GSL J Public Health Epidemiol

Global Scientific Library

Research Article

Body Burden of Persistent Organic Pollutants Were Negatively Associated with Adiponectin and Positively Associated with Glucose Intolerance Among Inuit in Canada

Zienczuk N[1], Egeland G[2] and Chan HM[1]*

[1]Centre for Advanced Research in Environmental Genomics and the Department of Biology, University of Ottawa, Ottawa, Ontario, Canada
[2]Norwegian Institute of Public Health and the Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

Abstract

Background: Persistent organic pollutants have been identified as potential risk factors for the development of obesity-associated metabolic diseases such as Type 2 Diabetes.

Objectives: We investigated the cross-sectional association between serum concentrations of Persistent Organic Pollutants (POPs) and markers of diabetes risk among non-diabetic Inuit adults in northern Canada using data collected by the International Polar Year Inuit Health Survey (2007-2008) in Canada.

Methods: A total of 2595 Inuit aged over 18 living in northern Canada participated in the Inuit Health Survey. Out of which, 792 non-diabetic participants completed the Oral Glucose Tolerance Test (OGTT) and were included in this study. Logistic regression models were constructed to evaluate the association between lipid-standardized serum concentrations of POPs and glucose intolerance. Linear regression was used to determine the association between serum POPs and adiponectin. All models were adjusted for age, sex, waist circumference, and smoking status. Analyses were conducted using STATA version 11.0 and a P-value <0.05 was considered statistically significant.

Results: Mean concentrations of all POPs included in the analyses were 2-fold higher in glucose intolerant versus normoglycemic participants (P<0.001). An increased odds for glucose intolerance was observed among participants with high concentrations of trans-nonachlor (OR=2.23; 95%CI=1.09,4.56), toxaphene Parlar50 (OR=2.03 95%CI=1.01, 4.06), PCB118 (OR=2.75; 95%CI=1.27; 5.98), and PCB138 (OR=2.14; 95%CI=1.00; 4.55). All POPs included in the analyses were significantly and negatively associated with adiponectin.

2. Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder currently burdening population worldwide. It is estimated that over 422 million people are suffering from T2DM (GLOBAL REPORT ON DIABETES WHO Library Cataloguing-in-Publication Data Global Report on Diabetes, 2016) [1]. Although diabetes has not reached epidemic proportions among Canadian Inuit, the prevalence has been increasing from xx % to YY% since the mid-1900s [2,3] and is reported to have doubled between 2001 from 2% and 4 % in 2006 (PHAC, 2011) reflecting an increasing trend that is of public health concern. The rapid increase in diabetes prevalence among Inuit is related to the drastic sociocultural and nutrition transitions the population is currently experiencing. Inuit in northern Canada have a strikingly high prevalence of obesity as well as dietary intake patterns [4] and a metabolic profile indicative of increased risk for diabetes [5]. However, emerging evidence suggests that nontraditional risk factors, such as exposure to environmental chemicals, may be contributing to the development of obesity and metabolic disorders [6].

***Corresponding Author:** Chan HM, Norwegian Institute of Public Health and the Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

Received: Nov 20, 2023; **Accepted:** Dec 05, 2023; **Published:** Dec 07, 2023

Persistent Organic Pollutants (POPs) comprise a wide range of chemicals derived from anthropogenic sources, including dioxins, polychlorinated biphenyls, organochlorine pesticides, brominated flame retardants, and perfluorinated acids (ref). Although most POPs of concern have been banned or severely restricted since the 1970's, these compounds are highly resistant to degradation and consequently persist in the environment for decades [7]. POPs are highly lipophilic, bio-accumulate, biomagnify, undergo long range transport through ocean and atmospheric processes, and accumulate in Arctic ecosystems (ref). Given that the Inuit Nunangat stretches across the circumpolar Arctic, Inuit have one of the highest exposures to POPs in the world (ref). Humans are primarily exposed to POPs through the consumption of animal fats. Owing to their lipophilicity, POPs accumulate in lipid compartments of human and animal tissues. Arctic homeotherms heavily rely on lipid energy stores, which are necessary for survival in the Arctic but also result in a greater capacity to accrue POPs. Since the traditional diet of Inuit is heavily lipid-based, food is a disproportionately significant pathway for exposure to POPs among Inuit (ref). According to recent biomonitoring studies, blood concentrations of POPs are higher among Inuit in the Canadian Arctic compared to the general Canadian population [8].

Since POPs have lipophilic physiochemical properties and are primarily stored in adipose tissue, adipose tissue is a target organ for toxicity [9]. Adipose tissue plays a central role in the pathogenesis of

T2DM as an active metabolic and endocrine organ that secretes an array of adipocytokines such as tumour necrosis factor-alpha (TNF), leptin, and adiponectin. Both the metabolic and endocrine functions of adipose tissue are critically involved in the maintaining insulin sensitivity and energy homeostasis. Immunity and metabolism are also closely linked processes and obesity is increasingly recognized as an inflammatory disease characterized by overproduction of pro-inflammatory adipocytokines, such as TNF , and decreased production of adiponectin and there is increasing evidence that POPs may contribute to this pathophysiological state [10]. Adiponectin is hormone predominantly secreted by adipocytes that acts as an anti-diabetic, anti-atherogenic, and anti-inflammatory adipocytokine [11]. Adiponectin is considered a protective adipokine due to its insulin-sensitizing effects and biomarker of adipose tissue function and is dose-dependently associated with decreased risk of T2DM in diverse ethnic groups [12]. Binding of adiponectin to its receptors in skeletal muscle and liver increases beta-oxidation of fatty acids, thereby reducing triglyceride content and increasing insulin sensitivity [13,14]. However, adiponectin levels decrease with increasing adiposity and are reduced in T2DM. Furthermore, an inverse association between serum POPs and adiponectin has been found in obese individuals, suggesting that interference with the endocrine-secretory capacity of adipose tissue may be a biologically plausible mechanism through which POPs increase the risk of developing T2DM [9].

Numerous epidemiological studies conducted over the last decade have found an association between Persistent Organic Pollutants (POPs) and diabetes, altered glucose homeostasis, insulin resistance, as well as the metabolic syndrome [15]. These findings suggest that exposure to POPs may be an additional risk factor that contributes to the development and progression of T2DM among the Inuit. Using data collected by the cross-sectional Inuit Health Survey (2007-2008) [5], the present study investigated if serum concentrations of POPs exhibit a cross-sectional association with prediabetic states of glycemia among highly exposed non-diabetic Inuit adults. We also explored the feasibility of using adiponectin as a biomarker for either POP effects or risk of diabetes. These findings will help to understand the roles of POPs in the development of dysglycemia at early stages in the natural history of T2DM.

3. Methods

3.1. Study design

The Inuit Health Survey (2007-2008) was a cross-sectional survey carried out in 36 Inuit communities in 3 regions of Inuit Nunangat. Details of the survey protocol are available elsewhere (Saudny-Unterberger 2012). Briefly, homes were randomly selected using a computerized random digit assignment or table. A total of 2796 households were approached, of which 1901 (68%) agreed to participate for a total of 2595 participants. All participants were Inuit, over the age of 18, and lived in Nunavut, Nunatsiavut, and the Inuvialuit Settlement Region. The survey consisted of a battery of interviewer-administered questionnaires and clinical assessments that collected information on indicators of health and well-being among Inuit adults in the Canadian Arctic and was developed in a participatory manner with members of the steering committees of the 3 Inuit jurisdictions. Participation was voluntary and informed consent was obtained from each participant. A certificate of Ethical Acceptability was obtained from the McGill Faculty of Medicine Institutional Review Board.

3.2. Inclusion criteria and definitions

Participants who completed the OGTT (n=831) were considered for inclusion in the present analyses while those who were previously diagnosed with diabetes and/or on any diabetes medication or treatments, as ascertained by medical charts, were excluded. The American Diabetes Association (ADA) guidelines were used to identify diabetes and pre-diabetes based on fasting and 2-hour plasma glucose concentrations and newly identified diabetics (fasting glucose >7mmol/L or 2-hour glucose> 11.1 mmol/L) were also excluded from the present study. Participants with impaired fasting glucose (fasting plasma glucose>5.6 mmol/L and <7 mmol/L) and/or impaired glucose tolerance (2-hour glucose>7.8 mmol/L and <11.1 mmol/L) were classified as Glucose Intolerant (GI) and compared with normoglycemic participants.

3.3. Questionnaires

All questionnaires were interviewer-administered by trained bilingual research personnel. Information was collected on various indicators of physical and mental health, nutrition, and environment of Inuit. Data collected pertaining to a history of diabetes, use of supplements and medicaments, sociodemographics, and smoking was used in the present analyses.

3.4. Anthropometric assessments

Waist Circumference (WC) measurements were obtained for determining the extent of abdominal obesity. Measurements to the nearest millimeter were made at the midpoint between the top of the hip and the last loose rib following the end of a normal expiration. Percent body fat was determined by bioelectrical impedance using a foot-to-foot Tanita scale (Tanita Corporattion Tokyo, Japan).

3.5. Blood collection and laboratory analyses

After fasting for a minimum of 8 hours, venous blood sample collection was performed by a registered nurse. Owing to logistical constraints, only a sub-sample of participants (approximately 30%) completed a 75g Oral Glucose Tolerance Test (OGTT). Following collection of the first blood sample, individuals with a fasting blood capillary glucose level < 7 mmol/L, participants were asked to consume a 75g glucose drink within 5 minutes and a second blood collection tool place 2 hours later. The test was not performed on individuals who reported taking medication for diabetes or had a fasting blood capillary glucose level > 7 mmol/L. Fasting and 2-hour blood samples were stored on ice or 4 C until transfer to the lab where they were processed and immediately stored at -80 C. Analysis of blood samples was arranged through Nutrasouce Diagnostics (Guelph, ON). Blood glucose levels were determined using the glucose hexokinase II method. Enzymatic colorimetric tests were used to determine fasting serum cholesterol

and triglycerides. Electrochemiluminescent immunoassay (ECLIA) was used to determine blood insulin levels at the Institut de Cardiologie et de Pneumologie de Quebec (IUCPQ) (Quebec City, QC).

3.6. Persistent organic pollutants

Detailed methods for analyses of POPs in plasma samples were reported in [8]. Briefly, POPs were extracted with hexane and cleaned up on florisil columns and measured by GC-MS on a DB-XLB column. POPs including oxychlordane, transnonachlor, DDE, toxaphene 50, PCB118, PCB156, PCB138, PCB153, and PCB180 that were previously reported to have endocrine disruptive properties (ref, Muir) were chosen to be included in the analysis of this study. All analyses were performed using lipid-standardized concentrations of POPs (ug/g lipid).

3.7. Statistics

The normality of the data was tested. Either non-parametric tests were used or appropriate data transformation was performed before parametric tests were used. Serum contaminant concentrations, HOMA-IR index, leptin, and adiponectin did not follow the Gaussian distribution; therefore, the Wilcoxon rank-sum non-parametric test of means was used for these parameters and geometric means (SE) are presented. Pearson's chi-squared test was used for categorical variables. Student's t-tests were used to compare differences in means by glucose tolerance status and sex. Multivariable-adjusted logistic regression was used to estimate Odds Ratios (ORs) and corresponding 95% Confidence Intervals (CI) for the association between serum POP concentrations and glucose intolerance using the equation log(p/1-p) = b-not + b1x1 + b2x2 etc. All of the POPs included in the present analyses were highly correlated with each other (r=0.68 to r=0.96), therefore, two logistic regression approaches were made to evaluate the association of glucose intolerance with each of the POPs by quartile. The first one was analyzing each POP concentration separately in separate logistic regression analysis by comparing quartile categories, using the lowest quartile (which included participants with concentrations below the LOD) as the reference group. The second approach was by summing the ranks of participants' POP concentrations within each of the three defined subclasses: OC pesticides (list them out), dioxin-like PCBs (list them out), and non-dioxin like PCBs (list). The cumulative rank score of each subclass was entered separately into a multivariable model as quartile categories. In both regression methods, biologically plausible risk factors for diabetes including age, sex, waist circumference (cm), and smoking status, were entered as covariates. Smoking was categorized as non-smokers versus current and former smokers. Because total energy intake (kilocalories) and physical activity (MET score) were not associated with glucose intolerance in simple regression models, nor did they improve overall model fit according to the Akaike Information Criterion (AIC), these variables were not included.

Multiple linear regression was used to evaluate the associations of serum POP concentrations with adiponectin. To account for potential confounding effects, we included age, sex, waist circumference, and smoking status as covariates. A Variance Inflation Factor (VIF) of 5 was used as an indicator of multicollinearity and effect modification was tested by simultaneously entering the main effects plus interaction terms into regression models. All analyses were performed using STATA version 11.0 statistical software package and we considered $P<0.05$ as statistically significant.

4. Results

A total of 831 participants completed an OGTT. After excluding diabetics, participants who fasted for < 7 hours, as well as those who reported taking anti-diabetic treatments or medications, the final study sample consisted of 792 non-diabetic Inuit adults. Table 1 shows the lipid-standardized serum distribution of POPs including four OC pesticides, 3 non-dioxin-like PCBs, and 2 dioxin-like PCBs in the study sample. All analytes were detected in >90% of the sample, with the exception of PCB 156 which was detected in 81% of the sample. Dioxin-like PCBs had the lowest median concentrations (15 and 7.3 ng/g lipid for PCB 118 and PCB 156, respectively). Median concentrations were in the range of 45 to 111 ng/g lipid for non-dioxin-like PCBs and 17 to 281 ng/g lipid for OC pesticides. Among all POPs, the highest median concentration of 281 ng/g lipid was observed for DDE.

Table 1: Distribution of lipid-standardized persistent organic pollutants (POP) concentrations among Inuit participants.

Analyte (ng/g lipid)	%>LOD	Geometric Mean (95%CI)	Median	Range
OC pesticides				
Oxychlordane	97.8	43 (38, 49)	48	0.2-2127
Transnonachlor	97.4	67 (59, 75)	80	0.8-3094
p,p'-DDE	99.5	258 (237, 282)	281	1.5-8189
Toxaphene (Parlar 50)	91.2	14 (12, 15)	17	0.3-855
Dioxin-like PCBs				
PCB 118	94.3	15 (14, 16)	15	0.7-619
PCB 156	81.1	6.4 (5.9, 7.1)	7.3	0.5-185
Non-dioxin like PCBs				
PCB 138	98	40 (36, 44)	45	0.8-935
PCB 153	99.8	101 (91, 112)	111	0.8-3207
PCB 180	99.2	53 (48, 59)	58	0.8-2453

Table 2: Characteristics of study subjects by glucose tolerance status and sex.

Variables	Normoglycemic	Glucose Intolerant	P value[a]	Male	Female	P value[a]
n (%)	658 (83)	134 (17)		316 (39)	488 (61)	
Male n (%)	255 (39)	57 (43)	0.41	-	-	
Age (years)	39.9 ± 13.2	51.1 ± 13.2	<0.001*	42.4 ± 14.0	41.4 ± 13.7	0.31
Smokers n (%)[b, c]	616 (94)	117 (90)	0.08	286 (93)	447 (94)	0.76
WC (cm)	92.1 ± 15.4	102 ± 16.6	<0.001*	92.0 ±14.6	94.8 ± 16.8	0.01*
% BF	29.9 ± 11.1	35.5 ± 10.3	<0.001*	23.3 ±8.86	35.7 ± 9.74	<0.001*
Serum lipids (g/L)	6.16 ± 1.37	6.81 ± 1.53	<0.001*	6.22 ± 1.52	6.31 ± 1.35	0.36
Adiponectin (ug/mL)[d]	10.4	9.15	0.32	10.32	10.27	0.37
Leptin (ug/mL)[d]	11.1	17	0.001*	4.2	18.8	<0.001*
OC pesticides (ng/g lipid)[d]						
Oxychlordane	38	84	<0.001*	67	32	<0.001*
Transnonachlor	58	137	<0.001*	101	51	<0.001*
p,p'-DDE	234	423	<0.001*	350	211	<0.001*
Toxaphene (parlar 50)	12	29	<0.001*	18	11	<0.001*
Dioxin-like PCBs (ng/g lipid)[d]						
PCB118	13	29	<0.001*	18	13	<0.001*
PCB156	5.8	11	<0.001*	11	4.6	<0.001*
Non-dioxin like PCBs (ng/g lipid)[d]						
PCB138	35	73	<0.001*	58	31	<0.001*
PCB153	89	179	<0.001*	160	74	<0.001*
PCB180	48	92	<0.001*	93	37	<0.001*

WC: Waist Circumference; %BF: Percent Body Fat; PCB: Polychlorinated Biphenyl

[a]Student's t-test for differences in means ± SD for normally distributed parameters, unless otherwise indicated.

[b]Pearson chi-square test.

[c]Smokers included current smokers and former smokers.

[d]Wilcoxon rank sum non-parametric test of means; median is presented.

Of the participants included in the present analyses, 134 (17.0%) were classified as glucose intolerant Table 2. Of the glucose intolerant participants, 89 (11.3%) had isolated impaired fasting glucose (IFG), 55 (6.97%) had isolated Impaired Glucose Tolerance (IGT), and 10 (1.26%) had both IFG and IGT. Glucose intolerant participants were significantly older (p<0.001) than normoglycemic participants. A similar proportion of males and females were glucose intolerant (18% and 16%, respectively). Smoking was highly prevalent among all study subjects, regardless of glucose tolerance status and sex. Glucose intolerant participants had a significantly higher mean waist circumference, percentage body fat, and total serum lipid concentration (p<0.001). Circulating adiponectin concentrations were comparable (p=0.32) among glucose intolerant and normoglycemic participants (9.06 ug/mL versus 9.42 ug/mL), however the concentration of leptin was significantly higher in glucose intolerant participants (17 ug/ml versus 11 ug/mL; p<0.001). Furthermore, females had a significantly higher leptin concentration than males (18.8 ug/mL and 4.2 ug/mL, respectively; p<0.001). Concentrations of all POPs analyzed were, on average, approximately two-fold higher in glucose intolerant participants and males than in normoglycemic participant ts and females, respectively (p<0.001).

4.1. Association Between POPs and Glucose Intolerance

Separate approach:

Subclass approach:

Similar and difference

Each POP was significantly and positively associated with glucose intolerance in separate models. After adjusting for age, sex, waist circumference, and smoking status, increased odds of glucose intolerance were observed at the highest versus lowest quartile of transnonachlor (OR=2.20; 95% CI=1.07; 4.51), toxaphene (OR=2.04; 95% CI=1.01; 4.09), PCB118 (OR=2.76; 95% CI=1.26; 6.03), and PCB 138 (OR=2.11; 95% CI=0.99; 4.49) Table 3, N.

Table 3: Adjusted a odds ratio (or) and 95%CI for glucose intolerance among Inuit adults by quartiles of POPs (ug/g **lipid).**

Analyte	Quartiles of Serum POPs (ug/g lipid)				P-trend
	Q1	Q2	Q3	Q4	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
OC Pesticides	Referent	1.58 (0.80; 3.10)	1.22 (0.60; 2.50)	2.25 (1.10; 4.60)*	
Oxychlordane	Referent	1.10 (0.57; 2.15	1.10 (0.55; 2.18)	1.73 (0.87; 3.45)	
Trans-nonachlor	Referent	1.62 (0.83; 3.15)	1.21 (0.59; 2.47)	2.26 (1.11; 4.61)*	
p,p'- DDE	Referent	1.33 (0.68; 2.60)	1.22 (0.61; 2.46)	1.99 (0.98; 4.05)#	
Toxaphene 50	Referent	1.60 (0.80; 3.19)	1.74 (0.89; 3.42)	2.11 (1.06; 4.20)*	
Dioxin-like PCBs		1.47 (0.71; 3.07)	1.46 (0.68; 3.14)	1.99 (0.87; 4.55)	
PCB118	Referent	2.31 (1.13; 4.73)*	1.45 (0.67; 3.14)	2.76 (1.27; 6.00)**	
PCB156	Referent	1.10 (0.53; 2.28)	1.37 (0.64; 2.90)	1.14 (0.48; 2.70)	
Non-dioxin-like PCBs		1.28 (0.64; 2.56)	1.10 (0.52; 2.31)	1.63 (0.75; 3.54)	
PCB138	Referent	1.46 (0.72; 2.96)	1.64 (0.79; 3.38)	2.11 (0.99; 4.49)*	
PCB153	Referent	1.45 (0.74; 2.86)	1.06 (0.51; 2.22)	1.73 (0.81; 3.68)	
PCB180	Referent	1.31 (0.64; 2.66)	1.34 (0.63; 2.83)	1.48 (0.65; 3.37)	
Σ ΠΟΠσ		1.63 (0.81; 3.30)	1.30 (0.61; 2.75)	2.50 (1.15; 5.43)*	

POPs: Persistent Organic Pollutants; DDE: Dichlorodiphenyltrichloroethane; PCB: Polychlorinated Biphenyl.

aAdjusted for age, sex, smoking status, waist circumference, Rank orders of individual POPs in each subclass were summed to obtain subclass values (ranks of all nine POPs were summed to obtain SumPOPs values)

In subclass analyses, the sum of ranks of POPs belonging to the OC pesticide subclass, in the highest versus lowest quartile, was significantly associated with glucose intolerance (OR=2.18; 95% CI=1.06; 4.48) after adjusting for the potential confounding variables. Furthermore, the sum of all POPs was significantly and positively associated with glucose intolerance in the highest versus lowest quartile (OR=2.50 95% CI =1.15; 5.43).

Linear regression analyses were performed to evaluate the association of each contaminant with adiponectin (Table 4). Each POP, except for PCB156, was significantly and negatively associated with adiponectin in separate linear regression models adjusted for age, sex, smoking status, and waist circumference.

Table 4: Association of serum adiponectin with serum POPs (ug/g lipid).

Analyte[c]	β (ΣE)[α]	β_{σ} [β]	P value	R^2
Oxychlordane	-0.36 (0.14)	-0.12	0.01	0.1
Trans-nonachlor	-0.48 (0.15)	-0.14	0.002	0.1
p,p'- DDE	-0.30 (0.20)	-0.066	0.14	0.09
Toxaphene 50	-0.43 (0.14)	-0.13	0.003	0.1
PCB118	-0.46 (0.20)	-0.11	0.02	0.1
PCB156	-0.04 (0.22)	-0.01	0.85	0.09
PCB138	-0.39 (0.19)	-0.1	0.04	0.1
PCB153	-0.40 (0.18)	-0.1	0.03	0.1
PCB180	-0.36 (0.20)	-0.09	0.07	0.09

5. Discussion

5.1. Key findings

Compared to bio monitoring data from the Canadian Health Measures Survey (2007-2009), geometric means of POPs in the present sample of Inuit adults were 2 to 11 times higher than those found in the Canadian general population (CHMS, 07/09). Increased odds for glucose intolerance were found among Inuit participants with POP exposure at the top 25th percentile. We found that, among non-diabetic Inuit adults who are highly exposed to environmental pollution in the Canadian high Arctic, serum concentrations of OC pesticides, dioxin-like PCBs, and non-dioxin-like PCBs were significantly associated with glucose intolerance. We also found that serum concentrations of POPs were significantly and inversely associated with circulating adiponectin concentrations after adjusting by age, sex, waist circumference, and smoking status. Our findings suggest that exposure to POPs may be an additional risk factor contributing to the increasing rate of T2DM among Inuit by promoting the development of a diabetic phenotype at early stages in the natural history of diabetes.

5.2. Comparison with other populations POPs and diabetes

Although causal inferences are not permitted based on cross-sectional data, the positive association between POPs and glucose intolerance in the present study is consistent with results from numerous epidemiological studies conducted in a variety of experimental contexts. In a recent review, it was concluded that the epidemiological evidence supports an association between POPs and diabetes [16], (Persistent Organic Pollutants and Diabetes: A Review of the Epidemiological Evidence, n.d.). In particular, the magnitude of the odds ratios for diabetes or diabetes-related outcomes was greatest for trans-nonachlor, DDE, and dioxin-like chemical exposures. Adding to the existing literature, we found that the odds of glucose intolerance were 2.04-2.75 times higher among non-diabetic participants with high concentrations of trans-nonachlor, toxaphene, dioxin-like PCB118, and non-dioxin-like PCB138 than among those with low concentrations in multivariable adjusted models (Model 2; Table 3). We chose to exclude diabetics to minimize the potential bias arising from serum lipids, which are highly elevated in diabetics and strongly associated with both diabetes and POPs. In accordance with our findings, high concentrations of PCB 118 and PCB138, as well as other PCBs, were associated with prediabetes in the general population of Catalonia and the association was observed in both obese and non-obese individuals belong to the general adult population of Spain [17]. In vitro and animal studies have shown that both dioxin-like PCB118 and non-dioxin-like PCB138 are obesogens due to their ability to promote fat cell development, increase the size of fat cells, and cause insulin resistance [18].

An association between POPs and prediabetes has also been found in Danish adults using impaired fasting glucose and impaired glucose tolerance as a marker of prediabetes [19]. In addition, this study also demonstrated a shift in substrate oxidation patterns towards higher lipid oxidation and lower glucose oxidation using the gold standard clamp technique. In the Faroe Islands, increased serum concentrations of PCBs due to high intake of traditional foods was associated with an increase in fasting glucose concentrations [19]. An association between POPs and the metabolic syndrome among nondiabetic US NHANES participants exposed to background levels of POPs has also been previously demonstrated and, similar to our findings, the strength of the association was greatest for OC pesticides [20]. A dose-response relationship between POPs and prediabetes was also observed in a heavily polluted area of Eastern Slovakia [21]. Our finding that POPs in each of the three subclasses were associated with dysglycemia is comparable to findings in a Native American population and First Nation community which demonstrated positive associations between non-dioxin like congeners with diabetes (Diabetes Prevalence in Relation to Serum Concentrations of Polychlorinated Biphenyl (PCB) Congener Groups and Three Chlorinated Pesticides in a Native American Population, n.d.) [22,23].

However, we found no association between DDE and glucose intolerance, similar to findings among a population in Spain [17] and in a cohort of Great Lakes sport caught fish consumers (Persistent Organic Pollutants and Biomarkers [24] of Diabetes Risk in a Cohort of Great Lakes Sport Caught Fish Consumers, n.d.) Similarly, DDE was associated with diabetes among Inuit in the Canadian Arctic [25] but not with prediabetes in the present study. These findings suggest that DDE effects manifest until the later stages in the pathogenesis of T2DM. Among Inuit in the Canadian Arctic, a recent study found a positive association between serum concentrations of PCBs and DDE and self-reported diabetes and fasting glucose concentrations [25]. High POP exposure (quartile 4 vs. quartile 1) was associated with a 3%-7% increase in fasting glucose concentration. If POPs lie on the causal pathway, then they should also be associated with markers Adding to the existing literature, we found a positive association between POPs and pre-diabetes among Inuit adults in the Canadian Arctic.

In subclass analyses, OC pesticides and the sum of all POPs were associated with glucose intolerance among Inuit in our study. Our finding that mixtures of POPs are associated with glucose intolerance are supported by experimental toxicity studies (R. J. Mailloux et al., 2014) [26]. Furthermore, mixtures of POPs found in Atlantic salmon also increased body weight, adipose-tissue specific and muscle insulin resistance, and triacylglycerol and cholesterol levels in the liver while also upregulating inflammatory pathway genes in adipose tissue in an animal model exposed to high fat crude versus high fat refined diet [27], highlighting the difficulties in examining present day diet-disease relationships to the fact that processing may also remove environmental contaminants. Although it is difficult to extrapolate in vitro results back to the biology of the intact organism and from animals to humans due to differences in the Arts hydrocarbon receptor (Ahr), which is responsible for dioxin-like PCB effects in adipose tissue [28], POPs stored in human AT samples were correlated with adipose tissue inflammation, characterized by macrophage infiltration, and increased adipocyte size as well as measures of glycemic and insulin sensitivity in [29]. Adipocytes and macrophages communicate through a paracrine signalling pathway involving TNFa and fatty acids that decreases adiponectin secretion and increases the secretion of pro-inflammatory factors from adipose tissue through the activation of the NFkB pat. An Interaction between PCB153 and high fat diet increased the expression

and nuclear translocation of NFkB and downstream inflammatory markets was also demonstrated in an animal model [30]. Furthermore, in mice fed either a control diet or 42% milk fat diet, PCB 153 was associated with increased visceral adiposity, hepatic steatosis, and altered adipocytokibe concentrations in high fat diet fed mice but not control mice [31] and, genes associated with B -oxidation were decreased in the liver while lipid biosynthesis genes were upregulated. These findings suggest that POPs may contribute a phenotypic shift in adipose tissue characterized by over-production of pro-inflammatory factors such as TNF-a, which is implicated in the development of insulin resistance and decreased adiponectin production - a protective adipokine that sensitizes hepatocytes to insulin by increasing the beta-oxxidation of fatty acid and also has anti-inflammatory properties [13].

5.3. New thing about POPs and adiponectin

In accordance with our hypothesis we found that serum concentrations of all POPs were inversely associated with adiponectin levels among Inuit in the Canadian arctic while holding other predictor variables constant. These novel findings suggest that adipose tissue is a target organ for toxicity among Inuit and interference with the endocrine secretory capacity of adipose tissue may be a potential mechanism through which POPs contribute to the development and progression of obesity-related disorders such as T2DM. These findings also suggest that POPs may promote some aspects of adipocyte dysfunction. The sum of all POPs contributed 1% of the explained variance in adiponectin concentrations (semi-partial R^2=0.01, p<0.01) However, the magnitude of the association between POPs and adiponectin levels was? marginal. For example, for a 1% increase in ….

A possible explanation for this may be related to the composition of the diet. The traditional diet of Inuit is high in beneficial nutrients such as omega 3 fatty acids which have been demonstrated to attenuate the PCB associated increase in the expression of pro-inflammatory markers (NFkB) when substituted for omega 6 fatty acids (Changing Ratios of Omega-6 to Omega-3 Fatty Acids Can Differentially Modulate Polychlorinated Biphenyl Toxicity in Endothelial Cells, n.d.) [32]. Given that POPs rank among endocrine disrupting chemicals and hypoadiponectinemia has been shown to precede the development of insulin resistance in animal models of obesity as well as in humans, interference with the endocrine secretory capacity of adipose tissue may be a relevant pathway through which POPs increase the risk of glucose intolerance among Inuit. Using an animal model, it has been demonstrated that mice with disruptions in the gene that codes for adiponectin exhibit diet-induced insulin resistance [33,34]. Although few epidemiological studies have examined the association between POPs and adiponectin, a negative association between PCB 153 concentrations and circulating adiponectin in obese women has also been previously reported [9]. Furthermore, a negative association between PCB 28, PCB 138, and PCB 153 and adiponectin concentration was also found in Individuals with a higher BMI value in a cross-sectional study of Korean men and women [35]. In a prospective study of veterans exposed to agent Orange, TCDD was negatively associated with adiponectin, however, the results were not statistically significant (kern). However, no association between POPs and adiponectin was found in a prospective cohort of Great Lakes sport caught fish consumers (Persistent Organic Pollutants and Biomarkers of Diabetes Risk in a Cohort of Great Lakes Sport Caught Fish Consumers, n.d.).

Our findings are supported by experimental studies that investigated the ability of specific classes of POPs to promote adipogenesis and alter the endocrine secretory profile of adipocyte [28, 36]. Found that dioxin-like PCBs were associated with adipocyte dysfunction. Adipocytokine levels were altered and the effects were mediated by the aryl hydrocarbon receptor; adiponectin mRNA expression was decreased and TNFa levels increased. Pro-inflammatory cytokines sunch as TNFa and IL-6 have been reported to decrease adiponectin expression [37] by suppressing the expression and transcriptional activity of transcription factors which positively regulate adiponectin transcription, including PPAR , C/EBP, and SREBP-1c [38-40]. Despite the up regulation of PPAR , by TCDD and PCB77, adiponectin expression was decreased. Although the molecular mechanisms underlying the association between POPs and adiponectin in our study are not fully understood, evidence exists to support divergent molecular mechanisms of POPs on diabetes [41,42].

Furthermore, in vitro and in vivo studies have shown that both dioxin-like PCB118 and non-dioxin-like PCB138 are obesogens due to their ability to promote fat cell development, increase the size of fat cells, and cause insulin resistance [18]. Adipocyte size is also an important determinant of adipokine secretion and it has been observed that large adipocytes favour increased expression of pro-inflammatory factors and decreased expression of adiponectin compared to smaller adipocytes [43]. Our finding that high concentrations of POPs are associated with lower adiponectin levels therefore supports the obesogen hypothesis that states that exposure to EDCs, particularly during early windows of developmental exposure, increases the commitment of cells to the adipocytic lineage, increases adipocyte differentiation hypertrophy, and increases the accumulation of lipids in fat cells [44]. The expansion of adipose tissue mass is also associated with up-regulation of inflammation related genes and increased macrophage infiltration [45]. The ability of xenobiotic agents to induce inflammation is well known. In humans, the strength of the association between plasma levels of POPs and circulating cytokine levels was investigated in First Nations adults living in two remote northern communities in Ontario and compared to a southern population [46]. It was found that First Nations people has mean plasma levels of PCBs and cytokines that were significantly greater than in Caucasians. Among the predictor variables included in statistical models, only high levels of PCBs accounted for a small but significant portion of the observed variance in cytokine levels. Furthermore, dioxins and dioxin-like PCBs were shown to primarily alter the expression of inflammatory pathway genes in adipocytes, both in vitro and in an animal model [47]. Therefore, our findings suggest that POPs stored in adipose tissue promote the development of a pro-inflammatory phenotype in adipose tissue characterized by decreased adiponectin production.

Although the mechanisms by which POPs increase the development of obesity and metabolic disease have not been fully elucidated, in vitro, animal, and human investigations have demonstrated that various classes of environmental chemicals modify epigenetic marks

on chromatin [48]. Epigenetics has been defined as the study of heritable changes in gene expression that occur in the absence of a change in the DNA sequence itself {{141 Junien,C. 2007;}} [49]. Well-characterized modifications known to affect the epigenome thus far include DNA methylation, histone modification, and disordered expression of microRNAs [49]. Regarding POPs, a significant inverse linear relationship with blood global DNA methylation in Alu-repeated elements was found for Dichloro-Diphenyl-Trichloroethane (DDT), Dichloro-Diphenyl-Dichloroethylene (DDE), -benzenehexachloride (-BHC), oxychlordane, -chlordane, mirex, several polychlorinated biphenyls (PCBs), and the total of all POPs in 70 Greenlandic Inuit exposed to some of the highest levels of POPs worldwide [50]. Increasing evidence is linking environmental exposures with epigenetic alterations that are in turn associated with changes in gene expression patterns and increased risk of various disease outcomes that can be passed on to subsequent generations. For example, exposure of mice to a high fat diet in utero induced a T2DM phenotype that was transmitted to the progeny and was associated with epigenetic modifications of adipocytokine, adiponectin, and leptin gene expression [51].

Therefore, although it is unlikely that the rapid increase in the rate of obesity worldwide has any genetic basis, epigenetic changes facilitated by dietary and environmental factors may be a more plausible explanation since epigenetic modifications can easily become established within a single generation. Although human developmental stages represent a period of developmental plasticity during which the number and size of fat cells can change, the number of fat cells in an individual is refractory to change after puberty. Thus, epigenetic modifications mediated by exposure to environmental contaminants, particularly early in development, may induce changes in the expression of archetypal adipocyte genes, and thus increase the propensity for development of obesity and metabolic disorders. Although epigenetic changes are mitotically and trans-generationally inheritable, they are also potentially reversible [52]. Due to this transient nature of the epigenome, there is a need for further studies to determine is epigenetic alterations observed in response to toxicants lie in the causal pathway between exposure and disease endpoints (i.e., T2DM). On the other hand, the reversible nature of epigenetic phenomena makes this an attractive area of research since epigenetic markers can potentially be used as biomarkers of past environmental exposure in humans and may provide novel preventative and therapeutic treatment strategies for obesity and metabolic diseases such as T2DM.

5.4. Adiponectin with diabetes risk

We also assessed the utility of adiponectin as a biomarker of diabetes risk by investigating the association of adiponectin with measures of adiposity, insulin resistance, and inflammation. adiponectin levels were inversely correlated with waist circumference, HOMA-IR, and CRP. The association is consistent with previous studies in the literature [53] and supports the role of adiponectin as a marker of T2DM risk among Inuit.

5.5. Confounding Factors and Approaches Used by Different Study (regression analysis)

Each model was adjusted for potential confounding factors in order to evaluate serum POPs as a risk factor independent of other known risk factors for pre-diabetes. Potential confounding factors in our study included age, sex, smoking, and waist circumference. POPs and obesity are inter-related, therefore, it is uncertain whether obesity should be included as a confounding factor. If obesity lies on the causal pathway between POPs and glucose intolerance, adjusting for obesity may underestimate risk. Furthermore, there may be confounding from variables not adjusted for in models such as alcohol and other contaminants. All POPs were highly correlated and could not be entered into models simultaneously due to multicollinearity issues, therefore, there may be residual confounding from other contaminants not entered into the model which limits our ability to estimate the independent effects of individual POPs. However, POPs exist as mixtures in the environment (Carson), therefore each POP likely serves as a marker for chemical mixtures.

In contrast, no association between serum POPs and glucose intolerance was found in a cross-sectional study of non-diabetic Inuit adults in Greenland. However, a significant inverse association was observed between serum POPs and insulin and HOMA-B suggesting that POPs may affect insulin secretion rather than insulin resistance and glucose metabolism. Impaired beta cell function due to POP exposure is a mechanism that is supported by experimental toxicity studies [54]. Alternatively, the null association among Inuit in Greenland may be due to lack of a true reference group due to contamination of the reference group with other POPs, which may lead to underestimated risk. To facilitate selecting a reference group with extremely low concentrations of POPs, we created summary measures by summing the ranks of individual POPs in each POP subclass. Differences between our study and previous studies also include that measurement of fasting and two-hour glucose concentrations to ascertain glucose intolerance as well as the use of serum adiponectin concentrations. Our finding of a link between serum POPs and two early biomarkers of diabetes risk at is a strength in our study since it allowed us to examine the link between serum POPs and diabetes risk at early stages in the pathogenesis of the disease.

No association between POPs and HOMA-IR, as a marker of insulin resistance, was found in the current study. Our results are consistent with findings among Inuit in Greenland [55] as well as in two First Nations communities in northern Canada [56]. In contrast with findings among Aboriginals residing at high northern latitudes, POPs were significantly associated with insulin resistance in southern populations, such as the general US population [20]. Given that northern populations have a higher body burden of POPs than southern populations [8], these epidemiological observations suggest that concentrations of POPs below a certain threshold promote the development of insulin resistance while concentrations above this threshold do not. Low-dose effects and nonmonotonic dose responses are characteristic features of a variety of endocrine disrupting chemicals, including POPs, and contradict traditional concepts in toxicology [57]. On the other hand, this discrepancy between epidemiological studies may be related to the inherent limitations of relying on the HOMA method to quantify insulin resistance. Although HOMA is a validated physiologically based structural model for estimating insulin resistance, the mathematical

estimates are derived from fasting glucose and insulin concentrations. Therefore, insulin resistance would be underestimated in diabetics with compromised pancreatic beta cell function.

6. Limitations

The primary limitation of our study is the cross-sectional design. The cross-sectional design of the study limits the ability to rule out reverse causality. POPs have apolar and lipophilic properties and therefore circulate with serum lipids [56]. However, distorted lipids are associated with insulin resistance and occur prior to the development of overt diabetes. High lipids relate to greater circulation of lipophilic organochlorines, therefore the potential for reverse causality is high. Therefore, further studies are needed to determine whether POPs lie on the causal pathway between exposure and disease. However, in our study, we excluded diabetics to minimize the potential bias arising from serum lipids. We also used lipid standardized concentrations of POPs in our analyses, however, studies have demonstrated a causal effect of PCBs on serum lipid levels) [57]. If serum lipids are an intermediate factor in the association between POPs and T2DM risk adjusting for lipids may underestimate risk. Another limitation of the study is that, you can't compare coefficients on logistic models directly. With linear models, this isn't a problem because the error variance is assumed to follow a normal distribution. But in logistic models, the error is model dependent and there's no basis for comparison. So while you could look at two models and see that - for example - the coefficient in one model is statistically significant wheras in another it is not (or more precisely, that there is a large difference in p-values across models on the same predictor), you couldn't actually test whether that difference is statistically significant.

7. Conclusion

Observed that high concentrations of POPs were associated with increased risk of glucose intolerance among Inuit in the Arctic. Furthermore, the inverse association between POPs and adiponectin supports the hypothesis that adipose tissue is a victim of abuse and endocrine disruption by POPs may be a relevant pathway through which POPs icontribute to the development and progression of T2DM in the adult Inuit population of the Canadian Arctic. Sum of all pops

8. Acknowledgements

Funding of the project is supported by the Northern Contaminant Program and the Canadian Institute of Health Research. N. Zoenczuk was a recipient of the Ontario Graduate Scholarship and HM Chan is supported by the Canada Research Chair Program.

References

1. GLOBAL REPORT ON DIABETES WHO Library Cataloguing-in-Publication Data Global report on diabetes. (2016).
2. Jørgensen, Marit E, Bjeregaard P, Borch-Johnsen K, Backer V, Becker U, et al. Diabetes and Impaired Glucose Tolerance Among the Inuit Population of Greenland. In Diabetes Care. 2002;25.
3. Murphy NJ, Schraer CD, Bulkow LR, Boyko EJ, Lanier AP. Diabetes mellitus in Alaskan Yup'ik Eskimos and Athabascan Indians after 25 yr. Diabetes Care. 1992; 15: 1390-1392.
4. Zienczuk N, Young TK, Cao ZR, Egeland GM. Dietary correlates of an at-risk BMI among Inuit adults in the Canadian high arctic: Cross-sectional international polar year Inuit health survey, 2007-2008. Nutrition Journal. 2012; 11.
5. Egeland GM, Cao Z, Young TK. Hypertriglyceridemic-waist phenotype and glucose intolerance among Canadian Inuit: The International Polar Year Inuit Health Survey for Adults 2007-2008. CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne. 2011; 183: E553-E558.
6. Janesick, A. S, & Blumberg, B. (2016). Obesogens: an emerging threat to public health HHS Public Access. Am J Obstet Gynecol, 214(5), 559-565. https://doi.org/10.1016/j.ajog.2016.01.1826
7. van Oostdam J, Donaldson SG, Feeley M, Arnold D, Ayotte P, Bondy G, et al. Human health implications of environmental contaminants in Arctic Canada: A review. The Science of the Total Environment. 2005; 351-352: 165-246.
8. Laird BD, Goncharov AB, Chan HM. (2013). Body burden of metals and persistent organic pollutants among Inuit in the Canadian Arctic. Environment International. 2013; 59: 33-40.
9. Mullerova D, Kopecky J, Matejkova D, Muller L, Rosmus J, Racek J, et al. Negative association between plasma levels of adiponectin and polychlorinated biphenyl 153 in obese women under non-energy-restrictive regime. International Journal of Obesity. 2008; 32: 1875-1878.
10. Myre M, Imbeault P. Persistent organic pollutants meet adipose tissue hypoxia: does cross-talk contribute to inflammation during obesity? Obesity Reviews: An Official Journal of the International Association for the Study of Obesity. 2014; 15: 19-28.
11. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature Reviews. Immunology. 2011; 11: 85-97.
12. Li Shanshan, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2009; 302: 179-188.
13. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocrine Reviews. 2005; 26: 439-451.
14. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003; 423: 762-769.
15. Taylor KW, Novak RF, Anderson HA, Birnbaum LS, Blystone C, Devito M, et al. (2013a). Evaluation of the association between Persistent Organic Pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. Environmental Health Perspectives. 2013a; 121: 774-783.

16. Taylor KW, Novak RF, Anderson HA, Birnbaum LS, Blystone C, Devito M, et al. Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. Environmental Health Perspectives. 2013b; 121: 774-783.

17. Gasull M, Pumarega J, Téllez-Plaza M, Castell C, Tresserras R, Lee DH, et al. Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia. Environmental Science & Technology. 2012; 46: 7799-7810.

18. Kim HY, Kwon WY, Kim YA, Oh YJ, Yoo SH, Lee MH, et al. Polychlorinated biphenyls exposure-induced insulin resistance is mediated by lipid droplet enlargement through Fsp27. Archives of Toxicology. 2017; 91: 2353-2363.

19. Færch K, Højlund K, Vind BF, Vaag A, Dalgård C, Nielsen F, et al. Increased serum concentrations of persistent organic pollutants among prediabetic individuals: potential role of altered substrate oxidation patterns. The Journal of Clinical Endocrinology and Metabolism. 2012; 97: E1705-13.

20. Lee DH, Lee IK, Porta M, Steffes M, Jacobs DR J. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetologia. 2007; 50: 1841-1851.

21. Ukropec J, Radikova Z, Huckova M, Koska J, Kocan A, Sebokova E, Drobna B, et al. (2010). High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail. Diabetologia. 2010; 53: 899-906.

22. Diabetes Prevalence in Relation to Serum Concentrations of Polychlorinated Biphenyl (PCB) Congener Groups and Three Chlorinated Pesticides in a Native American Population. (n.d.).

23. Philibert A, Schwartz H, Mergler D. An exploratory study of diabetes in a First Nation community with respect to serum concentrations of p,p'-DDE and PCBs and fish consumption. International Journal of Environmental Research and Public Health. 2009; 6: 3179-3189.

24. Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers. (n.d.). 2015.

25. Singh K, Chan HM. Persistent organic pollutants and diabetes among Inuit in the Canadian Arctic. Environment International. 2017; 101: 183-189.

26. Mailloux RJ, Florian M, Chen Q, Yan J, Petrov I, Coughlan MC, et al. Exposure to a northern contaminant mixture (NCM) alters hepatic energy and lipid metabolism exacerbating hepatic steatosis in obese JCR rats. PloS One. 2014; 9: e106832.

27. Ibrahim MM, Fjære E, Lock EJ, Naville D, Amlund H, Meugnier E, et al. Chronic consumption of farmed salmon containing persistent organic pollutants causes insulin resistance and obesity in mice. PloS One. 2011; 6: e25170.

28. Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environmental Health Perspectives. 2008; 116: 761-768.

29. Rolle-Kampczyk U, Gebauer S, Haange SB, Schubert K, Kern M, Moulla Y, Dietrich A, et al. (2020). Accumulation of distinct persistent organic pollutants is associated with adipose tissue inflammation. Science of the Total Environment. 2020; 748.

30. Wu H, Yu W, Meng F, Mi J, Peng J, Liu J, et al. Polychlorinated biphenyls-153 induces metabolic dysfunction through activation of ROS/NF-κB signaling via downregulation of HNF1b. Redox Biology. 2017; 12: 300-310.

31. Wahlang B, Falkner KC, Gregory B, Ansert D, Young D, Conklin DJ, et al. (2013). Polychlorinated Biphenyl 153 Is a Diet-dependent Obesogen Which Worsens Nonalcoholic Fatty Liver Disease In Male C57BL6/J Mice. J Nutr Biochem. 2013; 24: 1587-1595.

32. Changing ratios of omega-6 to omega-3 fatty acids can differentially modulate polychlorinated biphenyl toxicity in endothelial cells. (n.d.). 2015.

33. Li Shushu, Wang X, Yang L, Yao S, Zhang R, Xiao X, et al. Interaction between β-hexachlorocyclohexane and ADIPOQ genotypes contributes to the risk of type 2 diabetes mellitus in East Chinese adults. Scientific Reports. 2016; 6.

34. Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nature Medicine. 2002; 8: 731-737.

35. Lim J, Jee SH. Association between serum levels of adiponectin and polychlorinated biphenyls in Korean men and women. Endocrine. 2015; 48: 211-217.

36. Regnier SM, Sargis RM. Adipocytes under assault: environmental disruption of adipose physiology. Biochimica et Biophysica Acta. 2014; 1842: 520-533.

37. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001; 286: 327-334.

38. Zhang B, Berger J, Hu E, Szalkowski D, White-Carrington S, Spiegelman BM, et al. (1996). Negative regulation of peroxisome proliferator-activated receptor-gamma gene expression contributes to the antiadipogenic effects of tumor necrosis factor-alpha. Molecular Endocrinology (Baltimore, Md.). 1996; 10: 1457-1466.

39. Ron, D, Brasier, A. R, McGehee, R. E. J, & Habener, J. F. (1992). Tumor necrosis factor-induced reversal of adipocytic phenotype of 3T3-L1 cells is preceded by a loss of nuclear CCAAT/enhancer binding protein (C/EBP). The Journal of Clinical Investigation, 89(1), 223-233. https://doi.org/10.1172/JCI11556639

40. Sewter C, Berger D, Considine Rv, Medina G, Rochford J, Ciaraldi T, et al. Human obesity and type 2 diabetes are associated with alterations in SREBP1 isoform expression that are reproduced ex vivo by tumor necrosis factor-alpha. Diabetes. 2002; 51: 1035-1041.

Citation: Zienczuk N, Egeland G and Chan HM, Body Burden of Persistent Organic Pollutants Were Negatively Associated with Adiponectin and Positively Associated with Glucose Intolerance Among Inuit in Canada. GSL J Public Health Epidemiol; 2:112.

41. Remillard RB J, Bunce NJ. Linking dioxins to diabetes: epidemiology and biologic plausibility. Environmental Health Perspectives. 2002; 110: 853-858.

42. Vezina CM, Walker NJ, Olson JR. Subchronic exposure to TCDD, PeCDF, PCB126, and PCB153: effect on hepatic gene expression. Environmental Health Perspectives. 2004; 112: 1636-1644.

43. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. The Journal of Clinical Endocrinology and Metabolism. 2007; 92: 1023-1033.

44. Grün F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. Endocrinology. 2006; 147: S50-S55.

45. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW J. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation. 2003; 112: 1796-1808.

46. Imbeault P, Findlay CS, Robidoux MA, Haman F, Blais JM, Tremblay A, et al. (2012). Dysregulation of cytokine response in Canadian First Nations communities: is there an association with persistent organic pollutant levels? PloS One. 2012; 7: e39931.

47. Kim MJ, Pelloux V, Guyot E, Tordjman J, Bui LC, Chevallier A, et al. (2012). Inflammatory pathway genes belong to major targets of persistent organic pollutants in adipose cells. Environmental Health Perspectives. 2012; 120: 508-514.

48. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Current Opinion in Pediatrics. 2009; 21: 243-251.

49. Chuang JC, Jones PA. Epigenetics and microRNAs. Pediatric Research. 2007; 61: 24R-29R.

50. Rusiecki JA, Baccarelli A, Bollati V, Tarantini L, Moore LE, Bonefeld-Jorgensen EC. Global DNA hypomethylation is associated with high serum-persistent organic pollutants in Greenlandic Inuit. Environmental Health Perspectives. 2008; 116: 1547-1552.

51. Masuyama H, Hiramatsu Y. Effects of a high-fat diet exposure in utero on the metabolic syndrome-like phenomenon in mouse offspring through epigenetic changes in adipocytokine gene expression. Endocrinology. 2012; 153(6): 2823-2830.

52. Weaver IC, Champagne G, Brown FA, Dymov SE, Sharma S, Meaney S, et al. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2005; 25(47): 11045-11054.

53. Trujillo ME, Scherer PE. Adiponectin--journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. Journal of Internal Medicine. 2005; 257: 167-175.

54. Mailloux R, Fu A, Florian M, Petrov I, Chen Q, Coughlan MC, et al. A Northern contaminant mixture impairs pancreas function in obese and lean JCR rats and inhibits insulin secretion in MIN6 cells. Toxicology. 2015; 334: 81-93.

55. Jørgensen ME, Borch-Johnsen K, Bjerregaard P. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. Diabetologia. 2008; 51: 1416-1422.

56. Pal S, Blais JM, Robidoux MA, Haman F, Krümmel E, Seabert TA, et al. The association of type 2 diabetes and insulin resistance/ secretion with persistent organic pollutants in two First Nations communities in northern Ontario. Diabetes & Metabolism. 2013; 39: 497-504.

57. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR J, Lee DH, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocrine Reviews. 2012; 33: 378-455.

58. Brown JF J, Lawton RW. Polychlorinated biphenyl (PCB) partitioning between adipose tissue and serum. Bulletin of Environmental Contamination and Toxicology. 1984; 33: 277-280.

59. Schisterman EF, Whitcomb BW, Louis GM B, Louis TA. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environmental Health Perspectives. 2005; 113: 853-857.