Environmental Research 160 (2018) 298–305

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Association of blood polychlorinated biphenyls and cholesterol levels among Canadian Inuit

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ARTICLE INFO

Keywords:
Inuit
Canada
Cholesterol
Triglyceride
Blood PCB

ABSTRACT

Background: It has generally been thought that Inuit populations have low risk of cardiovascular disease due to high consumption of omega-3 fatty acids found in traditional marine-based diets. However, results of recent surveys showed that Inuit populations are experiencing increasing rates of cardiovascular disease and related risk factors.

Objective: The purpose of this study was to investigate if blood polychlorinated biphenyls (PCBs) are associated with high cholesterol and related parameters in Canadian Inuit, known risk factors for cardiovascular disease.

Methods: The Adult Inuit Health Survey (IHS, 2007–2008) included 2595 Inuit participants from three regions of the Canadian Arctic, of which 2191 could be classified as with or without high cholesterol. The high cholesterol outcome was defined by LDL-C > 3.36 mmol/L or taking medication(s) that reduce cholesterol, and was examined in adjusted logistic regression models with individual blood levels of PCB congeners, sum of dioxin-like PCBs (ΣDL-PCBs), or sum of non-dioxin-like PCBs (ΣNDL-PCBs). Statistically significant covariates for high cholesterol were ranked in importance according to the proportion of the model log likelihood explained. Continuous clinical parameters of total cholesterol, triglycerides, LDL-C, and HDL-C were examined in multiple linear regression models with ΣDL-PCBs or ΣNDL-PCBs.

Results: A total of 719 participants had high cholesterol (32.8%). PCBs were associated with increased risk of high cholesterol, and higher levels of serum triglycerides, total cholesterol, and LDL-C. No association was observed between PCBs and serum HDL-C. With respect to other statistically significant covariates for high cholesterol, the log likelihood ranking of PCBs generally fell between body mass index (BMI) and age.

Conclusion: Further work is needed to corroborate the associations observed with PCBs and lipids in Canadian Inuit and to examine if they are causal in the direction anticipated.

1. Introduction

It has generally been thought that Inuit populations have low risk of cardiovascular disease due to consumption of omega-3 fatty acids found in traditional marine-based diets. However, based on the results of recent surveys, Inuit populations are experiencing high rates of cardiovascular disease and related risk factors. In the Canadian region of Nunavik, the *Qanuippitaa* Survey found that 16.7% of Inuit adults have high blood pressure, 7.9% high cholesterol, 4.1% cerebrovascular disease, 2.3% coronary artery disease, and 6.7% other cardiovascular disease (PHAC, 2009). In the Aboriginal Peoples Survey 2012 of Canada, 12% of Inuit 15 years of age or over reported having high blood pressure and 5% reported diabetes (excluding gestational diabetes) (Wallace, 2014). The Inuit diet, therefore, does not seem to provide full protection against cardiovascular morbidity. Non-modifiable and modifiable factors both play important roles in contributing to the prevalence of cardiovascular disease in Inuit communities (Tvermosegaard et al., 2015).

The presence of high blood cholesterol is an important risk factor for the development of atherosclerosis and myocardial infarction. Cholesterol travels in the blood stream bound mainly to low-density lipoprotein cholesterol (LDL-C), which carries up to 70% of total serum cholesterol and is highly atherogenic, and to high-density lipoprotein cholesterol (HDL-C), which carries up to 30% of total serum cholesterol (NCEP, 2002). The very low density lipoproteins (VLDL) and chylomicron lipoproteins are rich in triglycerides and also have potential to promote atherosclerosis (NCEP, 2002). According to clinical practice guidelines, cholesterol lowering therapy should be initiated for secondary prevention in those with clinical atherosclerotic cardiovascular disease and for primary prevention in those with LDL-C ≥4.9 mmol/L, with diabetes 40–75 years of age, or with 10-year atherosclerotic cardiovascular disease risk ≥7.5% and 40–75 years of age (Stone et al.,

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http://dx.doi.org/10.1016/j.envres.2017.10.010
Received 21 June 2017; Received in revised form 27 September 2017; Accepted 6 October 2017
Available online 15 October 2017
0013-9351/

2014). The risk of atherosclerotic cardiovascular disease is reduced by 20% for every 1.0 mmol/L reduction in LDL-C (Stone et al., 2014).

Although risk factors for high cholesterol, such as diets high in saturated and trans-fatty acids and obesity, are well recognized among the medical community, the contribution of persistent organic pollutant (POP) exposure is unclear. Persistent organic pollutants accumulate in the circumpolar Arctic region primarily by long-range transport from southern latitudes and resist environmental degradation (AMAP, 2015a). These chemicals bioaccumulate and biomagnify in food chains. The Inuit are especially susceptible to POP exposures from the consumption of marine mammals. They have been shown to have higher body burden of polychlorinated biphenyls (PCBs) and organochlorine pesticides compared to the general Canadian population (Laird et al., 2013). Only a few studies in Inuit populations have investigated the effect of POPs on cardiovascular disease risk factors (Château-Degat et al., 2010; Valera et al., 2013a, 2013b). In a cross-sectional study of Inuit adults from Nunavik, PCBs and p,p′-dichlorodiphenyldichloroethylene (p,p′-DDE) were found to be associated with higher risk of hypertension (Valera et al., 2013a). Among Inuit from Greenland, dioxin-like PCBs and p,p′-dichlorodiphenyltrichloroethane (p,p′-DDT) were associated with higher risk of hypertension in younger respondents 18–39 years of age, but not in older respondents ≥ 40 years (Valera et al., 2013b). Perfluorooctanesulfonate (PFOS) plasma levels were negatively associated with triacylglycerol and ratio of total cholesterol to HDL-C in Nunavik (Château-Degat et al., 2010).

The purpose of this study was to investigate the association of PCBs, a ubiquitous group of POPs, on high cholesterol and related clinical parameters. This area of investigation has received little attention in Inuit, although studies have been conducted in other populations (Aminov et al., 2013; Goncharov et al., 2008). An investigation of PCBs and high cholesterol in Canadian Inuit will add to our understanding of potentially novel risk factors for this important condition.

2. Methods

2.1. Participants and data collection

The Adult Inuit Health Survey (IHS, 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. Also included in the survey were tests of clinical parameters and blood levels of PCBs. A total of 2595 Inuit who were 18 years of age or older participated in the survey (68% participation rate) and 2191 were classified as with or without high cholesterol. 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. Scientific Research Licenses for the IHS were obtained from relevant northern research institutions (the Aurora Research Institute, Northwest Territories and Qaujisaqtulirijikkut, Nunavut).

2.2. Exposures

The association with high cholesterol and related measures was explored with individual plasma PCB congeners (PCB-99, 105, 118, 138, 153, 156, 170, 180, 183, and 187) and PCB groupings of sum of dioxin-like PCBs (ΣDL-PCB) and sum of non-dioxin like PCBs (ΣNDL-PCB). 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. ΣDL-PCB and ΣNDL-PCB were calculated according to the following:

Table 1
Quartile concentration cut-off values.

	Lipid-Based (μg/g lipid)	Wet-Weight (μg/L)
PCB-99		
Q1	[0.0016, 0.0059]	[0.015, 0.0362]
Q2	(0.0059, 0.0189]	(0.0362, 0.12]
Q3	(0.0189, 0.0509]	(0.12, 0.33]
Q4	(0.0509, 0.648]	(0.33, 4.9]
PCB-105		
Q1	[0.0004, 0.0011]	[0.004, 0.005]
Q2	(0.0011, 0.0032]	(0.005, 0.02]
Q3	(0.0032, 0.0092]	(0.02, 0.057]
Q4	(0.0092, 0.111]	(0.057, 0.78]
PCB-118		
Q1	[0.0007, 0.0063]	[0.005, 0.038]
Q2	(0.0063, 0.0176]	(0.038, 0.11]
Q3	(0.0176, 0.0475]	(0.11, 0.31]
Q4	(0.0475, 0.631]	(0.31, 4.9]
PCB-138		
Q1	[0.0007, 0.0184]	[0.005, 0.1]
Q2	(0.0184, 0.0541]	(0.1, 0.32]
Q3	(0.0541, 0.135]	(0.32, 0.88]
Q4	(0.135, 1.99]	(0.88, 15]
PCB-153		
Q1	[0.0007, 0.0429]	[0.005, 0.25]
Q2	(0.0429, 0.134]	(0.25, 0.79]
Q3	(0.134, 0.352]	(0.79, 2.3]
Q4	(0.352, 6.18]	(2.3, 48]
PCB-156		
Q1	[0.0005, 0.0025]	[0.005, 0.0163]
Q2	(0.0025, 0.00795]	(0.0163, 0.048]
Q3	(0.00795, 0.0202]	(0.048, 0.13]
Q4	(0.0202, 0.412]	(0.13, 3.2]
PCB-170		
Q1	[0.0006, 0.00688]	[0.005, 0.04]
Q2	(0.00688, 0.0219]	(0.04, 0.13]
Q3	(0.0219, 0.0607]	(0.13, 0.39]
Q4	(0.0607, 1.37]	(0.39, 10]
PCB-180		
Q1	[0.0007, 0.0211]	[0.005, 0.12]
Q2	(0.0211, 0.0667]	(0.12, 0.4]
Q3	(0.0667, 0.186]	(0.4, 1.2]
Q4	(0.186, 4.77]	(1.2, 37]
PCB-183		
Q1	[0.0005, 0.0019]	[0.005, 0.01]
Q2	(0.0019, 0.0063]	(0.01, 0.038]
Q3	(0.0063, 0.0163]	(0.038, 0.11]
Q4	(0.0163, 0.291]	(0.11, 2.2]
PCB-187		
Q1	[0.0007, 0.0089]	[0.005, 0.049]
Q2	(0.0089, 0.026]	(0.049, 0.15]
Q3	(0.026, 0.0642]	(0.15, 0.42]
Q4	(0.0642, 0.94]	(0.42, 7.3]
ΣDL-PCB		
Q1	[0.0021, 0.0113]	[0.015, 0.064]
Q2	(0.0113, 0.0306]	(0.064, 0.182]
Q3	(0.0306, 0.0775]	(0.182, 0.509]
Q4	(0.0775, 1.14]	(0.509, 8.88]
ΣNDL-PCB		
Q1	[0.0331, 0.148]	[0.24, 0.822]
Q2	(0.148, 0.367]	(0.822, 2.2]
Q3	(0.367, 0.93]	(2.2, 6.02]
Q4	(0.93, 15.4]	(6.02, 120]

Abbreviations: DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl; Q = quartile.

$$\sum \text{DL} - \text{PCB} = \text{PCB} - 105 + \text{PCB} - 118 + \text{PCB} - 156$$

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

All contaminants were divided into quartile level on both wet-weight and lipid basis and the first quartile set as the reference category (Table 1 provides concentration ranges of each quartile for each

Table 2
Characteristics of sample population (IHS 2007–2008).

	Total (n = 2191)	With High Cholesterol[a] (n = 719)	Without High Cholesterol (n = 1472)
Age (years) - Mean (SD)	42.4 (15.3)	49.8 (14.5)	38.8 (14.4)
Gender – No. (%)			
Males	844 (38.5)	304 (42.3)	540 (36.7)
Females	1347 (61.5)	415 (57.7)	932 (63.3)
Region – No (%)			
Nunavut	1646 (75.1)	506 (70.4)	1140 (77.4)
ISR	280 (12.8)	101 (14.0)	179 (12.2)
Nunatsiavut	265 (12.1)	112 (15.6)	153 (10.4)
Education[b] - No. (%)			
None	161 (7.3)	87 (12.1)	74 (5.0)
Elementary	415 (18.9)	164 (22.8)	251 (17.1)
Secondary	1113 (50.8)	286 (39.8)	827 (56.2)
College/Trade School	325 (14.8)	112 (15.6)	213 (14.5)
University	67 (3.1)	29 (4.0)	38 (2.6)
BMI (kg/m^2) - Mean (SD)	28.4 (6.5)	30.1 (5.8)	27.5 (6.6)
Fasting Glucose (mmol/L) - Mean (SD)	5.1 (1.0)	5.3 (1.0)	5.0 (0.9)
LDL-C (mmol/L) – Mean (SD)	2.8 (1.0)	3.8 (1.0)	2.4 (0.6)
HDL-C (mmol/L) – Mean (SD)	1.5 (0.5)	1.4 (0.5)	1.5 (0.5)
Triglycerides (mmol/L) –Mean (SD)	1.3 (0.7)	1.6 (0.8)	1.2 (0.7)
Total Cholesterol (mmol/L) – Mean (SD)	5.0 (1.1)	5.9 (1.1)	4.5 (0.8)
Alcohol[c] - No. (%)			
Yes	1188 (54.2)	346 (48.1)	842 (57.2)
No	623 (28.4)	244 (33.9)	379 (25.7)
Never Drank	139 (6.3)	56 (7.8)	83 (5.6)
Current Smoker – No. (%)			
Yes	1476 (67.4)	405 (56.3)	1071 (72.8)
No	635 (29.0)	287 (39.9)	348 (23.6)

Abbreviations: BMI = body mass index; ISR = Inuvialuit Settlement Region; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation.

[a] LDL-C > 3.36 mmol/L or taking medication that lowers cholesterol.

[b] Partial or completed elementary school, secondary school, college or trade school, or university.

[c] Alcohol consumption in past 12 months.

examined contaminant). The lipid-based quartile concentrations were calculated by dividing wet-weight plasma concentration by total serum lipids. Total serum lipids were 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. Observations with missing values for contaminant or total serum lipid were excluded from analyses.

2.3. Outcomes

If respondents had an LDL-C > 3.36 mmol/L (NCEP, 2002) or were taking medication(s) that lower cholesterol, they were classified as having high cholesterol (N = 2191). Triglycerides, total cholesterol, LDL-C, and HDL-C were examined as continuous outcomes. Aside from LDL-C, these parameters were measured in serum under fasting conditions for at least eight hours. LDL-C was obtained by calculation using the Friedewald equation (Friedewald et al., 1972):

$$\text{LDL (mmol/}L\text{)} = \text{Total Cholesterol}–(\text{Triglyceride}/2.2)–\text{HDL} \quad (2)$$

The sample population for the continuous outcomes was limited to those who were not taking any medications that lower cholesterol (N = 1279).

2.4. Statistical analyses

Multiple logistic regression models were developed to examine association between PCBs and high cholesterol. Multiple linear regression models were developed for triglycerides, total cholesterol, LDL-C, and HDL-C. For linear regression models, the assumptions of linearity, normality, and homoscedasticity of residuals were verified qualitatively with plots. For high cholesterol, models were run separately using wet-weight quartile categories and lipid-based quartile categories. For triglycerides, total cholesterol, LDL-C, and HDL-C, models were run with wet-weight PCB quartile levels only because adjustment for lipids would mask any association with the outcome. Triglycerides and HDL-C were natural log transformed. The untransformed β coefficients for these outcomes, therefore, represent the factor by which they increase (β > 1) or decrease (β < 1) the outcome.

Covariates considered for inclusion in models were age; sex; marital status; education; income; alcohol intake; cigarette smoking; exercise as measured with total metabolic equivalent (MET) score based on walking, moderate activity, and vigourous activity; body mass index (BMI); blood levels of heavy metals (selenium, lead, mercury, and cadmium); total monounsaturated fatty acids (MUFA); total polyunsaturated fatty acids (PUFA); total saturated fats; total trans fatty acids (TFA); omega-3/omega-6 ratio; fasting glucose; systolic blood pressure; diastolic blood pressure; and family history (high cholesterol in parent). 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).

To evaluate the relative importance of the PCB covariate relative to other covariates in adjusted models of high cholesterol, the statistically significant factors were ranked based on the ratio of the −2 log likelihood (−2LL) of a single covariate model compared with the −2LL of the full model (Harrell, 2001). The ranking represents how much of the log likelihood of the full model is explained by a particular covariate. The ranking of covariates from models that incorporated wet-weight PCB quartile levels and lipid-based quartile levels were graphed separately.

Parameters in models were considered statistically significant if $p < 0.05$. All analyses were conducted in R version 3.3.1.

Table 3
Wet-weight PCB concentrations.

	Total (μg/L)		With High Cholesterol (μg/L)		No High Cholesterol (μg/L)	
	GM (Range)	N	GM (Range)	N	GM (Range)	N
PCB-99	0.11 (0.015–4.90)	2162	0.21 (0.015–4.90)	701	0.08 (0.015–3.30)	1431
PCB-105	0.02 (0.005–0.78)	2162	0.04 (0.005–0.66)	701	0.02 (0.005–0.78)	1431
PCB-118	0.10 (0.005–4.90)	2162	0.22 (0.005–4.10)	701	0.07 (0.005–4.90)	1431
PCB-138	0.28 (0.005–15.00)	2162	0.58 (0.005–15.00)	701	0.20 (0.005–12.00)	1431
PCB-153	0.72 (0.005–48.00)	2162	1.49 (0.005–41.00)	701	0.50 (0.005–48.00)	1431
PCB-156	0.04 (0.005–3.20)	2162	0.09 (0.005–2.10)	701	0.03 (0.005–3.20)	1431
PCB-170	0.12 (0.005–10.00)	2162	0.25 (0.005–9.80)	701	0.08 (0.005–10.00)	1431
PCB-180	0.38 (0.005–37.00)	2162	0.78 (0.005–34.00)	701	0.26 (0.005–37.00)	1431
PCB-183	0.04 (0.005–2.20)	2161	0.07 (0.005–2.20)	700	0.03 (0.005–1.90)	1431
PCB-187	0.14 (0.005–7.30)	2162	0.27 (0.005–4.80)	701	0.10 (0.005–7.30)	1431
ΣDL-PCB	0.18 (0.015–8.88)	2162	0.37 (0.015–6.83)	701	0.13 (0.015–8.88)	1431
ΣNDL-PCB	2.30 (0.24–119.50)	2159	4.24 (0.24–101.00)	698	1.69 (0.24–119.50)	1431

Abbreviations: DL-PCB = dioxin-like polychlorinated biphenyl; GM = geometric mean; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl.

3. Results

A total of 2191 (84.4%) respondents were classified as with or without high cholesterol for this study (Table 2). Of this sample, 32.8% had high cholesterol and 67.2% did not. The average age was about 42 years and the majority were female (61.5%). The average BMI of respondents was in the overweight category (28.4 kg/m^2). Other clinical parameters and risk factors, including fasting glucose, LDL-C, HDL-C, triglycerides, total cholesterol, alcohol consumption, and cigarette smoking, are presented in Table 2. Wet-weight PCB concentrations for respondents with and without high cholesterol and for the total population are provided in Table 3. All PCB concentrations were higher in the group with high cholesterol.

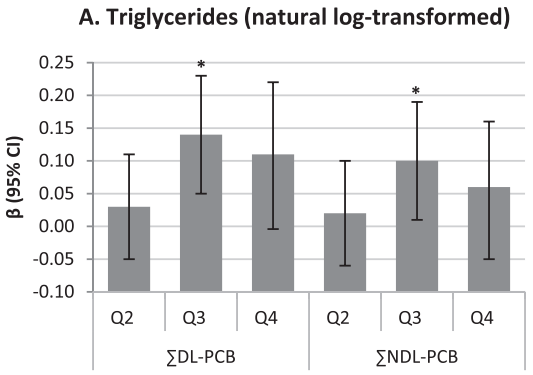
Table 4 shows the odds ratios for high cholesterol using wet-weight and lipid-based PCB quartile concentrations, adjusted for age, sex, education, alcohol consumption, smoking status, omega 3/6 ratio, selenium, fasting glucose, total MUFA, and total TFA. Wet-weight odd ratios were all positively associated with high cholesterol and a trend of increasing effect estimates from quartile 2 to quartile 4 appears. With lipid-based PCB concentrations, effect estimates were also in positive direction, although not all quartiles were statistically significant and the increasing trend from quartiles 2–4 is absent.

The β coefficients for wet-weight PCB quartile concentrations for triglycerides, total cholesterol, LDL-C, and HDL-C from adjusted regression models for ΣDL-PCB and ΣNDL-PCB are shown in Fig. 1. These analyses were restricted to respondents not taking any cholesterol

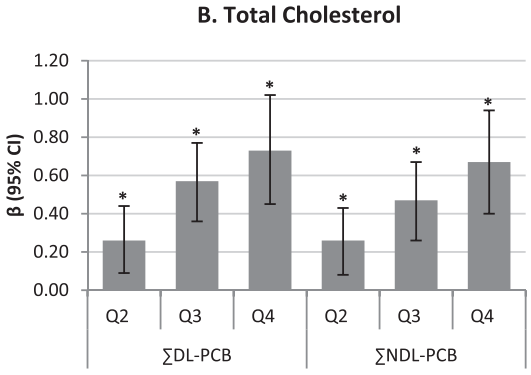
Table 4
Adjusted odds ratios for high cholesterol.

	OR (95% CI)				
		N	Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1
PCB-99	Wet	1798	2.00 (1.42, 2.84)***	2.31 (1.57, 3.42)***	3.78 (2.30, 6.23)***
	Lipid	1798	1.67 (1.20, 2.35)**	1.38 (0.95, 2.02)	1.66 (1.02, 2.70)*
PCB-105	Wet	1798	1.81 (1.27, 2.58)***	2.15 (1.50, 3.07)***	3.63 (2.25, 5.88)***
	Lipid	1798	1.75 (1.26, 2.46)**	1.39 (0.97, 1.99)	1.74 (1.08, 2.81)*
PCB-118	Wet	1798	2.31 (1.61, 3.33)***	2.95 (1.97, 4.46)***	4.90 (2.93, 8.25)***
	Lipid	1798	1.59 (1.13, 2.26)**	1.51 (1.03, 2.23)*	1.68 (1.01, 2.78)*
PCB-138	Wet	1798	1.97 (1.38, 2.84)***	2.68 (1.81, 4.00)***	4.55 (2.77, 7.53)***
	Lipid	1798	1.55 (1.10, 2.20)*	1.60 (1.09, 2.35)*	1.76 (1.09, 2.84)*
PCB-153	Wet	1798	1.79 (1.25, 2.58)**	2.51 (1.71, 3.71)***	3.91 (2.40, 6.40)***
	Lipid	1798	1.28 (0.91, 1.82)	1.46 (1.00, 2.15)†	1.48 (0.91, 2.41)
PCB-156	Wet	1798	1.82 (1.26, 2.65)**	2.98 (1.99, 4.48)***	4.80 (2.93, 7.91)***
	Lipid	1798	1.61 (1.13, 2.31)**	1.95 (1.32, 2.90)***	2.14 (1.33, 3.47)**
PCB-170	Wet	1798	1.68 (1.16, 2.44)**	3.48 (2.33, 5.24)***	4.70 (2.87, 7.75)***
	Lipid	1798	1.43 (1.01, 2.04)*	1.84 (1.24, 2.74)**	1.96 (1.22, 3.16)**
PCB-180	Wet	1798	1.54 (1.07, 2.23)*	3.14 (2.11, 4.71)***	3.74 (2.27, 6.20)***
	Lipid	1798	1.11 (0.78, 1.57)	1.59 (1.08, 2.35)*	1.48 (0.91, 2.40)
PCB-183	Wet	1797	2.13 (1.49, 3.06)***	2.58 (1.76, 3.81)***	4.66 (2.90, 7.53)***
	Lipid	1797	1.92 (1.36, 2.74)***	1.72 (1.16, 2.55)**	2.36 (1.48, 3.78)***
PCB-187	Wet	1798	1.74 (1.21, 2.52)**	2.79 (1.85, 4.23)***	4.60 (2.78, 7.65)***
	Lipid	1798	1.27 (0.89, 1.81)	1.55 (1.05, 2.31)*	1.69 (1.03, 2.76)*
ΣDL-PCB	Wet	1798	1.84 (1.27, 2.68)**	3.11 (2.08, 4.68)***	4.05 (2.41, 6.86)***
	Lipid	1798	1.55 (1.09, 2.21)*	1.70 (1.15, 2.53)**	1.74 (1.04, 2.90)*
ΣNDL-PCB	Wet	1796	2.08 (1.44, 3.01)***	2.83 (1.89, 4.25)***	4.61 (2.78, 7.67)***
	Lipid	1796	1.21 (0.86, 1.72)	1.39 (0.94, 2.05)	1.38 (0.84, 2.25)

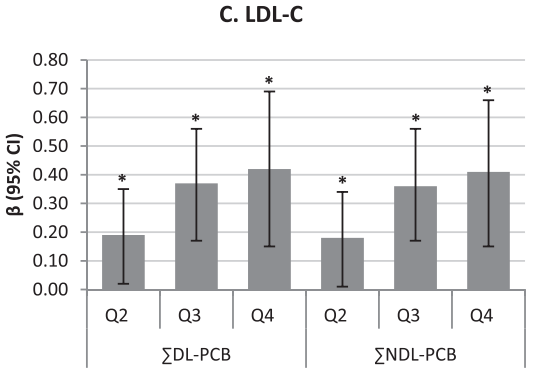
Adjusted for: age, sex, education, BMI, alcohol consumption, smoking status, omega3/6 ratio, selenium, fasting glucose, total MUFA, and total TFA.
Abbreviations: CI = confidence interval; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; OR = odds ratio; PCB = polychlorinated biphenyl; Q = quartile.
† $p = 0.05$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.



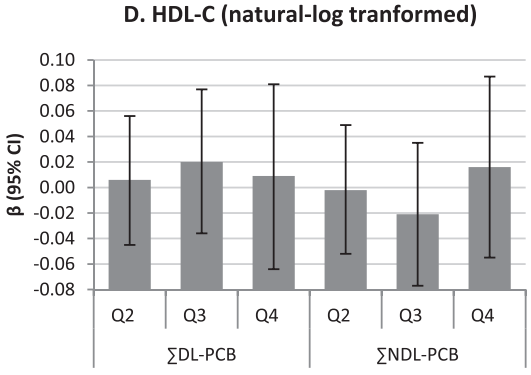
	%age Change (95% CI) ∑DL-PCB	%age Change (95% CI) ∑NDL-PCB
Q2 vs, Q1	3 (-5, 12)	2 (-6, 11)
Q3 vs. Q1*	15 (5, 26)	11 (1, 21)
Q4 vs. Q1	11 (0, 25)	6 (-5, 17)



	Change (95% CI) (mmol/L) ∑DL-PCB	Change (95% CI) (mmol/L) ∑NDL-PCB
Q2 vs, Q1*	0.26 (0.09, 0.44)	0.26 (0.08, 0.43)
Q3 vs. Q1*	0.57 (0.36, 0.77)	0.47 (0.26, 0.67)
Q4 vs. Q1*	0.73 (0.45, 1.02)	0.67 (0.40, 0.94)



	Change (95% CI) (mmol/L) ∑DL-PCB	Change (95% CI) (mmol/L) ∑NDL-PCB
Q2 vs, Q1*	0.19 (0.02, 0.35)	0.18 (0.01, 0.34)
Q3 vs. Q1*	0.37 (0.17, 0.56)	0.36 (0.17, 0.56)
Q4 vs. Q1*	0.42 (0.15, 0.69)	0.41 (0.15, 0.66)



	%age Change (95% CI) ∑DL-PCB	%age Change (95% CI) ∑NDL-PCB
Q2 vs, Q1	1 (-4, 6)	0 (-5, 5)
Q3 vs. Q1	2 (-4, 8)	-2 (-8, 4)
Q4 vs. Q1	1 (-6, 8)	2 (-5, 9)

Fig. 1. β coefficients of wet-weight quartile concentrations from adjusted models (Q1 = reference). * Statistically significant ($p < 0.05$). A. Triglycerides: adjusted for age, sex, education, current smoking status, exercise, BMI, fasting glucose, and systolic blood pressure. B. Total cholesterol: adjusted for age, sex, education, cadmium, BMI, selenium, systolic blood pressure, fasting glucose, and interaction between age + fasting glucose. C. LDL-C: adjusted for age, sex, education, marital status, cadmium, BMI, selenium, fasting glucose, systolic blood pressure, omega3/6 ratio, and interaction between age + fasting glucose. D. HDL-C: adjusted for age, sex, education, marital status, alcohol, BMI, fasting glucose, diastolic blood pressure, total MUFA, and omega 3/6 ratio.

medications (N = 1279). The corresponding increase in parameter levels are also provided in the tables below each figure. For triglycerides, quartile 3 vs. quartile 1 was statistically significant for ΣDL-PCB and ΣNDL-PCB (Fig. 1a). Total cholesterol and LDL-C were positively associated with ΣDL-PCB and ΣNDL-PCB with increasing trends from quartiles 2–4 (Fig. 1b and c). No significant association was found for ΣDL-PCB or ΣNDL-PCB with HDL-C (Fig. 1d).

The relative contribution of each statistically significant factor to the full model for high cholesterol is shown in Fig. 2. For models based on wet-weight PCB quartile concentrations (top-panel) or lipid-based PCB quartile concentrations (bottom-panel), the PCB factor generally falls between BMI and age. In the wet-weight models, the PCB factor contributes more to the −2LL of the full model compared with the lipid-based models.

4. Discussion

In this analysis we have shown that PCBs are associated with prevalence of high cholesterol, as measured by LDL-C or use of medication, as well as with triglycerides, total cholesterol, and LDL-C among the Canadian Inuit. For the outcome of high cholesterol, the risk estimates for wet-weight quartile PCB concentrations increased from quartile 2 to quartile 4. The largest odds ratio was for PCB-118 quartile 4 to quartile 1 (OR, 95% CI: 4.90, 2.93–8.25). The risk estimates for lipid-based PCB quartile concentrations also increased the risk for high cholesterol but without reaching statistical significance. The β coefficient estimates for wet-weight PCB quartile concentrations for total cholesterol and LDL-C were positive and demonstrated a trend of increase. In the relative ranking of statistically significant covariates, age was most important as expected. The placement of PCBs between age and BMI in both wet-

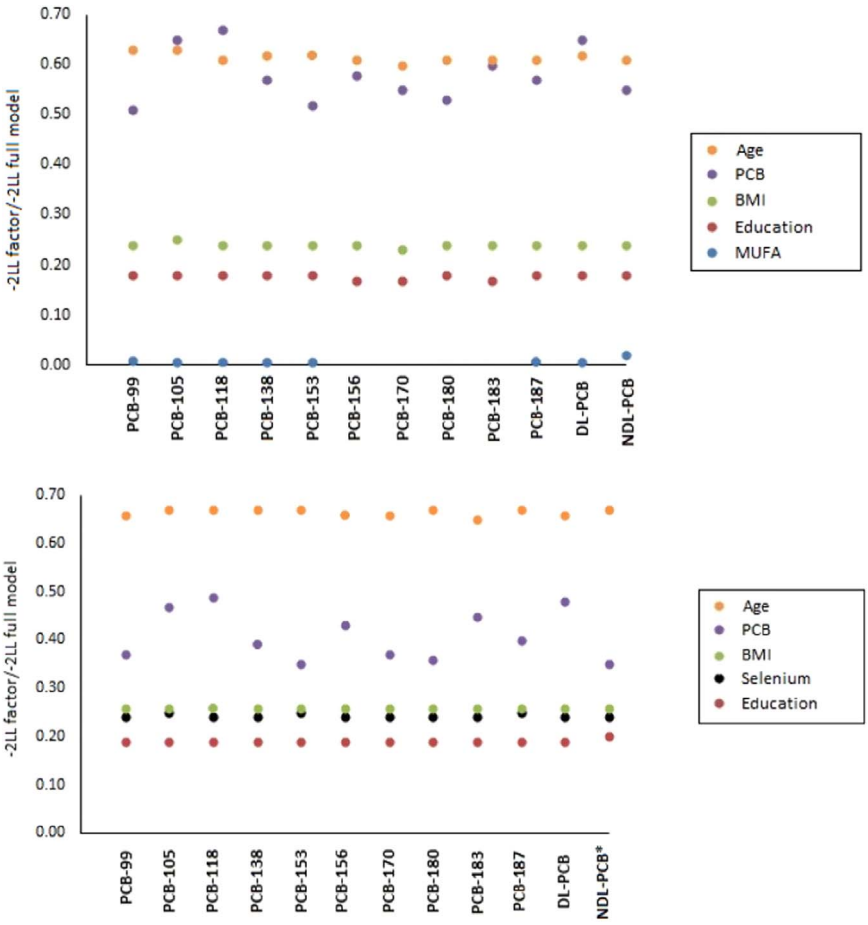


Fig. 2. Ranking of significant factors in adjusted models of high cholesterol and PCB quartile concentrations. Top – wet-weight; Bottom – lipid-based. *NDL-PCB in lipid-based model was not statistically significant.

weight and lipid models was an interesting finding, showing that the PCBs were important covariates in explaining the variation in outcome. To the authors' knowledge, there has been limited research on ranking the relative importance of environmental contaminants and well-established disease risk factors on health endpoints. The ranking places the risks of contaminants into context and further research in this area for other POPs and health outcomes should be pursued.

Several studies have shown positive association between PCBs and lipids in human populations (Aminov et al., 2013; Arrebola et al., 2014; Goncharov et al., 2008; Lee et al., 2011; Ljunggren et al., 2014; Patel et al., 2012; Penell et al., 2014; Tokunaga and Kataoka, 2003). In a cross-sectional study of 575 residents living close to a former Monsanto plant in Alabama, the sum total of 27 PCB congeners in serum was associated with total lipids, total cholesterol, and triglycerides (Aminov et al., 2013). The strongest associations were observed for PCB congeners with three, four, or at least eight substituted chlorine atoms (Aminov et al., 2013). Lee et al., 2011 also found that PCB congeners with seven or more chlorine atoms predicted higher BMI, triglycerides, and lower HDL-C in controls without diabetes. Arrebola et al. (2014) observed that PCB-138 and −180 were positively associated with triglycerides and total serum lipids, and PCB-153 with LDL-C in 298 adults from Southern Spain. In a highly exposed population (Yusho patients), PCBs were associated with higher total cholesterol and triglycerides, but not with HDL-C (Tokunaga and Kataoka, 2003). In a 5-year longitudinal study that examined change in lipids in seniors from Sweden 70–75 years of age, baseline levels of wet-weight or lipid-normalized non-dioxin like PCBs 194, 206, and 209 increased total serum cholesterol and LDL-C, and PCB-194 reduced HDL-C (Penell et al., 2014). Patel et al. (2012) screened for many environmental factors and lipids in an environment-wide association study in the United States. Higher triglycerides and lower HDL-C were associated with PCBs after adjusting for many factors. The pathway of PCBs to cardiovascular disease in a population of Akwesasne Mohawks was found to be mediated by an increase in serum lipids, using structural equation modeling (Goncharov et al., 2008).

Results from experimental studies using animal models support the hypothesis that PCB exposure alters lipid metabolism and blood lipid profile. In rats administered with PCB mixtures (e.g. Aroclor 1254, Aroclor 1242), increases in total cholesterol, HDL-C, triglycerides, and liver weights were observed (ATSDR, 2000). Mice exposed to soil from a Superfund site contaminated with PCBs for 4 weeks experienced doubling of liver weights (Imsilp and Hansen, 2005). A mixture of 22 contaminants, including PCBs, found in Inuit blood was studied for its effect on non-alcoholic fatty liver disease in obese JCR rats (Mailloux et al., 2014). In the liver of rats, the mixture increased the number of macrovesicular lipid droplets, total lipid content, total cholesterol, cholesterol ester, and mono- and polyunsaturated fatty acids (Mailloux et al., 2014). Individual congeners (e.g. PCB-105 and PCB-126) have also been found to increase serum cholesterol in rats (ATSDR, 2011, 2000). Changes in lipid profile may occur though cytochrome P450 enzyme induction (Imsilp and Hansen, 2005), epigenetic changes (Rusiecki et al., 2008), and up or down regulation of genes (Mailloux et al., 2014; Matsusue et al., 1999; Vezina et al., 2004). There is also evidence from experimental and epidemiological studies that PCBs may act as obesogens, although results are inconsistent with variation according to dose, timing of exposure (e.g. prenatal versus adult), and gender (de Cock and van de Bor, 2014; Lee et al., 2014).

The increasing trend observed with wet-weight PCB quartile level with prevalence of high cholesterol, total cholesterol, and LDL-C suggests a dose-response relationship. One possibility that cannot be ruled out from this analysis is a reverse association, i.e. higher total cholesterol or LDL-C results in higher wet-weight based PCB concentration. A

mechanism for this direction of association, however, is not clear. In addition, Goncharov et al. (2008) have shown that the association of serum lipids to serum PCBs is less plausible compared with the association of serum PCB to serum lipids by testing a nonrecursive feedback loop between PCBs and lipids. However, given that the lipid-based PCB analyses for high cholesterol produced significant effect estimates that did not increase with quartile level, further investigation about potential for dose-response and direction of association is needed.

The strengths of this study were its relatively large sample population, the adjustment of many important covariates, and the use of both wet-weight and lipid-based PCB concentrations for prevalence of high cholesterol. Lipid-based analyses were not conducted for triglycerides, total cholesterol, LDL-C, or HDL-C as this would have adjusted for the outcomes of interest. The prevalence of high cholesterol was based on LDL-C threshold or taking medication that lowers cholesterol, rather than self-report. The choice of this outcome has both its advantages and disadvantages. Since people with high cholesterol may be asymptomatic, self-report may underestimate actual prevalence and, therefore, an outcome based on LDL-C threshold or medication may be more reliable. However, this outcome omitted about 1% of respondents whose LDL was lowered without medication, such as through diet or exercise. The consumption of poor-quality store-bought foods, which contain large servings of carbohydrates, saturated fat, trans-fat, and cholesterol, is an important risk factor for high cholesterol and the metabolic syndrome. We adjusted for fasting glucose in all models, and additionally for total TFA in red blood cells when modeling the outcome of high cholesterol, which would account for the dietary contribution of sugars and trans-fats. It is possible that the results may be confounded by store-bought food consumption (i.e. if participants with higher PCB concentrations also consumed more poor-quality store-bought foods). Although we could not fully evaluate this possibility because only a few store items were evaluated in the IHS (i.e. drinks and chips, crisps, cheese puffs), participants with higher PCB levels would be expected to consume more traditional rather than store-bought foods given that POP exposures come primarily from traditional food sources. The limitations of this study were the cross-sectional design, which prevents any conclusions from being drawn about causality of the observed associations, and the absence of weighted estimates, which means that the observed associations are restricted to the sample population and cannot necessarily be generalized to all Canadian Inuit. Deciphering the individual effect of PCBs from other POPs is also difficult because Inuit are exposed to mixtures of contaminants which are highly correlated.

The importance of lipids in the development of cardiovascular disease requires that we have a sound understanding of all factors that adversely affect lipid profile so that prevention and treatment approaches are appropriately targeted. Further work is needed to corroborate the associations observed with PCBs and lipids in Canadian Inuit and to examine if they are causal in the direction anticipated. Although levels of PCBs are declining in Arctic air and biota overall, since 2000 the rate of decline has slowed and increases have been observed for PCB-52 and PCB-101, possibly due to reemission of PCBs from oceans and ice in response to climate warming (AMAP, 2015a). Levels of PCBs in human tissue are still high in some circumpolar regions, such as Eastern Canada and Greenland (AMAP, 2015b). Among the participants of the IHS, total PCB geometric mean concentration was four times higher than the general Canadian population, and up to nine times higher for elderly men (Laird et al., 2013). Therefore, continued monitoring of PCBs in the Arctic environment and assessment of health risks are required. Contaminant exposures in Inuit come primarily from traditional diets of marine mammal food sources. Traditional food sources also have many nutritional advantages compared with store-bought items, such as high levels of essential omega-3 fatty acids, as well as cultural benefits which cannot be easily replaced. Therefore, a study of the risks of contaminants and the benefits of traditional foods is needed to develop appropriate recommendations about dietary intakes.

Acknowledgements

We would like to thank all the participants of the Inuit Health Survey and the Steering Committee members for their guidance. We thank David Hu for reviewing the final manuscript. Funding support from the Northern Contaminants Program of the Government of Canada and the Canada Research Chair Program is acknowledged.

Funding Sources

Funding was provided from the Northern Contaminants Program of the Government of Canada and the Canada Research Chair Program.

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