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Associations of Peri-pubertal Serum Dioxins and Polychlorinated Biphenyls with Growth and Body Composition among Russian Boys in a Longitudinal Cohort

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Abstract

Background: Childhood exposure to organochlorines has been associated with alterations in somatic growth. We evaluated the associations of peri-pubertal serum levels of dioxin-like compounds (DLCs) and nondioxin-like polychlorinated biphenyls (NDL-PCBs), with adolescent growth, body composition, and near adult height (NAH) in a longitudinal cohort study of Russian boys.

Methods: 473 8–9 year-old boys had serum DLCs and associated toxic equivalents (TEQs) and NDL-PCBs concentrations measured. Physical examinations were performed at enrollment between 2003–2005, and annually over 11 years to 2016; annual bio-electric impedance analysis (BIA) of body composition began in 2006. We used mixed effects models to evaluate associations of quartiles of serum chemical concentrations with longitudinal measurements through age 19 of body mass index (BMI-Z) and height (HT-Z) z-scores, annual height velocity (HV), and BIA-derived height-adjusted fat (FMi) and fat-free mass (FFMi) indexes. Potential modification by age of the associations of chemical exposures with growth was evaluated. NAH (defined as HV<1 cm/year) and age at NAH attainment were estimated using parametric survival models accounting for right censoring.

Results: The medians of serum TEQs, DLCs, and NDL-PCBs were 21.1 pg TEQ/g lipid, 362 pg/g lipid, and 250 ng/g lipid, respectively. In multivariable models, higher serum concentrations of peri-pubertal TEQs, DLCs, and NDL-PCBs were associated with significantly lower BMI-Z, FMi, and FFMi over 11 years of follow-up. The differences in FFMi for boys with higher versus lower Σ TEQs and Σ NDL-PCBs increased with age. In multivariable models, higher NDL-PCBs were associated with lower HT-Z, with attenuation of the association with age (interaction $p<0.001$). The highest versus the lowest quartiles of NDL-PCBs were not associated with differences in NAH, but were associated with an average of 6 months later attainment of NAH.

Conclusions: Our findings suggest that dioxin and NDL-PCB exposures during childhood are associated with alterations in body composition and subsequent somatic growth.

Keywords

body composition; children's environmental health; cohort study; dioxins; height; polychlorinated biphenyls

Introduction

Dioxins and polychlorinated biphenyls (PCBs) are environmental contaminants that are ubiquitous because of their long environmental and biological half-lives (Milbrath et al. 2009) despite being banned or tightly regulated in many countries (UNEP 2004). Because organochlorine compounds (OCs) accumulate in adipose tissue and bioaccumulate in the food chain, humans are exposed primarily through dietary intake of high fat animal products including, for example, fish, meats, and dairy products (Burns et al. 2009; Gasull et al. 2011; Milbrath et al. 2009; Weber et al. 2018). Dioxin-like compounds (DLCs) and nondioxin-like PCBs (NDL-PCBs) have been identified as endocrine disrupting chemicals (Gore et al. 2015). As such, disruption of hormonal processes may be the mechanism underlying the

developmental and reproductive effects (Minguez-Alarcon et al. 2017; Parent et al. 2015; Vrijheid et al. 2016), and the increased risk for diabetes and cardiovascular disease (Humblet et al. 2008; Perkins et al. 2016; Song et al. 2016) associated with dioxins and PCBs.

Although a number of studies have examined the associations of DLCs and NDL-PCBs with childhood growth, especially obesity, the findings have been inconsistent and few have followed children to young adulthood. The association of intrauterine and early childhood exposure to high concentrations of PCBs and dioxin-like furans in contaminated cooking oil was evaluated in two accidental poisoning incidents in Japan (*Yusho*) (Yoshimura and Ikeda 1978) and Taiwan (*Yu-Cheng*) (Guo et al. 1995). These groups reported reduced growth during childhood, but have not reported on adolescent or young adult growth effects. Iszatt and colleagues pooled European studies to assess the relationship of: (1) perinatal DLCs in cord and breast milk samples with weight at age two years, and body mass index (BMI; kg/m²) at seven years (Iszatt et al. 2016), and (2) estimated pre- and post-natal NDL-PCB-153 exposures using a validated pharmacokinetic model with weight at two years (Iszatt et al. 2015). The observed associations appeared to depend not only on the specific OC, but also on the exposure period and gender. Although *prenatal* NDL-PCB-153 was not associated with growth, *post-natal* NDL-PCB-153 was associated with reduced weight, and perinatal DLC concentrations were associated with higher BMI, but only among girls.

Previously we reported that among boys in the Russian Children's Study (RCS), an ongoing prospective cohort study in Chapaevsk, Russia, higher peri-pubertal serum DLCs and NDL-PCBs were associated with reduced growth. However, this analysis was based on follow-up only to age 12 years, preceding the boys' pubertal growth spurt or attainment of near adult height (NAH) (Burns et al. 2011); thus, we were unable to assess whether the observed associations persisted into young adulthood. Our current analysis extends the analysis on the associations of peri-pubertal serum DLCs and NDL-PCBs with linear growth and body composition over 11 years of follow-up to young adulthood (19 years).

Material and Methods

Study population

The Russian Children's Study is a prospective cohort of 516 boys in Chapaevsk, Russia, who were enrolled at age 8–9 years (2003–2005) and followed annually to young adulthood (Burns et al. 2017; Sergeyev et al. 2017). This analysis includes the 473 boys in this cohort who had baseline dioxin, furan, and PCB measurements, with follow-up over 11 years to 2016. Orphans lacking baseline questionnaire data and boys with chronic medical conditions were excluded as described previously (Burns et al. 2009). The study was approved by the Human Studies Institutional Review Boards of the Chapaevsk Medical Association, Harvard T.H. Chan School of Public Health, Nemours Health Care System and Brigham and Women's Hospital. Before participation, the parent/guardian provided informed consent and the boys signed assent forms; at age 18 years, the young men signed informed consent forms.

At study entry, each boy's parent or guardian completed nurse-administered health and lifestyle questionnaires (Lee et al. 2003), ascertaining birth and medical history, and demographic and socioeconomic status (SES) information. A validated Russian Institute of Nutrition semi-quantitative food frequency questionnaire was used to characterize each child's diet (Martinchik et al. 1998; Rockett et al. 1997).

Physical examination and bio-electric impedance measurements

At study entry and every annual follow-up visit, the same trained research nurse and physician-investigator Oleg Sergeyev (O.S.) performed a standardized anthropometric examination (<http://wwwn.cdc.gov/nchs/nhanes/nhanes3/AnthropometricVideos.aspx>) according to a written protocol and standard procedures recommended by the U.S. Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 100 grams with a metric scale. Age-adjusted z-scores were calculated for height (HT-Z) and BMI (BMI-Z) at each annual visit using the World Health Organization (WHO) standards (WHO 2016). Annual height velocity (HV) was calculated by computing the difference in height between annual visits adjusted to one year increments (cm/year).

Beginning in 2006, annual bio-electric impedance (BIA) assessments were obtained by the same research nurse and physician-investigator (O.S.). BIA was measured using an 8-electrode Tanita BC-418MA segmental body composition analyzer with an electrical current frequency of 50 kHz. Clad only in underwear, the boys stood with bare feet contacting the four electrodes on the scale with hands clasping the four electrodes on the handles. Arms were held away from the trunk to prevent contact with other parts of the body, as recommended by the manufacturer (Tanita Corp., Tokyo, Japan). Whole-body estimates of fat-free mass (FFM) were calculated using the manufacturer's proprietary algorithm based on whole-body resistance between right hand and right foot, after entering the boys' age and height, and selecting the body type as 'non-athletic'. Fat mass (FM) was determined by the subtraction of FFM from body mass. The fat mass index (FMI) and fat-free mass index (FFMI) were calculated as FM and FFM divided by height squared, respectively (Wells et al. 2007).

Blood sample analyses

Serum aliquots prepared from fasting blood samples obtained at study entry were stored at -35°C until shipment on dry ice to the CDC for analysis. Analytes included 7 dibenzo-*p*-dioxins (dioxins: 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD), 10 dibenzofurans (furans: 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, OCDF), 4 co-planar PCBs (C-PCBs: 3,3',4,4'-TCB (77), 3,4,4',5-TCB (81), 3,3',4,4',5-PeCB (126), 3,3',4,4',5,5'-HxCB (169)), 6 mono-*ortho* substituted PCBs (M-PCBs: 2,3,3',4,4'-PeCB (105), 2,3',4,4',5-PeCB (118), 2,3,3',4,4',5-HxCB (156), 2,3,3',4,4',5'-HxCB (157), 2,3',4,4',5,5'-HxCB (167), 2,3,3',4,4',5,5'-HpCB (189)), 29 non-dioxin-like PCBs (NDL-PCBs: 28, 44, 49, 52, 66, 74, 87, 99, 101, 110, 128, 138–158, 146, 149, 151, 153, 170, 172, 177, 178, 180, 183, 187, 194, 195, 196–203, 199, 206, 209), and total lipids as

described previously (Burns et al. 2009). The reported detection limits have been published previously; values for each specimen and congener (analyte) varied depending on the actual specimen weight, serum lipid concentration, recovery of individual congeners (analytes) during sample cleanup, and the sensitivity of the specific mass spectrometer used to make the measurements (Burns et al. 2009). Measured values below the limit of detection (LOD) were assigned a value equal to the LOD/ 2 (Baccarelli et al. 2005). The OC concentrations were expressed as lipid-standardized concentrations (wet-weight concentrations divided by lipid concentrations) or as the lipid-standardized sum of the toxic-equivalency factor (TEF)-weighted dioxin-like concentrations (TEQs) (Van den Berg et al. 2006). Whole blood was analyzed for blood lead levels by Zeeman background-corrected, flameless graphite furnace, atomic absorption spectrometry (ESA Laboratories, Chelmsford, MA).

Statistical analysis

Mixed effects linear regression models were used to evaluate the associations of OC chemicals with BMI-Z, HT-Z, annual HV, log FMi, and FFMi measured over 11 years of follow-up (to age 19 years). FMi was log transformed because the distribution was right-skewed. Congeners were summed together to create categories of chemicals: dioxin-like chemicals (Σ DLC: dioxins, furans, C-PCBs); Σ TEQ: (dioxins, furans, C-PCBs, M-PCBs); and Σ NDL-PCBs (including M-PCBs). To assess dose-response trends, OC concentrations were modeled in quartiles. An autoregressive covariance structure was used to account for within-boy correlation in growth measures over time. We identified covariates associated with growth in the literature and then assessed their association with each study outcome in univariate models. For each growth outcome, we fit a full multivariable model including all covariates with univariate $p \leq 0.20$ for that outcome, and reduced to a final model retaining covariates with $p < 0.10$. In these core models, we included quartiles of OCs, and evaluated the associations between OCs and each growth outcome. Covariates for most models included birth characteristics, SES indicators, and age; models for body fat included nutritional factors; and models for HT-Z and NAH included baseline blood lead levels. Model specific covariates are indicated in table footnotes. We evaluated interactions between age (closest integer year) and higher versus lower OCs (dichotomized at the median) for each outcome using an overall Wald chi-square test for cross-product terms; if this interaction term was significant, we further evaluated age by OC quartile interaction terms. Parameter estimates were obtained using restricted maximum likelihood methods. We defined NAH as the first annual height at which the increment from the prior year (height velocity) was < 1 cm/year. We estimated both NAH and age at NAH for each OC quartile using parametric survival models accounting for right censoring (e.g. boys who had not yet attained NAH at their last study visit). All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as a two-sided p -value ≤ 0.05 .

In sensitivity analyses, we co-adjusted for Σ TEQs and Σ NDL-PCBs simultaneously because prior analyses (Burns et al. 2016) evaluating the relationships of Σ TEQs and Σ NDL-PCBs with pubertal timing had demonstrated correlations among these measures and possible confounding effects. Thus, we performed additional analyses to assess the robustness of the associations and independent contributions of Σ TEQs and Σ NDL-PCBs with body composition and height.

Results

Study population and serum levels of organochlorine compounds

Among 473 eligible boys with measured serum OCs, the distributions of birthweight and gestational age were comparable to U.S. and European populations (Martin et al. 2018; Zeitlin et al. 2017) (Table 1). Other perinatal and maternal characteristics, dietary composition, and socioeconomic indicators at study entry are in Table 1.

A wide range of serum Σ TEQ, Σ DLC, and Σ NDL-PCB concentrations were observed among the boys, with median (10th, 90th percentiles) of 21.1 TEQ pg/g lipid (9.9–51.8), 362 pg/g lipid (224–670), and 250 ng/g lipid (128–613), respectively (Supplemental Table 1). In the RCS, the 25th percentile of Σ TEQs (14.4 TEQ pg/g lipid) was comparable to the 95th percentile (14.0 TEQ pg/g lipid) observed among 12–29 year olds in the 2003–2004 U.S. National Health and Examination Survey (NHANES), whereas the 10th percentile of Σ NDL-PCBs (128 ng/g lipid) fell between the 90th and 95th NHANES percentiles (109, 139 ng/g lipid) (Burns et al. 2009; Patterson et al. 2009). For the majority of the congeners, concentrations were above the LOD in most (70% or more) samples. The median (range) of blood lead levels (BLLs) at age 8–9 years was 3.0 μ g/dL (0.5–31.0). Spearman correlations between Σ TEQs, Σ DLCs, and Σ NDL-PCBs were high, 0.74–0.82, whereas correlations between serum OCs and BLLs were lower, 0.15–0.19. Among the 473 boys included in this analysis, the median follow-up was 9 years (IQR: 8 to 10 years), with 81% followed to at least age 14 years and 63% to age 18–19 years.

Growth measures at entry and during follow-up

At study entry and at age 18–19 years, almost all of the boys' height and BMI measures (Table 1) fell between the 20th and 80th percentiles of the WHO Child Growth Standards. At age 18–19 years, 9% were classified as overweight (BMI-Z >1 to 2), 5% were obese (BMI-Z >2), and 8% were underweight (BMI-Z <−2) (de Onis et al. 2007). The greatest HV occurred at age 14 years (mean=7.7 cm/year). At age 18–19 years, 78% (n=233) of those still being followed had attained NAH.

Associations of serum organochlorine levels with body composition

In multivariable analyses, higher quartiles (Q2, Q3, and Q4) of Σ TEQs, Σ DLCs, and Σ NDL-PCBs compared to Q1 were associated with significantly lower BMI-Z, log FMI, and FFMi (Table 2). For most growth measures, the observed decrements in outcome relative to Q1 were similar for Q3 and Q4.

During follow-up to ages 18–19 years, the observed associations of quartiles of Σ TEQs and Σ DLCs with BMI-Z were relatively constant over time, with no significant interactions of these two exposure measures with age. However, the association of higher (median) Σ NDL-PCBs with BMI-Z varied by age (interaction p=0.01), with more pronounced Σ NDL-PCBs-associated decreases in BMI-Z at ages 11–12 years than at other ages (Supplemental Figure 1).

The associations of Σ TEQs, Σ DLCs, and Σ NDL-PCBs with log FMI were consistent as boys increased in age. However, associations of Σ NDL-PCBs (interaction $p=0.04$) and Σ TEQs (interaction $p=0.03$) with FFMi varied significantly across age groups. Among boys with higher (median) versus lower Σ NDL-PCBs and Σ TEQs, the differences in FFMi were greater in 12–19-year-olds than in 10–11-year olds (Figure 1; Supplemental Figure 2).

In models that included both Σ TEQs and Σ NDL-PCBs, the associations of Σ NDL-PCBs with BMI-Z, log FMI, and FFMi were modestly attenuated but remained significant, and the dose-response pattern did not change (Supplemental Table 2), whereas the associations of Σ TEQs with BMI-Z, log FMI, and FFMi were greatly attenuated and no longer significant (Supplemental Table 2).

Associations of serum organochlorine levels with height

In multivariable analyses, boys with higher levels of Σ NDL-PCBs had significantly lower HT-Z over eleven years of follow-up than those with lower levels (Supplemental Table 3). Adjusted mean HT-Z was similar for the upper three quartiles compared to Q1 (Q1: 0.32; Q2: 0.02; Q3 0.01; Q4 0.06), p -trend=0.03. For both Σ TEQs and Σ DLCs, the relationship with HT-Z was non-monotonic – that is, boys with concentrations in Q3 had significantly lower HT-Z than those in the lowest quartile, but the estimates for Q4 were not significantly different from Q1 (Supplemental Table 3).

There was a significant interaction between boys' age and quartiles of Σ NDL-PCBs for HT-Z ($p<0.001$). Further examination showed that, starting at age 15 years, the differences in HT-Z between the upper three quartiles compared to the lowest began to decrease and were greatly attenuated by age 19 years (Figure 2). Although there was no overall mean difference in HV by Σ NDL-PCBs levels, there was a significant interaction between quartiles of Σ NDL-PCBs and age for HV ($p<0.001$) (Figure 3). Comparing the highest quartile of Σ NDL-PCBs to the lowest, HV was lower at ages 12–13 years, but greater at ages 15–17 years. We observed no significant associations between OC quartiles and NAH (Table 3). However, increasing quartiles of serum OC levels were associated with significantly higher mean ages at NAH, and boys with OC levels in the highest quartile attained NAH approximately 6 months later, on average, compared to those in the lowest quartile (Table 3).

In a model for HT-Z that included both Σ TEQs and Σ NDL-PCBs, there were minimal changes in the Σ NDL-PCBs estimates associated with each quartile; as expected, due to the correlation between Σ TEQs and Σ NDL-PCBs, the confidence intervals were wider, reducing the statistical significance (data not shown). Both before (Supplemental Table 3) and after adjustment for Σ NDL-PCBs, Σ TEQs were not associated with HT-Z.

Discussion

In the RCS longitudinal cohort study of boys, we observed consistent associations of peri-pubertal serum OC concentrations with changes in adiposity and body composition that persisted over longer term follow-up to age 19 years. Specifically, higher serum concentrations of peri-pubertal Σ TEQs, Σ DLCs, and Σ NDL-PCBs were associated with lower BMI-Z, FMI and FFMi. Moreover, the age-associated expansion of FFMi lagged

among boys with higher versus lower Σ TEQs and Σ NDL-PCBs, especially after age 11 years. In contrast, attenuation over time of the association of higher quartiles versus the lowest quartile of peri-pubertal serum Σ NDL-PCBs with lower HT-Z resulted in no difference in NAH by exposure level. Although there was no significant difference in final NAH, boys in the highest quartile of NDL-PCBs reached NAH approximately 6 months higher age compared to boys in the lowest quartile. This may be a reflection of “catch up” growth associated with higher versus lower NDL-PCBs.

The effect of NDL-PCBs and DLCs on children’s growth has been a public health concern since the recognition of pervasive environmental and dietary contamination with these chemicals and the potential for some OCs to act as obesogens (Gore et al. 2015). In contrast to our analysis of peri-pubertal OC concentrations and growth through sexual maturity, most previous studies assessed the associations of OCs measured during the prenatal, perinatal, or lactational period with prepubertal growth. Because of potential differences in OC-growth relationships in boys compared with girls, interpreting our findings in the context of literature on boys is most informative.

The majority of longitudinal studies have not observed associations between prenatal nor lactational NDL-PCB concentrations and childhood BMI or other measures of adiposity (Criswell et al. 2017; Dallaire et al. 2014; de Cock et al. 2014; Hertz-Picciotto et al. 2005; Jackson et al. 2010; Karlsen et al. 2017; Lauritzen et al. 2018; Mendez et al. 2011; Pan et al. 2010; Patandin et al. 1998; Su et al. 2015; Vafeiadi et al. 2015; Valvi et al. 2014). Prenatal NDL-PCBs, however, were associated with higher BMI among both boys and girls in Belgium (Verhulst et al. 2009) and Spain (Agay-Shay et al. 2015; Valvi et al. 2012) at ages 3 and 6.5–7 years, respectively, although the association was attenuated in the Belgian study by age 7–9 years (Delvaux et al. 2014). Peri-natal Σ NDL-PCBs were only associated with higher BMIs among girls both in a childhood Faroe Island study (Tang-Peronard et al. 2014) and a North Carolina study of adolescents (Gladden et al. 2000). Consistent with our findings, other studies reported associations of higher pre- or peri-natal NDL-PCBs with lower weight and BMI during childhood (Guo et al. 1995; Iszatt et al. 2015; Jacobson et al. 1990; Lamb et al. 2006; Rylander et al. 2007; Yoshimura and Ikeda 1978), although Lamb and colleagues observed the association only among girls. Over time, the associations with lower weight and BMI were attenuated in the *Yusho* (Yoshimura and Ikeda 1978) and *Yu-Cheng* (Guo et al. 1995) cohorts, as well as in the only study with follow-up through adolescence (Lamb et al. 2006).

Of note, among published studies, only the *Yu-Cheng* study assessed body composition, comparing 25 randomly selected poisoning cases and control pairs (Guo et al. 1994). Consistent with our findings associating higher peri-pubertal serum Σ NDL-PCBs and Σ TEQs with lower FMI and FFMi, the *Yu-Cheng* study observed that higher *in utero* PCB and furan exposures were associated with lower soft and lean tissue mass at ages 6–13 years assessed by dual-photon absorptiometry (Guo et al. 1995). However, the *Yu-Cheng* study did not have biomarker measures of specific PCB and furan congener levels; thus, it cannot be determined whether the observed associations with lower soft and lean tissue mass were associated with exposures to NDL-PCBs, dioxin-like furans, or both (Guo et al. 1995).

In the RCS, we found strong associations between higher serum Σ TEQs and Σ DLCs and lower BMI-Z and fat and fat-free tissue mass. The only prior study to evaluate the association between prenatal and lactational DLCs and BMI with follow-up into adolescence did not report an association (Leijds et al. 2008), but this Dutch cohort was limited by small sample size (n=33). The majority of studies that have evaluated prenatal or lactational DLC exposures with measures of adiposity during childhood (Delvaux et al. 2014; Jackson et al. 2010; Patandin et al. 1998; Su et al. 2010; Su et al. 2015; Verhulst et al. 2009; Wohlfahrt-Weje et al. 2014) did not find associations. A pooled analysis of three European cohorts (n=251) did not report an association between peri-natal DLCs with BMI among boys at age 7 years, but did report a positive association among girls (Iszatt et al. 2016). To our knowledge, the only prior longitudinal study that was consistent with our findings was a Vietnamese study conducted in an area with historically high environmental levels of the dioxin-contaminated defoliant Agent Orange (Tai et al. 2016). Tai and colleagues (2016) found that higher perinatal TEQ exposures estimated from breast milk were associated with lower BMI and abdominal circumference among boys at age three years but greater abdominal circumference among girls.

Although overall we observed that higher peri-pubertal serum Σ NDL-PCBs concentrations were associated with lower height, the association was attenuated after age 13 years. Other longitudinal studies that have assessed associations between prenatal or lactational NDL-PCB concentrations and linear growth during childhood have generally observed no associations (Dallaire et al. 2014; de Cock et al. 2014; Gladen et al. 2000; Jackson et al. 2010; Jacobson et al. 1990; Karmaus et al. 2002; Pan et al. 2010; Patandin et al. 1998; Rylander et al. 2007; Su et al. 2015), or inconsistent findings. An analysis of a U.S. cohort born in the 1960s observed no associations between prenatal NDL-PCBs and height among boys at age 5 years, but did find a positive association among girls (Hertz-Picciotto et al. 2005). A New York City study reported a positive association between prenatal NDL-PCBs and height among boys, but not girls, at ages 4 and 7 years, which was attenuated by age 17 years (Lamb et al. 2006). A Belgian study and the *Yusho* study initially reported associations of higher early prenatal or early childhood NDL-PCBs, respectively, with lower childhood height, but these associations were attenuated as the children aged (Delvaux et al. 2014; Verhulst et al. 2009; Yoshimura and Ikeda 1978). The *Yu-Cheng* study reported that children with high *in utero* PCB and furan exposures were shorter than unexposed children, beginning at 6 months up to ages 6–13 years (Guo et al. 1995). This finding is consistent with our earlier analysis with follow up of the RCS boys to age 12 years (Burns et al. 2011); in the current analysis with follow-up to age 19 years, the Σ NDL-PCB-height association was attenuated. In keeping with this finding, we observed no significant association of serum peri-pubertal Σ NDL-PCB concentrations with NAH. We did, however, observe that the highest compared to the lowest quartile of Σ NDL-PCBs was associated with significant changes in HV over time and with a 6 month higher age at attainment of NAH. To the best of our knowledge, other studies have not evaluated the relationship of either prenatal or childhood PCB exposures with NAH or age at attainment of NAH.

We did not observe an association between peri-pubertal serum TEQs and height in our cohort. Most prior longitudinal studies did not report an association between higher prenatal nor lactational DLC concentrations and linear growth (Delvaux et al. 2014; Leijds et al. 2008;

Patandin et al. 1998; Verhulst et al. 2009), whereas a few reported that associations observed initially between prenatal TEQs and greater height were attenuated during later childhood (Su et al. 2010; Su et al. 2015; Wohlfahrt-Veje et al. 2014). The New York State (NYS) Angler Cohort (Jackson et al. 2010) and the afore mentioned Vietnamese study by Tai and colleagues (2016), observed associations between higher breast milk TEQs and lower height, but both had a relatively brief follow-up to ages 2 or 3 years, respectively. Moreover, the small (n=32) NYS study did not find the sum of dioxin-like PCB congeners (PCB-77, PCB-126, PCB-169) associated with height, only PCB-77. The larger Vietnamese study (n=217), observed higher TEQs associated with lower height only among boys, not girls (Tai et al. 2016).

NDL-PCBs and DLCs are endocrine-disrupting compounds, but there is limited data describing how these compounds affect pathways associated with growth. The primary mode of action for DLCs is mediated through the aryl hydrocarbon receptor (AhR) (Schechter et al. 2006). AhR's signaling pathway has extensive crosstalk with steroid hormone receptors, and inhibits testosterone biosynthesis (Brokken and Giwercman 2014; Sorg 2014). Animal and epidemiological studies suggest that NDL-PCBs interfere with thyroid hormone and steroid signaling and metabolism (Duntas and Stathatos 2015; Gore et al. 2015; Warner et al. 2012). Before puberty, growth hormone (GH), insulin-like growth factor-1 (IGF-1), and thyroid hormones all modulate growth (reviewed in (Murray and Clayton 2013)). At pubertal onset, the rise in sex steroids elicits an increase in GH and IGF-1 and mediates the sexually dimorphic expansion of fat and muscle mass, i.e., androgen stimulated muscle development among boys and estrogen stimulated fat deposition among girls (Wells 2007). Differential sensitivity to growth stimulating hormones and sex steroids at different stages of puberty may partly explain the inconsistencies in the epidemiologic literature assessing the relation of these endocrine-disrupting chemicals with growth. For example, boys may have reduced muscle expansion because of dioxin's anti-androgen actions, as is suggested by our finding of higher TEQs associated with lower fat-free mass, which is more evident with follow up through puberty.

Our summary measures were broadly based on organochlorines with dioxin-like versus nondioxin-like properties, without considering the potential estrogenic or anti-androgen properties of these chemicals. Our cohort was limited to boys, therefore, we were unable to address whether these chemicals may have sex specific effects. Since the serum OC concentrations in this cohort were higher than those observed in most population-based cohorts, e.g. the lowest quartiles of OCs in the RCS were comparable to the 95th percentiles among U.S. 12–29 year-olds (Burns et al. 2009, Patterson et al. 2009), the associations in the RCS may not be generalizable to other populations.

The RCS is a unique, prospective cohort with follow-up through the dynamic adolescent period into young adulthood, allowing us to determine if the associations we previously observed from ages 8 to 12 years (Burns et al. 2011) were robust and persisted into young adulthood. Most epidemiological studies have assessed the associations of either perinatal or lactation OC exposures with growth; in contrast, we focused on the peri-pubertal period, which is another window of sensitivity that includes the period immediately preceding pubertal onset and the ensuing androgen-driven linear growth and muscle mass expansion.

Our study design, with baseline measurement of serum OCs and height and BMI assessments over eleven years of follow-up, reduces the likelihood that the associations observed between peri-pubertal OCs and BMI-Z are due to reverse causality, i.e. higher serum OCs and lower BMI reflect the sequestration of lipophilic OCs in adipose tissue (Wolff et al. 2007). Our inclusion of BIA estimates of body composition, not used in other epidemiological studies of OCs and growth, provide additional insight into the nature of the associations of higher serum Σ TEQs and Σ NDL-PCBs with lower BMI-Z, since these OCs were also associated with lower FMI and FFMi. Moreover, the differences in FFMi became more pronounced during the follow-up period, with higher peri-pubertal serum Σ TEQ and Σ NDL-PCB levels associated with progressively lower fat-free mass, providing evidence that NDL-PCBs may affect fat-free mass expansion in males, as suggested by the *Yu-Cheng* findings (Guo et al. 1995). Another strength of the RCS is the measurement of multiple congeners of dioxins, furans, and PCBs among our cohort. This allowed us to directly evaluate the relationships of specific OCs with body composition and height, and to explore potential confounding by mixed exposures.

In our cohort, we observed strong effects of Σ TEQs and Σ NDL-PCBs on growth; this was particularly evident in the negative associations with body composition (BMI-Z, FMI, and FFMi). These results do not support the hypothesis that these OCs are obesogens; however, the association with decreased age-associated expansion of fat-free mass during adolescence may have implications for energy metabolism in adulthood, such as increasing the risk of type 2 diabetes mellitus. In contrast, the associations between NDL-PCBs and HT-Z diminished substantially over time. This analysis is the first to evaluate the associations of peri-pubertal serum DLC and NDL-PCB concentrations with serial outcome measures through young adulthood. Our findings emphasize the importance of longitudinal follow-up through pubertal growth to maturity, and suggest that growth may be sensitive to endocrine disrupting chemicals. Future research will explore the interrelationships between DLCs, NDL-PCBs and serum hormone concentrations to better understand the potential pathways by which these exposures may impact male growth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

µg/dL	micrograms per deciliter
ΣDLCs	Sum of dioxin-like chemicals
ΣNDL-PCBs	Sum of nondioxin-like polychlorinated biphenyls
ΣTEQs	Sum of toxic equivalencies
BLL	Blood lead levels
BMI	Body mass index, kg/m ²
BMI-Z	World Health Organization age- and sex-adjusted body mass index z-score
CDC	Centers for Disease Control and Prevention
C-PCBs	Co-planar PCBs
DLCs	Dioxin-like chemicals
EDCs	Endocrine disrupting chemicals
FMI	Fat Mass Index
FFMI	Fat-Free Mass Index
HT-Z	World Health Organization age- and sex-adjusted height z-score
HV	Height velocity, cm/year
LOD	Limit of detection
M-PCBs	Mono- <i>ortho</i> PCBs
NAH	Near adult height
ng/g lipid	nanograms per gram lipid
NDL-PCBs	Nondioxin-like PCBs
PCBs	Polychlorinated biphenyls
pg/g lipid	picogram per gram lipid
RCS	Russian Children's Study
SD	Standard deviation
SES	Socio-economic status
TEF	Toxic equivalency factor

TEQ

Toxic equivalents

WHO

World Health Organization

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Figure 1.

Age-Specific Adjusted^a Mean Fat Free Mass Index (95% CI) by Baseline High versus Low ΣNDL-PCB Concentrations (≥ versus < the median, 250 ng/g lipid)

^aAdjusted repeated measures linear regression model, including birthweight, no biological father in home, low household income, and age (years).

Figure 2.

Age-Specific Adjusted^a Mean Height Z-scores (95% CI) by Baseline Quartiles^b of ΣNDL-PCB Concentrations

^aAdjusted repeated measures linear regression model, including birthweight, parental education, high blood lead ($> 5\mu\text{g/dL}$), and age (years).

^bΣNDL-PCB quartiles (ng/g lipid): Q1 62 – 163; Q2 164 – 249; Q3 250 – 393; Q4 394 – 4248.

Figure 3.

Age-Specific Mean Height Velocity (95% CI) by Baseline Serum Quartiles^a of ΣNDL-PCB Concentrations

^a ΣNDL-PCB quartiles (ng/g lipid): Q1 62 – 163; Q2 164 – 249; Q3 250 – 393; Q4 394 – 4248.

Table 1:

Descriptive characteristics of the Russian Children's Study population of boys (N=473)

Growth measures ^{a,b}	Ages 8–9 years (N=473)	Ages 18–19 years (N=300)
Height z-score ^c	0.12 ± 1.00	0.14 ± 0.92
BMI z-score ^c	−0.19 ± 1.26	−0.34 ± 1.26
Height (cm)	130.1 ± 6.2	177.4 ± 6.8
Weight (kg)	27.1 ± 5.4	68.0 ± 14.0
BMI (kg/m ²)	15.9 ± 2.3	21.6 ± 3.9
Fat mass (kg) ^d	6.3 ± 3.4	10.1 ± 6.3
Fat-free mass (kg) ^d	26.5 ± 4.4	57.9 ± 8.6
FMI (fat mass index; kg/m ²) ^d	3.2 ± 1.5	3.2 ± 1.9
FFMI (fat-free mass index; kg/m ²) ^d	13.6 ± 1.4	18.4 ± 2.2
Overweight or obese	79 (17)	56 (14)
Pubertal onset (testicular volume >3 mL)	68 (14)	N/A
Sexual maturity (testicular volume ≥ 20 mL)	N/A	292 (97)
Birth and neonatal history ^b		
Birthweight (kg)	3.3 ± 0.5	
Gestational age (wks)	39.1 ± 1.7	
Breastfeeding duration (wks)	27.4 ± 34.2	
Preterm (<37 wk gestation)	41 (9)	
Maternal characteristics and exposures during pregnancy ^b		
Age at son's birth (years)	23.9 ± 5.1	
Alcohol consumption	59 (12)	
Tobacco smoking	36 (8)	
Any smoking in household	224 (48)	
Boys' daily dietary intake at study entry ^b		
Total calories (calories/day)	2820 ± 984	
Percent calories from carbohydrates	55 ± 7	
Percent calories from fat	34 ± 6	
Percent calories from protein	12 ± 2	
Household characteristics at study entry ^b		
Low parental education (secondary school)	37 (8)	
Low income (<175 U.S. dollars/month)	164 (35)	
Biological father resides in home	310 (66)	

Note: Values represent Mean ± standard deviation or *n* (%). Summary statistics were calculated among those with non-missing data for that characteristic.

^a Among boys with serum organochlorine compounds measured, 300 (63%) boys were enrolled at age 8 and 173 (37%) were enrolled at age 9.

^b Missing information: pubertal onset (n=3), sexual maturity at age 18–19 years (n=1), birth weight (n=3), gestational age (n=4), breastfeeding (n=11), mother's age at son's birth (n=5), maternal alcohol consumption (n=16), maternal tobacco smoke (n=13), any prenatal tobacco exposure (n=11), dietary information (n=3), parental education (n=4), household income (n=1).

^c WHO sex and age-adjusted z-scores: <http://www.who.int/childgrowth/en/>.

^d Measured at age 10 years, n=182

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Table 2.

Associations of serum toxic equivalents (Σ TEQs), dioxin-like compounds (Σ DLCs), and nondioxin-like polychlorinated biphenyls (Σ NDL-PCBs) with annual measures of body composition in the Russian Children's Study over eleven years of follow-up

Serum quartile	Body Mass Index (BMI) z-scores ^a		Log Fat Mass Index (FMI) ^b		Fat-Free Mass Index (FFMI) ^c	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Σ TEQs ^d						
Quartile 1	Reference		Reference		Reference	
Quartile 2	−0.60 (−0.87, −0.32)	<0.001	−0.22 (−0.32, −0.12)	<0.001	−0.70 (−1.13, −0.27)	0.002
Quartile 3	−0.85 (−1.12, −0.57)	<0.001	−0.30 (−0.40, −0.20)	<0.001	−1.17 (−1.60, −0.74)	<0.001
Quartile 4	−0.72 (−1.00, −0.44)	<0.001	−0.28 (−0.38, −0.18)	<0.001	−0.99 (−1.43, −0.56)	<0.001
Trend test		<0.001		<0.001		<0.001
Σ DLCs ^e						
Quartile 1	Reference		Reference		Reference	
Quartile 2	−0.49 (−0.77, −0.21)	<0.001	−0.20 (−0.30, −0.10)	<0.001	−0.54 (−0.98, −0.11)	0.02
Quartile 3	−0.66 (−0.94, −0.38)	<0.001	−0.23 (−0.33, −0.14)	<0.001	−0.85 (−1.28, −0.42)	<0.001
Quartile 4	−0.68 (−0.97, −0.40)	<0.001	−0.24 (−0.34, −0.14)	<0.001	−0.92 (−1.37, −0.48)	<0.001
Trend test		<0.001		<0.001		<0.001
Σ NDL-PCBs ^f						
Quartile 1	Reference		Reference		Reference	
Quartile 2	−0.61 (−0.88, −0.34)	<0.001	−0.28 (−0.38, −0.19)	<0.001	−0.74 (−1.17, −0.31)	<0.001
Quartile 3	−0.92 (−1.19, −0.65)	<0.001	−0.35 (−0.45, −0.25)	<0.001	−1.19 (−1.62, −0.75)	<0.001
Quartile 4	−0.93 (−1.20, −0.65)	<0.001	−0.37 (−0.46, −0.27)	<0.001	−1.23 (−1.66, −0.80)	<0.001
Trend test		<0.001		<0.001		<0.001

^a Adjusted repeated measures linear regression model, including birthweight, no biological father in home, low parental education, and age (years).

^b Adjusted repeated measures linear regression model, including birthweight, no biological father in home, low household income, percent dietary fat, and age (years).

^c Adjusted repeated measures linear regression model, including birthweight, no biological father in home, low household income, and age (years).

^d Σ TEQ quartiles (pg TEQ/g lipid): Q1 4.0 – 14.3; Q2 14.4 – 21.1; Q3 22.0 – 33.2; Q4 33.3 – 174.7

^e Σ DLC quartiles (pg/g lipid): Q1 123 – 278; Q2 279 – 361; Q3 362 – 494; Q4 495 – 2963

^f Σ NDL-PCB quartiles (ng/g lipid): Q1 62 – 163; Q2 164 – 249; Q3 250 – 393; Q4 394 – 4248

Table 3.

Adjusted mean near adult height (NAH) and age at NAH by quartiles of serum toxic equivalents (Σ TEQs), dioxin-like compounds (Σ DLCs), and nondioxin-like polychlorinated biphenyls (NDL-PCBs) concentrations among Russian boys, enrolled at ages 8–9 years and followed to 18–19 years.

Serum quartile	Near Adult Height (NAH: cm) ^a		Age at NAH (years) ^b	
	Mean (95% CI)	P-value	Mean (95% CI)	P-value
Σ TEQs ^c				
Quartile 1	178.5 (177.0, 180.0)	Ref	17.6 (17.4, 17.8)	Ref
Quartile 2	179.3 (177.7, 180.9)	0.47	17.8 (17.6, 18.0)	0.16
Quartile 3	178.8 (177.2, 180.3)	0.79	17.9 (17.7, 18.1)	0.02
Quartile 4	180.6 (179.0, 180.2)	0.06	18.2 (17.9, 18.4)	<0.001
Trend test		0.11		<0.001
Σ DLCs ^d				
Quartile 1	179.6 (178.0, 181.1)	Ref	17.6 (17.4, 17.8)	Ref
Quartile 2	178.6 (177.0, 180.1)	0.37	17.7 (17.5, 17.9)	0.63
Quartile 3	178.2 (176.7, 179.7)	0.22	18.0 (17.8, 18.2)	0.01
Quartile 4	181.23 (179.6, 182.9)	0.15	18.1 (17.9, 18.3)	0.001
Trend test		0.25		<0.001
Σ NDL-PCBs ^e				
Quartile 1	179.2 (177.7, 180.8)	Ref	17.7 (17.4, 17.9)	Ref
Quartile 2	178.9 (177.4, 180.4)	0.76	17.7 (17.5, 17.9)	0.57
Quartile 3	178.5 (177.0, 180.1)	0.55	17.9 (17.7, 18.1)	0.09
Quartile 4	180.5 (179.9, 182.1)	0.26	18.1 (17.9, 18.3)	0.002
Trend test		0.32		<0.001

^a Adjusted for birthweight, preterm vs. term, high (> 5 µg/dL) vs. low blood lead. Continuous covariates were estimated at the mean level and categorical covariates were weighted according to their relative proportion in the cohort.

^b Adjusted for mother smoked tobacco during pregnancy, low household income, and low parental education.

^c Σ TEQ quartiles (pg TEQ/g lipid): Q1 4.0 – 14.3; Q2 14.4 – 21.1; Q3 22.0 – 33.2; Q4 33.3 – 174.7

^d Σ DLC quartiles (pg/g lipid): Q1 123 – 278; Q2 279 – 361; Q3 362 – 494; Q4 495 – 2963

^e Σ NDL-PCB quartiles (ng/g lipid): Q1 62 – 163; Q2 164 – 249; Q3 250 – 393; Q4 394 – 4248;