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Environmental Contaminant Body Burdens and the Relationship with Blood Pressure Measures Among Indigenous Adults

Aleksandra M. Zuk[a,b,*], Eric N. Liberda[c], and Leonard J.S. Tsuji[a]

Background: Blood pressure (BP) increase cardiovascular disease (CVD) risk. Indigenous Canadians experience slightly higher CVD compared with nonIndigenous Canadians. This study examined the role of polychlorinated biphenyls (PCBs), other organic compound concentrations (OCs), and toxic metals on blood pressure measures among Indigenous Canadians.

Methods: Using data from the Environment-and-Health Study, the sample was restricted to adults with valid BP measures and detectable body burden mixtures. In total, n = 759 participants were eligible, of which, n = 447(59%) were females. Principal Component Analysis (PCA) was used to reduce the complexity of the contaminant data. Orthogonal principal component (PC) variables, and sum (∑) of contaminant compounds were used as independent predictors in modified Poisson regression models with robust variance estimation, deriving prevalence ratios (PR) for hypertension, that is, systolic BP (SBP) ≥140 ml of mercury (mmHg), or diastolic BP ≥90 mm Hg. Additionally, using multivariable generalized linear regression, sex-stratified continuous SBP measure was regressed on ∑ contaminant compounds.

Results: Two PCs were extracted from the PCA analysis. PCBs and OCs positively highly loaded on the first axis (PC-1). Lead loaded positively on the second (PC-2) axis. Hypertension was consistently associated with PC-1 across models, PR = 1.08 (95% confidence intervals = 1.003 to 1.172) fully adjusted model. Examining ∑ of contaminants, the strength of association with hypertension was strongest for ∑OCs compared with ∑PCBs. The measure of effect for continuous SBP measures with ∑ dichlorodiphenyltrichloroethane(*p,p'-DDT*) and dichlorodiphenyldichloroethylene(*p,p'-DDE*) concentrations although small was similar for both females and males, β = 0.04 (95% confidence intervals = 0.005 to 0.075) among females; however, for males the estimate is imprecise after adjusting for body mass index.

Conclusion: This cross-sectional analysis found that PCBs and OCs were associated with associated prevalent hypertension; and exposure to OC pesticides, particularity DDT/DDE were found to be associated with prevalent SBP measures among females and not males.

Keywords: Contaminants; Environmental exposure; Indigenous; Blood Pressure

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide.[1] Hypertension (high blood pressure) is a major risk factor for CVD,[2,3] with 25% of Canadians reporting this health condition.[1] More specifically, the recent clinical practice guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults notes that higher systolic blood pressure (SBP) has been consistently associated with increased CVD risk—even after stratification or adjustment.[3,4] Importantly, others have highlighted that the prevalence of hypertension has been progressively increasing among Indigenous persons in Canada, and CVD is now reported to be the leading cause of death in this population.[5] The progressive increase in hypertensive prevalence among Indigenous persons is particularly important because this observation remains despite improvements in awareness and treatments.[6] Others have suggested that study conclusions, such as, this could be due to racial

[a]*Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, Ontario, Canada;* [b]*School of Nursing, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada; and* [c]*School of Occupational and Public Health, Ryerson University, Toronto, Ontario, Canada.*

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Data availability: Datasets generated and analyzed for this study are available through the Cree Board of Health and Social Services of James Bay.

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**Corresponding author. Address: School of Nursing, Faculty of Health Sciences, Queen's University, 92 Barrie Street Kingston, Ontario K7L 3N6, Canada. Phone: +1-416-208-5088. E-mail address: amz4@queensu.ca (A. Zuk).*

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What this study adds

Cardiovascular disease disproportionally affects Indigenous adults. This article examines the association between environmental contaminant mixture of persistent organochlorine pollutants and toxic metals on blood pressure measure among Indigenous populations in Canada. Our findings highlight the importance of examining summed contaminant compounds and combined mixture effects of contaminants using principal component analysis, a data reduction technique. Specifically, exposure to organochlorine pesticides, particularity dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) were found to be associated with prevalent systolic blood pressure measures among females. Additional studies are needed examining the role of DDT and DDE on cardiovascular risk factors among Indigenous peoples, and particularly women.

or geographic factors,[7] and more specifically, disparities in the availability and uptake of healthcare[6]—an important observation given that many Indigenous communities in Canada are remote.

Indigenous First Nation residents of the eastern James Bay region of the *Eeyou Istchee* Territory in Quebec, Canada, live in varying degrees of isolation, with some communities having year-round access to roads, and others only being accessible by plane or boat. Many residents in these communities live, at least in part, a subsistence lifestyle involving traditional hunting activities. Although hunted wild game and meats present a cost-effective source of protein and maintain traditional activity practices, it may also lead to an increased risk of dietary exposure to environmental contaminants. We have previously reported on the body burdens of contaminants,[8,9] and their associations with diabetes and intima media thickness[10,11] in residents from the *Eeyou Istchee* territory. Various organic contaminant mixtures have shown associations with increases in blood pressure in some populations[12–14] but not in others.[15]

Henríquez-Hernández et al[16] found that some individual contaminants may exert positive effects on blood pressure, although others exert negative effects, and thus, highlight the complexity associated with assessing mixtures. Additionally, Brook et al[17] note that environmental factors, such as, temperature, noise, geographic latitude, altitude, and other nonmeasured pollutants may also contribute to alterations in blood pressure, further complicating its evaluation. Beyond organic environmental contaminants, toxic metals such as lead and cadmium, among others, have also been shown to increase risk of hypertension.[18,19] Given the additional risks to increased environmental contaminant body burdens, combined with varying degrees of isolation (and hence potentially reduced health care access) in the *Eeyou Istchee* territory, it is important to characterize the associations between environmental exposures and blood pressure measures, while identifying the main contributors to this effect, if any. Therefore, we evaluated the association between complex organic and metal/metalloid contaminant body burden mixtures with blood pressure measures among Canadian Cree (Indigenous) communities residing in the *Eeyou Istchee* territory in northern Quebec, Canada.

Methods

Data sources

Data for this analysis were obtained from the *Nituuchiscaayihtitaau Aschii* ("Learn about ourselves and our earth"), Multi-Community Environment-and-Health Study. This study was conducted in the *Eeyou Istchee* territory, located in the James Bay Region of northern Quebec, Canada (Figure 1). Detailed information about the Multi-Community Environment-and-Health Study is previously published.[20] Briefly, seven Cree communities participated in the study between 2005 and 2009. The primary objective of the study was to examine the influence of various lifestyle factors, environmental contaminant exposures, and diets and food consumption have on health and wellbeing. Participants who were enrolled were stratified according to age groups: adults (15–39 years, and 40 years older); and children (0–7 years and 8–14 years). Data were collected by research nurses who administered health-related questionnaires, conducted medical chart reviews to validate specific health information, and obtained clinical and physical measurements, which included collecting blood specimens by venipuncture. Ethics for this study was approved by following universities: McGill University (Montreal, Quebec), Laval University (Laval, Quebec), and McMaster University (Hamilton, Ontario), in partnership with the Cree Board of Health and Social Services of James Bay. All participants and their guardians provided both written and informed consent in Cree, English, or French.

Study population

Study recruitment and sampling details are described elsewhere.[20] For this analysis, the initial sample consisted of 1,425 study participants. Study participants between 20 and 80 years of age were included if the following health data were available: (1) valid SBP and diastolic BP (DBP) measures; (2) complete exposure profiles for 20 environmental contaminants, specifically, persistent organic pollutants (POPs) and toxic metals/metalloids; (3) completed both the health interview-questionnaires, and physical health assessment, including a fasting blood draw. The final analytical sample consisted of 759 Indigenous Cree adults from seven communities in the *Eeyou Istchee* territory of northern Quebec, Canada. A flow chart of the sample is presented in the eFig S1; http://links.lww.com/EE/A119.

Environmental contaminants analysis

The Institut National de Santé Publique du Québec Human Toxicology Laboratory (INSPQ), an accredited International Organization for Standardization 17,025 by the Standards Council of Canada carried out analyses for toxic metals and persistent organic pollutants (POPs). Toxic metals (Cadmium, Cd; Lead, Pb; Mercury, Hg; and Selenium) were measured in whole blood samples and assessed by inductively coupled plasma mass spectrometry (ICP-MS) via. the Perkin Elmer Sciex Elan 6000 ICP-MS (and dynamic reaction cell II for total Hg) instrument. Also, from participant blood draws, plasma samples were assessed for the following nine polychlorinated biphenyl congeners (PCB-99, -105, -118, -138, -153, -170, -180, -183, -187); and seven organochlorine pesticides or metabolites [mirex, oxy-chlordane, trans-Nonachlor, cis-Nonachlor, hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (*p,p'-DDT*), dichlorodiphenyldichloroethylene (*p,p'-DDE*)] by gas chromatography-mass spectrometry [GC-MS (INSPQ Method E-446)] on an Agilent 6,890 gas chromatograph equipped with an Agilent G2397A ECD and an Agilent 5,973 network mass detector. Limits of detection (LOD) for persistent organic pollutants, toxic metals, and metalloids are described and previously published.[8,9]

Outcome assessment

Blood pressure (BP) measurement protocols were according to the World Health Organization clinical guidelines for hypertension management.[20] Nurses during the direct physical examination (which included same day phlebotomy and blood collection) obtained three blood pressure readings in a seated position using mercury sphygmomanometers after participants rested for 5 minutes and refrained from eating and smoking for at least 30 minutes. SBP and DBP readings were measured in units of millimeters of mercury (mmHg), and only the last two BP measurements were used in calculating an overall SBP and DBP mean.[20]

Classification of blood pressure was according to the updated 2017 American College of Cardiology and American Heart Association (ACC/AHA) clinical practice guidelines for blood pressure in adults.[3] Hypertension (i.e., stage 2 hypertension) was defined by SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, or antihypertensive medication, which was based on the Drug Identification Number (DIN).

Risk factors

For each study participant, a trained research nurse conducted interviewer-administered health questionnaires, collecting sociodemographic, and health-related behavior information. The following risk factor information was attained: age (years-continuous) and sex. Questions relating to smoking habits were

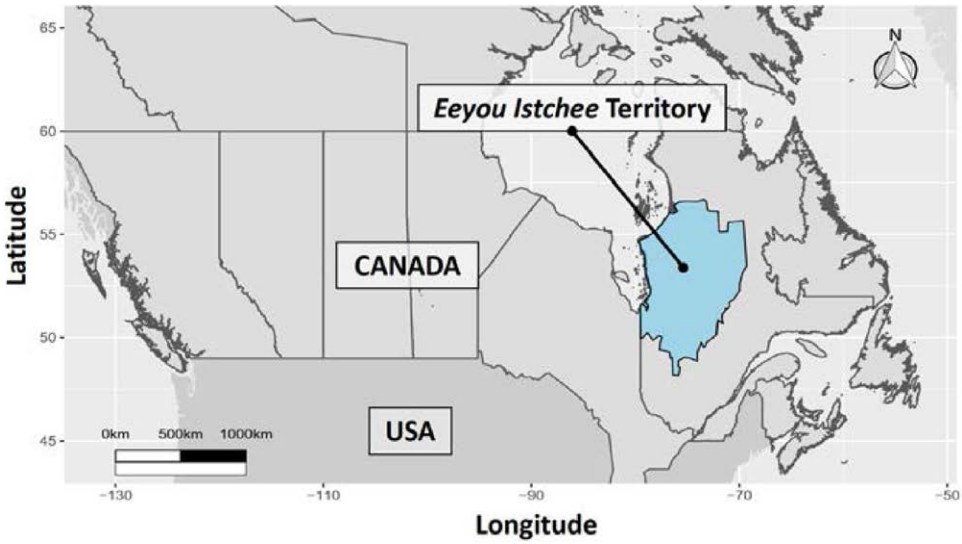


Figure 1. *Eeyou Istchee* Territory, Quebec, Canada.

broadly defined, that, smoking among participants was classified as those who self-reported being "current or occasional smokers" and "never or former smokers."

Anthropometric measures were taken during the physical assessment; body mass index (BMI, kg/m^2) was calculated as weight in kilograms (kg), divided by and height in meters squared (m^2). Total blood lipid adjusted concentrations (g/L) are calculated by equations described by Rylander et al.[21] Ascertainment of type 2 diabetes was verified for each individual. This was carried out through medical chart reviews by a research nurse for all consenting adults who underwent health-related questionnaires. Food frequency questionnaire assessed dietary intake of traditional (i.e., consumption of game animals, fish, birds, berries) and market (i.e., store bought) foods. The 24-hour recall estimated the following specific micronutrients, sodium, and potassium were measured in milligrams (mg) per day. However, due to possible underreporting of certain foods caution is warranted for absolute micronutrient intake values.[22]

Statistical analysis

Descriptive statistics for all variables are presented and stratified by clinically defined hypertension. Where appropriate, means (or geometric means) ± standard deviations (SD) are presented. Categorical variables are reported as frequencies and percentages. The analysis was conducted in two parts. First, Principal Component Analysis (PCA), a data reduction technique was conducted on the aforementioned PCBs, organic compound concentrations (OCs), and toxic metals, which were $\log_{10}$-transformed (variate + 1) to normalize distributions, and standardized in the PCA analysis.[23] PCA reduced the total number of 20 environmental contaminants into fewer uncorrelated orthogonal principal components (PCs) that explain the total variance of original observed contaminant concentrations. Only orthogonal PC were retained if the eigenvalues were equal to or greater than one. Therefore, the first retained PC (PC-1) explained the largest variance, with all subsequent PCs (e.g., PC-2) explaining a smaller proportion of the total variance that was not accounted for in the previous PC. PC loadings for each contaminant concentrations were important if the absolute value was 0.60 or greater. Importantly, the relative magnitude and patterns of PC loadings are meaningful rather than the sign of PC loadings.[24] PCA analysis derives orthogonal PC scores for each retained PC axes, which were then used as independent predictors in multivariable modified Poisson regression with robust error variance to estimate prevalence ratios (PR) and corresponding 95% confidence intervals (95% CI) using SAS PROC GENMOD procedures. The analysis regressed clinically defined hypertension on extracted PCs (i.e., PC-1 and PC-2); and sums (∑) of the following compounds: nine PCBs (∑9 PCBs, PCB-99, -105, -118, -138, -153, -170, -180, -183, -187), seven organochlorines (∑7 OCs, mirex, oxy-chlordane, trans-Nonachlor, cis-Nonachlor, hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (*p,p'-DDT*), dichlorodiphenyldichloroethylene (*p,p'-DDE*)), five organochlorines, which excluded *p,p'-DDT* and *p,p'-DDE,* and lastly (∑2 *p,p'-DDT* + *p,p'-DDE*) alone, adjusting for *a priori* covariates of the exposure-outcome relationship: age (continuous), sex, total lipids (continuous), smoking status (categorical), and BMI (continuous).

We further performed an analysis primarily focused on moderate to high PC contaminant loadings. Specifically, mercury (Hg), and the sum (∑) of the following compounds: ∑9 PCBs, ∑7 OCs, ∑5 OCs, and (∑2 *p,p'-DDT* + *p,p'-DDE*). We fit sex-stratified generalized linear regression model with an identity link and Gaussian distribution, regressing continuous measures of SBP on log transformed ($\log_{10}$) predictors, which are interpreted as the change in the average value of continuous SBP measures for every 1% increase in the predictor. Simple fit plots displaying the linear relationship between SBP and DBP on summed Σ contaminant body burdens found no meaningful relationship for DBP, and thus not further examined in this analysis (data not shown).

All statistical analyses were carried out using SAS v9.4 (SAS Institute, Inc., Cary, NC), and R (version 3.5.3; Vienna, Austria) generated all figures.

Results

Descriptive results

Population study characteristics are presented in Table 1. In total, there were 759 participants in this analysis, represented by mainly females 447 (59%). The overall mean age (±SD) for males and females was 39.5 ± 12.4 years and 41.4 ± 14.7 years, respectively. Hypertension (i.e., stage 2) was slightly higher for males (33.7%) than for females (31.2%). Among adults living with hypertension 25% reported taking medication for hypertension (i.e., drug identification number coded for high blood pressure). Overall, the mean body mass index (BMI) at examination was similar for both males and females, although, female adults with

Table 1.

Participant characteristics stratified by sex and hypertension status: Results from the *Nituuchischaayihtitaau Aschii*—Multi-Community Environment-and-Health Study (2005–2009)

			Total		Hypertension[b]		Normotensive	
Participant characteristics	**Sex stratified**	**% ≥LOD[a]**	**Frequency (N) or mean**	**% or SD**	**Frequency (N) or mean**	**% or SD**	**Frequency (N) or mean**	**% or SD**
Demographic								
Sex (n, %)	Female		447	58.9	139	31.2	308	68.9
	Male		312	41.1	105	33.7	207	66.3
Age (yrs)								
	Female		39.5	12.4	50.3	13.9	34.6	10.8
	Male		41.4	14.7	49.8	15.3	37.2	12.4
Risk factors								
Anthropometry								
Body mass index, BMI (kg/m^2)	Female		35.5	7.3	37.2	7.6	34.8	7.0
	Male		32.2	5.7	34.0	5.9	31.4	5.4
Health factors								
Smoking status, current, or occasional	Female		228	51.1	46	10.3	182	40.8
			218	48.9	92	20.6	126	28.3
Smoking status, former, or never (R)	Male		150	48.5	33	10.7	117	37.9
			159	51.5	72	23.3	87	23.3
Antihypertensive medication[c]	Female		112	25.1	112	25.1	0	0.0
	Male		75	24.0	75	24.0	0	0.0
Type 2 diabetes[d]	Female		91	22.3	66	16.2	25	6.1
	Male		44	15.4	36	12.6	8	2.8
Cardiometabolic								
Total lipids (g/L)[e]								
	Female		6.0	1.2	6.3	1.4	5.8	1.1
	Male		6.4	1.4	6.3	1.5	6.4	1.3
Contaminants[f]								
Metals/metalloids								
Cadmium, Cd (nmol/L)	Female	60.9	8.18	2.82	6.34	2.59	9.18	2.87
	Male	51.9	7.79	3.11	4.72	2.46	10.03	3.18
Mercury, Hg (nmol/L)	Female	82.8	15.79	3.88	30.66	3.80	11.70	3.52
	Male	85.9	21.40	3.95	35.45	3.95	16.57	3.68
Lead, Pb (μmol/L)	Female	70.0	0.12	2.93	0.17	2.83	0.10	2.86
	Male	90.7	0.19	2.53	0.22	2.59	0.17	2.47
Selenium, Se (μmol /L)	Female	99.8	2.13	1.16	2.21	1.21	2.10	1.14
	Male	99.7	2.24	1.14	2.27	1.16	2.22	1.13
PCBs								
PCB-99 (μg/L)	Female	56.4	0.05	3.75	0.12	4.04	0.03	2.96
	Male	65.7	0.06	3.37	0.09	3.54	0.04	3.02
PCB-105 (μg/L)	Female	48.3	0.03	2.80	0.06	3.37	0.02	2.12
	Male	50.0	0.03	2.37	0.04	2.76	0.02	2.03
PCB-118 (μg/L)	Female	82.6	0.09	4.78	0.27	4.33	0.05	3.76
	Male	87.8	0.09	4.00	0.17	4.18	0.07	3.51
PCB-138 (μg/L)	Female	94.4	0.02	1.40	0.02	1.61	0.01	1.24
	Male	98.1	0.02	1.39	0.02	1.53	0.02	1.29
PCB-153 (μg/L)	Female	98.7	0.43	5.68	1.36	4.41	0.26	4.91
	Male	99.7	0.68	4.66	1.25	4.38	0.50	4.39
PCB-170 (μg/L)	Female	81.7	0.10	4.82	0.30	4.15	0.06	4.03
	Male	91.7	0.17	4.43	0.30	4.36	0.13	4.12
PCB-180 (μg/L)	Female	96.9	0.33	5.75	1.04	4.46	0.20	4.96
	Male	98.7	0.57	5.00	1.07	4.67	0.42	4.73
PCB-183 (μg/L)	Female	62.2	0.05	3.64	0.12	3.72	0.03	2.91
	Male	79.8	0.06	3.48	0.11	3.58	0.05	3.16
PCB-187 (μg/L)	Female	85.5	0.13	5.18	0.40	4.37	0.08	4.35
	Male	92.0	0.21	4.66	0.39	4.43	0.16	4.38
OCs								
cis-Nonachlor (μg/L)	Female	46.8	0.03	2.55	0.05	2.91	0.02	2.02
	Male	59.6	0.03	2.62	0.03	2.62	0.03	2.24
Mirex (μg/L)	Female	73.4	0.07	4.51	0.18	4.26	0.04	3.70
	Male	84.0	0.11	4.82	0.20	4.84	0.08	4.45
Hexachlorobenzene (HCB) (μg/L)	Female	65.3	0.06	2.92	0.13	2.83	0.04	2.43
	Male	76.6	0.07	2.61	0.11	2.52	0.06	2.48
oxy-Chlordane (μg/L)	Female	66.4	0.04	3.01	0.09	2.99	0.03	2.48
	Male	80.1	0.05	2.83	0.08	2.99	0.04	2.49
Trans-nonachlor (μg/L)	Female	76.7	0.06	3.66	0.16	3.31	0.04	3.00
	Male	89.4	0.09	3.42	0.16	3.44	0.06	3.05
p'p'-DDT (μg/L)	Female	10.7	0.03	1.46	0.03	1.69	0.03	1.31
	Male	9.6	0.03	1.37	0.03	1.51	0.03	1.28
p'p'-DDE (μg/L)	Female	99.3	1.21	3.82	3.13	3.12	0.78	3.30
	Male	99.7	1.46	2.91	2.37	2.93	1.14	2.66

Missing values among adult females; BMI (n = 3, 0.002%); smoking status (n = 1, 0.002%). Missing values among adult males; BMI (n = 6, 0.019%); smoking status (n = 3, 0.009%).

[a]Percentage of contaminants above the level of detection (LOD);

[b]Hypertension (i.e., stage 2 hypertension) was defined by SBP≥140 mmHg or DBP≥90 mmHg, or antihypertensive medication;

[c]Antihypertensive mediation is based on the Drug Identification Number (DIN).

[d]Type 2 diabetes case aascertainment verified though medical chart reviews.

[e]Total lipid concentrations were determined using methods described by Rylander et al.[21]

[f]Presented are geometric means ± SD.

% inidcates percentage; BMI, body mass index; N, frequency value; OCs, Organochlorines; *p,p'-DDE*, Dichlorodiphenyldichloroethylene; *p,p'-DDT*, Dichlorodiphenyltrichloroethane; PCBs, Polychlorinated biphenyls; R, reference category.

hypertension had slightly higher mean BMI than male adults with hypertension, 37.2 kg/m^2 ± 7.6, and 34.0 kg/m^2 ± 5.9. Half of female participants (51.1%) self-reported being "current and occasional" smokers compared with "former or never" smokers. For both sexes, only 10% self-report being "current and occasional" smokers among adults with hypertension.

Contaminant Principal Component Analysis loadings

The PC loadings generated from PCA are shown in Figure 2. In total, two PC axes were retained (i.e., had eigenvalues values greater than one). The first PC (PC-1) explained 73% of the total variance from the original log transformed contaminant body burdens. PC-1 highly and positively loaded for all PCBs, OCs (highly lipophilic), and moderately loaded on mercury (slightly lipophilic), indicating that those participants with higher PC scores exhibit differential exposures, higher burden of PCBs and organochlorine pesticides, with mercury showing a smaller contaminant body burden. The second axis, PC-2 moderately loaded on lead (Pb), and only explained 5.6% of the total variance.

PCA biplot is shown in Figure 3, representing orthogonal PC axes overlaid with hypertension among Indigenous Cree adults in the *Eeyou Istchee* territory.

Prevalence ratios (PR) were estimated using multivariable modified Poisson regression with robust error variance. Prevalent stage 2 hypertension was regressed on retained orthogonal PCs and shown in Table 2. Across all adjusted models, only PC-1, which loaded highly and positively on PCBs, OCs, and moderately on mercury (Hg) was associated with hypertension (PR = 1.08, 95% CI= 1.003 to 1.172) , i.e., as PC-1 axis scores increase, PCBs, OCs exhibit strong positive loadings and moderate Hg loadings. The strength of association was slightly stronger for PC1 than for PC2, which accounted for almost three-fourths of the total variance. Further adjusting for micronutrient values did not change the strength of association (data not shown).

Main effects for sums of contaminant body burdens and stage 2 hypertension

Using the information from the PCA, a data reduction technique, we examined sums (Σ) of contaminant body burdens for primary contaminant loadings (i.e., PCBs, OCs, Hg, and Pb) and prevalent stage 2 hypertension. As shown in Table 3, across all adjusted models, the sizes of the effect estimates show the strength of association was stronger for sums of Σ7 OCs, Σ DDT/DDE, and Σ5 OCs, which excluded *p,p'-DDT* and *p,p'-DDE*, followed by sum of Σ PCBs after adjusting for confounders in model 3, PR 1.53 (95% CI = 1.17 to 2.00), PR 1.52 (95% CI = 1.16 to 1.98), PR 1.38 (95% CI = 1.09 to 1.75), PR 1.29 (95% CI = 1.06 to 1.57), respectively. There was no appreciable difference in the strength of association after accounting micronutrient values (data not shown).

Sums of contaminant body burdens and systolic blood pressure

Tables 4 and 5 show sex-stratified multivariable generalized linear regression models examining the association between sums (Σ) of contaminant body burdens and SBP measures. Sums

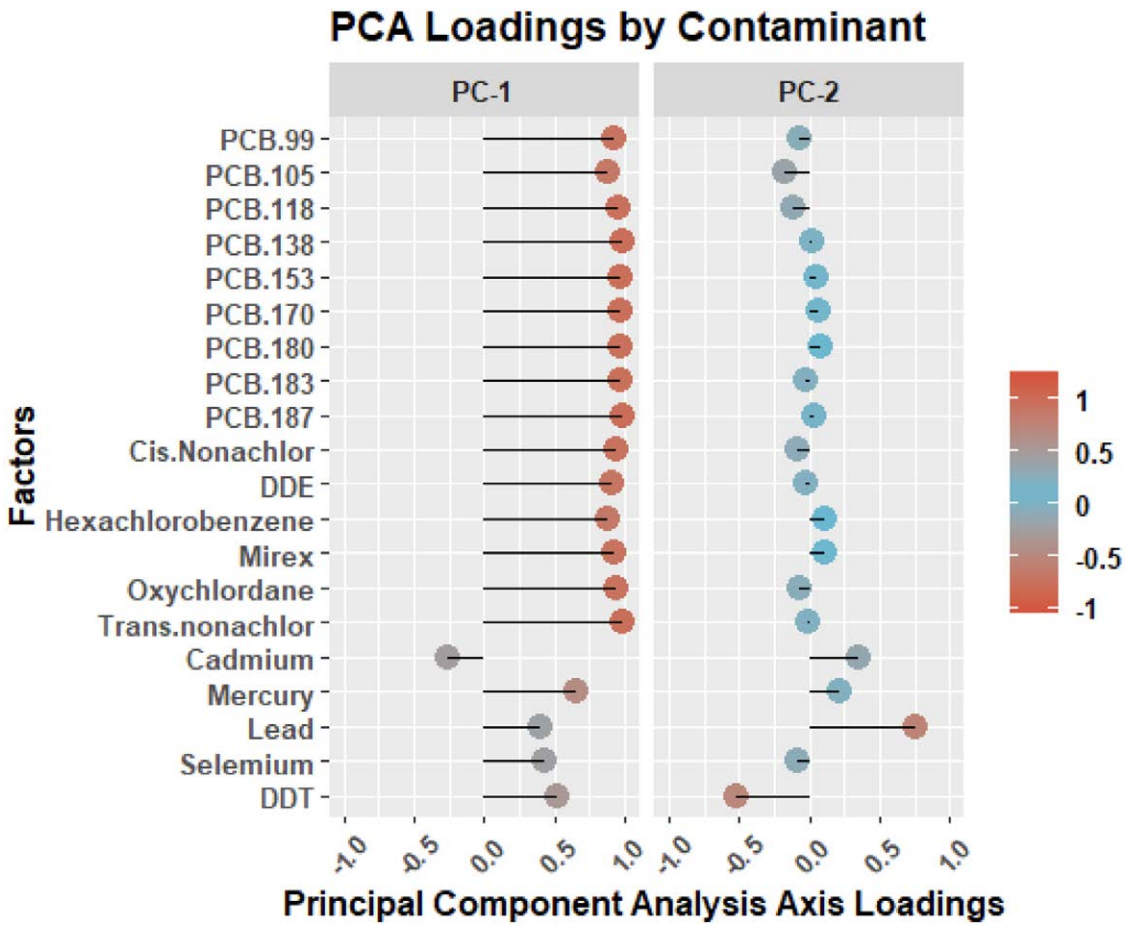


Figure 2. PCA loadings of environmental contaminants among Indigenous cree adults in the *Eeyou Istchee* territory. PCA indicates Principal Component Analysis.

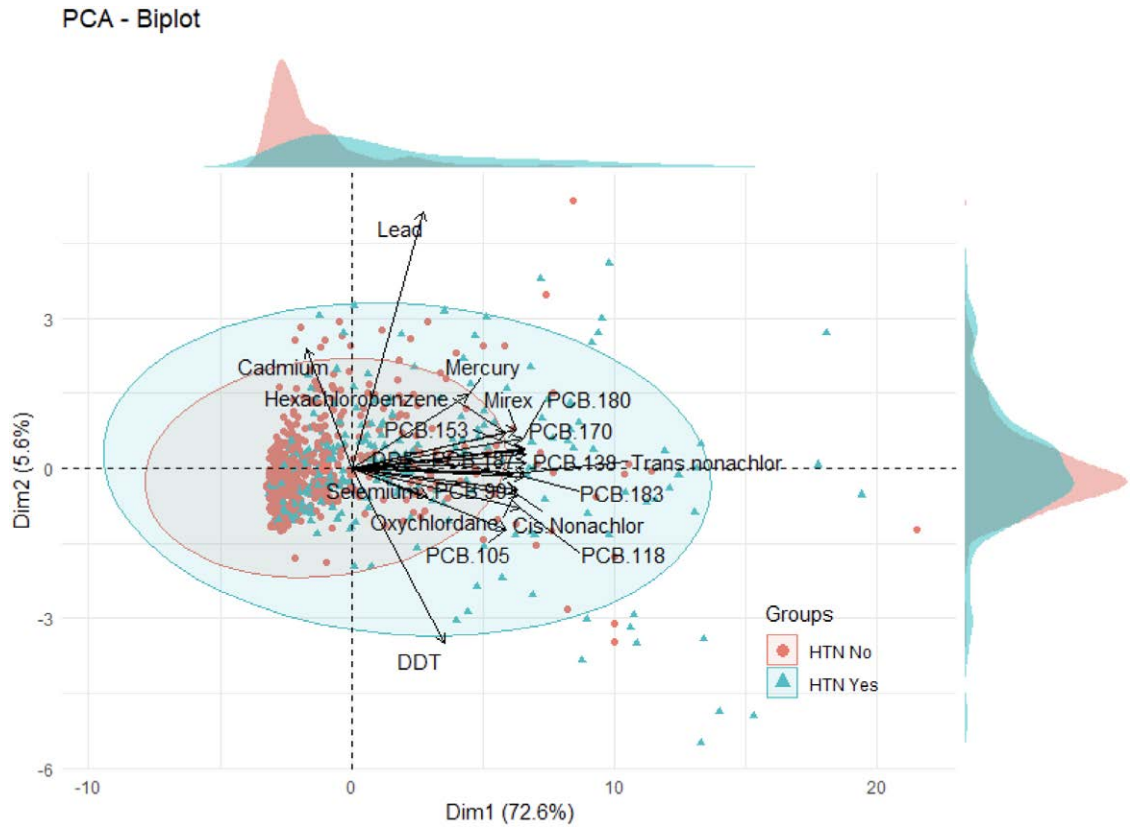
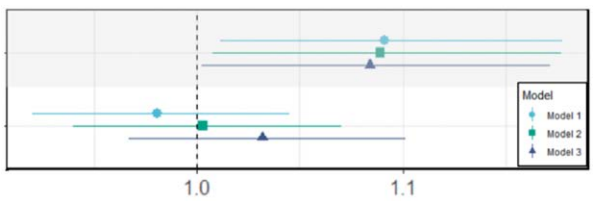


Figure 3. PCA biplot and hypertension status among Indigenous cree adults in the *Eeyou Istchee* territory. Main effects of PCA and stage 2 hypertension. PCA indicates Principal Component Analysis.

Table 2.

Multivariable adjusted prevalence ratios (95% CI) for prevalent stage 2 hypertension and orthogonal principal component axes among adults over 20 years of age using data from the *Nituuchischaayihtitaau Aschii*—Multi-Community Environment-and-Health Study (2005–2009)

		Modified poisson regression models		
		Prevalence ratio (PR)		
		Model 1	**Model 2**	**Model 3**
PC-1	PR	**1.091**	**1.089**	**1.084**
	95% CI	(1.011–1.178)	(1.008–1.177)	(1.003–1.172)
	P	**0.025**[a]	**0.031**[a]	**0.043**[a]
PC-2	PR	0.981	1.003	1.032
	95% CI	(0.921–1.045)	(0.940–1.070)	(0.967–1.101)
	P	0.554	0.931	0.342



Model 1: age, sex, total lipids; model 2: model 1, plus smoking; model 3: model 2, plus BMI
Bolded values indicate statistical significance: [a]$P < 0.05$.
CI indicates 95% confidence intervals; PC1 and PC2, first and second orthogonal principal components axes.

(Σ) of the highly and moderately loaded contaminants, that is, PCBs, OCs, and the lipophilic mercury (Hg) were examined on continuous blood measures of blood pressure. Among females, sum of Σ7 OCs was associated with SBP across all adjusted models, the strength of association similar across all models, $\beta = 0.04 (95\%\,\text{CI} = 0.003 \text{ to } 0.078)$ in the final adjusted model. Additionally, when examining only the sum of two OCs, the sum of Σ of *p,p'-DDT* and *p,p'-DDE* alone with SBP across all adjusted models, the estimates are similar in strength with Σ7 OCs, $\beta = 0.04 (95\%\,\text{CI} = 0.005 \text{ to } 0.075)$, showing similar changes in magnitude and precision after adjusting for confounders. However, a weaker and less precise association was found when examining only Σ5 OCs (i.e., excluding *p,p'-DDT* and *p,p'-DDT*) with SBP among females. The strength of association for Σ9 PCBs and toxic metal Hg was found to be even weaker compared with OCs, although results showed slightly improved precision. Among males only the sum of Σ of *p,p'-DDT* and *p,p'-DDE* alone was associated with SBP across the minimally and adjusted models (i.e., model 1 and 2); however, when adjusting for BMI the strength of association for Σ of *p,p'-DDT* and *p,p'-DDE* was slightly attenuated with an imprecise estimate. Furthermore, among males, the magnitude of effect for Σ of 5 OCs, which excluded the Σ of *p,p'-DDT* and *p,p'-DDE* was largely reduced compared with the association between Σ of 7 OCs and continuous measures of SBP. Minimally adjusted models (i.e., age) are provided in eTable 1; http://links.lww.com/EE/A119.

Table 3.

Multivariable adjusted prevalence ratios (PR, 95% CI) for prevalent stage 2 hypertension and sums (Σ) of environmental contaminants including continuous measures among adults over 20 years of age using data from the *Nituuchischaayihtitaau Aschii*—Multi-Community Environment-and-Health Study (2005–2009)

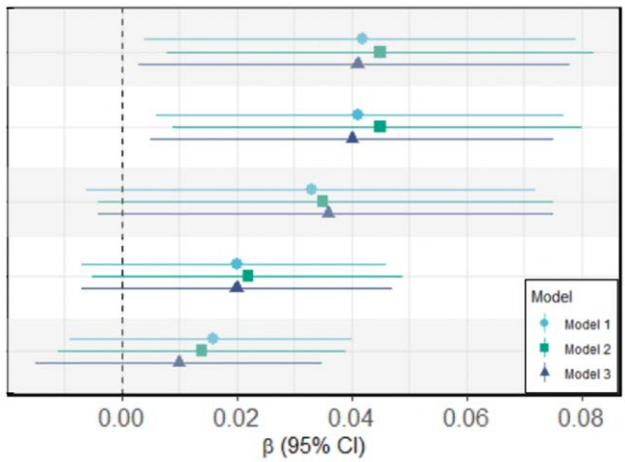
	Model 1	Model 2	Model 3
Σ Sum of environmental contaminants	**PR (95% CI)**	**PR (95% CI)**	**PR (95% CI)**
Σ 7 OCs	1.64 (1.25–2.14)	1.61 (1.23–2.11)	1.53 (1.17–2.00)
Σ DDT/DDE	1.65 (1.26–2.15)	1.62 (1.25–2.12)	1.52 (1.16–1.98)
Σ 5 OCs	1.40 (1.10–1.76)	1.39 (1.09–1.75)	1.38 (1.09–1.75)
Σ PCBs	1.32 (1.08–1.60)	1.31 (1.08–1.59)	1.29 (1.06–1.57)
Hg	1.20 (0.99–1.46)	1.18 (0.98–1.44)	1.16 (0.96–1.42)
Pb	1.12 (0.88–1.40)	1.15 (0.92–1.45)	1.18 (0.94–1.49)

Σlog10-transfomed predictors; PR per one-log10-transfomed predictor increase.
Model 1: age, sex, total lipids; model 2: model 1, plus smoking; model 3: model 2, plus BMI.
Bolded values indicate statistical significance: $P < 0.05$.
CI indicates confidence intervals; DDT/E, dichlorodiphenyltrichloroethane (*p,p'*-DDT) and dichlorodiphenyldichloroethylene (*p,p'-DDE*); Hg, mercury; OCs, organochlorines pesticides; Pb, lead; PCBs, polychlorinated biphenyls; PR, prevalence ratio.

Table 4.

Sex-stratified female multivariable generalized linear regression models between SBP measures and sums (Σ) of environmental contaminants including continuous measures among participants from the *Nituuchischaayihtitaau Aschii*—Multi-Community Environment-and-Health Study

		Generalized Multivariable Linear Regression Models: ∑Log10 transformed predictors on SBP measures among females		
∑ Sums		**Model 1**	**Model 2**	**Model 3**
∑ 7 OCs	B	**0.042**	**0.045**	**0.041**
	95% CI	(0.004–0.079)	(0.008–0.082)	(0.003–0.078)
	P	**0.029**[a]	**0.018**[a]	**0.033**[a]
∑ DDT DDE	B	**0.041**	**0.045**	**0.040**
	95% CI	(0.006–0.077)	(0.009–0.08)	(0.005–0.075)
	P	**0.022**[a]	**0.013**[a]	**0.027**[a]
∑ 5 OCs	B	0.033	0.035	0.036
	95% CI	(–0.006–0.072)	(–0.004–0.075)	(–0.004–0.075)
	P	0.099	0.078	0.077
∑ PCB	β	0.020	0.022	0.020
	95% CI	(–0.007–0.046)	(–0.005–0.049)	(–0.007–0.047)
	P	0.147	0.106	0.141
Hg	B	0.016	0.014	0.010
	95% CI	(–0.09–0.040)	(–0.011–0039)	(–0.015–0.035)
	P	0.222	0.266	0.451



∑log10-transformed predictors represents the average value of SBP for 1% increase in the predictor.
Model 1: age, sex, total lipids; Model 2: model 1, plus smoking; Model 3: model 2, plus BMI
Bolded values indicate statistical significance: [a]$P < 0.05$.
CI indicates 95% confidence intervals; DDT DDE, DDT/E, dichlorodiphenyltrichloroethane (*p,p'*-DDT) and dichlorodiphenyldichloroethylene (*p,p'-DDE*); Hg, mercury; OCs, organochlorines; PCBs, polychlorinated biphenyls; SBP, systolic blood pressure measures.

Simple fit plots displaying the linear association between DBP on summed Σ contaminant body burdens found no meaningful relationship in either direction, and therefore not examined in this analysis (data not shown).

Discussion

This cross-sectional analysis demonstrated that PCBs, OCs and the mercury positively correlated with the first principal axes (PC-1) from PCA, a data reduction tool.

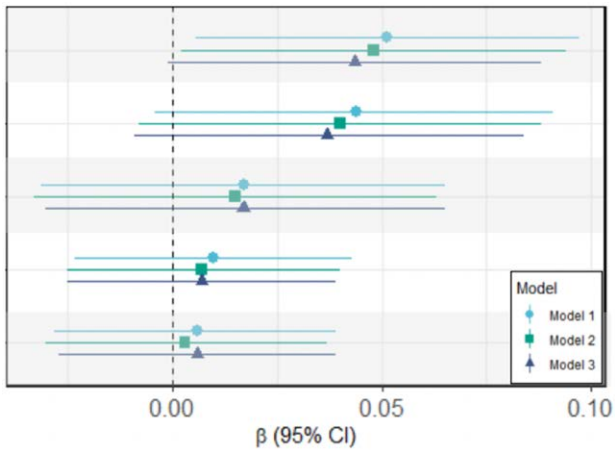
PC-1 was associated with stage 2 hypertension. When further examined, summed OCs had a stronger association than summed PCBs with prevalent hypertension among Indigenous adults. Summed concentrations of *p,p'-DDT* and *p,p'-DDE* appeared to be driving the association among Indigenous women and less likely for adult Indigenous men even after adjusting for body mass index.

Pesticides such as DDT have been banned in Canada since 1985, although its use was permitted until 1990,[25] and continues to be found in the environment.[26] Historically, several occupational studies in the United States have shown an association between pesticides and blood pressure measures. In a small case-control study (i.e., 23 cases and 20 controls) pesticide-exposed male workers from the South Carolina Community Pesticide Study show that *p,p'-DDT* was elevated in blood levels, and reported that SBP was significantly correlated with *p,p'-DDT* among the exposed group compared with controls, although, DBP was not associated with *p,p'-DDT* exposure.[27]

Table 5.

Sex-stratified male multivariable generalized linear regression models between SBP and sums (Σ) of environmental contaminants including continuous measures among participants from the *Nituuchischaayihtitaau Aschii*—Multi-Community Environment-and-Health Study

		Generalized Multivariable Linear Regression Models		
		∑Log10 transformed predictors on SBP measures among males		
∑ Sums		**Model 1**	**Model 2**	**Model 3**
∑ DDT DDE	β	**0.051**[a]	**0.048**[a]	0.044
	95% CI	(0.006–0.097)	(0.002–0.094)	(−0.001–0.088)
	P	**0.027**[a]	**0.041**[a]	0.056
∑ 7 OCs	β	0.044	0.040	0.037
	95% CI	(−0.004–0.091)	(−0.008–0.088)	(−0.009–0.084)
	P	0.072	0.099	0.116
∑ 5 OCs	B	0.017	0.015	0.017
	95% CI	(−0.031–0.065)	(−0.033–0.063)	(−0.030–0.065)
	P	0.0489	0.547	0.480
∑ PCB	B	0.010	0.007	0.007
	95% CI	(−0.023–0.043)	(−0.025–0.040)	(−0.025–0.039)
	P	0.547	0.655	0.678
Hg	β	0.006	0.003	0.006
	95% CI	(−0.028–0.039)	(−0.030–0.037)	(−0.027–0.039)
	P	0.745	0.840	0.725



∑log10-transformed predictors represents the average value of SBP for 1% increase in the predictor
Model 1: age, sex, total lipids; model 2: model 1, plus smoking; model 3: model 2, plus BMI.
Bolded values indicate statistical significance: [a]P < 0.05.
CI indicates 95% confidence intervals; DDT DDE, DDT/E, dichlorodiphenyltrichloroethane (*p,p'*-DDT) and dichlorodiphenyldichloroethylene (*p,p'-DDE*); Hg, mercury; OCs, Organochlorines; PCBs, Polychlorinated biphenyls; SBP, systolic blood pressure measures

In a large occupational study, a national health status program across 13 states examined pesticide-exposed U.S workers between 1971 and 1973, which showed that the sum of DDT and DDE was significantly higher among participants selfreporting subsequent hypertension than those that did not four to 6 years later, 1974–1977.[28] More recently, data from a prospective Child Health and Development birth cohort in the US examined prenatal *p,p'DDT* exposure among women (n = 527) between 1959 and 1967 and self-reported physician-diagnosed medicated hypertension among adult female offspring (39–47 years of age) in 2005–2008. This study shows that compared with the lowest category, the second and third highest tertiles of prenatal *p,p'DDT* was significantly associated with medicated hypertension across all adjusted models.[29]

Similarly, African women who participated in the Venda Health Examination of Mothers, Babies and their Environment study show that serum concentrations of *p,p'DDT* and *p,p'DDE* at the time of delivery significantly increased the odds of self-reported and medical chart reviewed hypertensive disorders in pregnancy.[30] In Sweden, data from the Northern Sweden Health and Disease study examined both cross-sectional and longitudinal measurements (i.e., 10 years apart) of plasma concentrations of different persistent organic pollutants (POPs) on hypertension among middle-aged adults. Those enrolled at baseline between 1990 and 2003 were followed-up during 2000–2013; this study showed that *p,p'DDE* and dioxin-like PCBs (but not nondioxin-like PCBs) were associated with hypertension when examined cross-sectionally and longitudinally; however, after adjusting for lipids and body mass index, *p,p'DDE* was no longer significantly associated with hypertension.[12] These findings are similar to ours among males, where after adjusting for body mass index, hypertension was attenuated and imprecise with sums of *p,p'DDT and p,p'DDE*. However, a cross-sectional study of Swedish elderly (i.e., 70 years and older) showed that *p,p'DDE* was associated with prevalent hypertension even after adjusting for body mass index and other covariates,[31] as was found in our analysis among females participants.

Among Inuit from Arctic regions, exposure to *p,p'DDT* and *p,p'DDE* in the overall sample was only significantly associated with prevalent hypertension in the unadjusted models.[15] However, when stratified by age groups (i.e., 18 to 39 years, and ≥40 years of age), *p,p'DDE* in the unadjusted model among older adults was associated with hypertension, but not in the fully adjusted models; whereas *p,p'DDT* was shown to be associated with hypertension among younger adults in both unadjusted and adjusted models, although, among older adults, *p,p'DDT* was only associated with hypertension in the unadjusted model.[15] In a meta-analysis of predominately cross-sectional studies (n = 10), Park et al[32] examined the association between POPs and hypertension. The overall effect of POP exposures was significantly associated with increased odds of hypertension. Specifically, subgroup analyses following pooled random-effects of six studies showed that *p,p'DDT* increased the odds of hypertension (odds ratio 1.10; 95% CI = 1.03 to 1.18). This association remained significant even when examining studies that only reported: lipid-adjusting analyses; measuring POPs using high resolution gas chromatography/high-resolution mass spectrometry; or pooled definitions of hypertension.

Exposure to organochlorides pesticides (i.e., *p,p'DDT and p,p'DDE)* in the environment (e.g., soil, water, or air) are a health concerns as OCs have been linked with various adverse health effects (e.g., type 2 diabetes, liver cancer).[11,33] Bioaccumulating in the food chain, exposure sources of *p,p'DDT* and its metabolites may be found in food items such as meat and fish. In humans, these compounds are lipophilic bioaccumulating in fatty tissues with slow elimination rates, estimated elimination half-life for *p,p'DDE and p,p'DDT* is 6–7 years and 2 years, respectively.[34,35]

Previously widely used, organochlorine pesticides that persist in the environment (e.g., *p,p'DDT*), as previously discussed, are shown to be associated with hypertension in various populations and across research settings indicating a trend toward consistent evidence. These findings therefore have important public health implications because Indigenous people are disproportionality exposed to environmental contaminants as a result of historical industrial development (e.g., hydroelectric development and long-range transport in Artic and subarctic regions).[36,37] Additionally, among Indigenous peoples, cardiovascular health research lacks female-specific data.[5] Possible biologic mechanisms have been proposed in relation to *p,p'DDE* and cardiovascular effects. For example, among men *p,p'DDE* has antiandrogenic effects acting on the androgen receptor, which is shown to be inversely associate with testosterone.[38] Testosterone is important for CV health, and low testosterone levels are inversely linked with intima-media thickness, hypertension, and CVD events such as myocardial infarctions.[39] Among women, particularly postmenopausal, the imbalance between fallen estrogen levels, and testosterone (i.e., stable or increased) quantified by the free androgen index, rather than testosterone levels alone, may possibly partially predict CVD risk.[39] However, further research is needed to elucidate these relationships for both men and women.[39] In our study, summed concentrations of *p,p'-DDT* and *p,p'-DDE* were found to be associated with continuous SBP measures among women but among men the strength of association was similar although the estimate is imprecise after adjusting for obesity. Additionally, mean body mass index was higher for females, which these compounds are known to bioaccumulate in adipose tissues. When examining summed concentrations of *p,p'-DDT* and *p,p'-DDE* alone, and summed organochlorines the association was strongly associated with prevalent clinically defined hypertension, even after adjusting for BMI. Importantly, the environmental exposure of *p,p'-DDT* and *p,p'-DDE* on SBP measures represent subclinical associations across all population age groups, whereas, the classification of clinically defined hypertension is highly age dependent (i.e., older age groups, including possibly postmenopausal women). Furthermore, as described in aforementioned literature we cannot rule out the possible historical prenatal exposure to *p,p'DDT* among women in this cross-sectional study with development of hypertension into adulthood (the nature of this study design preclude such interpretations), or even possibly prenatal *p,p'DDE* exposure and obesity.[40]

Even though there are epidemiologic studies examining the association between persistent organic pollutants with hypertension, the overall number of studies is still limited, and more are needed to elucidate the mechanism of OCs and blood pressure measures. The results from our study align with the current literature. This is the first study to examine the association between complex contaminant body burdens (i.e., mixtures) and blood pressure measures among Indigenous adults living in James Bay, northern Quebec, who are at higher risk of environmental exposures such as POPs and toxic metals,[8,9] including the subarctic bioaccumulation of DDT. Among this same population, only one other study examined the long-term effect of toxic mercury exposure on blood pressure measures,[41] and thereby this article adds to the literature showing the possible contribution of (*p,p'DDT+p,p'DDE)* exposures and prevalent continuous blood pressure measures among Indigenous adults. Furthermore, this study highlights the importance of conducting sex-stratified analysis among Indigenous peoples as there is limited female-specific cardiovascular health research, which takes into account exposure to mixture of chemicals. However, several key limitations should be considered. Notably, this is a cross-sectional analysis with the exposures and outcomes all measured at the same timepoint. Hence, a temporal relationship precludes causal association. Furthermore, the study did not collect health information on smoking intensity, that is, cigarette pack-per-day, which is a better measure when modeling CVD events.[42] Additionally, the study lacked biochemical measures of cotinine, a breakdown product of nicotine exposure.

In conclusion, exposure to OC pesticides, particularity DDT and DDE were found to be associated with prevalent SBP measures among females and not males. Additional studies are needed especially prospective and perinatal studies examining this aforementioned association among Indigenous peoples.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

Acknowledgments

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References

1. Padwal RS, Bienek A, McAlister FA, Campbell NR; Outcomes Research Task Force of the Canadian Hypertension Education Program. Epidemiology of hypertension in Canada: an update. *Can J Cardiol*. 2016;32:687–694.
2. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension*. 2020;75:285–292.
3. Whelton PK, Carey RM, Aronow WS, et al. *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task*. Vol. 71. Lippincott Williams and Wilkins; 2018:1269–1324.
4. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2:775–781.
5. Prince SA, McDonnell LA, Turek MA, et al. The state of affairs for cardiovascular health research in indigenous women in Canada: a scoping review. *Can J Cardiol*. 2018;34:437–449.
6. Tobe SW, Yeates K, Campbell NRC, et al. Diagnosing hypertension in Indigenous Canadians (DREAM-GLOBAL): a randomized controlled trial to compare the effectiveness of short message service messaging for management of hypertension: main results. *J Clin Hypertens (Greenwich)*. 2019;21:29–36.
7. Howard G, Prineas R, Moy C, et al. Racial and geographic differences in awareness, treatment, and control of hypertension: the reasons for geographic and racial differences in stroke study. *Stroke*. 2006;37:1171–1178.
8. Liberda EN, Tsuji LJ, Martin ID, et al. Plasma concentrations of persistent organic pollutants in the Cree of northern Quebec, Canada: results from the multi-community environment-and-health study. *Sci Total Environ*. 2014;470–471:818–828.
9. Nieboer E, Martin ID, Liberda EN, Dewailly E, Robinson E, Tsuji LJS. Body burdens, sources and interrelations of selected toxic and essential elements among the nine Cree First Nations of Eeyou Istchee, James Bay region of northern Quebec, Canada. *Environ Sci Process Impacts*. 2017;19:727–741.
10. Liberda EN, Zuk AM, Tsuji LJS. Complex contaminant mixtures and their associations with intima-media thickness. *BMC Cardiovasc Disord*. 2019;19:289.
11. Zuk AM, Tsuji LJS, Nieboer E, Martin ID, Liberda EN. Examining environmental contaminant mixtures among adults with type 2 diabetes in the Cree First Nation communities of Eeyou Istchee, Canada. *Sci Rep*. 2019;9:15909.
12. Donat-Vargas C, Åkesson A, Tornevi A, et al. Persistent organochlorine pollutants in plasma, blood pressure, and hypertension in a longitudinal study. *Hypertension*. 2018;71:1258–1268.

13. Goncharov A, Pavuk M, Foushee HR, Carpenter DO; Anniston Environmental Health Reseach Consortium. Blood pressure in relation to concentrations of PCB congeners and chlorinated pesticides. *Environ Health Perspect*. 2011;119:319–325.
14. Valera B, Ayotte P, Poirier P, Dewailly E. Associations between plasma persistent organic pollutant levels and blood pressure in Inuit adults from Nunavik. *Environ Int*. 2013;59:282–289.
15. Valera B, Jørgensen ME, Jeppesen C, Bjerregaard P. Exposure to persistent organic pollutants and risk of hypertension among Inuit from Greenland. *Environ Res*. 2013;122:65–73.
16. Henríquez-Hernández LA, Luzardo OP, Zumbado M, et al. Blood pressure in relation to contamination by polychlorobiphenyls and organochlorine pesticides: results from a population-based study in the Canary Islands (Spain). *Environ Res*. 2014;135:48–54.
17. Brook RD, Weder AB, Rajagopalan S. "Environmental hypertensionology" the effects of environmental factors on blood pressure in clinical practice and research. *J Clin Hypertens (Greenwich)*. 2011;13:836–842.
18. Prozialeck WC, Edwards JR, Nebert DW, Woods JM, Barchowsky A, Atchison WD. The vascular system as a target of metal toxicity. *Toxicol Sci*. 2008;102:207–218.
19. Rosin A. The long-term consequences of exposure to lead. *Isr Med Assoc J*. 2009;11:689–694.
20. Bonnier-Viger Y, Dewailly E, Egeland G, Nieboer E, Pereg D. Nituuchischaayihtitaau Aschii Multi-community environment-and-health longitudinal study in Iiyiyiu Aschii: Mistissini Technical report: summary of activities, results and recommendations. In: Pereg D, Nieboer E, eds. *Cree Board of Health and Social Services of James Bay*. 2007. http://www.creehealth.org/sites/default/files/Environmental%20Health%20Study-%20Technical%20Report%20of%20Mistissini.pdf. Accessed December 20, 2020.
21. Rylander L, Björkdahl CM, Axmon A, et al. Very high correlations between fresh weight and lipid-adjusted PCB-153 serum concentrations: irrespective of fasting status, age, body mass index, gender, or exposure distributions. *Chemosphere*. 2012;88:828–831.
22. Nieboer E, Dewailly E, Egeland G, Château-Degat M-L, Bonnier-Viger Y. Nituuchischaayihtitaau Aschii Multi-community environment-and-health longitudinal study in Eeyou Istchee: Eastmain and Wemindji. Technical report: Summary of 2007 activities, results and recommendations. In: Nieboer E, Robinson E, Petrov K, eds. *Public Health Report Series 4 on the Health of the Population*. Cree Board of Health and Social Services of James Bay; 2011.
23. O'Rourke N, Hatcher L. *A Step-by-Step Approach to Using SAS for Factor Analysis and Structural Equation Modeling*. Sas Institute; 2013.
24. Jolliffe IT, Cadima J. Principal component analysis: a review and recent developments. *Philos Trans A Math Phys Eng Sci*. 2016;374:20150202.
25. Environment Canada Chemicals Management Division. Dichlorodiphenyltrichloroethane. 2013. https://www.ec.gc.ca/toxiques-toxics/Default.asp?lang=En&n=98E80CC6-1&xml=13272755-983C-4DF5-8EA2-E734EFC39869. Accessed December 20, 2020.
26. Government of Canada Indigenous and Northern Affairs Canada. Persistent organic pollutants (POPs) fact sheet series: dichlorodiphenyltrichloroethane (DDT). 2011. https://www.aadnc-aandc.gc.ca/eng/1316102914633/1316103004743. Accessed December 20, 2020.
27. Richardson JA, Keil JE, Sandifer SH. Catecholamine metabolism in humans exposed to pesticides. *Environ Res*. 1975;9:290–294.
28. Morgan DP, Lin LI, Saikaly HH. Morbidity and mortality in workers occupationally exposed to pesticides. *Arch Environ Contam Toxicol*. 1980;9:349–382.
29. La Merrill M, Cirillo PM, Terry MB, Krigbaum NY, Flom JD, Cohn BA. Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: a longitudinal birth cohort study. *Environ Health Perspect*. 2013;121:594–599.
30. Murray J, Eskenazi B, Bornman R, et al. Exposure to DDT and hypertensive disorders of pregnancy among South African women from an indoor residual spraying region: the VHEMBE study. *Environ Res*. 2018;162:49–54.
31. Lind PM, Penell J, Salihovic S, van Bavel B, Lind L. Circulating levels of p,p'-DDE are related to prevalent hypertension in the elderly. *Environ Res*. 2014;129:27–31.
32. Park SH, Lim JE, Park H, Jee SH. Body burden of persistent organic pollutants on hypertension: a meta-analysis. *Environ Sci Pollut Res Int*. 2016;23:14284–14293.
33. VoPham T, Bertrand KA, Hart JE, et al. Pesticide exposure and liver cancer: a review. *Cancer Causes Control*. 2017;28:177–190.
34. Jackson E, Shoemaker R, Larian N, Cassis L. Adipose tissue as a site of toxin accumulation. *Compr Physiol*. 2017;7:1085–1135.
35. Ritter R, Scheringer M, MacLeod M, Schenker U, Hungerbühler K. A multi-individual pharmacokinetic model framework for interpreting time trends of persistent chemicals in human populations: application to a postban situation. *Environ Health Perspect*. 2009;117:1280–1286.
36. Luginaah I, Smith K, Lockridge A. Surrounded by chemical valley and 'living in a bubble': the case of the Aamjiwnaang First Nation, Ontario. *J Environ Planning Manage*. 2010;53:353–370.
37. Wong F, Shoeib M, Katsoyiannis A, et al. Assessing temporal trends and source regions of per-and polyfluoroalkyl substances (PFASs) in air under the arctic monitoring and assessment programme (AMAP). *Atmos Environ*. 2018;172:65–73.
38. Blanco-Muñoz J, Lacasaña M, Aguilar-Garduño C, et al. Effect of exposure to p,p'-DDE on male hormone profile in Mexican flower growers. *Occup Environ Med*. 2012;69:5–11.
39. Elagizi A, Köhler TS, Lavie CJ. Testosterone and cardiovascular health. *Mayo Clin Proc*. 2018;93:83–100.
40. Cano-Sancho G, Salmon AG, La Merrill MA. Association between exposure to p,p'-DDT and its metabolite p,p'-DDE with obesity: integrated systematic review and meta-analysis. *Environ Health Perspect*. 2017;125:096002.
41. Valera B, Dewailly E, Poirier P. Impact of mercury exposure on blood pressure and cardiac autonomic activity among Cree adults (James Bay, Quebec, Canada). *Environ Res*. 2011;111:1265–1270.
42. Nance R, Delaney J, McEvoy JW, et al. Smoking intensity (pack/day) is a better measure than pack-years or smoking status for modeling cardiovascular disease outcomes. *J Clin Epidemiol*. 2017;81:111–119.