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Abstract

Background: The body burden of metals and persistent organic pollutants (POPs) is particularly high in populations that rely on fish and other marine species for sustenance. This exposure has been associated with an increased risk of type 2 diabetes, but results remain contrasted.

Objective: We studied this association in two Indigenous populations of northern Québec (Canada) with markedly different prevalences of diabetes and levels of exposure to POPs and mercury.

Methods: As part of health surveys conducted in 2004-2009, diabetes prevalence and glucose metabolism (glucose, insulin, HOMA-IR, HOMA-B) in non-diabetic fasting adults were assessed using similar protocols in two populations: Inuit from Nunavik (n=877) and Cree from *Eeyou Istchee* territory (n=780). Blood mercury, plasma polychlorinated biphenyls (PCBs), organochlorine (OC) pesticides/metabolites and polybrominated diphenylethers (PBDEs) levels were measured in samples collected at the time of examination. Logistic and linear regressions and restricted cubic splines analyses were conducted adjusting for sex, age, waist circumference, smoking and omega-3 fatty acid content in plasma phospholipids.

Results: Diabetes prevalence was higher in Cree (20%) than in Inuit (7%), whereas environmental exposure was 2 to 3-fold greater in Inuit than in Cree participants. In the range of exposure common to the two populations, we observed similar linear increases in the risk of diabetes with increasing contaminant exposure. Among Cree participants, fasting glucose was positively associated with plasma PBDE level, and HOMA-B negatively associated with concentrations of ∑PCBs, dichlorodiphenyldichloroethylene, PBDEs and ∑OC pesticides. Among Inuit participants, a trend towards reduced insulin secretion was observed in association with most contaminants, but the relation was nonlinear (greater reduction at intermediate levels of exposure). A significant increase in fasting glucose levels was observed at elevated blood mercury levels (> 16 µg/L).

Conclusion: The observed association between POPs exposure and diabetes risk in the two populations studied should be confirmed using prospective design. Our results suggest the need for additional research on the physiopathological process through which POPs exposure may induce type 2 diabetes in these Indigenous populations.

Keywords: persistent organic pollutants, mercury, diabetes, glucose, insulin, First Nations, Inuit

Human subjects research review

All study components were reviewed and approved by the ethics committees of the participating institutions (McMaster, Laval and McGill universities). Community consent was obtained through formal resolutions, and all individual participants provided informed written consent.

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing among Indigenous populations of Canada with a projection of 214% overall increase between 2000 and 2030 (Leung, 2016). However there are large disparities among Indigenous populations: age-adjusted T2DM prevalence is much higher in First Nations peoples (17.2% when living on reserve; 10.3% off reserve) than in Metis (7.3%) or Inuit (5.0%) (similar to the general Canadian population) (PHAC, 2011). Specific genetic polymorphisms conferring susceptibility to T2DM have been identified among some First Nations populations (Hegele et al., 2003) and Inuit (Manousaki et al., 2016). These genotypes, in combination with lifestyle changes and dietary transition, may partly explain the differences in T2DM prevalence between Indigenous populations. At different periods of time in their history, these populations have faced profound societal changes, as a result of residential schools and other legacies of colonization, resulting in a shift away from traditional lifestyles and diet. Initially composed of local and highly nutritious fish, seafood, marine and terrestrial mammals, wild birds and plants, these are now increasingly replaced by imported nutrient-poor, energy-dense processed foods. Concomitantly, a reduction of the daily level of physical activity has occurred. Both are major risk factors of obesity, which is a major driver of T2DM. Conversely, despite their modest contribution to total energy intake, traditional foods are still an integral part of Indigenous cultures, and continue to largely contribute to diet quality and nutrient intakes (Willows et al 2019; Kenny et al 2019 ; Batal and Decelles 2019).

Unfortunately, worldwide increase of industrial activity has brought chemical contamination of the environment, bioaccumulation and biomagnification of metals and persistent organic pollutants (POPs) including polychlorinated biphenyls (PCBs) in some freshwater fish and marine species, and ultimately, to an increased body burden of these contaminants in populations that rely on these species for sustenance (AMAP, 2015). Thus, despite the many benefits of traditional foods, some of them can also be a source of exposure to environmental contaminants, especially predatory fish and marine mammals that are at the top of the food chain. Whereas several fish species are often consumed by different Indigenous communities, marine mammals are almost uniquely consumed by Inuit communities (Noreen et al 2018; Lemire et al, 2015). This translates into a high exposure to mercury and PCBs, but also to elevated intakes of marine food nutrients, such as omega-3

polyunsaturated fatty acids, iron, selenium, iodine and lipophilic vitamins, in Inuit communities (AMAP, 2015; Lemire et al., 2015; Laird et al., 2013).

Recent reviews have concluded that body burden of several of these contaminants has been associated with an increased risk of T2DM (Lee et al., 2014; Thayer et al., 2012; Taylor et al., 2013; Roy et al., 2017). This contamination could therefore contribute to the rising epidemics of diabetes in several Indigenous populations of Canada. High exposure levels to these contaminants have been reported in several of these communities (Liberda et al., 2014; Donaldson et al., 2010). The role of this exposure in T2DM onset has been studied, with conflicting results, among Inuit populations in Greenland (Jorgensen et al., 2008; Jeppesen et al., 2015) and Canada (Inuvialuit Settlement Region, Nunavut and Nunatsiavut) (Singh et al., 2017), and among First Nations in Manitoba and Ontario (Marushka L et al., 2017). Possible reasons for these discrepancies include different population characteristics such as exposure levels or prevalence of other T2DM risk factors, and different methods used to assess glucose metabolism, environmental exposures and dose-response relationships.

In the present study, we evaluated the associations between POPs and mercury exposure with altered glucose metabolism in two Indigenous populations of Northern Quebec, Canada that exhibit different exposure levels and different genetic backgrounds. Similar methods were used in both populations for assessing exposure to these contaminants and health outcomes.

2. Methods

2.1. Population and data collection

Comprehensive environmental health surveys were conducted between 2004 and 2009 in two Indigenous populations living in Northern Quebec (Inuit of Nunavik, Cree of *Eeyou Istchee*) using similar protocols. The *Qanuippitaa?* Nunavik Health Survey was conducted during the summer of 2004 among Inuit adults (aged 18years and over) from 14 Nunavik villages. A clinical and paraclinical exam was organized onboard the Canadian Coast Guard Icebreaker *Amundsen.* Each individual who agreed to participate in the survey signed a consent form. The study protocol was approved by the ethics committee of Laval University; more details are available in Rochette and Blanchet (2007). The

Multi-community Environment-and-Health Study is a cross-sectional investigation that was carried out in nine Cree communities located in the *Eeyou Istchee* territory between 2005 and 2009 collecting similar clinical and personal information. All of the study's components were reviewed and approved by the ethics committees of the participating institutions: McMaster, Laval and McGill universities. Community consent was obtained through formal resolutions, and all individual participants provided informed written consent. More details about this second study is available in Nieboer et al. (2013).

The enrolled individuals answered a series of questionnaires documenting lifestyle and dietary habits, and diagnosed health conditions including diabetes. Subsequently, a series of tests and anthropometric measurements (height, weight, waist circumference) were conducted during a clinical session and blood samples were collected for measures of glucose metabolism and biomarkers of exposure to environmental contaminants. Medical records were also reviewed for several health outcomes including diabetes and medication use.

Among the 914 Inuit participants who participated in the clinical session in 2004, 37 were excluded because of missing values on essential variables (disease, glucose), 62 (7.1%) were identified with a diagnosis of diabetes and 815 were considered non-diabetic. Among these 815 a priori non-diabetic participants, 144 were in a non-fasting state and were excluded, leaving 671 participants for which biological measures were performed; 161 of them also underwent an oral glucose tolerance test (OGTT). Out of 881 Cree participants, 101 could not be assessed for diabetic status and 158 had diagnosed diabetes (20.3%). Biological measures were performed for the remaining 599 subjects a priori non-diabetic, in fasting state, with full data on main covariates (only 59 were also submitted to OGTT and data will not be reported).

2.2. Diagnosis of T2DM and laboratory analyses

Prevalent T2DM among participants was assessed from previous diagnosis confirmed by medical chart review, or from consumption of antidiabetic drugs as indicated in medical records (more details are given in supplemental file 1).

Fasting plasma insulin (pmol/L) was measured with the chemiluminescent detection immunoassay system (ADVIA Centaur CP Immunoassay system; Bayer HealthCare, Toronto, ON. Canada). Blood glucose (mmol/L) was quantified by a spectrophotometric assay (Vitros 950; Ortho-Clinical

Diagnostics) (Chateau-Degat et al., 2009). All analyses were performed by the Clinical Biochemistry Laboratory of the Centre Hospitalier de l'Université Laval (CHUL), Québec. We used the homeostasis model assessment (HOMA) to assess insulin resistance (HOMA-IR) and pancreatic β-cell function (HOMA-B) (Matthews et al., 1985; Song et al., 2007). The HOMA-IR score was calculated for each participant using the following formula: HOMA-IR = [fasting glucose (mmol/L)] × [fasting insulin (mIU/L) /22.5]. The HOMA-B (or HOMA β-cell) was calculated as follows: HOMA-B = [20 x fasting insulin (mIU/L)] / [fasting glucose (mmol/L) – 3.5].

2.3. Exposure assessment

We analyzed plasma samples of participants to determine their body burden of the following POPs: 7 polychlorinated biphenyls (PCBs) congeners (IUPAC nos.105, 118, 138, 153, 156, 170 and 180) (NIOSH, 1977; Patterson et al., 1991); 13 organochlorine (OC) pesticides or metabolites (aldrin, ß-hexachlorocyclohexane [HCH], α-chlordane, γ-chlordane, oxychlordane, *trans*-nonachlor, *cis*-nonachlor, *p,p'*-dichlorodiphenyltrichloroethane, *p,p'*-dichlorodiphenyldichloroethylene [DDE], hexachlorobenzene [HCB], mirex, toxaphene congeners Parlar no. 26 and Parlar no. 50 [toxaphene 26+50]), and 5 brominated organic compounds (polybrominated biphenyl [PBB] congener no. 153, polybrominated diphenyl ethers [PBDEs] congeners nos. 47, 99, 100, and 153). Total mercury (Hg) and omega-3 polyunsaturated fatty acids (omega-3 PUFAs) were quantified in whole blood and plasma phospholipids, respectively (Liberda et al.. 2014; Rochette and Blanchet, 2007). Data for PBDE 47, PBDE 153, and toxaphene congeners were not available for some Cree participants, leaving 519 subjects for analysis relative to these compounds.

Organohalogenated compounds were extracted from plasma using solid-phase extraction. The resulting extract was cleaned on florisil columns and analysed by high resolution gas chromatography–mass spectrometry (HRGC–MS) at the *Centre de Toxicologie du Québec*. Limits of detection (LODs) were based on a signal-to-noise ratio of 3:1 for all compounds. LODs changed over the course of the projects, due to instrument optimization; the most conservative (highest) LOD values were assigned to each compound: 0.005 µg/L: toxaphene congeners; 0.02 µg/L: all PCBs congeners, aldrin, α-chlordane, γ-chlordane, oxychlordane, mirex, *trans*-nonachlor, PBB 153, PBDE nos. 99, 100 and 153; 0.03 µg/L: PBDE 47; 0.04 µg/L: HCB; 0.05 µg/L: ß-HCH, DDT; 0.09 µg/L: DDE. Intra-day precision (typically <3%), inter-day precision (mostly ≤ 10%, but 25–35% for the brominated

compounds) and recoveries (mostly ≥ 70%) were all in the acceptable range. The measurement of whole blood total mercury (Hg) concentration was performed by ICP-MS at the *Centre de Toxicologie du Québec* and the complete analytic method was detailed elsewhere (Valera et al. 2009). LOD for the determination of Hg was 0.12 µg/L.

Cholesterol and triglycerides were analyzed using a Hitachi 917 Chemistry Analyzer. Total plasma lipids (as an adjustment variable for lipophilic contaminants) were then estimated from cholesterol and triglyceride levels. Plasma phospholipids were isolated from the lipid extract by chromatography, and the fatty acid profile, including DHA and EPA (omega-3 PUFAs), was determined by capillary gas–liquid chromatography as described by Jacobson et al. (2008).

2.4. Statistical analysis

Because glucose, insulin, HOMA-IR and HOMA-B values were substantially skewed, we used a logarithmic transformation of these variables for the analysis. Two extreme values were also winsorized to reduce the impact of outliers. Imputations were performed for missing values on main covariates and the results were bootstrapped in order to take into account the complex survey design (Inuit study).

Ten contaminant categories were created: ∑PCBs (105,118,138,153,156,170,180), dioxin-like PCBs (105+118+156), DDE, HCB, mirex, oxychlordane+*trans*-nonachlor, PBDE (47+153), toxaphene (26+50), ∑OC pesticides (HCB, mirex, oxychlordane, *trans*-nonachlor, DDE), and Hg. Contaminant concentrations were grouped in tertiles (µg/L) in each study population. Omega-3 PUFAs concentration was considered as a continuous variable.

All multivariate models were adjusted for age (years), sex, waist circumference (cm), smoking (never smoker, ex-smoker, occasionally, daily – for Cree; current non-smoker, occasional smoker, daily smoker – for Inuit), omega-3 PUFAs (% of total fatty acids by weight in plasma phospholipids) and total lipids (g/L) (when appropriate).

Odds ratio of T2DM for each group of contaminants was estimated by logistic regression in each population separately. Linear trend tests for odds ratios and percent changes were obtained using orthogonal polynomial contrast on risk factor levels. Accordingly, the median values for each tertile

were used to create polynomial coefficients, using the SAS proc IML. The latter coefficients were then applied in the contrast statement to achieve a dose response trend. Likewise, within each population, an interaction term between the risk factor components (∑PCBs, DDE) and waist circumference (above and below the median) was also tested.

The shape of dose-response associations for the main contaminants (∑PCBs and DDE), was also explored using spline regression modeling in order to detect non-linear relationship between the exposure (ng/g plasma lipids) and the outcome that would not otherwise be captured with the exposure categorization (tertiles). Restricted cubic spline was selected to insure stability at tails. A model including three knots (5th, 50th and 95th percentiles) allowed an adequate fit of the data. Graphs are represented as the log(odds) of T2DM by contaminant levels. Log(Odds) were derived at minimum value (reference value) of the exposure. To test whether the shape of the outcome-exposure relationship is different between the two populations (Inuit and Cree), an interaction term (population by exposure components) was used. An overall model was first assessed; the model estimates were then contrasted at specific range of data points for each population to derive the log(Odds) function.

Regressions models were also used in order to evaluate the relationship between environmental contaminants and biomarkers of glucose metabolism among non-diabetic participants. Percent of change coefficients $((exp(\beta)-1)x100)$ were calculated (as the dependent variables were log-transformed) to provide a measure of change for the selected glucose metabolism marker that occurs for any tertile of exposure compared to the reference (lower tertile).

Statistical analyzes were performed by SAS software, version 9.4 (SAS Institute. Cary. NC).

1. Results

The prevalence of T2DM was 20.3% among Cree and 7.1% among Inuit. Table 1 contains descriptive data for markers of glucose metabolism in fasting adult participants from both populations. Although median age at enrollment (33-34 years) was similar in the two groups, all indicators of metabolic disturbances (waist circumference, fasting glucose, fasting insulin) were markedly higher in the Cree population. Conversely, plasma concentrations of all POPs (except PBDE), of Hg and omega-3 PUFAs (Table 2) were higher in the Inuit compared to the Cree population. When grouped into tertiles, the second tertile of environmental contaminants and nutrients distributions in the Inuit population was

approximately equivalent to the third tertile in the Cree population. Due to low percentage of detection of toxaphene 26+50 in the Cree population, results relative to these compounds are not reported. Concentrations of several of these contaminants were highly correlated (r>0.9 between ∑PCBs, DDE, mirex, and oxychlordane+transnonachlor) (Supplemental File 2).

All contaminant concentrations, except PBDE and Hg, were associated with an increased risk of prevalent T2DM in the Cree population (Table 3). In the Inuit population, significant trends were observed for ∑PCBs, mirex, and ∑OC pesticides. When modelling non-linear dose-response curves of log(Odds) in association with ∑PCBs and DDE, including Cree and Inuit populations with the same reference value, the interaction was not statistically significant (Figures 1-2). Within the range of exposure common to the two populations (<1200 ng/g lipids for DDE, <2300 ng/g lipids for ∑PCBs), the risk of T2DM increased in a similar fashion among Cree and Inuit but kept increasing beyond this range only among Inuit. Interaction between plasma ∑PCBs or DDE levels and waist circumference did not reach statistical significance. However among Inuit, linear trends of risk of T2DM with contaminant levels are observed only among subjects with waist circumference above median, whereas in the Cree population, linear trends of risk of T2DM are observed in both strata. (Supplemental File 3)

In the Inuit population free of previously diagnosed diabetes, higher plasma concentrations of ∑PCBs, dioxin-like PCBs and some OCs (HCB, mirex, toxaphene) were associated with decreasing levels of fasting insulin (up to a 13% decrease), but not with increasing fasting glucose levels (Table 4). However, the decrease in insulin was not linearly related to exposure, as it was more pronounced in the second tertile of exposure. Similar patterns of associations were observed for HOMA-IR or HOMA-B levels, with decreased levels occurring in the intermediate range of concentrations. In the subsample of Inuit participants submitted to the OGTT test (n=161), a linear decrease in glucose level was observed in association with higher concentrations of mirex. A notable exception in the direction of these associations was the positive association between DDE concentration and an increase in insulin and in HOMA-IR levels (up to 9%) (Figure 3). Increased blood Hg concentration was associated with a linear increase in fasting glucose (+3% in the third tertile of exposure) and this association was more pronounced in the subsample submitted to the OGTT test (+26% in the third tertile).

In the Cree population free of previously diagnosed diabetes, fewer changes in markers of glucose metabolism were observed in association with exposure to POPs (Table 5). An increase in fasting glucose was observed in association with PBDE plasma level, and a decrease in HOMA-B with increasing concentrations of ∑PCBs, dioxin-like PCBs, DDE, PBDE and ∑OC pesticides, although the shape of the relationship was not always linear (Figure 4).

4. Discussion

Our results obtained in two different Northern Quebec Indigenous population indicate similar dose-response associations between POPs exposure and T2DM risk, despite markedly different exposure levels, glucose metabolism measures and diabetes prevalence. However, the patterns of association between exposure and biomarkers of glucose metabolism differed between the two groups of non-diabetic adults, suggesting different processes linking environmental contaminants to diabetes onset in these populations, perhaps linked to abdominal obesity.

The two populations studied present contrasted characteristics at baseline, both in terms of T2DM prevalence (20% among Cree, 7% among Inuit) and markers of glucose metabolism (altered among Cree), and in terms of exposure to environmental contaminants (higher among Inuit). In the Cree study population, the median fasting plasma glucose level (5.32 mmol/l) and waist circumference (108.9 cm) were at the cutoff points for definition of metabolic syndrome (Goldenberg et al., 2013). Conversely, blood levels of total PCBs and ∑OC pesticides were 2 to 3 times, and mercury level up to 7 times higher among Inuit compared to Cree.

Previous studies pertaining to POPs exposure and risk of diabetes in different Inuit populations have reported contrasted results. Among Inuit from Greenland, a previous cross-sectional study conducted between 1999 and 2002 (Jorgensen et al., 2008) reported plasma concentrations of total PCBs and OCs at least 4 times higher than in the present study in Nunavik. However, contrary to our findings, no association was observed between exposure to POPs and diabetes prevalence. As suggested by the authors, because very high levels of exposure are present in their population, the range of exposures

may not have been large enough to reveal associations with metabolic dysfunctions (see Figure 2). Nevertheless, both in Inuit populations from Greenland and Nunavik (present study), an inverse association with insulin levels is observed: in Greenland, Jorgensen et al. (2008) reported inverse associations between stimulated insulin level and total PCBs or several OC pesticides, whereas in Nunavik we also found inverse associations between fasting insulin and these contaminants (stimulated insulin was not measured in our study). In the Adult Inuit Health Survey conducted in Nunavut, Inuvialuit Settlements and Nunatsiavut in the Canadian Arctic (Nunavik not included) in 2007-2009, POPs blood plasma levels were similar to those observed in our Nunavik Inuit population (Singh et al., 2017). In this cross-sectional survey, they reported an association between POPs exposure and (self-reported) diabetes as well as fasting glucose. The latter finding is hard to interpret however, since the authors apparently did not exclude prevalent cases of diabetes when performing these statistical analyses. The potential impact of mercury exposure on glucose metabolism was studied previously in the Inuit population of Greenland (Jeppesen et al., 2015). The authors reported a positive association between mercury exposure and T2DM prevalence and with fasting glucose and 2h-glucose; the relationship appeared linear in their range of exposure levels (median 17.3 µg/L; range: 0.05-490 µg/L). Whereas we do not find an association between mercury exposure and T2DM prevalence in the Nunavik Inuit population, similar associations with 2h-glucose are observed, but statistical significance was reached only in the higher exposure range (our third tertile > 16 µg/L) for fasting glucose.

In summary, our results combined to those obtained in similar studies conducted in other Inuit populations suggest an association between POPs exposure and diabetes prevalence. Moreover, our results obtained in non-diabetic individuals suggest that reduced insulin secretion, rather than early signs of insulin resistance, is associated with increasing contaminant concentrations, but mostly at intermediate levels of exposure. The existence of non-monotonic dose-response curves in these associations has already been suggested (Lee et al., 2014). Although we did not find an association between mercury exposure and T2DM prevalence, our results suggest that an increase in glucose levels may occur at blood mercury levels above 16 µg/L, which is coherent with the data from a previous study among Greenlandic Inuit (Jeppesen et al., 2015).

The risk of diabetes in relation with POPs exposure was previously studied in the Mohawk population of Akwesasne, a First Nations community located along the St Lawrence River in New York State, USA (Codru et al., 2007). In this cross-sectional study, blood concentrations of total PCBs, DDE, HCB and mirex were 2 to 3 times higher than those observed in the Cree participants in our study. The authors reported positive associations between elevated serum concentrations of PCBs, DDE and HCB and diabetes prevalence, but a negative association with mirex. An update of this analysis has subsequently been published (Aminov et al., 2016) with an extended sample of the same Mohawk population. Serum concentrations of 101 PCB congeners and 3 pesticides (DDE, HCB, mirex) were measured and statistical analyses included mutual adjustment for concentrations of other POPs. Significant associations were reported between diabetes prevalence and serum levels of low-chlorinated non-dioxin-like PCBs congeners and HCB. Another large study conducted among First Nations adults in Ontario, Canada focused on risks and benefits of fish consumption in relation with T2DM risk (Marushka L et al., 2017). Globally, a frequent consumption of fish (>= once a week), and the estimated DDE and PCBs intakes from fish, were associated with increased risk of T2DM. Our study is the first to report an association between PBDE exposure and impairment of glucose metabolism in a First Nations population, and these results add to the growing knowledge on the potential health effects of brominated flame retardants (Kim et al., 2014).

In summary, in coherence with results of other studies conducted in First Nations populations, we observed an association of POPs exposure with diabetes prevalence. In addition, among non-diabetic participants, we observed a decrease in HOMA-B, indicative of reduced β-cell function, in association with ∑PCBs, DDE, PBDE and ∑OC pesticides exposures.

With regard to the effect of POPs on insulin levels, there is in-vitro evidence indicating that POPs can directly reduce insulin secretion of beta cells at very low doses, following a non-linear relationship (Lee et al., 2017). Results from the latter study also suggest the possibility that a compensatory over-secretion of insulin among individuals exhibiting insulin resistance may mask a direct effect of POPs on pancreatic beta-cell function. Accordingly, a recent review article on POPs and T2D concluded that the role of POPs would be more prominent in the development of beta-cell dysfunction-dominant T2D rather than insulin resistance-dominant T2D (Lee et al., 2018).

Assuming that a similar linear dose-response relationship exists between the main POPs exposures and T2DM risk among Cree and Nunavik Inuit populations, in their common range of exposure (<1200 ng/g lipids for DDE, <2300 ng/g lipids for ∑PCBs - that concern the majority of the two populations), the population fraction of T2DM attributable to POPs exposure is likely to be higher among Inuit compared to Cree, because exposure levels are higher among Inuit. This potential impact is likely to decline over the next decades, because of decreasing environmental levels and human body burden of most POPs in the Arctic (AMAP 2015), except for PBDE.

A number of limitations are present in our study. Although we had the opportunity to study a large number of POPs, several of them are highly correlated. Some combinations of contaminants are driven by one main compound: for example, ∑OC pesticides concentrations are largely explained by DDE, especially among Cree where DDE represents 82% of ∑OC pesticide concentration. The large number of tests performed has increased the likelihood of positive findings. However, due to high correlations among several POPs, significant associations found with some specific compound (such as DDE or mirex) may be attributed to the mixture rather than to the compound itself. Diagnosis of diabetes was based on medical records, an improvement over studies relying only on self-reported diabetes, but we cannot exclude that some cases may have been missed. Some potential confounders such as alcohol consumption, physical activity or family history of diabetes were difficult to assess with precision in these two populations and could not be taken into account. Most of the contaminants measured in our study persist for many years in the body; however simultaneous cross-sectional assessment of blood contaminant levels and disease status may also have introduced measurement error or even reverse causation, due to the lipophilic properties of several POPs (Zong et al., 2018). In addition, the duration of disease (median 5.5 years among Cree, 3.3 years among Inuit) may also have introduced behavior changes (including dietary) that modified their current circulating levels of pollutants. Despite these potential limitations, common to most cross-sectional studies on this issue, our study relied on a detailed assessment of contaminants and nutrients biomarkers in two large population samples. The originality of our analysis lies in parallel observations of disturbances of glucose metabolism and diagnosed T2DM in two Indigenous populations of Canada with contrasted characteristics.

Conclusion

The observed link between POPs exposure and T2DM risk in the two populations studied should be confirmed using preferably a prospective design. Our results also suggest the need for additional research on the physiopathological process through which POP exposure may induce type 2 diabetes in these Indigenous populations.

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Variable[a]	Inuit		Cree
	Total Population (n=671)	Subsample OGTT (n=161)	Total Population (n=599)
Age (years)	32.9 [24.4-43.6]	38.8 [27.2-50.1]	33.8 [25.1-43.9]
% men	53.0	57.3	43.6
Waist circumference (cm)	88.6 [79.9-98.8]	90.1 [80.9-100.2]	108.9 [99.8-118.9]
% ever smoker	77.7	74.0	90.5
Fasting glucose (mmol/l)	4.36 [3.97-4.69]	4.49 [4.23-4.75]	5.32 [4.97-5.78]
Fasting insulin (pmol/l)	42.4 [33.6-60.8]	43.9 [33.7-65.7]	129.5 [85.1-195.3]
HOMA-IR	1.18 [0.90-1.74]	1.30 [0.91-1.90]	4.54 [2.89-7.29]
HOMA- B[b]	144.0 [100.8-249.6]	125.0 [97.0-215.6]	197.0 [135.9-281.4]

a: continuous variables are presented as median and interquartile range [Q1-Q3]
b: n=622 Inuit, measures below 3.5 mmol/L are excluded.

Table 1: Characteristics of the Inuit and Cree adult populations (non-diabetic, fasting state)

	N	%>LOD	P10	P25	P50	P75	P90	Max
Inuit								
∑PCB (ng/g)	671	100	78	175	366	850	2000	8342
dioxin-like PCB (ng/g)	671	99.42	6.5	14	30	66	149	689
p,p'-DDE (ng/g)	671	100	129	233	421	818	1672	8307
HCB (ng/g)	671	99.59	14	25	52	116	228	1246
Mirex (ng/g)	671	91.05	1.6	4.3	9.6	24	55	293
Oxychlordane + *trans*-nonachlor (ng/g)	671	100	38	74	159	429	974	6395
PBDE (47 +153) (ng/g)	669	85.5	<LD	2.7	8.3	15	35	402
Toxaphene 26 + 50 (ng/g)	671	98.14	7.6	14	32	80	177	968
∑OC pest (ng/g)	671	100	207	375	698	1471	3131	14688
Hg (µg/L)	671	100	2.46	5.32	10.3	20.7	38.2	152
Omega-3 (% total FA)	671	100	5.19	6.78	9.03	11.7	14.3	19.5
Cree								
∑PCB (ng/g)	599	99.3	17	45	169	542	1548	13200
dioxin-like PCB (ng/g)	599	88.1	<LD	4.6	16	51	160	1978
p,p'-DDE (ng/g)	599	99.8	38	64	143	355	823	7144
HCB (ng/g)	599	99.8	3.3	3.8	8.0	16	32	240
Mirex (ng/g)	599	78.8	<LD	1.8	7.7	30	94	645
Oxychlordane + *trans*-nonachlor (ng/g)	599	92.8	1.1	4.0	11	28	67	483
PBDE 47 +153 (ng/g)	479	82.5	<LD	5.1	9.8	18	33	219
Toxaphene 26 + 50 (ng/g)	479	39.9	<LD	<LD	<LD	2.4	5.6	53
∑OC pest (ng/g)	599	100	46	73	175	442	1088	8212
Hg (µg/L)	599	100	0.41	0.98	3.00	7.99	16.5	82.2
Omega-3 (% total FA)	598	100	4.92	5.35	5.95	6.77	7.74	17.4

Σ PCB = sum (105+118+153+156+170+180); dioxin-like PCB = sum (105+118+156);
Σ OC pest = sum (HCB+mirex+oxychlordane+*trans*-nonachlor+*p,p'*-DDE); FA: fatty acids

Table 2: Blood levels of POP (ng/g lipids), mercury (Hg) and omega-3 polyunsaturated fatty acids in Inuit and Cree adult populations (non-diabetic, fasting state)

	Inuit (n=877)			Cree (n=778)		
Variable/Tertiles	**OR[a]**	**95% CI**		**Variable/Tertiles**	**OR[a]**	**95% CI**
∑PCB[b] (µg/L) **<1.42** (ref)	1			**∑PCB[b]** (µg/L) **<0.59** (ref)	1	
1.42-4.40	1.20	[0.33 – 4.35]		**0.59-3.02**	1.86	[0.98 – 3.51]
>4.40	4.37	[1.27 – 15.08]		**>3.02**	2.50	[1.20 – 5.24]
P Trend	0.003			**P Trend**	0.025	
Dioxin-like PCB[c] (µg/L) **<0.12** (ref)	1			**Dioxin-like PCB[c]** (µg/L) **<0.06** (ref)	1	
0.12-0.36	1.11	[0.29 – 4.29]		**0.06-0.29**	2.46	[1.26 – 4.81]
>0.36	2.51	[0.75 – 8.44]		**>0.29**	3.63	[1.70 – 7.76]
P Trend	0.060			**P Trend**	0.002	
***p.p'*-DDE** (µg/L) **<1.8** (ref)	1			***p.p'*-DDE** (µg/L) **<0.60** (ref)	1	
1.8-4.5	1.15	[0.33 – 3.97]		**0.60-2.20**	2.31	[1.18 – 4.55]
>4.5	2.35	[0.68 – 8.06]		**>2.20**	3.14	[1.43 – 6.91]
P Trend	0.115			**P Trend**	0.008	
HCB (µg/L) **<0.21** (ref)	1			**HCB** (µg/L) **<0.03** (ref)	1	
0.21-0.63	0.72	[0.19 – 2.69]		**0.03-0.10**	1.90	[0.99 – 3.64]
>0.63	2.20	[0.55 – 8.74]		**>0.10**	3.59	[1.72 – 7.52]
P Trend	0.104			**P Trend**	0.001	
Mirex (µg/L) **<0.035** (ref)	1			**Mirex** (µg/L) **<0.02** (ref)	1	
0.035-0.12	0.57	[0.18 – 1.86]		**0.02-0.17**	1.99	[1.06 – 3.73]
>0.12	2.35	[0.84 – 6.55]		**>0.17**	2.48	[1.16 – 5.30]
P Trend	0.019			**P Trend**	0.042	
Oxychlordane *trans*-nonachlor (µg/L) **<0.67** (ref)	1			**Oxychlordane *trans*-nonachlor** (µg/L) **<0.05** (ref)	1	
0.67-2.16	0.51	[0.15 – 1.78]		**0.05-0.17**	2.49	[1.23 – 5.05]
>2.16	2.11	[0.70 – 6.36]		**>0.17**	5.83	[2.58 – 13.2]
P Trend	0.064			**P Trend**	<0.001	
∑OC pest[d] (µg/L) **<2.92** (ref)	1			**∑OC pest[c]** (µg/L) **<0.73** (ref)	1	
2.92-8.13	0.58	[0.15 – 2.30]		**0.73-2.73**	2.78	[1.38 – 5.61]
>8.13	2.54	[0.79 – 8.16]		**>2.73**	3.93	[1.73 – 8.92]
P Trend	0.018			**P Trend**	0.003	
PBDE 47+153 (µg/L) **<0.02** (ref)	1			**PBDE 47+153** (µg/L) **<0.04** (ref)	1	
0.02-0.08	1.16	[0.55 – 2.45]		**0.04-0.09**	1.40	[0.78 – 2.53]
>0.08	0.90	[0.40 – 2.04]		**>0.09**	0.99	[0.54 – 1.81]
P Trend	0.716			**P Trend**	0.773	
Toxa 26+50 (µg/L) **<0.13** (ref)	1					
0.13-0.43	0.71	[0.20 – 2.55]				
>0.43	1.82	[0.54 – 6.13]				
P Trend	0.159					
Mercury (µg/L) **<7.21** (ref)	1			**Mercury** (µg/L) **<1.84** (ref)	1	

3

	7.21-17.2	0.72	[0.26 – 1.96]	**1.84-6.61**	1.91	[1.07 – 3.41]
	>17.2	1.18	[0.42 – 3.31]	**>6.61**	1.09	[0.56 – 2.15]
P Trend		0.551	**P Trend**		0.668	

a: adjusted for age, sex, waist circumference, smoking, omega-3 PUFAs, total lipids (except for mercury models);
b: ΣPCB = sum (105+118+138+153+156+170+180); c: dioxin-like PCB = sum (105+118+156); d: ΣOC pest = sum (HCB+mirex +oxychlordane+*trans*-nonachlor+*p.p'*-DDE)

Table 3: Odds Ratio of T2DM according to tertiles of circulating concentrations of POP and Hg in Inuit and Cree adult populations

Variable/Tertiles		Glucose %change [95%CI][a]	Insulin %change [95%CI][a]	Homa-IR %change [95%CI][a]	Homa-B %change [95%CI][a]	2h-Glucose %change [95%CI][a]
∑PCB[b] (µg/L)	< 1.37 (ref)	0	0	0	0	0
	1.37-4.08	-0.01 [-2.49 – 2.54]	-10.1 [-17.8 – -1.75]	-10.1 [-18.9 – -0.30]	-15.4 [-25.6 – -3.69]	-8.39 [-20.4 – 5.45]
	>4.08	0.81 [-2.51 – 4.24]	-2.97 [-13.6 – 8.93]	-2.18 [-14.2 – 11.49]	-11.0 [-24.2 – 4.60]	-9.24 [-28.4 – 14.97]
P Trend		0.591	0.922	0.822	0.398	0.531
Dioxin-like PCB[c] (µg/L)	<0.12 (ref)	0	0	0	0	0
	0.12-0.32	0.43 [-1.89 – 2.80]	-9.99 [-17.3 – -2.07]	-9.71 [-18.1 – -0.49]	-10.4 [-20.9 – 1.59]	-1.51 [-15.7 – 14.99]
	>0.32	0.78 [-2.37 – 4.04]	-0.72 [-11.2 – 11.01]	-0.12 [-12.1 – 13.49]	-5.32 [-19.4 – 11.27]	1.65 [-21.9 – 32.27]
P Trend		0.658	0.556	0.544	0.814	0.854
p,p'-DDE (µg/L)	<1.80 (ref)	0	0	0	0	0
	1.80-4.00	-1.25 [-3.67 – 1.24]	-1.84 [-9.92 – 6.97]	-2.85 [-12.1 – 7.35]	-3.85 [-15.1 – 8.94]	7.19 [-6.23 – 22.54]
	>4.00	1.17 [-1.60 – 4.01]	8.02 [-1.89 – 18.93]	9.38 [-1.84 – 21.89]	-2.30 [-15.2 – 12.57]	10.07 [-10.1 – 34.78]
P Trend		0.188	0.045	0.033	0.857	0.412
HCB (µg/L)	<0.20 (ref)	0	0	0	0	0
	0.20-0.59	-1.94 [-4.31 – 0.49]	-9.07 [-16.2 – -1.39]	-10.9 [-18.9 – -2.20]	0.59 [-10.7 – 13.30]	0.40 [-11.7 – 14.13]
	>0.59	-1.44 [-4.76 – 2.00]	-5.52 [-16.7 – 7.18]	-7.05 [-19.2 – 6.94]	3.83 [-14.6 – 26.23]	2.10 [-16.3 – 24.55]
P Trend		0.596	0.661	0.583	0.692	0.834
Mirex (µg/L)	<0.03 (ref)	0]	0	0	0	0
	0.03-0.10	-0.37 [-2.74 – 2.06]	-12.7 [-19.9 – -4.79]	-12.9 [-21.0 – -3.96]	-14.4 [-24.9 – -2.36]	-7.94 [-20.3 – 6.28]
	>0.10	0.37 [-2.67 – 3.51]	-7.24 [-17.7 – 4.49]	-6.86 [-18.5 – 6.43]	-12.8 [-25.7 – 2.27]	-18.5 [-34.6 – 1.58]
P Trend		0.716	0.548	0.650	0.219	0.068
Oxychlordane+*trans*-nonachlor (µg/L)	<0.65 (ref)	0	0	0	0	0
	0.65-1.98	0.05 [-2.31 – 2.46]	-1.89 [-10.3 – 7.36]	-1.94 [-11.6 – 8.77]	-3.72 [-15.0 – 9.05]	6.73 [-7.70 – 23.42]
	>1.98	0.02 [-3.03 – 3.17]	2.61 [-8.04 – 14.50]	2.45 [-9.47 – 15.94]	-0.84 [-15.0 – 15.69]	11.57 [-12.5 – 42.23]
P Trend		0.999	0.491	0.557	0.935	0.438
∑OC pest[d] (µg/L)	<2.88 (ref)	0	0	0	0	0
	2.88-7.27	-0.99 [-3.28 – 1.36]	-3.06 [-11.2 – 5.87]	-4.11 [-13.3 – 6.10]	-6.28 [-16.9 – 5.75]	3.05 [-9.96 – 17.92]
	>7.27	1.29 [-1.63 – 4.30]	7.30 [-3.60 – 19.43]	8.53 [-3.91 – 22.57]	-3.96 [-17.3 – 11.50]	12.83 [-9.88 – 41.26]
P Trend		0.228	0.083	0.071	0.774	0.272

PBDE 47+153 (µg/L)	<0.02 (ref)	0	0	0	0	0
	0.02-0.07	0.60 [-1.72 – 2.98]	2.91 [-5.39 – 11.94]	3.33 [-6.10 – 13.71]	-4.75 [-16.0 – 7.97]	8.37 [-5.92 – 24.83]
	>0.07	0.67 [-1.55 – 2.95]	-2.47 [-10.3 – 6.08]	-2.06 [-11.0 – 7.75]	-7.85 [-19.0 – 4.85]	7.75 [-6.50 – 24.18]
P Trend		0.594	0.436	0.543	0.225	0.385
Toxa 26+50 (µg/L)	<0.13 (ref)	0	0	0	0	0
	0.13-0.39	-2.05 [-4.26 – 0.21]	-8.91 [-16.3 – -0.84]	-10.9 [-19.2 – -1.78]	-0.21 [-11.4 – 12.43]	1.07 [-13.5 – 18.15]
	>0.39	-1.30 [-4.06 – 1.55]	-0.99 [-10.8 – 9.88]	-2.28 [-13.1 – 9.88]	2.78 [-12.6 – 20.90]	8.38 [-14.8 – 37.81]
P Trend		0.633	0.635	0.749	0.701	0.471
Mercury (µg/L)	<6.81 (ref)	0	0	0	0	0
	6.81-16.4	0.35 [-2.12 – 2.88]	2.85 [-5.14 – 11.52]	3.00 [-6.24 – 13.16]	1.63 [-10.8 – 15.81]	3.85 [-10.8 – 20.89]
	>16.4	2.56 [-0.10 – 5.28]	1.94 [-6.84 – 11.55]	4.49 [-5.81 – 15.92]	-6.35 [-17.2 – 5.92]	26.23 [2.63 – 55.25]
P Trend		0.039	0.779	0.455	0.201	0.018

a: % change adjusted for age, sex, waist circumference, smoking, omega-3 PUFAs, total lipids (except for mercury models);
b: ΣPCB = sum (105+118+138+153+156+170+180); c: dioxin-like PCB = sum (105+118+156); d: ΣOC pest = sum (HCB+mirex +oxychlordane+*trans*-nonachlor+*p.p'*-DDE).

Table 4: Adjusted percentage change (%) in markers of glucose metabolism according to POPs (µg/L) and Hg (µg/L) in the adult Inuit diabetes-free population (n=671)

Variable/Tertiles		Glucose %change [95%CI][a]	Insulin %change [95%CI][a]	Homa-IR %change [95%CI][a]	Homa-B %change [95%CI][a]
∑PCB[b] (µg/L)	<0.41 (ref)	0	0	0	0
	0.41-2.29	2.59 [-0.84 – 6.14]	-2.01 [-10.8 – 7.62]	1.02 [-9.24 – 12.43]	-10.2 [-18.9 – -0.63]
	>2.29	1.53 [-2.85 – 6.11]	-7.88 [-18.4 – 4.02]	-5.87 [-18.1 – 8.14]	-13.7 [-24.3 – -1.51]
P Trend		0.774	0.162	0.290	0.066
Dioxin-like PCB[c] (µg/L)	<0.05 (ref)	0	0	0	0
	0.05-0.22	2.33 [-1.06 – 5.84]	-2.28 [-11.0 – 7.24]	0.51 [-9.61 – 11.77]	-10.0 [-18.6 – -0.48]
	>0.22	2.26 [-2.10 – 6.82]	-3.72 [-14.6 – 8.58]	-0.92 [-13.6 – 13.7]	-10.7 [-21.6 – 1.72]
P Trend		0.479	0.582	0.853	0.203
p,p'-DDE (µg/L)	<0.5 (ref)	0	0	0	0
	0.5-1.5	0.95 [-2.46 – 4.48]	-6.17 [-14.6 – 3.14]	-4.99 [-14.7 – 5.85]	-10.6 [-19.3 – -0.92]
	>1.5	3.14 [-1.50 – 8.00]	-1.30 [-13.0 – 12.0]	2.29 [-11.5 – 18.2]	-9.41 [-21.1 – 3.96]
P Trend		0.176	0.871	0.529	0.327
HCB (µg/L)	<0.02 (ref)	0	0	0	0
	0.02-0.08	1.21 [-2.10 – 4.63]	-3.05 [-11.6 – 6.26]	-1.71 [-11.5 – 9.15]	-8.92 [-17.5 – 0.59]
	>0.08	-1.59 [-5.71 – 2.71]	-2.10 [-13.0 – 10.2]	-3.32 [-15.5 – 10.6]	-0.70 [-12.6 – 12.8]
P Trend		0.331	0.814	0.641	0.760
Mirex (µg/L)	<0.02 (ref)	0	0	0	0
	0.02-0.12	2.11 [-1.34 – 5.67]	0.84 [-8.27 – 10.9]	3.38 [-7.20 – 15.2]	-5.73 [-14.9 – 4.48]
	>0.12	0.17 [-4.02 – 4.54]	-4.14 [-14.8 – 7.85]	-3.49 [-15.6 – 10.4]	-6.24 [-17.5 – 6.57]
P Trend		0.740	0.385	0.420	0.461
Oxychlordane + *trans*-nonachlor (µg/L) <0.03 (ref)		0	0	0	0
	0.03-0.12	0.30 [-3.18 – 3.90]	-4.97 [-13.8 – 4.72]	-4.17 [-14.2 – 7.07]	-8.06 [-17.3 – 2.16]
	>0.12	2.20 [-2.61 – 7.24]	-6.56 [-18.2 – 6.70]	-3.84 [-17.4 – 11.9]	-12.7 [-24.4 – 0.83]
P Trend		0.330	0.393	0.717	0.094
∑OC pest[d] (µg/L)	<0.57 (ref)	0	0	0	0
	0.57-1.88	1.07 [-2.35 – 4.61]	-6.99 [-15.4 – 2.26]	-5.70 [-15.4 – 5.08]	-11.9 [-20.5 – -2.32]
	>1.88	3.55 [-1.21 – 8.54]	-3.15 [-14.9 – 10.24]	0.76 [-13.1 – 16.82]	-12.3 [-23.8 – 0.89]

P Trend		0.136	0.903	0.673	0.159
PBDE 47+153 (µg/L)	<0.04 (ref)	0	0	0	0
	0.04-0.09	0.25 [-3.26 – 3.89]	-2.15 [-11.2 – 7.79]	-1.92 [-12.3 – 9.74]	-2.06 [-11.8 – 8.77]
	>0.09	3.73 [0.08 – 7.51]	-4.97 [-13.8 – 4.72]	-1.91 [-12.4 – 9.78]	-11.0 [-19.9 – -1.16]
P Trend		0.035	0.305	0.760	0.024
Mercury (µg/L)	<1.54 (ref)	0	0	0	0
	1.54-5.29	-0.74 [-3.94 – 2.57]	5.79 [-3.34 – 15.78]	5.35 [-4.97 – 16.80]	6.10 [-3.79 – 17.02]
	>5.29	1.67 [-2.21 – 5.71]	1.05 [-9.22 – 12.48]	3.01 [-8.86 – 16.43]	-4.51 [-15.0 – 7.27]
P Trend		0.286	0.889	0.805	0.224

a: % change adjusted for age, sex, waist circumference, smoking, omega-3 PUFAs, total lipids (except for mercury);
b: ΣPCB = sum (105+118+138+153+156+170+180); c: dioxin-like PCB = sum (105+118+156); d: ΣOC pest = sum (HCB+mirex +oxychlordane+*trans*-nonachlor+*p.p'*-DDE)

Table 5: Adjusted percentage change (%) in markers of glucose metabolism according to POPs (µg/L) and Hg (µg/L) in the adult Cree diabetes-free population (n=599)
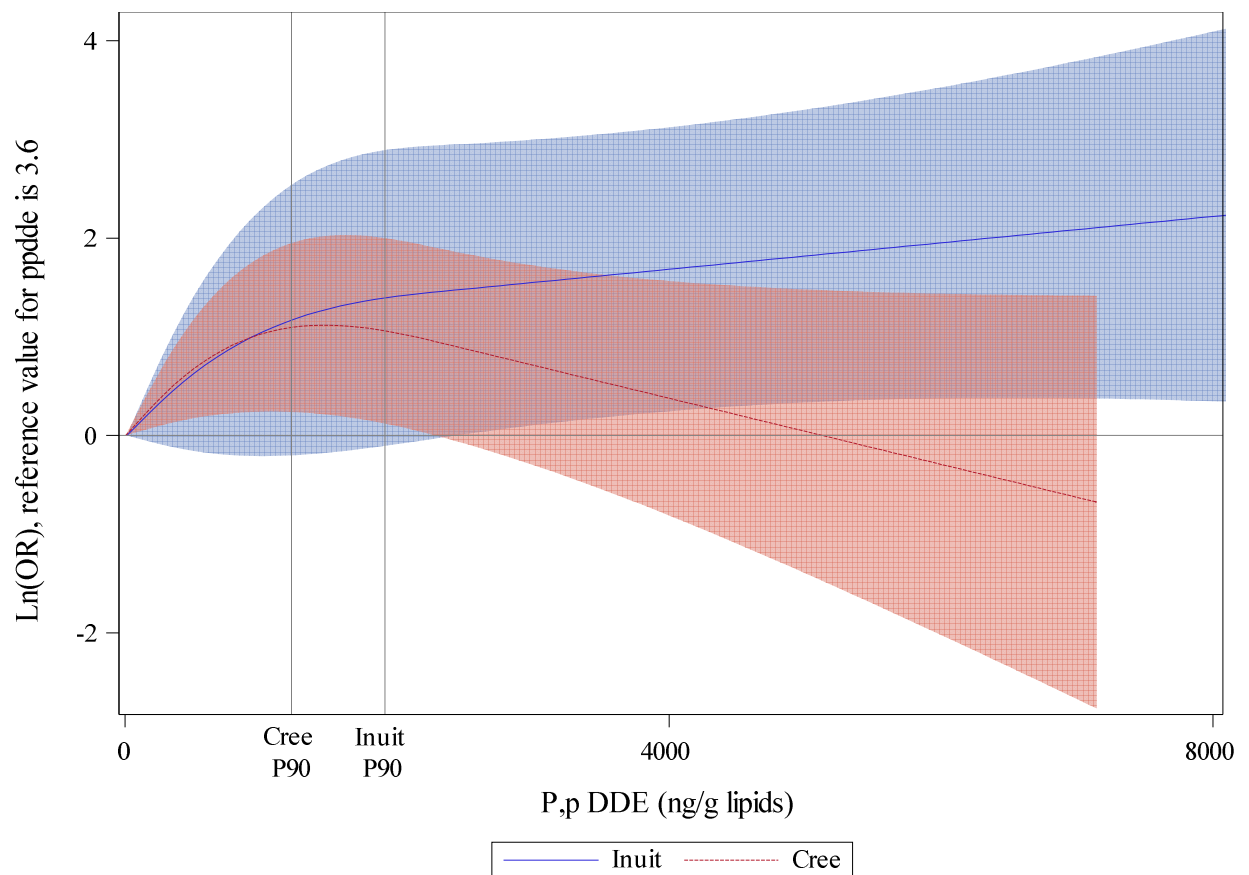
Figure 1: Generalized additive model (using restricted cubic spline with 3 knots) of the relationship between *p,p'*-DDE plasma concentration (ng/g lipids) and the risk of T2DM in Inuit and Cree populations
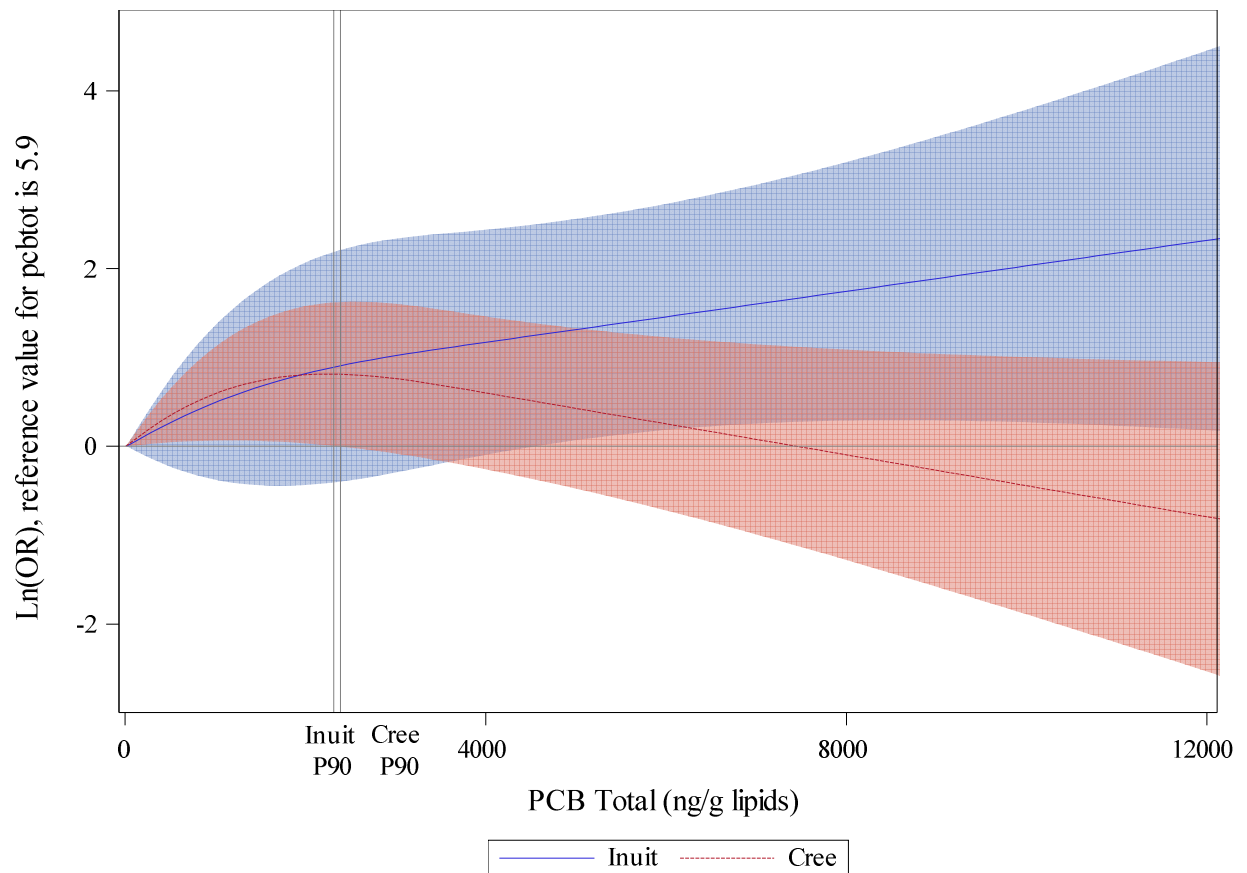
Figure 2: Generalized additive model (using restricted cubic spline with 3 knots) of the relationship between ΣPCB plasma concentration (ng/g lipids) and the risk of T2DM in Inuit and Cree populations
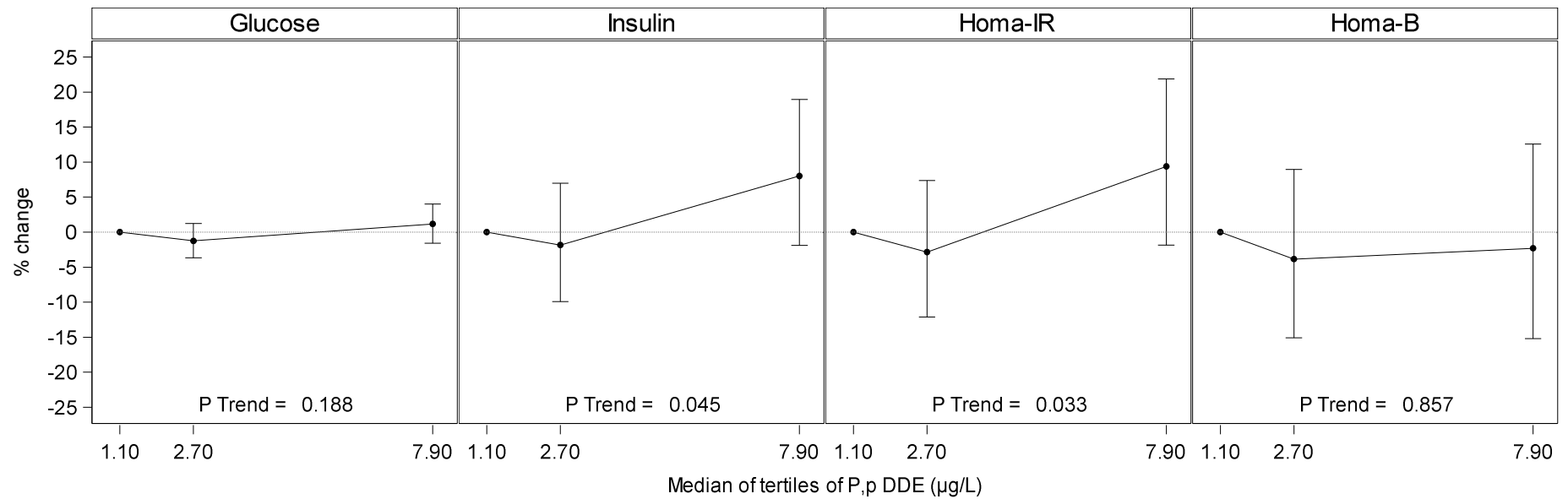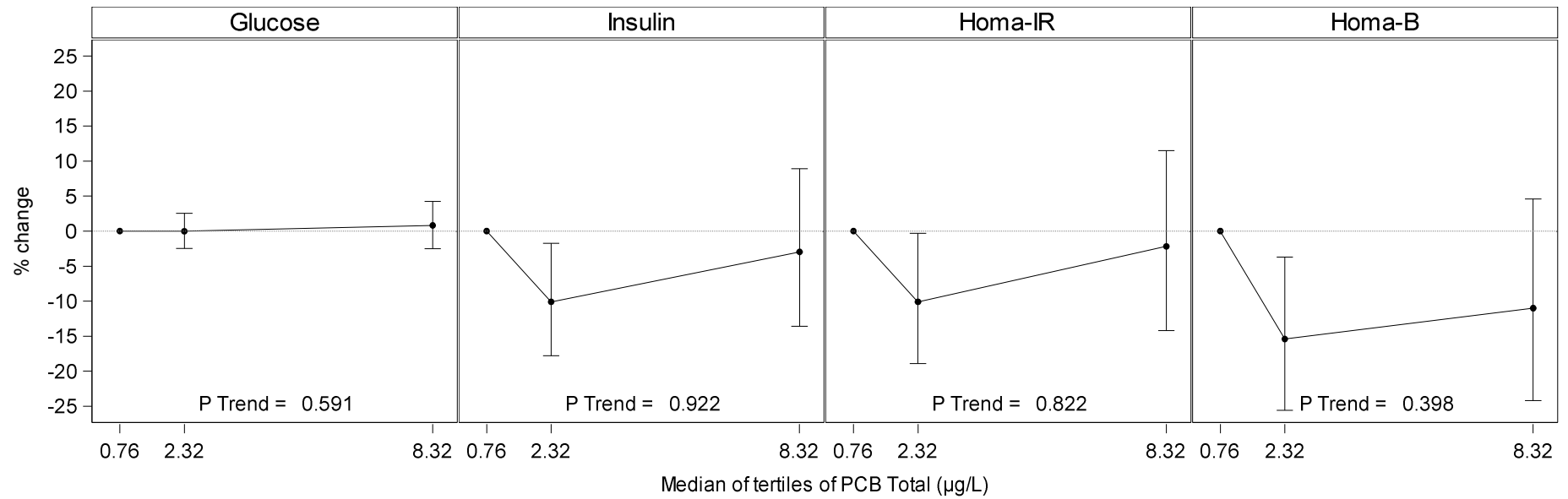
Figure 3 : Adjusted percentage change (%) in markers of glucose metabolism according to total PCBs (µg/L) and DDE (µg/L) (Inuit diabetes-free population   n=671)

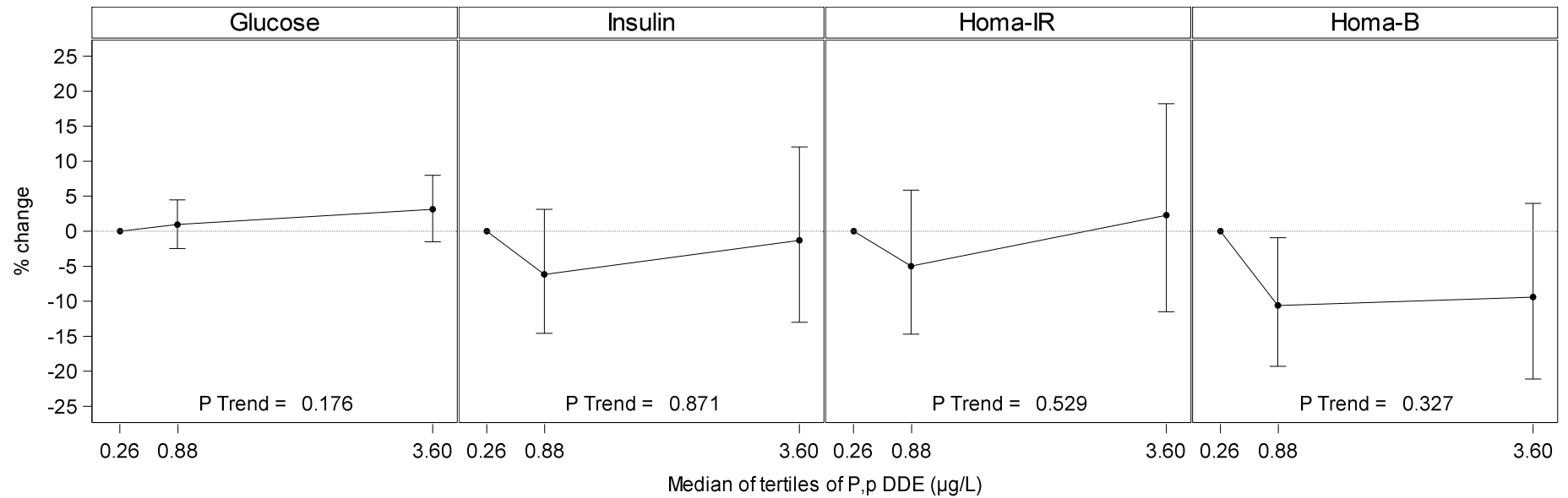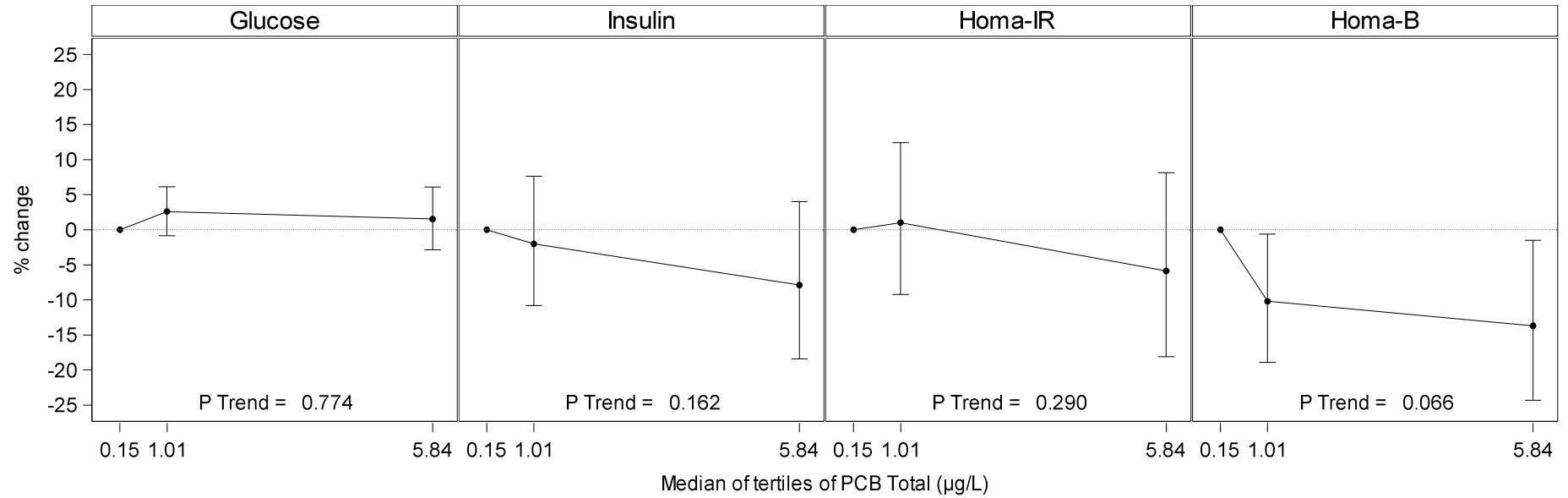Figure 4: Adjusted percentage change (%) in markers of glucose metabolism according to total PCBs (µg/L) and DDE (µg/L) (Cree diabetes-free population n=599)

Highlights:

. Several Indigenous people of Canada are exposed to mercury and mixtures of POPs

. Levels of exposure are much higher in Inuit compared to Cree

. In both populations, risk of diabetes increased with exposure to several POPs

. In diabetes-free Inuit, reduced insulin secretion was associated with several POPs

Declaration of interests

x The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: