Serum Dioxins and Polychlorinated Biphenyls Are Associated With Growth Among Russian Boys

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KEY WORDS

children, BMI, height, environment, epidemiology, polychlorinated biphenyls, polychlorinated dibenzodioxins, polychlorinated dibenzofurans, lead

ABBREVIATIONS

PCB—polychlorinated biphenyl
PCDD—polychlorinated dibenzo-*p*-dioxin
PCDF—polychlorinated dibenzofuran
C-PCB—coplanar polychlorinated biphenyl
M-PCB—mono-ortho polychlorinated biphenyl
NDL-PCB—nondioxinlike polychlorinated biphenyl
SES—socioeconomic status
WHO—World Health Organization
CDC—Centers for Disease Control and Prevention
HV—height velocity
LOD—limit of detection
BLL—blood lead level
TEQ—toxic equivalent
AhR—aryl hydrocarbon receptor

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WHAT'S KNOWN ON THIS SUBJECT: The disruption of childhood growth has been linked with deleterious effects on health in both childhood and adulthood. There is limited evidence from epidemiological studies that prenatal and postnatal exposure to dioxins and polychlorinated biphenyls affects childhood growth.

WHAT THIS STUDY ADDS: In this study serum dioxins and polychlorinated biphenyls were measured in a cohort of Russian boys, who then underwent follow-up examinations for 3 years. The results showed that higher levels of serum dioxins and polychlorinated biphenyls were associated with lower BMI and linear growth.

abstract

OBJECTIVE: We evaluated the associations of serum dioxins and polychlorinated biphenyls (PCBs) with longitudinally assessed growth measurements among peripubertal Russian boys.

METHODS: A total of 499 boys from Chapaevsk, Russia, aged 8 to 9 years were enrolled in the study from 2003 to 2005 and were followed prospectively for 3 years. Blood samples were collected and physical examinations were conducted at entry and repeated at annual study visits. Multivariate mixed-effects regression models for repeated measures were used to examine the associations of serum dioxins and PCBs with longitudinal measurements of BMI, height, and height velocity.

RESULTS: Serum dioxin (total 2005 toxic equivalency [TEQ] median: 21.1 pg/g lipid) and PCBs (median sum of PCBs: 250 ng/g lipid) were measured in 468 boys. At study entry and during 3 years of follow-up, >50% of the boys had age-adjusted BMI and height z scores within 1 SD of World Health Organization—standardized mean values for age. Boys in the highest exposure quintile of the sum of dioxin and PCB concentrations and total TEQs had a significant decrease in mean BMI z scores of 0.67 for dioxins and TEQs and 1.04 for PCBs, compared with boys in the lowest exposure quintile. Comparison of the highest versus the lowest quintile revealed that higher serum PCB concentrations were associated with significantly lower height z scores (mean z-score decrease: 0.41) and height velocity (mean decrease: 0.19 cm/year) after 3 years of follow-up.

CONCLUSIONS: Our findings suggest that exposures to dioxins and PCBs are associated with reduced growth during the peripubertal period and may compromise adult body mass, stature, and health. *Pediatrics* 2011;127:e59–e68

Children may be especially sensitive to the effects of endocrine-disrupting chemicals, such as dioxins, furans, and polychlorinated biphenyls (PCBs).¹ Evidence is accumulating that exposures to these substances affect linear growth and body composition. Prenatal exposure to chlorinated aromatic chemicals, such as dioxin-like compounds (polychlorinated dibenzofurans [PCDFs, furans], coplanar PCBs [C-PCBs], mono-ortho PCBs [M-PCBs]), and nondioxin-like PCBs (NDL-PCBs), has been found to be associated with reduced birth weight and length, independent of gestational age.^{2–4} Prenatal and postnatal exposures to chlorinated compounds may alter postnatal growth.^{5–8} The disruption of childhood growth has been linked with altered pubertal onset,⁹ psychosocial and cognitive difficulties,^{10,11} reduced height in adulthood,¹² and increased risk for obesity, insulin resistance, type 2 diabetes mellitus,^{13–15} and hip fracture.¹⁶ Although body burdens of chlorinated chemicals have decreased over time,^{17,18} children continue to be exposed. Furthermore, these compounds have long biological half-lives because they are stored in adipose tissue and are slowly metabolized.^{19,20} To investigate childhood exposure to chlorinated chemicals, we targeted Chapaevsk, Russia, a town highly contaminated with dioxins and PCBs from discharge from locally produced industrial and agricultural chemicals.^{21,22} We report data on the associations of serum dioxins and PCBs at study entry with serial measures of growth and adiposity during 3 years of follow-up in this ongoing study of Russian boys.

METHODS

Study Population

The Russian Children's Study is a prospective cohort study of 499 boys in Chapaevsk, Russia, which has been previously described in detail.²³ The

boys, identified by using the town-wide health insurance information system, were enrolled from 2003 to 2005, when they were 8 or 9 years old. Enrollment exclusion criteria included being institutionalized or having a severe chronic illness that could have had an impact on childhood growth. The present analysis was restricted to 489 boys, after the exclusion of 10 boys for chronic illnesses that could affect growth. The study was approved by the human studies institutional review boards of the Chapaevsk Medical Association, Harvard School of Public Health, Brigham and Women's Hospital, and University of Massachusetts Medical School. For each study participant, the parent or guardian signed an informed consent form and the boy signed an assent form.

At study entry, the boys underwent a physical examination and blood collection. The mother or guardian completed nurse-administered health and lifestyle questionnaires,^{24,25} which included information on birth, family and child medical histories, occupational and residential history, and measures of socioeconomic status (SES) such as household income and parental education. Birth weight and gestational age were obtained from medical records. A validated Russian Institute of Nutrition semiquantitative food-frequency questionnaire was used to ascertain the child's dietary intake during the previous year.^{26,27}

Physical Examination

At study entry and annual follow-up visits a standardized anthropometric examination (www.cdc.gov/nchs/products/elec_prods/subject/video.htm) was performed by a single study investigator (Dr Sergeyev) who followed a written protocol and was without knowledge of the boys' dioxin and PCB levels. Height was measured to the nearest 0.1 cm by using a stadiometer.

Weight was measured to the nearest 100 g with a metric scale. Age-adjusted *z* scores were calculated for height and BMI by using the World Health Organization (WHO) standards (www.who.int/childgrowth), and for weight by using the Centers for Disease Control and Prevention (CDC) standards (www.cdc.gov/growthcharts/clinical_charts.htm), because WHO standards are unavailable for this age group. We calculated annual height velocity (HV) by computing the difference in height between visits, adjusted to 1-year increments.

Blood Sample Analyses

Blood samples were collected at study entry for measurements of dioxin, furan, PCB, and lead concentrations. Serum was stored at -35°C until shipment on dry ice to the CDC, Atlanta, GA, for analysis. Serum samples, including method blank and 2 quality-control samples, were spiked with a mixture of $^{13}\text{C}_{12}$ -labeled PCDDs/PCDFs/C-PCBs as internal standards and extracted by a C_{18} solid-phase extraction followed by a multicolumn automated cleanup and enrichment procedure.²⁸ The analytes were separated on a DB-5 MS capillary column and quantified using selected-ion-monitoring high-resolution (10 000 resolving power) mass spectrometry (high-resolution gas chromatographic–isotope dilution/high-resolution mass spectroscopic analysis).²⁹

For the analysis of M-PCBs and NDL-PCBs, the samples were spiked with $^{13}\text{C}_{12}$ -labeled PCBs, extracted by either large-volume²⁸ or small-volume³⁰ solid-phase extraction, and analyzed by using high-resolution gas chromatography/mass spectrometry in selected-ion monitoring.³¹ Lipid content was determined from enzymatic measurements of total cholesterol and triglycerides; total lipids were then estimated by using the Phillips equation.³² Dioxin ($n = 473$) and PCB ($n = 468$) congener con-

centrations were available for the boys; measured values below the limit of detection (LOD) were assigned a value equal to the LOD divided by the square root of 2.³³

For blood lead levels (BLLs) a 3.0-mL venous blood sample was collected and analyzed by Zeeman background-corrected flameless graphite furnace atomic absorption (ESA Laboratories, Chelmsford, MA), as described previously.³⁴ The LOD was 1.0 $\mu\text{g}/\text{dL}$.

Statistical Analysis

We evaluated the associations of serum dioxin and PCB concentrations at age 8 to 9 years among 473 boys with age-adjusted BMI and height z scores and annual HV measured during the 3 years of follow-up (through ages 11–12 years). Individual serum dioxin, furan, and PCB congener concentrations were used to calculate lipid-adjusted summary measures: total 2005 toxic equivalencies (TEQs), a measure of toxicity for dioxin-like compounds; the sum of PCDD/PCDF/C-PCB concentrations; and the sum of PCB (M-PCB/NDL-PCB) concentrations. Using a conservative approach that did not require an assumption of linearity, we divided the summary measures into quintiles, with the lowest quintile as the reference. We used mixed-effects regression models for repeated measures with an unstructured covariance to examine the associations of the summary measures with growth outcomes. Initially we evaluated univariate associations, then fit a full multivariate model including all covariates with $P \leq .20$ and reduced to a final core model for all analyses retaining covariates that were significant or marginally significant ($P < .10$) predictors of at least 1 outcome. Included in the final core model was each boy's age, birth weight, gestational age, household income, high ($>5 \mu\text{g}/\text{dL}$) versus low BLL, and nutritional covari-

TABLE 1 Descriptive Characteristics of the Russian Children's Study Population ($N = 489$)

	8-y-Old Boys ($n = 306$)	9-y-Old Boys ($n = 183$)
Growth measurements at study entry according to age group, mean (SD) ^a		
Height, cm	128.5 (5.9)	133.2 (5.9)
Height z score ^b	0.18 (1.03)	0.08 (0.97)
Weight, kg	26.5 (5.4)	28.5 (5.8)
Weight z score ^c	−0.08 (1.16)	−0.26 (1.08)
BMI	15.9 (2.3)	16.0 (2.4)
BMI z score ^b	−0.10 (1.30)	−0.29 (1.25)
Birth and neonatal history, mean (SD) ^a	All Boys ($N = 489$)	
Birth weight, kg	3.4 (0.5)	
Gestational age, wk	39.1 (1.7)	
Duration of breast feeding, wk	28.0 (34.9)	
Maternal characteristics and exposures during pregnancy, n (%) ^a		
Mother's age < 25 y at son's birth	315 (64)	
Mother overweight at study entry	180 (37)	
Maternal alcohol consumption	60 (12)	
Maternal tobacco smoking	36 (7)	
Any household tobacco smoking	231 (47)	
Household characteristics, n (%) ^a		
Parental education, maximum, n (%)		
Secondary education or less	41 (8)	
Junior college/technical training	293 (59)	
University graduate	161 (33)	
Household income, n (%)		
$< \text{US}\$175/\text{mo}$	178 (36)	
$\text{US}\$175\text{--}250/\text{mo}$	127 (26)	
$> \text{US}\$250/\text{mo}$	193 (39)	
Both parents living in the home at study entry	302 (62%)	

^a Missing information: birth weight ($n = 3$), gestational age ($n = 4$), breastfed ($n = 11$), mother's age ($n = 5$), mother overweight ($n = 39$), mother drank alcohol during pregnancy ($n = 16$), mother smoked during pregnancy ($n = 13$), any household smoking ($n = 11$), parental education ($n = 4$), and household income ($n = 1$).

^b WHO age-adjusted z scores (see www.who.int/childgrowth).

^c CDC age-adjusted z scores (see www.cdc.gov/growthcharts).

ates (total caloric intake and percent calories from protein, fat, and carbohydrate).³⁵ Maternal prenatal alcohol and tobacco consumption were not included because they were not associated with growth in our study ($P > .20$). Household income was divided into 3 levels with US monetary equivalents of: < 175 , $175\text{--}250$, or > 250 dollars per month. Because of limited laboratory availability, 119 of the serum dioxin and PCB samples were analyzed in 2004, and the remainder (354) in 2007. We performed sensitivity analyses in which we used an indicator for year of sample analysis (2007 vs 2004). Parental height and BMI were missing for 30% of fathers and 7% of mothers. To assess confounding by parental height and BMI,

we compared the regression estimates from the final multivariate models to the same models including parental height and BMI.

RESULTS

Study Population and Biological Levels of Environmental Chemicals

Among 489 eligible boys enrolled in the study, birth weight and gestational age ranges were consistent with WHO Child Growth Standards (www.who.int/childgrowth/standards) (Table 1). The percentage of calories from dietary protein (mean: 11.6%), fat (mean: 34.1%), and carbohydrate (54.3%) were within nutritionally appropriate ranges for this age group and gender.³⁶ Birth, maternal, and household

TABLE 2 Distribution of Measured Dioxins and PCBs (Serum) and Lead (Blood) Among Russian Boys Aged 8 to 9 Years in the Russian Children's Study ($N = 473$)

	<i>n</i>	Percentile				
		10th	25th	Median	75th	90th
Total PCDD/PCDF/C-PCB concentrations, pg/g lipid ^a	473	224	279	362	495	670
Total PCB concentrations, ng/g lipid ^{a,b}	468	128	164	250	394	613
2005 TEQs, pg TEQ/g lipid ^a	468	9.9	14.4	21.1	33.2	51.8
Lead, $\mu\text{g}/\text{dL}$ ^c	481	2.0	2.0	3.0	5.0	7.0

^a Samples below the LOD were assigned a value equal to the LOD divided by the square root of 2.

^b Sum of noncoplanar PCBs (IUPAC [International Union of Pure and Applied Chemistry] numbers 18, 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 118, 128, 138/158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196/203, 201, 206).

^c Samples below the LOD were assigned a value of 0.5 $\mu\text{g}/\text{dL}$.

characteristics are presented in Table 1; 86% of the boys were breastfed.

The serum TEQ, dioxin, furan, and PCB concentrations had wide ranges for the 473 boys (Table 2), with medians that greatly exceeded those reported in the United States and Europe.^{18,37} Additional details regarding the boys' serum levels of specific dioxin, furan, and PCB congeners are provided elsewhere.²³ BLLs are presented in Table 2 and have been previously reported.^{34,38} The retention rate was 88% after 3 years of follow-up.

Growth Measures at Entry and During Follow-up

At study entry, the boys' height, weight, and BMI ranges (Table 1) were consistent with the WHO³⁹ and CDC Child Growth Standards.⁴⁰ At enrollment, 18% of the boys were overweight (defined as >1 SD above the mean),³⁹ 6% were underweight (defined as >2 SD below the mean),⁴¹ and 3% of the boys' heights were >2 SD below the mean. During follow-up, the boys' height, weight, and BMI z scores were similar to those of their baseline examinations

(Fig 1). The mean (SD) of HV at ages 8 to 12 years were 5.3 (0.8), 5.3 (0.9), 5.1 (1.0), and 5.1 (1.4) cm/year, respectively, which suggested that most of the boys had not begun their pubertal growth spurt. However, the 11- to 12-year HV data were incomplete because only 35% of the boys had reached the age of 12 years at their third-year visit. After adjustment for other covariates, we observed that increasing age was associated with significantly higher BMI z scores and significantly lower height z scores and HV during the study follow-up.

Boys' Characteristics, Household Income, and BLLs as Predictors of Growth Measures

In multivariate models, boys with higher birth weight had significantly higher BMI z scores for the 3-year follow-up period. The lowest compared with the highest household income was associated with marginally lower BMI z scores for the 3-year follow-up period. There was no association of

FIGURE 1

Median (25th and 75th percentiles) height, BMI, and weight z scores over time among boys in the Russian Children's Study ($N = 489$). ^a Data are from the WHO; ^b data are from the CDC.

TABLE 3 Associations of Serum Dioxins and PCBs With Measures of Growth in the Russian Children's Cohort

Exposure	2005 TEQ Quintiles, pg TEQ/g Lipid ^a		PCDD/PCDF/C-PCB Quintiles, pg/g Lipid ^b		PCB Quintiles, ng/g Lipid ^c	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Annual WHO age-adjusted BMI z scores, <i>n</i>	461	—	466	—	461	—
Quintile 1 (lowest)	Reference	—	Reference	—	Reference	—
Quintile 2	−0.53 (−0.86 to −0.19)	.002	−0.46 (−0.79 to −0.12)	.007	−0.81 (−1.14 to −0.48)	<.001
Quintile 3	−0.67 (−1.01 to −0.33)	<.001	−0.75 (−1.08 to −0.42)	<.001	−0.90 (−1.24 to −0.57)	<.001
Quintile 4	−0.84 (−1.18 to −0.50)	<.001	−0.57 (−0.91 to −0.24)	<.001	−1.01 (−1.34 to −0.68)	<.001
Quintile 5 (highest)	−0.67 (−1.01 to −0.33)	<.001	−0.67 (−1.01 to −0.33)	<.001	−1.04 (−1.37 to −0.71)	<.001
Trend test	—	<.001	—	<.001	—	<.001
Annual WHO age-adjusted height z scores						
Quintile 1 (lowest)	Reference	—	Reference	—	Reference	—
Quintile 2	−0.20 (−0.46 to 0.06)	.14	−0.32 (−0.58 to −0.06)	.02	−0.37 (−0.64 to −0.11)	.01
Quintile 3	−0.42 (−0.68 to −0.15)	.002	−0.43 (−0.69 to −0.17)	.001	−0.46 (−0.72 to −0.19)	<.001
Quintile 4	−0.36 (−0.62 to −0.10)	.007	−0.35 (−0.61 to −0.08)	.01	−0.40 (−0.67 to −0.14)	.003
Quintile 5 (highest)	−0.21 (−0.48 to 0.06)	.12	−0.22 (−0.48 to 0.05)	.11	−0.41 (−0.67 to −0.14)	.003
Trend test	—	.07	—	.13	—	.01
Annual HV, cm/year, <i>n</i>	439	—	444	—	439	—
Quintile 1 (lowest)	Reference	—	Reference	—	Reference	—
Quintile 2	−0.05 (−0.13 to 0.23)	.57	−0.09 (−0.26 to 0.09)	.32	−0.12 (−0.30 to 0.05)	.17
Quintile 3	−0.04 (−0.22 to 0.13)	.63	−0.21 (−0.39 to −0.04)	.02	−0.14 (−0.32 to 0.04)	.12
Quintile 4	−0.06 (−0.24 to 0.12)	.51	−0.22 (−0.39 to −0.04)	.02	−0.28 (−0.46 to −0.10)	.002
Quintile 5 (highest)	−0.04 (−0.22 to 0.15)	.71	−0.13 (−0.31 to 0.05)	.17	−0.19 (−0.37 to −0.01)	.04
Trend test	—	.39	—	.06	—	.01

Mixed-effects repeated-measures regression model adjusted for age; birth weight; gestational age; household income; total calories consumed; percent of calories from dietary protein, fat, and carbohydrate; and BLL. CI indicates confidence interval.

^a TEQ quintiles (Q): Q1: 4.0–12.6; Q2: 12.7–18.5; Q3: 18.6–24.8; Q4: 25.0–36.7; Q5: 36.8–174.7.

^b PCDD/PCDF/C-PCB quintiles: Q1: 123–264; Q2: 265–329; Q3: 330–414; Q4: 415–536; Q5: 537–2963.

^c PCB quintiles: Q1: 62–151; Q2: 152–209; Q3: 210–294; Q4: 295–434; Q5: 435–4248.

high blood lead levels with BMI z scores.

Similarly, after adjustment, boys with higher birth weight and preterm birth (<37 weeks) had significantly greater height z scores for the 3-year follow-up period. In addition, the lower household income groups had marginally lower height z scores and HV for the 3-year follow-up period compared with the highest income group. High BLLs ($\geq 5 \mu\text{g/dL}$) were associated with significantly lower height z scores ($P < .001$), and marginally lower HV ($P = .06$) in models adjusted for serum dioxins and PCBs. The mean height z score was 0.39 lower in boys with high BLLs compared with those with low BLLs.

Multivariate Associations of Serum Dioxins and PCBs With Growth Measures

In multivariate models, boys with higher quintiles of total TEQs, sum of

PCDD/PCDF/C-PCB concentrations, and sum of PCB concentrations had significantly lower BMI z scores for the 3-year follow-up period compared with boys with the lowest quintiles (Table 3; Fig 2A). The pattern across higher quintiles was similar for total TEQs and sum of PCDD/PCDF/C-PCB concentrations with a nonlinear dose-response. In contrast, the adjusted mean BMI z scores showed a monotonic decrease over serum PCB quintiles (Table 3). After conversion from z scores, the mean BMIs for 11-year-old boys were 16.1 and 18.2 for the highest versus the lowest serum PCB quintiles, respectively.

Boys with higher serum PCB quintiles had significantly lower adjusted height z scores for the 3-year follow-up period compared with boys with the lowest serum PCB quintile; the dose-response was nonlinear with a saturation effect. That is, we observed no additional incremental effect on growth for expo-

sures above the second quintile (Table 3; Fig 2B). In 11-year-old boys, the mean heights were 143.5 and 146.2 cm for the highest and the lowest serum PCB quintiles, respectively. Although higher quintiles of total TEQs and sum of PCDD/PCDF/C-PCB concentrations were associated with lower height z scores, the relationships seemed to be nonlinear. Boys with higher quintiles of the sum of PCB concentrations compared with the lowest quintile had significantly lower annual HV for the 3-year follow-up period, with a nonlinear dose response (Table 3). After adjustment for covariates, boys with the highest quintile of serum PCBs compared with boys with the lowest had a mean HV that was decreased by 0.19 cm/year (average 0.6 cm shorter in height after 3 years of follow-up). Neither total TEQs nor sum of PCDD/PCDF/C-PCB concentrations were consistently associated with HV (Table 3).

FIGURE 2

A, Adjusted differences in BMI z scores between quintiles of serum TEQs and serum PCDD/PCDF/C-PCB and PCB concentrations versus the lowest quintile. B, Adjusted differences in height z scores between quintiles of serum TEQs and serum PCDD/PCDF/C-PCB and PCB concentrations versus the lowest quintile. Q indicates quintile.

Sensitivity analyses that were adjusted for year of blood sample analysis did not affect the associations of serum total TEQ, PCDD/PCDF/C-PCB, and PCB quintiles with measures of growth (results not shown). In sensitivity analyses that included parental height and BMI, both maternal and paternal height had a significant positive association with boys' height. In addition

paternal BMI had a significant positive association with boys' BMI (mean increase: 0.09 in z score for each 1-unit increase in father's BMI). However, the inclusion of parental height and BMI in the models did not affect the associations between serum total TEQ, PCDD/PCDF/C-PCB, or PCB quintiles with measures of growth; thus, we did not include them in the final analyses.

DISCUSSION

In the present study, we found an association of higher peripubertal serum total TEQs and PCDD/PCDF/C-PCB and PCB concentrations with lower prospectively assessed BMI z scores among Russian boys. Higher sums of PCB concentrations were also associated with lower prospectively assessed height z scores and HV, although heights for >75% of the boys fell within 1 SD of the mean for age.³⁹ The pattern of the observed associations suggests that PCBs may have a greater effect than dioxins on childhood growth, especially linear growth.

Associations between prenatal dioxin and PCB exposures with lower birth length have been reported,^{4,42} but most studies have not identified effects on later childhood stature.^{5,7,43–46} Studies have found positive cross-sectional associations between dioxins⁴⁷ and a dioxin-like PCB congener 118⁴⁸ with girls' or boys' height, respectively, but no longitudinal associations related to prenatal exposures.⁴⁷ Results of another longitudinal study of prenatal PCB exposure showed reduced linear growth only in the first year of life.⁸ In most of these studies the study participants had much lower dioxin and PCB exposures than our cohort, which may account for differences in results across studies. In the Yu-Cheng cohort,⁶ Taiwanese children exposed in utero to high levels of PCBs and PCDFs from contaminated cooking oil were shorter than children matched for age (6–13 years), gender, and other familial and SES characteristics. The results of this study support our finding that childhood PCB exposure may be associated with decreased height. We are not aware of other studies in which investigators assessed the associations of dioxin and PCB exposures with HV. The consistency of our serum PCB associations with both lower height z

scores and HV suggests that PCBs may affect childhood stature by slowing linear growth.

Consistent with our previous cross-sectional findings,²³ serum dioxins and PCBs were inversely associated with longitudinal measures of BMI. Results of other cross-sectional studies have also revealed inverse associations between serum dioxins and PCBs with BMI in children.^{18,48,49} Rapid childhood growth and increasing BMI may result in dioxins and PCBs being distributed over a larger body-mass volume with proportionally more of these substances sequestered in adipose tissue, thereby decreasing serum concentrations. Thus, the association of lower BMI with higher serum dioxins and PCBs may reflect a dilutional effect⁵⁰ rather than a causal pathway. Because the mean BMI z scores in our study did not change over the 3-year follow-up period, our longitudinal analyses that used serial BMI z scores may partially account for the dilutional effect.

Prenatal exposure to PCBs,^{5,7} but not dioxins,^{8,46,47} has been associated with lower childhood weight. In the Yu-Cheng cohort, however, prenatal PCDF and PCB exposure was not associated with childhood weight but was significantly associated with reduced lean muscle mass.⁶ Therefore, exposure to dioxins and PCBs may alter the ratio of lean muscle mass to body fat. In the present analysis, however, we could not determine if our observed associations between serum dioxins and PCBs with BMI z scores were attributable to differences in body composition, such as reduced lean muscle mass versus body fat, because BMI is a crude approximation of body fat.

We found that perinatal factors, such as birth weight and gestational age, were associated with childhood BMI and height z scores. Consistent with

other studies,^{51,52} higher birth weight was positively associated with a greater increase in BMI and height z scores over time. Premature birth (<37 weeks' gestation) was associated with a greater increase in height z scores over 3 years, which may suggest compensatory growth. Infant and childhood compensatory growth has been seen with preterm birth in other cohorts.^{53,54} In our study population, similar to other cohorts,^{54,55} lower household income, a measure of SES, was associated with lower BMI and height z scores, as well as lower HV. In Russia, lower SES families may have limited access to nourishing foods and to health care, both of which have an impact on childhood growth. In the present study, high BLLs ($\geq 5\mu\text{g/dL}$) were significantly associated with lower height z scores and marginally associated with lower HV. The association of high BLL with height is consistent with our previous findings,³⁴ and with findings reported by others.^{56–59}

During the 3-year follow-up period, increasing age was inversely associated with height z score and velocity. This association may be an artifact of the enrollment process, because the 12-year-old data were available only for the 9-year-olds enrolled in 2003 who were born 2 to 3 years earlier (1994) than the other boys. Starting at enrollment this subgroup (35%) had consistently lower height z scores than the rest of the cohort but their scores were comparable those of the boys in our previously reported cross-sectional study.²⁵ Consequently, the inverse association of age with height measures should be interpreted with caution because we do not yet have complete 12-year-old data for the boys born in 1996–1997.

Although our data were collected prospectively, our exposure estimates were from the midchildhood period, not the perinatal period; thus

we may have missed a more susceptible critical window. However, the peripubertal concentrations of serum dioxins and PCBs may be a surrogate for prenatal exposure, because childhood levels often track closely with prenatal levels,⁶⁰ especially in a primarily breastfed population such as ours. At study entry, we excluded boys with severe chronic illnesses. If their illnesses were caused by perinatal exposure to dioxins, furans, and PCBs, the association of these exposures with growth may be underestimated in our analyses. These boys' serum dioxin and PCB concentrations were among the highest observed among contemporary general population samples,²³ with the 25th percentile for serum total TEQs twice the mean values of similarly aged German boys,¹⁸ which made it difficult to investigate the effects of very low exposures. We had incomplete information on parental height and weight, but the results of our sensitivity analyses suggest that these variables were not important confounders.

We chose to examine summary measures of dioxins and PCBs, not classes of congeners or individual congeners. This decision was made on the basis of a priori information on the biological mechanisms of dioxins and PCBs. Dioxins' actions are primarily mediated through the aryl hydrocarbon receptor (AhR), which regulates the expression of a large number of genes involved in normal development and homeostasis.^{61–63} NDL-PCBs do not bind the AhR and are postulated to exert their effect through other mechanisms such as disruption of thyroid hormone homeostasis.^{64,65} Our summary dioxin measures include PCDDs, PCDFs, C-PCBs, and M-PCBs; consequently our results may reflect a combination of mechanisms and we

may have been unable to detect associations because of specific compound classes (PCDDs, PCDFs, C-PCBs, M-PCBs, NDL-PCBs).

CONCLUSIONS

Higher peripubertal serum dioxin and PCB concentrations among Russian boys were associated with reduced measures of growth during 3 years of follow-up. These associations were stronger for the sum of PCB concentrations, which suggests that effects on growth are not primarily AhR mediated. Most of these boys had not reached their period of maximal pubertal growth, thus in the future we will assess whether the amplitude or duration of the peak growth velocity is affected, which

may further compromise adult stature. Despite limited information on fat and lean muscle mass, we found exposure associations with BMI, a surrogate for adiposity that provides a crude measure of body composition. Our ongoing prospective study design, and the recent addition of body composition data by bioelectric impedance, will enable us to clarify in future analyses whether the effects on growth and BMI are attributable to an overall growth inhibition or also to an alteration in body composition. The potential for disruption of childhood growth by environmentally and biologically persistent compounds has important public health implications, because disruption of childhood

growth has been associated with increased risk for adult disease.

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