HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

Environ Res. 2020 October ; 189: 109924. doi:10.1016/j.envres.2020.109924.

Effects of polychlorinated biphenyls exposure on physical growth from birth to childhood and adolescence: A prospective cohort study

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Abstract

Background/aims—Given that their traditional lifestyle and diet still relies on fish and other marine species for sustenance, the Inuit are highly exposed to polychlorinated biphenyls (PCBs) and PCBs are increasingly linked to obesity. However, evidence is not consistent regarding which periods of exposure are most relevant. In this study, we examine whether in utero, childhood, and adolescent exposure to PCBs are related to physical growth at adolescence.

Method—Inuit adolescents from Canada (N=212) enrolled in a prospective longitudinal cohort study since birth were assessed for height, weight, body mass index (BMI), fat mass index (FMI) and fat free mass index (FFMI) at 18 years of age. PCB 153 concentrations were quantified in blood samples obtained at birth (umbilical cord), 11, and 18 years of age. Maternal

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E.T and S.C.: developing the analysis plan, performing data analysis, interpretation of data, primarily responsible for writing the article, Y.C., N.F.-D., M.D.-C.: contribution in analysis plan, analysis and interpretation of data, article revision. G.M., J.L.J., S.W.J. and P.A.: Principal investigator (PI) and co-PIs of the longitudinal study since its conception, contribution in designing and carrying out the study, interpretation of data and article revision. R.E.B.: co-PI of the adolescence follow-up of the study, contribution in designing and carrying out the adolescence follow-up, interpretation of data and article revision.

Declaration of competing interests

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109924.

anthropometrics were measured and those for the newborns collected from medical records. Data on biological mothers and participants' sociodemographic characteristics and food security were collected using interviews. Multiple linear regression analyses were used to test associations between PCB 153 concentrations and adolescent anthropometric measures.

Results—Cord PCB 153 was not related to height or FFMI at adolescence. By contrast, analyses showed that cord PCB 153 was related to higher BMI, FMI and marginally to weight in girls but not boys. Child PCB 153 was not related to height, weight or FFMI in adolescence. Child PCB 153 was related to lower BMI and FMI at adolescence in both sexes, particularly among those considered overweight or obese during childhood. Adolescent PCB 153 was not associated with any outcome.

Conclusion—This study suggests that prenatal exposure to PCBs may have a long-term effect on growth in early adulthood among girls and identifies the peri-pubertal period as another window of sensitivity for the action of PCBs. Our findings also suggest that exposure to PCBs and body size be documented in multiple time periods from infancy to adulthood.

Keywords

Polychlorinated biphenyls; Childhood; Adolescence; Body weight; Body height

1. Introduction

A growing body of evidence suggests that early exposure to environmental contaminants, such as persistent organic pollutants (POPs; including polychlorinated biphenyls (PCBs)) are potential risk factors for obesity and abnormal growth beginning as early as the 1st year of life and persisting through adulthood. However, findings are not consistent regarding sensitive exposure periods, the period of maximum sequelae and whether the effects reported from birth persist beyond childhood. According to a review of 24 previous studies on the relation between POPs and obesity in human, the effect of PCBs on weight is largely dose-dependent and depends on timing of exposure, congeners and sex of the individual (Tang-Péronard et al., 2011). A number of prospective studies have been published more recently (Cupul-Uicab et al., 2013; Delvaux et al., 2014; Hoyer et al., 2014; Iszatt et al., 2015; Karlsen et al., 2017; Lauritzen et al., 2018; Tang-Péronard et al., 2014; Vafeiadi et al., 2015; Valvi et al., 2012, 2014). The evidence for a causal impact of prenatal and early life exposure on child growth and obesity is moderate for dichlorodiphenyldichloroethylene (DDE), prevalent POP (Vrijheid et al., 2016), but it is still considered sparse for PCBs.

A few mechanisms of actions are hypothesized to explain the association with higher weight: i) interaction of PCBs with Peroxisome Proliferator-Activated Receptor Gamma PPARγ (the principal regulator of adipogenesis) and Retinoid X Receptor (RXR) responsible of adipogenesis, lipid storage and imbalances in adipocytokine (Evans et al., 2004; Polyzos et al., 2012); ii) endocrine signaling transduction failure and interference by the hypothalamus-pituitary-thyroid axis (Santos--Silva et al., 2018) combined with an effect on anti-androgenic/xeno-estrogenic action through the inhibition of the androgen receptors, enhancement of the estrogen or reduction of peripheral androgen conversion (Darbre, 2017), all suggest different responses among girls and boys; iii) exposure to PCBs in animal studies

was linked to changes in cytokine production, lipid, and glucose metabolism leading to subsequent weight gain as a result of interaction with gut microbiota (Zhang et al., 2015).

The Inuit in Northern Quebec are highly exposed to environmental contaminants through their lifestyle, geographical settings, and consumption of traditional food. PCBs and other POPs are brought to the Arctic Ocean from around the world via sea currents as well as atmospheric transport and deposition, contaminating the marine mammals' fat and fish as well as game meat (AMAP, 1998; Dewailly, 2006; Muckle et al., 2001). Being resistant to environmental degradation, highly fat-soluble and biomagnified through the Arctic food chain, this group of chemicals represents an ongoing exposure hazard to indigenous communities (Cupul-Uicab et al., 2015; Rosenbaum et al., 2017).

We previously reported significant associations between exposure to PCB 153 and body size in 11-year-old Inuit children: prenatal exposure was positively related to height, whereas childhood exposure was associated with reduced height, weight and head circumference (Dallaire et al., 2014). Whether PCBs have a lasting effect on growth into adolescence and early adulthood remains understudied. Here we present results from the follow-up of the Nunavik Child Development Study (NCDS) cohort into adolescence. We hypothesise that in utero or subsequent exposure (childhood and adolescence) to PCBs will continue to be associated with physical growth (weight, height, body mass index (BMI) during adolescence.

2. Materials and methods

2.1. Study population and data collection

The NCDS is a prospective longitudinal cohort study aiming to document the effects of pre- and postnatal exposures to environmental contaminants on child development. The cohort is composed of 491 mothers initially recruited from the Cord Blood Monitoring Program (CBMP), targeting prenatal exposure to environmental contaminants present in marine food (Dewailly et al., 1993). Mothers were recruited between November 1993 and December 1996 from the 14 Inuit communities of the Nunavik region of Québec, located north of the 55th parallel. The cohort was then supplemented with 221 additional mothers, recruited as part of the National Institutes of Health/National Institute of Environmental Health Sciences prospective infancy study (NIH-infancy), from the three largest communities on the Hudson Bay coast (Puvirnituq, Inukjuak, and Kuujjuarapik) between November 1995 and March 2002 (Jacobson et al., 2008; Muckle et al., 2001). At mean age 11 years (range 9–14 years), a subsample of these children and their primary caregivers (N = 294; 247 from the CBMP and 47 from the NIH-infancy study) participated in a follow-up designed to examine effects of pre- and postnatal exposure to environmental contaminants on child growth and neurobehavior (NCDS-childhood (Jacobson et al., 2015)), which took place between September 2005 and February 2010. Detailed recruitment methods for the CBMP, the NIH-infancy and the NCDS-childhood follow-ups are described elsewhere (Dallaire et al., 2014; Dewailly et al., 1993; Jacobson et al., 2008; Ruiz-Castell et al., 2015). Inclusion criteria for the NCDS-childhood cohort were gestation duration ≥35 weeks and birth weight ≥2.5 kg, and the exclusion criteria included multiple deliveries, major birth anomalies and neurological or chronic health problems in children potentially affecting growth (e.g., liver

disease, asthma). Two participants had borderline low birth weight (2.44–2.50 kg), but sensitivity analyses excluding them revealed no difference in coefficients estimates (data not shown). The participants were re-examined at adolescence (NCDS-adolescence) between January 2013 and February 2016. Inclusion criteria for this most recent follow-up were participation in NCDS-childhood, living in Nunavik at the time of the follow-up, and ability to meet with the research team in one of Nunavik's three main villages. Those who were identified as suffering from severe health or neurological problems unrelated to exposure at the NCDS-childhood interview (epilepsy n=2; head trauma n=1: meningitis n=1; multiple sclerosis n=1) were excluded from the NCDS-adolescent follow-up. An additional 49 participants of the NCDS-childhood study were not eligible because they were deceased (n=9), incarcerated (n=12), had moved away or could not be reached (n=28). Formal refusal to participate in the follow-up was expressed by 28 adolescents. Thus, the remaining 212 adolescents participated in the current study.

Blood samples were obtained from the umbilical cord at birth (30 mL) and venous blood samples from the 11-year-old children (20 mL) and the 18-year-old adolescents (30 mL) for assessment of exposure to chemicals. Samples were then centrifuged to separate plasma, which was stored at −80°C in vials prewashed with hexane for later analysis for PCB 153, Pb and lipid concentrations.

Written informed consents were signed by biological mothers at recruitment, principal caregivers at the childhood follow-up (with verbal assents obtained from children) and by the adolescents in the last follow-up. The adolescents received an electronic music device (Ipod shuffle) valued at 50$ CAN as compensation for their time. The NCDS is supported by key Inuit representatives and public health authorities. The Université Laval and Wayne State University ethics committees approved the infancy and childhood follow-ups, and the ethics committee of the Centre de Recherche du CHU de Québec-Université Laval approved the consent and study procedures at adolescence follow-up.

2.2. Growth assessment at adolescence

Standing height was measured with a calibrated stadiometer with participants standing barefoot straight against a wall, with their heels on a hard surface and looking straight ahead. Two measurements were taken, plus a third one in case of a >5 mm difference. The final height (cm) was the average of the two closest measurements. Adolescent weight (kg), fat mass (kg) and fat-free mass (kg) were assessed using a Tanita Total Body Composition Analyzer (TBF-310). BMI, FMI and FFMI (kg/m^2) were calculated as total weight, fat mass and fat free mass divided by squared height, respectively.

2.3. Exposure to PCB 153 and co-exposure to Pb and Hg

Cord PCB 153 and other prevalent PCB congeners (International Union of Pure and Applied Chemistry numbers 28, 52, 99, 101, 105, 118, 128, 138, 156, 170, 180, 183 and 187) were measured in purified plasma extract using an HP 5890 high-resolution gas chromatograph equipped with dual-capillary columns (HP Ultra I and Ultra II) and dual Ni-63 electron capture detectors (Hewlett-Packard, Palo Alto, CA, USA). The extract was obtained by concentrating a mixture of 1:1:3 ammonium sulfate:ethanol:hexane and plasma from the

cord blood through two Florisil columns (60–100 mesh; Fisher Scientific, Nepean, Ontario, Canada). Detailed analytical methods are described elsewhere (Muckle et al., 2001). Child and adolescent blood PCB concentrations (99, 101, 105, 118, 128, 138, 153, 156, 163, 170, 180, 183 and 187) were quantified using Agilent 6890 Network gas chromatograph (Wilmington, DE) equipped with 7683 series automatic injector Agilent and an Agilent 5973 Network mass spectrometer. Carried by the helium gas, the gas chromatograph was fitted with an Agilent 60 m DB-XLB column (0.25 mm i.d, 0.25 μm film thickness). Limits of detection (LOD) for cord PCBs was 0.02 μg/L, < 0.05 μg/L for children, and 0.15 μg/L for all PCB congeners except PCB 52 for adolescent blood samples. We selected PCB 153 as representative of the mixture because it is the most abundant and persistent among PCBs (Ayotte et al., 2003).

Total mercury (Hg) concentrations in umbilical cord blood samples were determined using cold vapor atomic absorption spectrometry (Pharmacia Model 120; Pharmacia, Piscataway, NJ, USA). Cord blood lead (Pb) levels were determined by graphite furnace atomic absorption with Zeeman background correction (Perkin Elmer model ZL 4100; Perkin Elmer, Norwalk, CT, USA). Child blood Pb concentrations were quantified by inductively coupled plasma mass spectrometry (ICP-MS) using a Perkin-Elmer Sciex Elan 6000 DRC II. LOD for cord blood Pb samples was 0.02 μg/dL and 0.002 μg/dL for children blood samples. All blood samples were analyzed at the Centre de Toxicologie du Québec (Québec City, Québec, Canada) that is accredited by the Canadian Association for Environmental Analytical Laboratories.

All samples were above the limit of detection for all contaminants of interest.

2.4. Covariates and potential confounders

Gestational age (weeks), birth weight (kg), birth length (cm), and child's sex were collected from medical records. Biological mother's pre-pregnancy maternal weight (kg) and height (cm) were obtained from medical records, infancy or childhood follow-ups. Background family characteristics concerning biological mother age at delivery (years), maternal parity before the target child, tobacco smoking during pregnancy (yes/no), alcohol use during pregnancy (yes/no), child's breast-feeding status (yes/no) and breastfeeding duration were collected through interviews conducted during the infancy or childhood follow-ups. Child BMI z-score was computed using the World Health Organization's guidelines (de Onis et al., 2007). Adolescent characteristics: age (years) at the testing, substance abuse (number of binge drinking episodes in previous year and daily cannabis use) and household food security status (assessed by the eight questions from the adult section of the US Food Security Survey Module (Bickel et al., 2000)). Socioeconomic status of the principal provider at the adolescent follow-up was assessed using the Hollingshead (2011) index, in which a higher score on a scale from 8–66 represents higher socio-economic status on four dimensions: marital status, employment status, educational attainment and occupational prestige.

We selected age at adolescent testing and sex as a priori covariates in all models. Adolescent height was also considered an obligatory covariate in all weight models. In models of the association of exposure during childhood with adolescent growth parameters, baseline

growth parameters and age at childhood assessment were included in the models. Prenatal and postnatal models were mutually adjusted for exposure. Potential confounders were selected by directed acyclic graph (DAG) with the DAGitty environment (Textor et al., 2017). A single DAG was created to represent variables at four time points: prenatal, birth, childhood and adolescence (Supplemental material, Fig. S1). Covariates selected for the prenatal models were prepregnancy maternal anthropometric measures, maternal age at delivery, maternal parity before the target child, prenatal mercury (Hg) and lead (Pb) exposures. Covariates selected for postnatal models were maternal anthropometric measures, birth anthropometric measures, gestational age and postnatal Pb exposure.

Total blood lipids were always added to models with the corresponding PCB 153 concentrations. In each plasma sample collected, total cholesterol and triglycerides were measured by standard enzymatic procedures, and phospholipids were determined according to the enzymatic method (Takayama et al., 1977) using a commercial kit (Wako Pure Chemical Industries, Richmond, VA, USA). Total plasma lipids (g/L) was estimated according to a formula developed by Phillips et al. (1989) and included as a covariate to adjust for the wet weight concentration of the corresponding PCB 153 expressed in μg/L.

2.5. Statistical analyses

Data preparation—We screened the data for completeness and visually assessed the normality of distribution for all continuous variables. We proceeded to a natural logarithmic transformation to improve the skewed distribution of the blood PCB 153 Pb and Hg concentrations.

Multiple regression models—We first investigated associations of prenatal exposure (cord blood concentrations of PCB 153) with adolescent outcomes (height, weight, BMI, FMI and FFMI) in multiple regression linear models. Associations between child and adolescent exposure with adolescent outcomes were then examined, with and without prenatal concentrations. We checked the correlation matrix for collinearity between all variables included in the model. Based on earlier studies that showed differential effects by sex, interaction terms between contaminants exposure and participant sex were introduced in our analyses (Gladen et al., 2000; Lamb et al., 2006). Based on previous findings, an interaction term between prenatal exposure and sex was also added in the child and adolescent models. In models of the association of exposure between childhood with adolescent growth parameters, adjustment for BMI z-score at childhood was included to control for the possibility that the concentration of PCB 153 may have been diluted because of increased adipose tissue (Domazet et al., 2020). The possible interaction between child PCB 153 and childhood BMI z-score was also examined, and the corresponding slopes of the relation were calculated in normal and overweight/obese children according to IOTF classification (Cole et al., 2000; Medehouenou et al., 2015).

Missing data analyses—To examine possible selection bias, we compared the participants lost since childhood follow-up with those who completed the adolescent follow-up on selected variables. We found no significant differences between participants during adolescence and missing participants for maternal anthropometrics, maternal age, parity,

smoking and alcohol consumption during pregnancy, and duration of breastfeeding (not shown). Concentrations of cord blood PCB 153 and total lipids in our sample were comparable to those of the lost participants. Therefore, the loss of participants during follow-up was considered unlikely to influence our results.

The hypothesis of missing completely at random was rejected based on Little's MCAR test (X^2 MCAR = −6.0; p-value = 0.001). Since we found no indication of systematic missingness, we estimated the regression models using the full information maximum likelihood (FIML) estimator (Graham, 2009), which uses all available information to estimate each model's parameters instead of relying only on complete cases. There was no major difference in parameter estimate or inference compared to complete cases model.

Descriptive statistics were computed with the R 3.5.0 software (R Core Team, 2018) and the EnvStats package (Millard, 2013). The lavaan package was used to estimate regression models with FIML method (Rosseel, 2012). Standard errors for all model estimates were calculated from 1,000 bootstrap replicates.

3. Results

3.1. Descriptive and bivariate analyses

Characteristics of the study participants are shown in Table 1. Biological mothers were on average 24 years of age at delivery, had already given birth to 2 children. Alcohol use and smoking during pregnancy were very prevalent, and about 40% of mothers were either obese or overweight before pregnancy. As traditional Inuit adoption is prevalent, about a quarter of the children were not breastfed because they were adopted at birth by a close family member. By contrast, non-adopted children were mostly breastfed. A majority of adolescents were living in socioeconomically disadvantaged conditions, with a mean score of 28.6, which is the equivalent of semi-skilled workers according to the Hollingshead (2011) classification. One third had experienced severe food insecurity during the year before the interview. One of three participants was either obese or overweight in adolescence. Both cord and child blood PCB 153 concentrations were comparable between boys and girls, except for adolescent blood PCB 153 concentrations, which were higher in boys (mean difference = 0.07 μg/L, p-value = 0.004).

Correlations of cord PCB 153 with child and adolescent PCB 153 concentrations were moderate (Spearman's coefficients 0.39 and 0.41), and that between the child and adolescent PCB 153 concentrations was strong (0.83). The correlations between independent variables were all under 0.40.

3.2. PCB 153 concentrations associations with adolescent anthropometric measures

Associations of cord PCB 153 concentrations with adolescents' height, weight, BMI, FMI and FFMI are presented in Table 2. Cord blood PCB 153 concentrations were not associated with height or FFMI at adolescence. However, significant sex-modification associations were found for weight (marginally), BMI and FMI, and sex-specific analyses indicated that cord PCB 153 was related to greater weight, BMI and FMI among girls and after controlling

for co-exposure to cord Pb and Hg, and child blood PCB 153. By contrast, cord blood PCB 153 was unrelated to weight, BMI and FMI in adolescent boys.

Baseline growth parameters at childhood examination were taken into account when studying the association between child PCB 153 and growth at adolescence (Table 3). No interaction with sex was observed (data not shown). Child PCB 153 concentrations were associated to lower FMI in adolescence. Significant interactions between child BMI z-score and child PCB 153 blood concentration were observed: whereas marginal inverse associations were observed among normal weight children, significant inverse associations between child PCB153 and adolescent BMI and FMI were observed among overweight/obese children. Finally, concurrent PCB 153 exposure was not related to adolescent growth parameters (Supplementary Table 1).

4. Discussion

In this study, prenatal exposure to PCB 153 was associated with higher BMI and FMI at adolescence in girls. Child PCB 153 was related to lower BMI and FMI at adolescence, particularly among children considered overweight or obese. Height at adolescence was not associated with exposure to PCB 153 at any of the ages (prenatal, childhood or concurrent).

In a previous follow-up of the same population, prenatal exposure to PCB 153 was not associated with anthropometric parameters at birth nor during childhood (average=11.3 years old), whereas childhood (concurrent) exposure was associated with shorter height and lower sweight at that age. In these analyses, no differential association by sex was observed (Dallaire et al., 2014). The significant association observed in the longer follow-up at age 18 years reported here suggests that the sex-specific changes in body proportions occurring at adolescence may be a more suitable period to uncover long term consequences of prenatal and childhood exposure to PCBs.

A large number of longitudinal birth cohort studies and reviews have explored the role of prenatal exposure to POPs, especially PCBs, on child growth. Inconsistent findings for PCBs may be related to different mixtures of PCBs and other POPs to which study populations are exposed, to different background exposure levels, to different periods of growth being assessed in the various cohorts, or to unidentified sex-specific results. Tang-Péronard et al. (2011) summarized published studies in 2011 by classifying relations between prenatal exposure to PCBs and obesity development according to population exposure level and sex of the child. They proposed that in populations with high exposure levels (>4.0 μg/g of lipids) - including the Yucheng population (Guo et al., 1995), fishermen families in Sweden (Rylander et al., 2007) or in Michigan (Blanck et al., 2002; Jacobson et al., 1990) - toxic effects, i.e., exposure associated with a lower weight, might prevail. Conversely, in low (<1 μg/g lipids) or moderate exposure (1 to 4 μg/g lipids) levels populations associations with a higher weight is often observed in girls only (Gladen et al., 2000; Hertz-Picciotto et al., 2005; Verhulst et al., 2009). Since the Tang-Péronard et al. (2011) review, new studies including extended follow-up of previous cohorts (Delvaux et al., 2014; Valvi et al., 2014) were performed in low or moderate exposure levels populations. Unfortunately, their findings did not clarify the association between prenatal exposure to PCBs and obesity

development: 8 studies published since 2011 reported no association between prenatal PCBs exposure and weight development (Cupul-Uicab et al., 2013; Delvaux et al., 2014; Hoyer et al., 2014; Iszatt et al., 2015; Karlsen et al., 2017; Lauritzen et al., 2018; Vafeiadi et al., 2015; Valvi et al., 2014), whereas 2 reported an increase in weight/BMI among girls at 5–6 years (Tang-Péronard et al., 2014; Valvi et al., 2012). Our findings are in line with these previous cohorts of moderate exposure, suggesting that prenatal exposure to PCBs may have an impact on weight among girls during childhood (Tang-Péronard et al., 2014; Valvi et al., 2012) and up to puberty (Gladen et al., 2000).

The role of postnatal exposure to PCBs on child growth has been the object of a smaller number of studies. Several cross-sectional studies reported inverse associations between obesity and concurrent PCBs blood concentrations (Dhooge et al., 2010; Tang-Péronard et al., 2011), but this may be attributed to reverse causation, namely that the blood concentration of PCBs has been diluted due to increased adipose tissue (Wolff et al., 2007). In prospective studies, two situations of exposure were considered: i) early postnatal (lactational) exposure with a follow-up of a few years; ii) exposure in childhood (8–10 years) with a follow-up to adolescence or early adulthood. In the first set of eight studies (Grandjean et al., 2003; Hoyer et al., 2014; Iszatt et al., 2015; Jacobson et al., 1990; Karlsen et al., 2017; Pan et al., 2010; Patandin et al., 1998; Rogan et al., 1987), most reported no association between lactational exposure and child weight or BMI, only two reported an association between cumulative postnatal exposure and decreased weight (Grandjean et al., 2003; Iszatt et al., 2015). The second set of studies included two prospective cohorts of children enrolled at 8–10 years and followed for 10 years or more (Burns et al., 2020; Tang-Péronard et al., 2015) with PCBs concentrations measured in child blood at inclusion. In these two populations, there are suggestions of decreased growth at some points in follow-up in association with blood PCBs concentrations in childhood: a reduced BMI z-score and waist circumference in 20- to 22-year-old Danish girls (decrease not observed at the 14- to 16-year follow-up) (Tang-Péronard et al., 2015), and lower BMI z-score and altered body composition with higher exposure to non-dioxin-like PCBs in Russian boys (no girls in this cohort) up to age 19 (Burns et al., 2020). Our findings of a decrease in weight with higher concentrations of PCB 153 in childhood are consistent with these two comparable cohorts, suggesting the peri-pubertal period may be another window of sensitivity to the action of PCBs. Median PCBs exposure levels in childhood were comparable in the three cohorts: 0.18 μg/g lipids in the Danish cohort, 0.25 (non-dioxin-like PCBs) μg/g lipids in the Russian cohort and 0.20 μg/g lipids in the present Inuit cohort. Our study results also highlighted differential associations of postnatal PCB 153 exposure according to obesity status during childhood with the later adolescent BMI and FMI suggesting that the detrimental effect of exposure to PCBs during childhood may be especially of concern among overweight or obese children. In fact, higher content of adipose tissue, which is the natural lipid storage location, during childhood may increase the half-lives of PCBs acting as an ongoing internal exposure source (Milbrath et al., 2009). Their condition may predispose them to weight loss since PCBs cause disruption of thyroid hormone homeostasis involved in fat metabolism at multiple levels (Duntas, 2002; Duntas and Stathatos, 2015; Pelletier et al., 2003). One possible mechanism is the modification of thyroid hormones release from anterior pituitary. In a second model, PCBs may alter thyroid hormones transport by competing effectively for

binding proteins in plasma, however, the modification of the conversion of peripheral tetraiodothyronine as result of exposure to PCBs is also a possible action (Chauhan et al., 2000; Cheek et al., 1999; Langer, 2010). Finally, PCBs may reduce thyroid hormone half-life via the enhancement of thyroid hormones glucuronidation in the liver and therefor increase their biliary excretion (Martin et al., 2012).

4.1. Strength and limitations

Ours is the first study to report effects of both prenatal and childhood PCB exposure on adolescent growth. In addition to its longitudinal design, the main strengths of this study are the focus on a homogenous ethnic group exposed to a well-characterized mixture of environmental contaminants through contamination of diet including traditional food (Muckle et al., 2001) and additional adjustment for lead exposure.

This study has certain limitations. Associations with exposure to PCB 153, considered a proxy for the organochlorine chemicals family, should, in fact, be attributed to the whole mixture characteristic of this population, such as DDE or other highly intercorrelated POP (Muckle et al., 2001). DDE have been associated with an increasing risk of obesity after prenatal exposure in a number of previous studies (Vrijheid et al., 2016). We used five indicators for assessment of growth and of the various components of obesity at key time periods. However, despite the number of tests performed, study of these various outcomes should not be considered independent testing of multiple associations, since we were looking for consistent and interpretable associations between outcomes and between time periods. Although our study covers a long time span, it lacks repeated measures on the chronology of growth (growth curves) including episodes of weight loss, and detailed measurements of body composition at all assessments. Similarly, we were not able to consider intermediate outcomes (i.e., sex, parathyroid, thyroid and pituitary hormones), which would provide insight about mechanisms and pathways of action of the contaminants on body size changes. Although we controlled for many potential confounders, we cannot exclude residual bias due to unmeasured confounders, such as paternal anthropometric characteristics, participants' childhood and adolescent physical activity, and characterization of diet, such as caloric and fat intake. An additional limitation is the relative small size of the cohort at the final follow-up and its power repercussion in sex-stratified analyses. Finally, we cannot rule out that other prenatal determinants of human growth, such as maternal smoking and alcohol use during pregnancy and low SES, may have enhanced the persistent effects of PCBs on growth. Although this may limit the generalizability of our findings to other populations, this finding likely represents the risk of high PCB exposure found in other populations.

5. Conclusion

Prenatal exposure to PCBs may have a long-lasting effect on growth through young adulthood, particularly among girls. This study also identifies the peri-pubertal period as another window of sensitivity to the action of PCBs. In addition, our findings support the recommendation that exposure to chemicals and body size should be documented at multiple developmental periods up to adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are extremely grateful to the Nunavik population, all the people involved in this study and the Nunavik Nutrition and Health Committee for their useful comments on this manuscript.

This longitudinal research was funded by the Institute of Indigenous People's Health from the Canadian Institutes of Health Research (NRF130242), NIH/National Institute of Environmental Health Sciences (R01-ES007902); the Northern Contaminants Program from Government Canada; and the Lycaki-Young Fund from the State of Michigan. None of the funding sources was involved in the conception, analysis or interpretation of the data.

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Table 1

Descriptive characteristics of the study sample.

Variables	N	Mean ± SE	n (%)	Median	Range
Family characteristics					
Maternal age at delivery (years)	212	23.69 ± 5.67		22.25	15.00 – 42.00
Parity before delivery of the child	212	1.97 ± 1.79		2.00	0.00 – 8.00
Pre-pregnancy maternal weight (kg)	175	59.47 ± 10.24		58.10	41.50 – 108.00
Maternal height (cm)	159	154.51 ± 5.09		153.90	144.10 – 170.80
Pre-pregnancy maternal BMI (kg/m^2) [a]	128	25.24 ± 3.50		24.61	17.20 – 37.04
Normal			75 (58.59)		
Overweight			37 (28.91)		
Obese			16 (12.50)		
Smoking during pregnancy (% yes)	206		177 (85.92)		
Alcohol use during pregnancy (% yes)	184		100 (54.35)		
Birth characteristics					
Gestational age (weeks)	212	39.20 ± 1.44		39.00	36.00 – 44.00
Sex (% girls)	212		118 (55.66)		
Birth weight (kg)	212	3.48 ± 0.46		3.50	2.44 – 4.74
Birth length (cm)	211	51.11 ± 2.29		51.00	45.00 – 65.00
Breastfeeding status	203				
None			52 (25.62)		
0 < 3 months			36 (17.73)		
3 < 6 months			24 (11.82)		
≥6 months			91 (44.83)		
Cord blood PCB 153 (μg/L) [b]	205	0.22 (2.11)		0.22	0.04 – 2.42
Cord blood lead (μg/dL) [b]	204	3.80 (1.84)		3.73	0.83 – 17.80
Cord blood mercury (μg/dL) [b]	204	1.52 (2.15)		1.53	0.18 – 9.93
Cord blood total lipids (g/L)	205	2.59 (0.82)		2.49	1.59 – 4.40
Child characteristics					
Age (years)	212	11.34 ± 0.71		11.37	9.32–14.00

Variables	N	Mean ± SE	n (%)	Median	Range
Blood PCB 153 (μg/L)[b]	209	0.25 (2.57)		0.23	0.02 – 3.40
Blood lead (μg/dL)[b]	210	2.34 (1.86)		2.07	0.54 – 12.80
Blood total lipids (g/L)	209	5.08 (0.18)		5.00	3.00 – 9.70
Height (cm)	208	141.6 ± 7.33		141.00	126.20 – 167.75
Weight (kg)	208	39.99 ± 10.15		37.40	27.65 – 88.10
BMI z-score	208	0.78 ± 0.87		0.67	−1.11 – 4.16
Adolescent characteristics					
Age (years)	212	18.47 ± 1.11		18.48	16.01 – 21.88
Socioeconomic status of principal provider[c]	207	28.59 ± 13.01		28.00	8.00 – 61.00
Food security status [e]	201				
Food secure			37 (18.41)		
Moderate food insecurity			88 (43.78)		
Severe food insecurity			76 (37.81)		
Height (cm)	209	162.24 ± 7.75		162.00	145.00 – 187.00
Weight (kg)	209	62.55 ± 11.74		60.50	39.20 – 121.90
BMI (kg/m^2)	209	23.74 ± 3.94		23.00	17.00 – 48.80
Normal			152 (72.73)		
Overweight			43 (20.57)		
Obese			14 (6.70)		
Body fat (%)	209	20.57 ± 9.53		19.20	4.60 – 48.40
Fat free mass (kg)	209	49.27 ± 8.09		47.20	36.70 – 82.60
Fat mass (kg)	209	13.38 ± 8.39		11.10	2.10 – 57.30
Fat mass index (kg/m^2)	209	5.17 ± 8.39		4.22	0.84 – 22.95
Fat free mass index (kg/m^2)	209	18.61 ± 1.86		18.33	15.01 – 26.41
Blood PCB 153 (μg/L) [b]	211	0.18 (2.49)		0.18	0.02 – 1.90
Blood lead (μg/dL) [b]	212	1.63 (2.00)		1.52	0.35 – 18.13
Blood total lipids (g/L)	211	5.10 (0.96)		4.90	2.90 – 8.10

d Either married, in relationship or cohabited with a partner.

[a]The International Classification of adult underweight, overweight and obesity according to BMI (WHO, 2011).

[b] Geometric mean (geometric standard deviation).

[c] Assessed on the Hollingshead Index (2011).

[e] Based on Health Canada criteria: food security (score <2), moderate food insecurity (2≥ score <6) and severe food insecurity (score ≥6; Health Canada, 2007; USDA, 2006)

Table 2

Associations of cord blood PCB 153 concentrations with adolescents' height, weight, BMI, FMI and FFMI according to sex (n = 212).

Outcomes		Beta coefficient (p-value)			
		Baseline model	Sex interaction model		
		Global coefficient	Sex-modification test	Boys' coefficient	Girls' coefficient
Height (cm)	Model 1	0.03(0.95)	2.12 (0.02)	−0.99 (0.16)	1.73 (0.09)
	Model 2 [a]	0.32 (0.52)	0.69 (0.43)	0.03 (0.96)	0.72 (0.28)
Weight (kg)	Model 1	0.74 (0.49)	5.31 (0.02)	−1.82 (0.14)	3.50 (0.05)
	Model 2 [b]	1.67 (0.16)	3.00 (0.10)	0.29 (0.81)	3.28 (0.06)
Body mass index (kg/m^2)	Model 1	0.26 (0.42)	1.46 (0.05)	−0.37 (0.34)	1.09 (0.07)
	Model 2 [c]	0.56 (0.22)	1.67 (0.02)	−0.27 (0.52)	1.40 (0.03)
Fat mass index (kg/m^2)	Model 1	0.40 (0.11)	1.25 (0.01)	−0.20 (0.29)	1.05 (0.02)
	Model 2 [c]	0.74 (0.0[C])	1.38 (0.03)	0.05 (0.86)	1.42 (0.001)
Fat free mass index (kg/m^2)	Model 1	−0.14 (0.44)	0.11 (0.74)	−0.19 (0.41)	−0.08 (0.75)
	Model 2 [c]	−0.24 (0.26)	0.23 (0.46)	−0.35 (0.14)	−0.12 (0.69)

Notes: Cord and child blood concentrations (μg/L) were log-transformed. Parameter estimates and p-values were obtained by multiple linear regression and 1000 bootstrap samples. All models were adjusted for sex, age at adolescent examination and cord blood total lipids. Model 2 additionally adjusted for maternal age at delivery, maternal parity before the target child, cord blood mercury concentrations, cord blood lead concentrations, child blood PCB 153 concentrations and total child blood lipids.

[a] Adjusted for birth and maternal height.

[b] Adjusted for birth weight, pre-pregnancy maternal weight, and adolescent height.

[c] Adjusted for birth weight and pre-pregnancy maternal body mass index.

Table 3

Associations of child blood PCB 153 concentrations with adolescents' height, weight, BMI, FMI and FFMI according to child BMI (n = 212).

Outcomes		Beta coefficient (p-value)			
		Child PCB 153 coefficient	Child BMI * PCB 153 interaction test	IOTF reference [a]	
				Normal weight (n=166)	Overweight and Obese (n=42)
Height (cm)	Model 1 [b]	−0.10 (0.80)	−0.42 (0.25)	0.11 (0.80)	−0.80 (0.29)
	Model 2 [c]	0.16 (0.65)	−0.21 (0.44)	0.03 (0.94)	−0.17 (0.76)
Weight (kg)	Model 1 [d]	0.15 (0.81)	−1.15 (0.02)	0.90 (0.14)	−1.99 (0.16)
	Model 2 [e]	−0.55 (0.43)	−0.76 (0.18)	−0.02 (0.97)	−1.88 (0.15)
Body mass index (kg/m^2)	Model 1 [f]	−0.01 (0.95)	−0.44 (0.03)	−0.03 (0.87)	−1.16 (0.04)
	Model 2 [g]	−0.40 (0.11)	−0.40 (0.07)	−0.45 (0.09)	−1.59 (0.008)
Fat mass index (kg/m^2)	Model 1 [f]	−0.07 (0.65)	−0.37 (0.04)	−0.05 (0.79)	−0.90 (0.05)
	Model 2 [g]	−0.49 (0.01)	−0.38 (0.04)	−0.39 (0.06)	−1.40 (0.003)
Fat free mass index (kg/m^2)	Model 1 [f]	0.06 (0.48)	−0.09 (0.38)	0.01 (0.90)	−0.27 (0.14)
	Model 2 [g]	0.12 (0.28)	−0.02 (0.79)	−0.005 (0.97)	−0.16 (0.48)

Notes: Cord and child blood concentrations (μg/L) were log-transformed. Parameter estimates and p-values were obtained by multiple linear regression and 1000 bootstrap samples. All models were adjusted for sex, age at adolescent examination and total lipids. Model 2 additionally adjusted for gestational age, child blood lead concentrations, cord blood PCB 153 and cord blood total lipids. When an interaction between prenatal exposure and sex was found in cord models, the interaction term was also added.

[a] International Obesity Task Force references for sex and age specific child BMI classification (Cole et al., 2000).

[b] Adjusted for height and age at childhood examination.

[c] Adjusted for birth height, maternal height, height and age at childhood examination.

[d] Adjusted for weight and age at childhood examination.

[e] Adjusted for birth weight, pre-pregnancy maternal weight, weight and age at childhood examination and adolescent height.

[f] Adjusted for childhood BMI z-score.

[g] Adjusted for birth weight, pre-pregnancy maternal body mass index and childhood BMI z-score.