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Depressed height gain of children associated with intrauterine exposure to polycyclic aromatic hydrocarbons (PAH) and heavy metals: The cohort prospective study

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ABSTRACT

Fetal exposure to environmental toxicants may program the development of children and have long-lasting health impacts. The study tested the hypothesis that depressed height gain in childhood is associated with prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAH) and heavy metals (lead and mercury).

The study sample comprised 379 children born to non-smoking mothers among whom a total of 2011 height measurements were carried out over the 9-year follow-up period. Prenatal airborne PAH exposure was assessed by personal air monitoring of the mother in the second trimester of pregnancy and heavy metals were measured in cord blood. At the age of 3 residential air monitoring was done to evaluate the level of airborne PAH, and at the age 5 the levels of heavy metals were measured in capillary blood.

The effect estimates of prenatal PAH exposure on height growth over the follow-up were adjusted in the General Estimated Equation (GEE) models for a wide set of relevant covariates. Prenatal exposure to airborne PAH showed a significant negative association with height growth, which was significantly decreased by 1.1 cm at PAH level above 34.7 ng/m^3 (coeff.$=-1.07$, $p=0.040$). While prenatal lead exposure was not significantly associated with height restriction, the effect of mercury was inversely related to cord blood mercury concentration above 1.2 μg/L (coeff.$=-1.21$, $p=0.020$),

The observed negative impact of prenatal PAH exposure on height gain in childhood was mainly mediated by shorter birth length related to maternal PAH exposure during pregnancy. The height gain deficit associated with prenatal mercury exposure was not seen at birth, but the height growth was significantly slower at later age.

1. Introduction

Height gain in early life has been recognized as an important biological marker for the toxicity of environmental exposures in the fetal period. It was found that growth restriction in early life was associated not only with short stature of adults (Sorensen et al., 1999), but also with a number of poor health outcomes later in life (Barker, 2006). Beside genetic factors (Pietilainen et al., 2002; Silventoinen et al., 2000), height growth in childhood is to be determined by early nutrition (Martin et al., 2002), social factors (Gulliford et al., 1991; Rona et al., 1978), and psychosocial stress (Montgomery et al., 1997; Pine et al., 1996). Since long epidemiologic studies have demonstrated that environmental factors, such as maternal smoking affect not only birth outcomes but postnatal growth as well (Butler and Goldstein, 1973; Day et al., 1992; Fogelman and Manor, 1988; Fox et al., 1990; Fried et al., 1999; Vik et al., 1996). The effect of intrauterine exposure to toxic heavy metals has also been evaluated and the mechanism of placental transfer and its impact on fetuses and children's health documented (Caserta et al., 2013). In particular, the early exposure to lead (Jelliffe-Pawlowski et al., 2006; Shukla et al., 1991) and mercury (Bellinger, 2008; Gardner et al., 2013; Järup, 2003; Jedrychowski et al., 2006) was found to correlate with infant growth and development. Very recent investigations have documented negative effects of prenatal exposure to polycyclic aromatic hydrocarbons (PAH) on birth outcomes and neurodevelopment (Choi et al., 2006; Dejmek et al., 2000; Edwards et al., 2010; Perera et al., 1998, 2003, 2009).

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PAH compounds are the most common atmospheric pollutants and are mainly derived from coal and other fossil fuel burning by stationary sources and diesel and gasoline engine powered vehicles. Major indoor sources of airborne PAH also include emissions from residential heating (e.g., coal or wood stoves, fireplaces, kerosene heaters), unvented gas appliances, environmental tobacco smoke, and fumes from cooking, grilling, and frying of food (Guillen et al., 1997; IARC, 2010; Junninen et al., 2009; Zedeck, 1980). The biological importance of toxic PAH compounds for children's growth results from the fact that these toxicants readily cross the placenta and interfere with DNA replication and fetal development (Jedrychowski et al., 2012; F. Perera et al., 2005; F.P. Perera et al., 2005).

Although the effects of early life environmental toxic contaminants have been often examined in respect to height at a specific age, their effects on the growth pattern of children is not fully understood. To undestand the impact of early life factors on children's growth, it is necessary to examine height gain longitudinally at different ages in the context of environmental background. The results of longitudinal studies on growth of children could have been biased if they failed to correct for interrelationship between heights of children at various ages or disregarded the impact of birth length and maternal body size on height trajectories.

Our study is part of an ongoing comparative longitudinal investigation on the health impact of prenatal exposure to outdoor/indoor air pollution in infants and children being conducted in New York City and Krakow. One of the goals of the study is to assess the role of individual prenatal exposure to PAH with concurrent exposure to heavy metals (lead and mercury) in order to examine when the particular effects start and how strong and persistent they are through the childhood.

2. Methods and material

The present analysis was restricted to 379 term-babies (born >36 weeks of gestation) who took part in the 9 year follow-up. The design of this prospective cohort study and the population selection were described previously (Jedrychowski et al., 2003). Women who were residents of Krakow, one of the major cities in Poland, and attended ambulatory prenatal clinics in the first and second trimesters of pregnancy were eligible for the study. A total of 505 enrolled pregnant women gave birth between January 2001 and February 2004. Enrollment included only nonsmoking women with singleton pregnancies between the ages of 18 and 35 years who were free from such chronic diseases as diabetes and hypertension. On enrollment, a detailed questionnaire was administered to each subject to elicit demographic data, medical and reproductive history, date of last menstrual period, occupational exposures, and smoking practices of others present at home. Information about height of women and pre-pregnancy maternal weight was obtained from the interview. At the delivery the birth outcomes (weight, length and head circumference) were recorded. Every three months in the first two years of the newborn's life and every 6 months, thereafter mothers participated in a detailed face-to-face interview on their children's health and environmental conditions.

Individual prenatal exposure to airborne PAH was measured in the second trimester of pregnancy and cord blood lead and mercury levels were used as a biomarker of fetal exposure to heavy metals. At ages of 3–9 children were invited annually for pediatric examination during which height measurements were done. At the age of 3 residential air monitoring was done to evaluate the level of exposure to airborne PAH, and at the age 5 the levels of heavy metals were measured in capillary blood. Children living with a smoker in the household were treated as environmental tobacco smoke (ETS) positive.

In the analysis of outcome (height gain), beside exposure variables we included a wide set of potential confounders (maternal height as an indicator of genetic potential; birth length, prepregnancy maternal weight, gestational weight gain, prenatal and postnatal ETS, breastfeeding as an indicator of nutrition in infancy, maternal education as a proxy for social class and standard of living, and parity as a proxy of family size).

2.1. Personal monitoring of PAH exposure over pregnancy

Monitoring of personal PAH exposure was carried out in all pregnant women over a 48-h period during the second trimester of pregnancy. The women were instructed how to use the personal monitor by a trained staff member and were asked to wear the monitoring device during the daytime hours for two consecutive days and to place it near the bed at night. On the second day, the air monitoring staff assistant and interviewer visited the woman's home to change the battery-pack and to complete the questionnaire on the household characteristics. They checked faultless operating of the monitoring device or exchanged it in case of the evident failure. In the study we used a sampling pump to draw air through a polyurethane foam (PUF) sampler for the measurement of PAH. The single pump/two impactors sampling method has been developed at Harvard School of Public Health (Dr. J. Spengler) and applied to particles and gases (Choi et al., 2008). The instrument draws air at a constant flow rate of 4 l per minute (LPM). Flow rates were calibrated (with filters in place) prior to the monitoring, and checked again after changing the battery-pack on the second day and at the conclusion of the monitoring. As previously described (Camann and Whyatt, 2001; Tonne et al., 2004), the PUF cartridges were analyzed at Southwest Research Institute in San Antonio, Texas, where determination of the total PAH (benzo(a)anthracene, benzo(b) fluoranthene, benzo(k)fluoranthene, benzo(g,h,i) perylene, benzo(a)pyrene, chrysene/isochrysene, dibenzo(a,h)anthracene, indeno(1,2,3-c,d) pyrene, and pyrene) in extracts was performed.

2.2. Blood sample collection and analysis

A maternal blood sample (30–35 mL) was drawn at delivery into an EDTA-treated vacutainer tube. Approximately the same amount of venous blood was drawn from the clamped umbilical cord and put into another vacutainer tube. The tube then was inverted several times to mix the EDTA and blood to prevent coagulation. For chemical analysis blood samples were refrigerated without processing and shipped to the Centers for Disease Control and Prevention (CDC) for chemical analysis, where serum cotinine, plasma mercury and lead levels in cord and capillary blood were measured using high-performance liquid chromatography atmospheric-pressure ionization tandem mass spectrometry (CDC, 2003).

2.3. Statistical analysis

The purpose of the statistical analysis was to measure the mean effect of prenatal PAH exposure on the height growth. To identify potential confounders, associations between population characteristics and the outcome variables were investigated. Differences between subgroups with lower and higher PAHs exposure were tested by χ^2-statistics (categorical variables) or by t-test (numerical variables). Initially, the relationship between prenatal PAH exposure and height of children at each specific age was evaluated with linear univariate regression; however, in order to assess the average effect of the exposure on height growth over

the follow-up measured at birth and later annually from 3 to 9 years of age, the generalized estimating equation (GEE) model was applied to account for the correlation between series of observations obtained from the same child (Hardin and Hilbe, 2012). Models computed multivariable regression coefficients of the outcome variable on the main predictor variables (prenatal exposures to PAH, lead and mercury) accounting for potential confounders or modifiers (maternal height, maternal education, maternal age, pre-pregnancy maternal weight, gestational weight gain, parity, child's gender, prenatal and postnatal ETS, residential PAH at the age of 3, season of residential PAH monitoring, and blood levels of lead and mercury measured at the age of 5). All exposure variables (PAH, lead, mercury) were introduced in the GEE models after transformation to ordinal scales by tertiles. Interaction between exposure variables was explored, however due to lack of significance an interaction term was not included in final models. All statistical analyses were carried out with STATA 13.1 version software for Windows.

3. Results

Personal measurements of prenatal exposure to PAHs in the children showed that the geometric mean (gmean) of total PAH was 20.5 ng/m^3 (95% CI: 18.3–23.1) and postnatal residential PAH was 27.4 ng/m^3 (95% CI: 23.2–32.4); the corresponding gmeans of cord blood cotinine, mercury and lead were 0.12 ng/mL (95% CI: 0.10–0.14), 0.89 μg/L (95% CI: 0.83–0.95) and 1.21 μg/dL (95% CI: 1.17–1.26). There was only a significant, but weak positive Spearman correlation (r_s) between PAH airborne and cord blood mercury levels (r_s=0.121, $p<0.05$). Plasma cord blood cotinine levels were inversely correlated with cord blood merucry levels ($r_s=-0.121$, $p<0.05$), but positively with cord blood lead concentrations (r_s=0.131, $p<0.05$). Levels of mercury and lead measured in capillary blood of children at the age of 5 were 0.45 μg/L (95% CI: 0.41–0.49) and 2.05 μg/dL (95% CI: 1.07–2.14). Only cord blood lead correlated positively with capillary lead blood levels (r_s=0.305, $p<0.05$).

Table 1 compares characteristics of the total recruited sample and those who were followed through age 9. It shows that maternal characteristics did not differ across the groups, but there were statistically significant differences in birth outcomes or prenatal levels of PAH and cord lead.

In the follow-up, the mean height of children increased with age by about 6–7 cm per year. The data did not suggest that children had entered their prepubertal growth spurt (Table 2, Fig. 1). As expected, children's height at a particular age significantly correlated with maternal height, birth length and actual height achieved in the preceding year (Supplemental Table 1A). Birth length and maternal height were the strongest predictors of children's height at each age (Supplemental Table 2A, Fig. 2).

Table 3 shows the associations (Spearman correlation coefficients) between annual height of children and prenatal and postnatal exposure. While prenatal PAH exposure significantly correlated only with birth length, mercury significantly correlated with height measured at each age, but not length at birth. Cord blood lead inversely correlated with height at the age of 5–8. Postnatal lead level was found to correlate negatively with height measured in all age groups except for birth length and height at the age of 9. Residential PAH levels were not associated with children's height (data not shown).

The constructed GEE multivariable model (Table 4) assesses the mean height growth of children over the follow-up resulting from the main exposure variables (PAH, mercury and lead categorized by tertiles). These models incorporated all potential confounding variables, which appeared to be significantly associated with the outcome variable in the univariate analysis. Prenatal exposure to airborne PAH showed a significant negative association with height of children, which significantly decreased by 1 cm at the expsoure level above 34.7 ng/m^3 (coeff.=−1.07, p=0.040). While prenatal exposure to lead was not associated with height growth, the impact of mercury showed a height growth deficit of 1.21 cm at the cord mercury level above 1.2 μg/dL (coeff.=−1.21, p=0.020). The interaction between the effects of prenatal PAH and

Table 1
Characteristics of the total group of enrolled subjects and the study sample included in the follow up.

Variables	Total sample recruited, N=505	Study sample, N=379	p Values for difference
Maternal characteristics			
Education (years)	15.6 ± 2.75	15.7 ± 2.74	0.672
Pre-pregnancy height (cm)	165.1 ± 5.46	165.0 ± 5.30	0.832
Pre-pregnancy weight (kg)	58.2 ± 8.44	58.3 ± 8.42	0.678
Pre-pregnancy BMI (kg/m^2)	21.4 ± 2.93	21.4 ± 2.87	0.853
Children's chracteristics			
Girls	247 (48.9%)	182 (48.0%)	0.732
Parity (2 or more)	188 (37.2%)	138 (36.4%)	0.990
Gestational age (weeks)	39.3 ± 1.57	39.5 ± 1.11	0.0001
Birthweight (g)	3401.3 ± 486.40	3458.7 ± 436.79	0.0110
Length at birth (cm)	54.5 ± 2.96	54.9 ± 2.61	0.0064
Breastfeeding exclusive (weeks)	4.9 ± 3.81	5.0 ± 3.75	0.464
Breastfeeding (weeks)	43.0 ± 29.51	44.8 ± 29.17	0.234
Prenatal ETS	135 (26.7%)	98(25.9%)	0.711
Postnatal ETS (1–3years)	92(20.6%)	73(22.1%)	0.494
Postnatal ETS (4–6years)	81 (26.0%)	63(26.4%)	0.899
Postnatal ETS (7–9years)	49 (18.2%)	37(18.1%)	0.982
Prenatal exposure			
Personal total PAHs (ng/m^3)	24.82 (22.36–27.55)	20.52 (18.27–23.06)	0.0016
missing	3	–	
Pb cordblood (μg/dL)	1.29 (1.24–1.34)	1.21 (1.17–1.26)	0.0007
missing	45	–	
Hg cordblood (μg/L)	0.88(0.83–0.94)	0.89 (0.83–0.95)	0.718
missing	115	–	
Cotinine cordblood (ng/mL)	0.13 (0.11–0.15)	0.12 (0.10–0.14)	0.454
missing	21	8	
Postnatal exposure			
Pb blood (μg/dL)	2.07 (1.99–2.16)	2.05 (1.97–2.14)	0.713
Hg blood (μg/L)	0.46 (0.43–0.50)	0.45 (0.41–0.49)	0.464
Cadm blood (μg/L)	0.38 (0.34–0.42)	0.37 (0.33–0.41)	0.570
missing	261	175	
Residential PAH (ng/m^3)	20.2 (17.6–23.1)	27.4(23.2–32.4)	0.0003
missing	184	160	

Table presents mean ± standard deviation, n (%) and geometric mean (95% CI)

Table 2
Mean height and weight by age of children (with 95% CI) followed-up through 9 years of age.

	N	Height (cm)	Weight (kg)
Birth length	379	54.8 (54.6–55.1)	3.46 (3.41–3.50)
At age 3	280	98.7 (98.3–99.2)	15.2 (15.0–15.5)
Age 4	253	105.8 (105.3–106.2)	17.3 (17.0–17.6)
Age 5	244	112.9 (112.3–113.4)	19.8 (19.4–20.1)
Age 6	236	119.2 (118.6–119.8)	22.5 (22.0–22.9)
Age 7	214	126.1 (125.4–126.8)	25.9 (25.3–26.5)
Age 8	207	131.7 (131.0–132.4)	28.7 (27.9–29.4)
Age 9	205	137.5 (136.7–138.2)	32.3 (31.5–33.2)

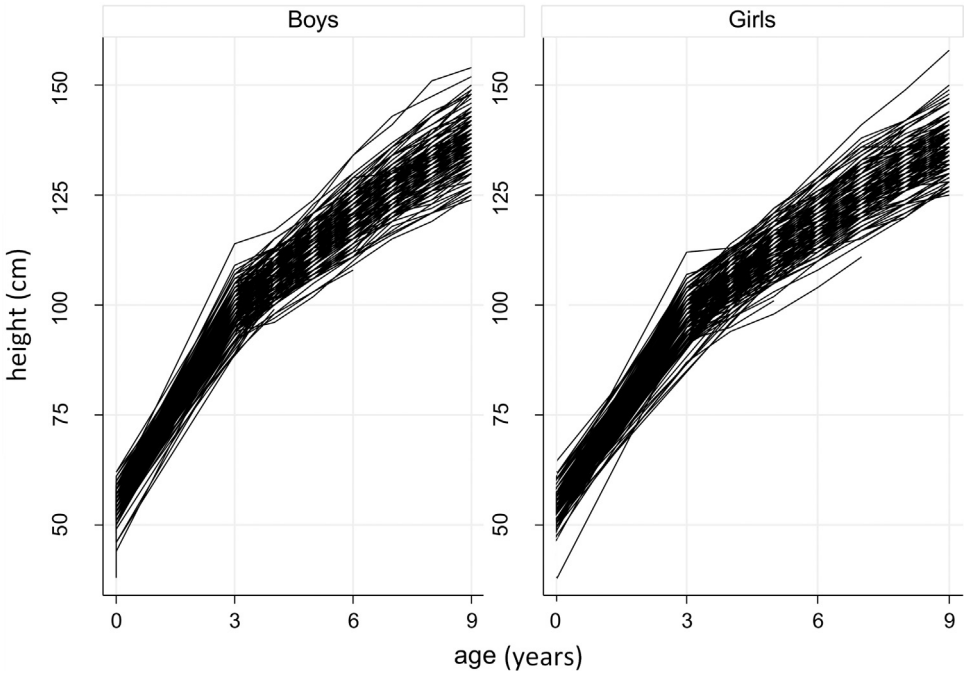

Fig. 1. Observed height trajectories of boys and girls in the study period.

cord blood mercury exposure was insignificant. As expected, the mean height growth in girls was slower than that in boys (coeff. = −1.30, p=0.001) and maternal height had a positive strong effect on height growth, which amounted to 2.16 cm at the maternal height of 168 cm or more (coeff. = 2.16, $p < 0.0001$). Pre-pregnancy weight had an additional positive effect on the height

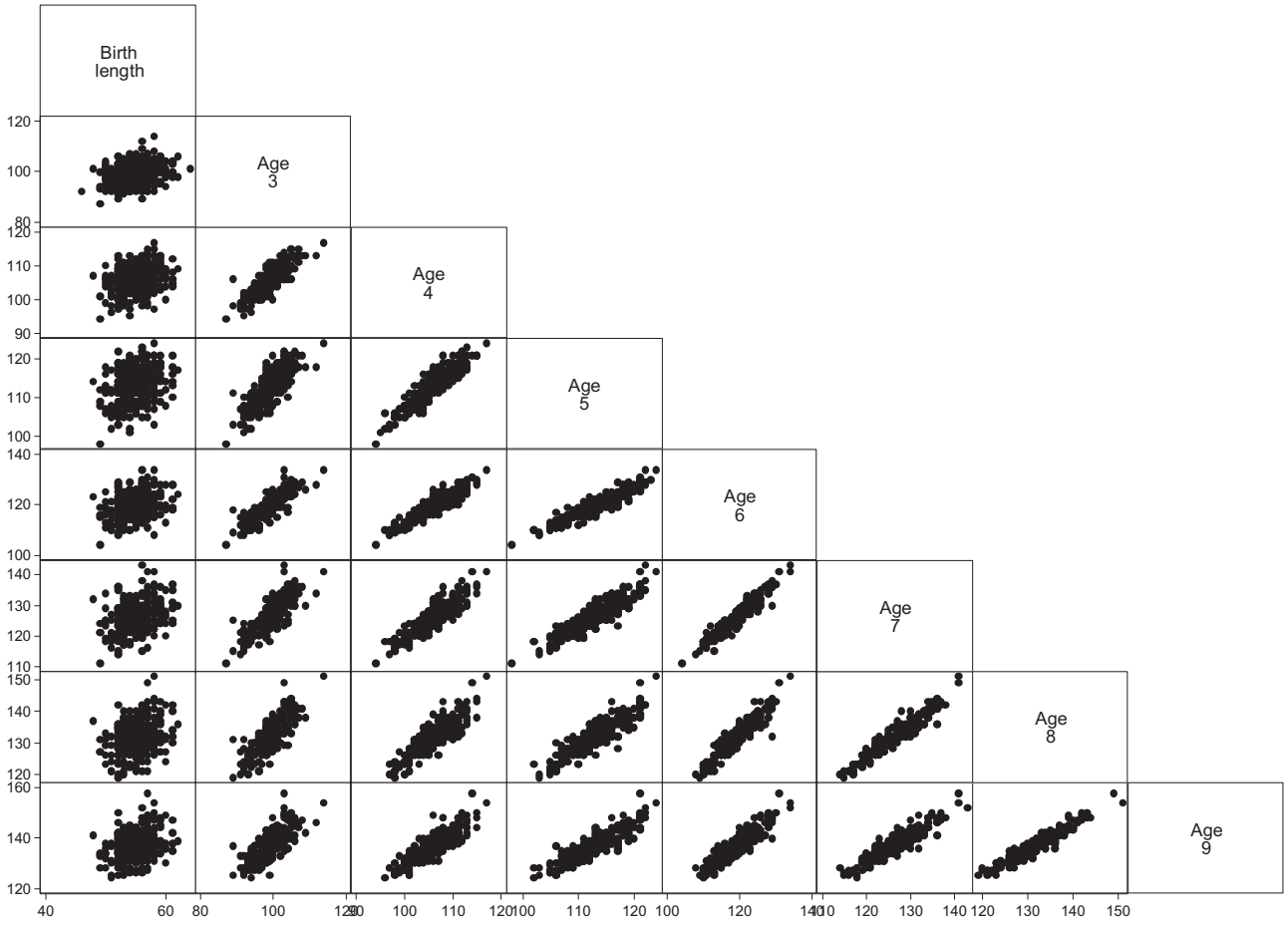

Fig. 2. Graph matrix of correlation between birth length and height of children achieved at each age.

Table 3
Correlation between height (crude data) and prenatal (cord blood) and postnatal exposure to metals (capillary blood at age 5) by age of children.

Age	Prenatal exposure			Postnatal exposure	
	Airborne PAH	Mercury	Lead	Mercury	Lead
At birth	−0.092*	−0.103	0.040	−0.127	0.040
Age 3	−0.043	−0.243*	−0.087	−0.187*	−0.087*
Age 4	−0.040	−0.209*	−0.177	−0.181*	−0.177*
Age 5	−0.029	−0.212*	−0.187*	−0.153	−0.187*
Age 6	0.025	−0.212*	−0.197*	−0.144	−0.197*
Age 7	0.035	−0.256*	−0.181*	−0.159	−0.190*
Age 8	0.020	−0.220*	−0.178*	−0.142	−0.178*
Age 9	−0.032	−0.222*	−0.171	−0.158	−0.171

* Significant at p level < 0.05.

Table 4
Effect of potential predictors on height change over the follow-up. GEE regression model (number of observations = 2011, number of groups = 379, average observations per group = 5.3).

Predictors	Coeff.	z	$p > z$	95% Conf. interval	
Prenatal airborne PAH concentration (ng/m^3)[a]					
< =9.2	Reference				
9.3–34.7	−0.380	−0.80	0.426	−1.317	0.557
> 34.7	−1.073	−2.05	0.040	−2.099	−0.047
Cord blood Hg (μg/L)[a]					
< =0.7	Reference				
0.71–1.20	−0.245	−0.48	0.629	−1.237	0.748
> 1.2	−1.210	−2.33	0.020	−2.227	−0.192
Cord blood Pb in (μg/dL)[a]					
< =1.0	Reference				
1.1–1.4	−0.671	−1.40	0.161	−1.610	0.267
> 1.4	−0.736	−1.38	0.166	−1.779	0.307
Prepregnancy maternal weight (kg)[a]					
< =54	Reference				
54.1–60.0	0.806	1.58	0.113	−0.192	1.804
> 60	1.239	2.35	0.019	0.204	2.275
Maternal height (cm)[a]					
< =163	Reference				
164–168	1.678	3.51	0.000	0.741	2.615
> 168	2.159	3.83	0.000	1.054	3.265
Weight gain in pregnancy (kg)[a]					
< =13.0	Reference				
13.1–17.0	−0.322	−0.65	0.517	−1.297	0.652
> 17.0	1.014	2.00	0.046	0.018	2.010
Maternal education (years)[b]	0.104	1.31	0.191	−0.052	0.260
Sex of child (girls)	−1.297	−3.22	0.001	−2.087	−0.508
Age of child[b]	9.132	167.92	< 0.0001	9.025	9.238
Parity	−0.964	−2.24	0.025	−1.808	−0.121

[a] Tertiles.
[b] Continuous.

gowth (coeff. = 1.24, $p = 0.019$ at maternal weight of 60 kg and more) and children of mothers with high gestational weight gain (> 17 kg) had enhanced height growth by about 1.0 cm (coeff. = 1.01. $p = 0.046$). Older siblings showed a disadvantage in height growth compared with the first born babies (coeff. = −0.96, $p = 0.025$)

4. Discussion

This is the first study that showed that the height growth deficit in children monitored over a nine-year period is significantly associated with prenatal airborne PAH levels above 35 ng/m^3. The impact of the PAH exposure was adjusted for a very wide set of covariates, which could have modified the effect size. The finding that prenatal airborne PAH exposure may result in children's height deficit is consistent with the reports from epidemiologic investigations demonstrating a detrimental PAH impact on birth outcomes (Choi et al., 2006; Dejmek et al., 2000; Perera et al., 1998, 2003). Our earlier published results have indicated that fetal PAH exposure was significantly associated with reduced birth length by 0.5 cm/ln-unit of PAH airborne concentration (Choi et al., 2006). As the prenatal PAH level was associated only with birth length and the catch-up effect in the follow-up was not observed, this may imply that the height deficit in the postnatal period would be mediated by a shorter birth length attributable to prenatal PAH exposure.

The mechanism of fetal toxicity of PAH on birth outcomes is not yet fully understood, but it may involve the induction of apoptosis after DNA damage, anti-estrogenic effects and binding to human aryl hydrocarbon receptor to induce P450 enzymes to receptors for placental growth factors, resulting in decreased exchange of oxygen and nutrients (Davila et al., 1996; Herbstman et al., 2012; Lutz et al., 1998; Manchester and Perera, 1998; Page et al., 2002; Perera, 2011). The present analysis of the Krakow cohort provides evidence that the birth length deficit "persisted" later in childhood. The persisted height deficit associated with prenatal PAH exposure could eventually be explained by some interference in fetal programing, which could have resulted from fetal DNA changes induced by the exposure. This assumption is supported by the fact that the impact of birth length on height of children (standardized beta regression coefficients) was constant and significant in all height prediction equations considered for separate age groups.

The study also revealed that the low-dose prenatal exposure to mercury affects height gain in childhood, however, contrary to PAH exposure, the growth restriction could not be demonstrated in newborns. Mercury, like PAH, is a global toxicant occurring in different forms (organic, metallic, and inorganic) in the human environment (Clarkson, 1997, 2002; Goldman and Shannon, 2001). Its compounds are easily absorbed by inhalation, digestion, and skin contact; they rapidly bind to erythrocytes and are carried throughout the body, pass through the blood–brain barrier and placenta (Caserta et al., 2013; Counter and Buchanan, 2004; Doi et al., 1984; Kajiwara et al., 1997). Up to now a great many research efforts were focused particularly on the effects of mercury exposure on neurodevelopment of children (Castoldi et al., 2001; Grandjean et al., 1997; Lederman et al., 2008; Reuhl and Chang, 1979). Although the specific mechanism of growth retardation in children associated with mercury exposure is not yet well-known, it is assumed that it may be attributable to its function as a disruptor of endocrine system, which controls maturation, development and body growth. Endocrine disruptors can target various endocrine active organs, such as the hypothalamic–pituitary–gonad, thyroid, and adrenal axes (Diamanti-Kandarakis et al., 2009; Meeker, 2012; Schug et al., 2011; Solomon and Schettler, 2000; WHO, 2012). As they affect hormone synthesis, secretion, metabolism and body growth, this may well explain observed children's growth restriction resulting from mercury exposure. However, the primary target of mercury compounds is the central nervous system, which plays a complex role in regulating endocrine function within the body (Naveau et al., 2011). It may be hypothesized that growth restriction would be a secondary phenomenon possibly resulting from subclinical impairment of brain cells by mercury. However, the hypothesis has to be corroborated by solid experimental studies.

The results of our study confirmed that maternal height is an important biological determinant of birth length and height growth in childhood and pointed to additional biological factors being relevant in growth of children, such as maternal pre-pregnancy weight and gestational weight gain. Both factors may have an independent impact on prenatal programing of body growth in

offspring. One hypothesis explaining the association between gestational weight gain and offspring development refers to neurological aspects of body growth regulation and the brain–gut interaction. It has recently been shown that powerful appetite stimulating neuropeptides such as neuropeptide Y (NPY) and cholecystokinin, play important roles in the interaction between the brain, digestive system, and fat stores in controlling food intake and regulating hunger and satiety (Beck, 2006). Evidence from animal studies has suggested that fetal hyperinsulinism resulting from high food supply in gestation can elevate the expression of neuropeptide Y neurons in the arcuate hypothalamic nucleus, which may result in hyperphagia and body growth in offspring (Plagemann et al., 1999; Kalra et al., 1999).

Our study confirmed as well that the older siblings showed a disadvantage in height growth compared with the first born babies. Parity and the number of children at home may be a proxy not only for socioenvironmental factors operating in early childhood, but also for a higher risk of viral infections introduced into the household by older siblings, which in turn may affect children's development. On the other side, maternal attention being spread over multiple children may mean that mothers are less responsive to each child's particular needs.

The study sample was restricted to non-smoking women recruited from only one city, therefore, our results may not be fully representative for the general pollution. Weaknesses of the study include the relatively small sample size and the short measurement time of prnetal PAH exposure. Since the additional prenatal PAH measurements performed in the subsample of pregnant women both in the second and third trimesters were significantly correlated (Choi et al., 2008), we considered the single personal monitoring during the second trimester, a reasonable indicator of prenatal airborne PAH exposure over the last two pregnancy trimesters. Despite known seasonal variation in air pollution levels related to heating with coal in Krakow, the potential effect of measurement season on our results was mitigated by the fact that monitoring was evenly distributed across seasons (Choi et al., 2008). Strength of the study is the prospective cohort design and long follow-up period, where the assessment of personal prenatal expsosure to airborne PAH and heavy metals in blood and the measurement of the residential individual exposure were carried out with the same methods. In addition, a new set of relevant confounders of the relationship between exposure variables and children's height, such as maternal pre-pregnacy weight and gestational weight gain were introduced in the statistical GEE model. Other potential predictors of height growth in children, such as chronic diseases of mothers or maternal active tobacco smoking, have been removed through entry criteria to our study.

In conclusion, the results of the present study have shown that besides maternal height and birth length, maternal pre-pregnancy weight and gestational weight gain are relevant predictors of height gain in childhood. The study provided evidence that airborne prenatal PAH exposure above 35 ng/m^3 is associated with a significant height gain deficit, which may be helpful in establishing preventive guidelines regarding this exposure. Prenatal low-dose exposure to mercury, also associated with height gain deficit, appears later in childhood and might be a kind of secondary phenomenon to the even subclinical impairment of fetal development of the central nervous system.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2014.08.047.

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