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# Persistent organic pollutants and diabetes among Inuit in the Canadian Arctic

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ABSTRACT

Type 2 diabetes is a chronic metabolic disease that is of increasing concern in Inuit communities. Behavioural factors such as physical inactivity and poor diet are well-known risk factors. Exposure to persistent organic pollutants (POPs) has emerged as an additional factor in the pathogenesis of diabetes.

In this study, association between polychlorinated biphenyls (PCBs) and p,p′-dichlorodiphenyldichloroethylene (p,p′-DDE) with diabetes in Canadian Inuit was examined.

Data from the Adult Inuit Health Survey (2007–2008) of Inuit participants from the Canadian Arctic were analyzed. Self-reported diabetes (excluding gestational diabetes) and clinical measurement of fasting glucose were examined as outcomes. Association with individual PCB congeners, sum of dioxin-like PCBs (∑DL-PCB), non-dioxin-like PCBs (∑NDL-PCB), total PCBs (∑PCB), and p,p′-DDE were investigated using multiple regression models adjusted for confounding factors. Using different methods to incorporate serum lipids, highest vs. lowest quartile exposures to PCB-105, PCB-118, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, ∑PCB, and p,p′-DDE were associated with increased risk of diabetes. For these PCBs, odds ratios (ORs) ranged from 1.9–3.5 (lower 95% CI: 0.8–1.4, upper 95% CI: 4.4–9.0) and for p,p′-DDE the OR was 2.5 (lower 95% CI: 1.1–1.2, upper 95% CI: 5.9–6.0). The highest vs. lowest quartile exposure to most PCBs and p,p′-DDE were associated with an increase of fasting glucose by 3–7%.

PCBs and p,p′-DDE were associated with increased risk of diabetes and higher fasting glucose level in a cross-sectional survey of Canadian Inuit. Cause-effect relationships of PCBs and p,p′-DDE with diabetes and diabetes-related outcomes need to be further investigated in a cohort study.



## 1. Introduction

Diabetes is a chronic metabolic disease with incidence rates increasing around the world ([WHO] World Health Organization, 2016). In Canada, the prevalence of diabetes was 6.8% (2.4 million Canadians) in 2009 and is expected to rise to 3.7 million people by 2019 ([PHAC] Public Health Agency of Canada, 2011). Nine out of ten have type 2 diabetes, which is characterized by increased hepatic glucose output, reduced insulin secretion, and insulin resistance ([CDA] Canadian Diabetes Association, 2016). Although type 2 diabetes is generally diagnosed in adults over the age of 40 years, this condition is increasingly being detected in adolescents and children ([PHAC] Public Health Agency of Canada, 2011). Since people with diabetes are more likely to be hospitalized and to require specialist care, the healthcare costs of diabetes are also significant. By 2020, diabetes-associated costs to the Canadian healthcare system are estimated to reach 16.9 billion dollars per year ([CDA] Canadian Diabetes Association, 2011).

The Canadian Inuit population comprises nearly 60,000 people and about 75% reside in the northern Canadian regions of Nunatsiavut, Nunavik, Nunavut, and the Inuvialuit Settlement Region (Statistics Canada, 2011). Although diabetes prevalence in Canadian Inuit is similar to the general Canadian population, it is on the rise with increase from 2% in 2001 to 5% in 2012 (Tait, 2006; Wallace, 2014). This rise of prevalence in Inuit communities is of concern because diabetes is an independent risk factor for cardiovascular disease and leads to several health complications. Many risk factors for diabetes, such as physical inactivity, high caloric intake, shift in dietary pattern, and obesity are prevalent in the Inuit (Jørgensen, 2010). In addition, upstream factors that impact the social determinants of health such as housing conditions, food insecurity, employment opportunities, and access to healthcare also have an impact on diabetes prevalence ([PHAC] Public Health Agency of Canada, 2011). The Aboriginal Peoples Survey 2012 reported that 30% of Inuit 18 years of age or older were overweight and 26% were obese based on body mass index (BMI) (Wallace, 2014). In addition, 41% of Inuit 15 years of age or older experienced food insecurity in the past 12 months compared with 8% of the general Canadian population (Wallace, 2014).

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Global pollution and long-range transport have caused accumulation of persistent organic pollutants (POPs) in the Arctic environment (Donaldson et al., 2010). Marine mammals have high concentrations of POPs, particularly in fat, due to biomagnification of contaminants to the top trophic levels of the food chain (Donaldson et al., 2010). Many studies have shown that Inuit have high exposure and body burden of POPs because of their traditional diets that include marine mammals (Donaldson et al., 2010). The association between POPs and diabetes has been investigated in human populations around the globe (Sharp, 2009; Taylor et al., 2013). In a review of epidemiological studies, the strongest positive association with type 2 diabetes was found with organochlorine pesticides and polychlorinated biphenyls (PCBs) (Taylor et al., 2013). In the Arctic, a cross-sectional study of 692 adult Greenlandic Inuit found that POPs were not associated with diabetes or impaired glucose tolerance but there was an inverse association with stimulated insulin concentration and homeostasis model assessment of beta cell function (HOMA-B) (Jørgensen et al., 2008). This study suggested that POPs may affect insulin secretion rather than insulin resistance. In a smaller study of 101 participants from a Canadian First Nations community, self-reported diabetes was positively associated with p,p′-dichlorodiphenyldichloroethylene (p,p′-DDE) and PCBs (Philibert et al., 2009).

The purpose of this study was to investigate if there is association between blood PCBs or p,p′-DDE concentrations and diabetes in a sample population of Canadian Inuit. Self-reported diabetes (excluding gestational diabetes) and measured fasting glucose were examined in this study. This is the first study, to our knowledge, that has evaluated the relationship between POP exposures and diabetes in this population.

## 2. Methods

### 2.1. Participants and data collection

The Adult Inuit Health Survey (2007–2008) was a cross-sectional survey of Canadian Inuit across 33 coastal communities and three inland communities in the Inuvialuit Settlement Region, Nunavut Territory, and Nunatsiavut and was conducted as part of the International Polar Year program (Saudny et al., 2012). The survey included questionnaires about health status, chronic diseases, and behaviours such as exercise, smoking and alcohol intake. For self-reported conditions, respondents were asked the question "Did a doctor or a nurse ever tell you that you suffered from diabetes (other than during pregnancy)". Also included in the survey were tests of clinical parameters such as fasting glucose and blood levels of PCBs and organochlorine pesticides. A total of 2595 Inuit who were 18 years of age or older participated in the survey (68% participation rate) and 2172 provided blood samples. The following PCB congeners were measured in blood plasma: PCB-28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 163, 170, 180, 183, and 187. PCB-163 was omitted from analyses because about 56% of observations were not reported. Pregnant women were excluded. All work was approved by the research ethics boards of the University of Northern British Columbia, McGill University and the University of Ottawa.

### 2.2. Exposures

The association with diabetes was explored with individual PCB congeners (PCB-99, 105, 118, 138, 153, 156, 170, 180, 183, 187); PCB groupings - sum of dioxin-like PCBs ($\sum$ DL-PCB), sum of non-dioxin like PCBs ($\sum$ NDL-PCB) and total PCBs ($\sum$ PCB); and the organochlorine pesticide metabolite, p,p′-DDE. Details of analytic methods and quality control procedures have been described previously (Laird et al., 2013). Samples were analyzed by the Laboratoire de Toxicologie at the Institut National de Santé Publique du Québec. In this study, we grouped the PCB congeners into sum of dioxin-like PCBs ($\sum$ DL-PCB), sum of non-dioxin like PCBs ($\sum$ NDL-PCB) and total PCBs ($\sum$ PCB).

$$\sum \text{DL-PCB} = \text{PCB-105} + \text{PCB-118} + \text{PCB-156}$$
$$\sum \text{NDL-PCB} = \text{PCB-28} + \text{PCB-52} + \text{PCB-99} + \text{PCB-101} + \text{PCB-128} + \text{PCB-138} + \text{PCB-153} + \text{PCB-170} + \text{PCB-180} + \text{PCB-183} + \text{PCB-187}$$
$$\sum \text{PCB} = \sum \text{DL-PCB} + \sum \text{NDL-PCB}$$

All contaminants were divided into quartile level on both lipid and wet-weight basis and the first quartile was set as the reference category (Table 1 provides concentration ranges of each quartile for each examined contaminant). The lipid-based quartile concentrations were calculated by dividing wet-weight concentration by total serum lipid. Total serum lipid was derived from total cholesterol and triglycerides using the equation (Bernert et al., 2007):

$$\text{Total lipids (mg/dL)} = 2.27 * \text{total cholesterol} + \text{triglycerides} + 62.3 \quad (1)$$

Values below the limit of detection were recoded as half the detection limit value (Supplementary Table 1). Observations with missing values for contaminant or total serum lipid were excluded from analyses.

### 2.3. Outcomes

Self-reported diabetes (excluding gestational diabetes) and measured fasting glucose were examined in this study. Type 1 and 2 diabetes were not differentiated, however, it could be assumed that the majority of the self-reported cases would be type 2 based on the epidemiology of diabetes ([PHAC] Public Health Agency of Canada, 2011 p.8). The natural logarithm transformation of fasting glucose was included in models. If respondents indicated that they did not have diabetes but reported that they were taking a medication for diabetes, they were reclassified as positive. Seven respondents were reclassified as positive based on medication use.

### 2.4. Statistical analyses

Multiple logistic regression models were developed to examine association between PCBs, p,p′-DDE, and diabetes self-reported dichotomously. Multiple linear regression models were also developed for fasting glucose. For linear regression models, the assumptions of linearity, normality, and homoscedasticity of residuals were verified qualitatively with plots. Models were run using wet-weight quartile categories, quartiles based on wet-weight divided by total serum lipids, and wet-weight quartile categories with total serum lipids as a covariate. The latter two are termed lipid standardized and lipid adjusted according to the nomenclature of Schisterman et al. (2005). All model results are available in Supplementary Tables 2 and 3. Here, results based on lipid standardized and lipid adjusted modeling are presented.

Covariates considered for inclusion in models were age; sex; marital status; education; income; total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), alcohol intake, cigarette smoking, exercise as measured with total metabolic equivalent (MET) score based on walking, moderate activity, and vigourous activity; BMI; blood levels of heavy metals (selenium, lead, mercury, and cadmium); total monounsaturated fatty acids (MUFA), total polyunsaturated fatty acids (PUFA), total saturated fats, omega-3 fatty acids, omega-6 fatty acids, and omega-3/omega-6 ratio in red blood cells; family history (diabetes in parent or sibling), and medication use. Covariates were examined in univariate analyses with each outcome and were considered for inclusion in full models based on statistical significance, missing data, and available degrees of freedom. Collinearity among covariates was tested with the variance inflation factor (VIF).

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