 2).

The sum of PFOS, PFOA, PFHxS and PFNA concentrations in serum was higher in Anishinabe participants compared to Innu participants.

![Table 1](https://example.com/Table1.png)

**Table 1** Characteristics of the JES!-YEH! participants from four Anishinabe and Innu communities in Quebec, Canada.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants (n = 186)</th>
<th>Anishinabe participants (n = 106)</th>
<th>Innu participants (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Min-max)</td>
<td>Median (Min-max)</td>
<td>Median (Min-max)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>10 (3–19)</td>
<td>9 (3–19)</td>
</tr>
<tr>
<td>3–5 years old</td>
<td>36 (19.4)</td>
<td>23 (21.7)</td>
<td>13 (16.3)</td>
</tr>
<tr>
<td>6–11 years old</td>
<td>74 (39.8)</td>
<td>45 (42.5)</td>
<td>29 (36.3)</td>
</tr>
<tr>
<td>12–19 years old</td>
<td>76 (40.8)</td>
<td>38 (35.8)</td>
<td>38 (47.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>89 (47.8)</td>
<td>52 (49.0)</td>
<td>37 (46.3)</td>
</tr>
<tr>
<td>Male</td>
<td>97 (52.2)</td>
<td>54 (51.0)</td>
<td>43 (54.7)</td>
</tr>
<tr>
<td>Urinary cotinine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.50 (0.55–2700.00)</td>
<td>0.55 (0.55–1500.00)</td>
<td>0.55–2700.00)</td>
</tr>
<tr>
<td>Non-smoker (&lt; 30 μg/L)</td>
<td>155 (83.8)</td>
<td>98 (93.3)</td>
<td>57 (71.3)</td>
</tr>
<tr>
<td>Smoker (&gt; 100 μg/L)</td>
<td>25 (13.5)</td>
<td>7 (6.7)</td>
<td>18 (22.5)</td>
</tr>
<tr>
<td>Urinary iodine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.94 (0.07–3.6)</td>
<td>2 (1.9)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Severe deficiency (&lt; 0.16 μmol/L)</td>
<td>7 (3.8)</td>
<td>2 (1.9)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Mild deficiency (&lt; 0.39–0.78 μmol/L)</td>
<td>54 (29.2)</td>
<td>29 (27.6)</td>
<td>25 (31.3)</td>
</tr>
<tr>
<td>Mild deficiency (&lt; 0.79–1.57 μmol/L)</td>
<td>68 (36.8)</td>
<td>41 (39.0)</td>
<td>27 (33.8)</td>
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<tr>
<td>Ample supply (&gt; 1.58–2.36 μmol/L)</td>
<td>31 (16.8)</td>
<td>20 (19.0)</td>
<td>11 (13.8)</td>
</tr>
<tr>
<td>Excessive supply (&gt; 2.37 μmol/L)</td>
<td>12 (5.9)</td>
<td>7 (6.7)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>BMI z-score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.42 (−2.26–4.8)</td>
<td>1.21 (−2.26–3.65)</td>
<td>2.10*** (−0.89–4.83)</td>
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<tr>
<td>BMI category&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>2 (1.1)</td>
<td>2 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Normal (≥ 18.5–23)</td>
<td>60 (32.6)</td>
<td>46 (43.4)</td>
<td>14 (17.9)</td>
</tr>
<tr>
<td>Overweight (≥ 23–25)</td>
<td>50 (27.2)</td>
<td>37 (34.9)</td>
<td>13 (16.7)</td>
</tr>
<tr>
<td>Obese (&gt; 25)</td>
<td>72 (39.1)</td>
<td>21 (19.8)</td>
<td>51 (65.4)</td>
</tr>
</tbody>
</table>

Significant difference for continuous variables between participants from Anishinabe and Innu communities assessed by Wilcoxon test (**p < 0.001; ***p < 0.01; *p < 0.05).

<sup>a</sup> Cut-off proposed by the INSPQ.
<sup>b</sup> Cut-off proposed by WHO and Health Canada.
<sup>c</sup> Cut-off proposed in Cole and Lobstein (2012).
Table 2
Serum concentrations of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexanesulfonate (PFHxS) and perfluorooctanoic acid (PFNA) (μg/L) in participants from JES!-YEH!, by nation and age, compared to the general Canadian population (CHMS cycle 2, 2009-2011, age 12-19).

<table>
<thead>
<tr>
<th>PFASs</th>
<th>JES!-YEH!</th>
<th>CHMS cycle 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-5 yo</td>
<td>6-11 yo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFOS</td>
<td>1.01</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>(0.95–1.09)</td>
<td>(0.83–1.14)</td>
</tr>
<tr>
<td></td>
<td>(0.99–2.34)</td>
<td>(0.53–2.80)</td>
</tr>
<tr>
<td>PFOA</td>
<td>0.85</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>(0.81–0.89)</td>
<td>(0.72–0.96)</td>
</tr>
<tr>
<td></td>
<td>(0.83–1.19)</td>
<td>(0.77–1.08)</td>
</tr>
<tr>
<td>PFHxS</td>
<td>0.38</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>(0.35–0.42)</td>
<td>(0.25–0.44)</td>
</tr>
<tr>
<td></td>
<td>(0.36–1.19)</td>
<td>(0.30–0.91)</td>
</tr>
<tr>
<td>PFNA</td>
<td>2.09</td>
<td>2.25</td>
</tr>
<tr>
<td></td>
<td>(1.75–2.51)</td>
<td>(1.53–3.22)</td>
</tr>
<tr>
<td></td>
<td>(2.10,</td>
<td>(2.45,</td>
</tr>
<tr>
<td></td>
<td>(2.0–29.00)</td>
<td>(2.0–15.00)</td>
</tr>
<tr>
<td>Sum PFASs</td>
<td>5.31</td>
<td>4.99</td>
</tr>
<tr>
<td></td>
<td>(4.90,</td>
<td>(4.90,</td>
</tr>
</tbody>
</table>

PFOS, PFOA, PFHxS and PFNA were detected over the LOD in all samples.

PFAs (μg/L): geometric mean 95% CI, (median, min-max).

E Use data with caution (coefficient of variation between 16.6 and 33.3%).

F Data is too unreliable to be published (coefficient of variation > 33.3%).

* Significant difference in PFAS serum concentrations between participants with different age groups (p < 0.05).

a Significant difference in PFAS serum concentrations between participants from Anishinabe and Innu communities (p < 0.05).

c Significant difference in PFAS serum concentrations between participants with different age groups in Anishinabe communities (p < 0.05).
across all age groups (p < 0.0001). Among Anishinabe participants, the sum of PFASs was significantly higher among those aged 6 to 11 years old (p < 0.0001) (Table 2).

PBDE-47 was only measured in CHMS Cycle 1 (2007–2009) and for participants aged 20 years old and above. Still, serum PBDE-47 concentrations adjusted for serum lipids in JES!-YEH! were not statistically different from those aged 20 to 39 years old (Supplemental material Table S1). All other PBDEs (PBDE-99, PBDE-100, PBDE-153, and PBDE209) are not reported since they were not detected in > 40% of samples (data not shown).

PFNA concentrations were only moderately correlated with PFOA (ρ = 0.47, p < 0.0001), PFHxS (ρ = 0.51, p < 0.0001), and to a much lesser extent to PBDE-47 (ρ = 0.17, p = 0.02). Conversely, PFNA concentrations were not significantly correlated with PFOS (ρ = 0.14, p = 0.14) (Supplemental material Table S2).

3.3. Thyroid parameters

Almost all participants (n = 185, 99.5%) had free T4 within normal age-specific paediatric ranges. Free T4 concentrations tended to be higher in Anishinabe participants, although the difference was not statistically significant (p = 0.10) (Table 3). Free T4 levels were higher in participants aged 3 to 11 years old compared those aged 12 to 19 years old (p < 0.0001). Free T4 levels were not statistically different between sex (p = 0.30), iodine categories (p = 0.98) or cotinine categories (p = 0.45). According to the age-specific paediatric ranges, 175 participants (94%) had TSH concentrations within the normal range while 10 participants (5.4%) had TSH concentrations higher than 20 pmol/L.

In participants aged 3 to 11 years old compared those aged 12 to 19 years old (p < 0.0001). Among Anishinabe participants, TSH serum concentrations were lower in participants aged 12–19 years old compared to those aged 3–5 years old (p = 0.0015), and higher in boys (p = 0.0036) and among non-smokers (p = 0.0034). Conversely, TSH levels were not statistically different between iodine categories (p = 0.83).

Anti-TPO levels and thyroglobulin were normal for 96.8% and 84% of the participants, respectively. No significant differences were observed between nations, sex or age-groups. Anti-TPO level is a measure to detect autoimmune thyroid disease (Portman et al., 1985), while thyroglobulin is a precursor of thyroid hormones. Anti-thyroglobulin is also used as a measure to detect autoimmune thyroid disease. However, it is important to note that the mechanisms triggering its production are not fully understood and that 10% of the disease-free populations in the United States show higher levels of this antibody (Hollowell et al., 2002).

3.4. Associations between PFASs and thyroid parameters

A significant positive association was found between PFNA and free T4 concentrations (Table 4). Conversely, no significant associations were found between PFOS, PFOA and PFHxS concentrations and free T4 levels. When stratifying by nation and by sex, the positive association between PFNA and free T4 concentrations remained strong and significant for the Anishinabe and Innu participants, and among male participants. A positive significant association was observed between PFOS and free T4 concentrations in Anishinabe participants. Overall, the associations between free T4 and the different PFASs were not significantly modified by the inclusion of the other PFASs and PBDE-47 into the models, and the interaction terms between PFAS concentrations and age sex were not significant.

No significant associations were found between PFAs concentrations and TSH or thyroglobulin levels in the adjusted models (Tables S3 and S4). When stratifying the PFOA model by nation, a positive significant association between PFOA and TSH concentrations was observed among Innu participants.

Removing from the adjusted models the participants with anti-TPO levels over 34 did not change the associations between free T4 levels

### Table 3

<table>
<thead>
<tr>
<th>Thyroid parameters</th>
<th>All participants (n = 186)</th>
<th>Anishinabe participants (n = 106)</th>
<th>Innu participants (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Median (Min-max)</td>
<td>n (%)</td>
<td>Median (Min-max)</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>16.00</td>
<td>16.00</td>
<td>16.00</td>
</tr>
<tr>
<td>Below age-specific paediatric reference range</td>
<td>1 (0.5)</td>
<td>(10.00–22.00)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Normal age-specific paediatric reference range</td>
<td>185 (99.5)</td>
<td>106 (100.0)</td>
<td>79 (98.7)</td>
</tr>
<tr>
<td>Above age-specific paediatric reference range</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>TSH (mUI/L)</td>
<td>2.13</td>
<td>2.11</td>
<td>2.19</td>
</tr>
<tr>
<td>Below age-specific paediatric reference range</td>
<td>0 (0.0)</td>
<td>(0.43–8.18)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Normal age-specific paediatric reference range</td>
<td>175 (94.1)</td>
<td>98 (92.5)</td>
<td>76 (95.0)</td>
</tr>
<tr>
<td>Above age-specific paediatric reference range</td>
<td>11 (5.9)</td>
<td>7 (6.6)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Anti-TPO (kUI/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (0–34 kUI/L)</td>
<td>180 (96.8)</td>
<td>103 (97.2)</td>
<td>77 (96.3)</td>
</tr>
<tr>
<td>Excessive (&gt; 34 kUI/L)</td>
<td>6 (3.2)</td>
<td>3 (2.8)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Thryglobulin (μg/L)</td>
<td>11.2</td>
<td>11.2</td>
<td>11.3</td>
</tr>
<tr>
<td>Deficient (&lt;1.60 μg/L)</td>
<td>6 (3.2)</td>
<td>(0.05–41.0)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Normal (1.60–50 μg/L)</td>
<td>179 (96.8)</td>
<td>102 (96.2)</td>
<td>77 (97.5)</td>
</tr>
<tr>
<td>Excess (&gt; 50 μg/L)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Anti-thyroglobulin (kUI/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;4 kUI/L)</td>
<td>156 (84.0)</td>
<td>87 (82.0)</td>
<td>69 (87.3)</td>
</tr>
<tr>
<td>Excessive (≥4 kUI/L)</td>
<td>29 (16.0)</td>
<td>19 (18.0)</td>
<td>10 (12.7)</td>
</tr>
</tbody>
</table>

Significant difference for continuous variables between participants from Anishinabe and Innu communities assessed by Wilcoxon test (**p < 0.001; ***p < 0.01; *p < 0.05).

a Age-specific paediatric reference TSH range (2.5–97.5 percentiles) (mU/L) (Kapelari et al., 2008): 3–5 years old: 0.8–6.26 mU/L; 6–11 years old: 0.8–5.40 mU/L; 12–19 years old: 0.5–4.61 mU/L.

b Age-specific paediatric reference free T4 range (2.5–97.5 percentiles) (pmol/L) (Kapelari et al., 2008): 3–5 years old: 10.5–22.4 pmol/L; 6–11 years old: 10.6–20.9 pmol/L; 12–19 years old: 10.4–22.6 pmol/L.

c Cut-off proposed in Jatzko et al. (2014).

d Cut-off proposed by the Laboratoire Multidisciplinaire du CHUL.

e Cut-off proposed in Kitahara et al. (2012).
4. Discussion

The aim of the project was to assess and compare exposure to PFASs and investigate associations between exposure to PFASs and levels of thyroid parameters among children and youth from four First Nations communities in Quebec. While concentrations of older PFASs (PFOA, PFOS, PFHxS) were lower than those reported in the general Canadian population in CHMS Cycle 2 (2009–2011), PFNA concentrations measured among Anishinabe participants in this study realized in 2015 were 3 times higher than those measured among CHMS participants aged 12 to 19 years in 2009–2011 (Health Canada, 2012). Moreover, Anishinabe participants presented a very large range of exposure to PFNA, which was particularly elevated among Anishinabe participants aged 6 to 11 years old. Interestingly, PFNA concentrations in Innu participants were lower than those reported in CHMS Cycle 2. With respect to thyroid parameters, although few participants presented abnormal free T4 status, a significant and consistent positive association was found between PFNA exposure and T4 levels, but not with TSH or thyroglobulin. These results are consistent with the few studies on endocrine disruption effects of PFAs reported among children and youth (Lin et al., 2013; Lopez-Espinosa et al., 2012).

PFASs with >8 carbon chains (such as PFNA) were used as a replacement of older PFASs (e.g. PFOS, PFOA), which production was phased out in 2002 in the United States (Paul et al., 2009). As the United States were the primary supplier for these substances in Canada, their imports have been significantly limited since 2002. Moreover, PFOS is not manufactured in Canada (Government of Canada, 2018). PFOS was added to the Stockholm Convention in 2009, while PFOS is under review (Stockholm Convention, 2018). PFOS was used as a replacement of older PFASs (PFOA, PFOS, PFHxS) were lower than those reported in the general Canadian population in CHMS Cycle 2 (2009–2011), PFNA concentrations measured among Anishinabe participants in this study realized in 2015 were 3 times higher than those measured among CHMS participants aged 12 to 19 years in 2009–2011 (Health Canada, 2012). Moreover, Anishinabe participants presented a very large range of exposure to PFNA, which was particularly elevated among Anishinabe participants aged 6 to 11 years old. Interestingly, PFNA concentrations in Innu participants were lower than those reported in CHMS Cycle 2. With respect to thyroid parameters, although few participants presented abnormal free T4 status, a significant and consistent positive association was found between PFNA exposure and T4 levels, but not with TSH or thyroglobulin. These results are consistent with the few studies on endocrine disruption effects of PFAs reported among children and youth (Lin et al., 2013; Lopez-Espinosa et al., 2012).

Exposure to PFNA among in Anishinabe participants in JES!-YEH! conducted in 2015 (median 3.0 μg/L) was systematically higher than in other similar studies. For example, Lopez-Espinosa et al. (2012) reported lower median serum PFNA concentrations in children aged 1–5 years old (1.4 μg/L), 6–10 years old (1.8 μg/L) and 10–17 years old (1.4 μg/L). The PFNA geometric mean reported by Lin et al. (2013) in children aged 12 to 19 years old was also greatly lower compared to Anishinabe participants from the same age group (0.91 μg/L versus 3.01 μg/L). In obese children aged 8–12 years old from a recent study in Ohio, the median serum PFNA concentration was 0.24 μg/L (Khalil et al., 2018). In 940 adolescents (15–19 years old) from Norway and in 51 children (5 years old) from the Faroe Islands, the median PFNA serum concentrations (0.50 and 0.72 μg/L, respectively) were also lower than what we reported in the JES!-YEH! study (Averina et al., 2018; Dassuncao et al., 2018). Interestingly, serum concentrations of PFNA steadily increased from 1999 to 2008 in children aged 12 to 19 years old who participated in the National Health and Nutrition Examination Survey in the United States (Kato et al., 2011). In the 2007–2008 survey, the median serum concentration of PFNA for this age group was 1.42 μg/L, which is still 2 times lower than those measured in 12–19 years old Anishinabe participants in the present study. More recently, a similar mild but increasing trend was also reported in children and adults from Australia with median serum concentrations at 0.5 μg/L in 2002 and 0.8 μg/L in 2011 (Toms et al., 2014).

PFAs with >8 carbon chains (such as PFNA) were used as a replacement of older PFASs (e.g. PFOS, PFOA), which production was phased out in 2002 in the United States (Paul et al., 2009). As the United States were the primary supplier for these substances in Canada, their imports have been significantly limited since 2002. Moreover, PFOS is not manufactured in Canada (Government of Canada, 2018). PFOS was added to the Stockholm Convention in 2009, while PFOA is considered for listing and PFHxS is under review (Stockholm
Concentration of PFASs in different dust samples, possibly resulting – suggest that high PFAS exposure in this context was fairly recent. Sta-
were higher in 6 to 11 years old children and did not primarily increased in the environment make their local or regional sources very challenging to the Quebec/Labrador region in 2017 (L. Chan, personal communication). Moreover, no cleaning pro-
duced increased exposure to PFNA in association with high seafood consumptions in children aged 1 to 17 years old living near a petrochemical plant in the US. Thyroid hor-
mones biosynthesis is controlled by a precise feedback mechanism. The production of TSH in the anterior pituitary gland by thyrotrope cells sends a signal to the follicular cells of the thyroid to synthesize T4 (Smith et al., 2002), which is then converted to T3, the biologically active hormone. Once in the circulation, an important portion of T3 and T4 will bind to transport proteins (Refetoff, 2015). The increase in circulating le-
vels of T4 and T3 is a key component of the regulatory feedback, as it leads to the inhibition of TSH production. Finally, the active hormone T3 will bind to specific nuclear receptors: the thyroid hormone receptors (TRs) (Oppenheimer et al., 1987; Smith et al., 2002). In our study, no association was found between PFNA exposure and TSH levels. This could be explained by the hypothesis put forward by Gutshall et al. (1989) who studied the effects of perfluoro-o-decanoic acid (PFDA) on thyroid hormone levels in rats, and found that PFDA did not exert effects directly on thyroid hormones synthesis, but displaced thyroid hormones from their binding protein sites and increased free T4 levels in circulation. Another hypoth-
"estis that could explain the absence of a negative association between PFNA and TSH levels is the very high proportion of overweight or obesity found in our study population (66.3%). Indeed, thyroid hormone resistance and derangement in the hypothalamic-pituitary axis are more prevalent in overweight or obese individuals, and these two conditions are known to increase the circulating TSH levels (Reinehr, 2010).

When stratifying the models by sex, the association between PFNA concentrations and free T4 levels remained statistically significant in male participants. These results are aligned with other similar studies, where exposure to PFASs such as PFNA and PFOS were associated with increased levels of total T4 in boys (Lopez-Espinosa et al., 2012). It is known that PFASs can alter the activity of the androgen receptor in vitro (Kjeldsen and Bonefeld-Jorgensen, 2013), and exposure to PFASs has been associated with disruption of reproductive hormones in children and young adults (Goudarzi et al., 2016; Itoh et al., 2016; Lopez-Espinosa et al., 2016; Tsai et al., 2015). Moreover, there is increasing evidence of crosstalk between the thyroid hormone and androgen axis (Flood et al., 2013), which could par-
entially explain the differences observed between girls and boys in our study.

When stratifying the models by sex, the association between PFNA concentrations and free T4 levels were statistically significant in both studied nations, suggesting that endocrine disruption effects of PFNA could be observed also lower levels of exposure. Further studies using a larger sample size are needed to investigate the possible plateau effect of PFNA exposure on increasing free T4 concentrations.

Thyroid hormones play major roles in growth, metabolism, and brain maturation and function. During childhood, thyroid dysfunction has been associated with neurological and behavioral abnormalities (Venero et al., 2005), including language and attention deficits, poorer memory skills and fine neuromotor impairments (Zoellner and Rovet, 2004). Interestingly, Hoffman et al. (2010) reported a positive but nonsignificant association between PFNA serum concentrations in children aged 12–15 years old from the United States and the diagnosis of attention-deficit/hyperactivity disorder (ADHD). In a study of 8 years old children from Ohio, USA, increased exposure to PFNA at 8 years old was associated with poorer executive function and poorer behavior regulation among boys (Vuong et al., 2018). Higher concentrations of
PFNAs in 8 years old children from Taiwan were also associated with lower verbal IQ (Wang et al., 2015). Moreover, thyroid hormones also play a major role in the regulation of behavior and mood, through their action on neurotransmitters like serotonin (Bauer et al., 2003). Thus, the endocrine disruption effects of PFAS in children and youth may have a significant impact on their global development.

Among the limitations of the study, it is important to note the cross-sectional design, which does not necessarily indicate causal mechanisms, as well as the absence of T3 measurements, which would have enabled a more comprehensive understanding of the participants’ thyroid function. Although the sample size is small, and the sampling strategy was not fully on a random basis, a major strength of the present study is the inclusion of First Nations children and youth, as they are not represented in CHMS or FNBI studies. The ability to adjust for several potential confounders is also an asset. The inclusion of other potential thyroid-disrupting chemicals in the multiple regression models strengthens our interpretation of the association between PFNA exposure and thyroid parameters specifically.

5. Conclusion

PFNAs exposure among Anishinabe participants in this study was among the highest reported for children and youth until today (Averina et al., 2018; Dassuncao et al., 2018; Lin et al., 2013; Lopez-Expinosa et al., 2012; Wu et al., 2015). A positive association between PFNA and free T4 concentrations, but not with TSH, was also observed, primarily among male participants. To our knowledge, this is the first study reporting PFNAS exposure and associations between PFNAS exposure and thyroid parameters levels in First Nations youth. First Nations communities already face important health inequities (Frohlich et al., 2006), and a disproportionate environmental burden may exacerbate these disparities (Miranda et al., 2009). Further studies to understand the sources of exposure to PFASs, especially PFNA, and the sex-specific and dose-response relationships between PFAS and thyroid parameters as well as other health-related outcomes are strongly needed to foster the inclusion of all PFAS in the Stockholm Convention, ban these chemicals in consumer goods, and better prevent the impacts of emerging environmental exposures on the health of children and youth.

Acknowledgements

We greatly thank the participants, their parents and legal guardians and community partners in Lac Simon, Winneway – Long Point First Nation, Nutashkuan and Unamen Shipu without whom this work could not have been successfully accomplished as well as the research team who helped in the study design and collected the data. This study was funded by Health Canada and the Nasivik Research Chair in Ecosystem Approaches to Northern Health.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.04.029.

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