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In utero exposure to a brominated flame retardant and male growth and development

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Abstract

Whether environmental exposures alter the timing of puberty is the subject of increasing interest as pubertal age may have consequences for long term health. This study examines the association between exposure to a brominated flame retardant, polybrominated biphenyl (PBB), and puberty and growth. The population consists of sons born to women accidentally exposed to PBBs during 1973–74. Sons 5 to 17 years reported Tanner Stages and answered questions regarding current growth in a mailed questionnaire. Sons 18 to 30 years of age participated in a telephone interview in which they reported retrospective measures of development. Among sons 5–17 years, those with highest exposure (>3 ppb) were less likely to report advanced Tanner stage genital development (OR=0.4, 95% CI: 0.2–0.9) and were less likely to report advanced pubic hair development (OR=0.5; 95% CI: 0.2–1.0), after adjusting for current age, compared to those with lowest exposure (<= 1 ppb). No differences were seen in growth among sons 5–17. However, among sons 18–30 years, those with higher exposure were more likely to weigh less and have lower BMI as adults (test of trend p=0.01 and 0.04, respectively). They were less likely to recall being tall (OR=0.5; 95% CI 0.2–0.9) or heavy (OR=0.6; 95% CI 0.3–1.1) compared to their peers at age 11 years. These results suggest that sons exposed to PBBs in utero may be more likely to have delayed puberty. Further research is needed to corroborate these findings among structurally related compounds and shed light on the biological mechanisms that may be disrupted during puberty and development.

Keywords

Polybrominated Biphenyls; brominated flame retardant; growth; development; maternal exposure; environmental exposure; puberty; male; adolescent development

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Introduction

The development of the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-adrenal axis begin in utero, and continue through the cascading events leading to puberty, sexual maturation and the capacity to produce offspring. The timing and pace of puberty differs among individuals and populations and appears to have consequences for long term health and well-being (1). In addition, there is evidence of a secular trend towards the earlier maturation of girls (2,3) and some indication of a secular trend toward earlier growth and puberty among boys (4). Whether environmental exposures have altered the timing of puberty has been a subject of increasing interest (5).

The Michigan Long-Term Polybrominated Biphenyl (PBB) Study provides a unique opportunity to assess the effects of human exposure to a brominated flame retardant, PBB, on puberty. In 1973–74, Michigan residents were exposed to substantial PBB levels through contaminated animal and dairy products when NutriMaster®, a nutritional cattle feed supplement, was inadvertently replaced with FireMaster®, a brominated flame-retardant. In 1976–77, the Michigan Department of Community Health (MDCH) enrolled ~4,000 individuals with a range of exposure levels into a registry for long term health monitoring (6). This cohort of exposed individuals and their offspring (who were subsequently enrolled into the cohort) has been followed through the present time.

PBB production in the US ceased in 1979. However, concern remains for long-term health effects given continued production of and exposure to similar brominated flame-retardants (7,8). PBBs are stable, persistent pollutants possessing extremely long half-lives; estimates range from eleven to twenty eight years depending on the initial level of exposure (9,10). PBBs are transferred across the placenta, and the fetus may be exposed in utero (7,11,12). Furthermore, neonates may be exposed through breast feeding as PBBs are concentrated in breast milk (over 100-fold compared to maternal serum) (11,12).

Previously we utilized the prospective design of the Michigan Long-Term PBB Study to examine endocrine and growth outcomes among females exposed to PBB in utero and through breastfeeding. Breastfed daughters who were highly exposed in utero experienced earlier menarche (13), but did not differ in height and weight from unexposed daughters (14). Studies of effects of structurally similar compounds (including PCB, DDE, and PCDD/Fs) on puberty in boys (15–20) are not consistent. The current study investigates associations between in utero PBB exposure and growth and developmental outcomes among the male offspring of cohort members.

Methods

The study population, drawn from the Michigan Long-Term PBB Study, included male offspring of female cohort members. Female cohort members were potentially exposed to PBB between the time when contaminated feed was delivered to some Michigan farms (~May, 1973) and the time at which those farms were quarantined (~May, 1974). We considered sons born after July 1, 1973 to have potential in utero PBB exposure, and they were included in the study. We identified 809 sons between the ages of five and 30 years

between 2003–2006. The Institutional Review Boards at MDCH and at Emory University approved the study. Participants gave informed consent or assent.

PBB exposure assessment

Maternal serum PBB levels were measured when the mother enrolled in the cohort using gas chromatography with electron-capture detection. PBB quantitation was based on PBB-153, the main congener involved in the PBB incident (6). The limit of detection (LOD) for serum PBB was 1 part per billion (ppb). Samples were collected from non-fasting participants, and serum lipid levels were not available.

Maternal serum PBB level at the time of conception, estimated using a PBB decay model, was a surrogate for the son's in utero PBB exposure. Briefly, the decay model included BMI at initial PBB measurement, parity, age, smoking, and breastfeeding. Predicted and measured PBB levels were highly correlated (concordance correlation coefficient R=0.90) (21). The estimated date of conception was calculated by subtracting the gestational age from the date of birth.

Questionnaires

The questionnaire used and mode of response differed by age of the participant. Sons 5 to 17 years of age were sent a questionnaire about their health and development (hereafter referred to as the parent-son questionnaire). Three age-specific versions contained minor wording differences. Parents of sons aged 5–10 years were asked to complete the questionnaire for their son(s). Parents of sons aged 11–16 years were given the choice of completing the questionnaire themselves, completing it with the help of their son, or allowing their son to complete it. Sons aged 17 years were asked to complete the questionnaire themselves. Sons aged 18 years and older were asked to participate in a telephone interview about their health including retrospective questions about puberty and growth.

Questionnaires were sent to 436 sons age 5–17 years (181 were 5–10 years of age; 214 were 11–16 years; 41 were 17 years of age). Of those sent, 30 were returned unopened, and we were unable to locate a correct address for these individuals. 280 questionnaires were completed (69% of those not returned unopened). Of these, 32 sons did not have maternal PBB measurements and were excluded from this analysis.

We attempted to contact 373 sons, between the ages of 18 and 30 years, to participate in a telephone interview. Of these, we were unable to locate 42 and one was deceased. We were unable to reach an additional 75 men for whom we believe we had correct contact information. Of the 255 men contacted, 226 completed the telephone interview (89%). Of these, 10 sons did not have maternal PBB measurements and were excluded from this analysis.

In the parent-son questionnaire, participants reported current height and weight and described the current state of their growth spurt (not begun, barely started, definitely underway, seems completed), voice change status (not started, just started, definitely underway, seems complete), and underarm and facial hair growth (not begun to grow, barely started to grow, hair growth is definitely underway, hair growth seems completed). Standard

Tanner Stage diagrams (for both genital and pubic hair development) were used to assess the genital and pubic hair development (22). For children ages 5–10 years, only stages 1–3 were shown in the Tanner stage diagrams. Based on data from NHANES III, we expected no boys to reach Tanner stage 4 for pubic hair before age 11, and less than 0.1% to have reached Tanner stage 4 for genital development before age 11 years (4 23). Children ages 11–17 were asked to match their development to any of the five Tanner stage diagrams. Covariates which might affect growth or development were assessed including: sports participation, dietary supplementation (protein, DHEA, Andro, Hydroxycut, Nitric oxides, and vitamins), medication use (oral steroids, human growth hormone, Ritalin/Adderall, Insulin, and Testosterone) and health problems (thyroid disease, diabetes, cancer, and asthma).

In the telephone interview, in addition to being asked questions about their current height and weight, participants aged 18 years and over were asked to retrospectively assess their growth and pubertal development. They were asked to recall their height (taller, shorter, or about average) and weight (thinner, heavier or about average) relative to their peers at 11 years of age. They reported the age at which they grew the fastest and the age at which pubic hair first appeared. Covariates which might affect growth or development were assessed including: medications use (oral steroids, human growth hormone, Ritalin), health problems (thyroid disease, cancer, asthma, diabetes), and sports participation.

Gestational age at birth was obtained from birth certificates (66%), maternal pregnancy records (18%) when birth certificates were not available, or maternal telephone interview responses (15%) when neither of the prior was available. Similarly, birth weight was obtained from birth certificates (87%), PBB cohort files (8%), or maternal medical records (4%).

Statistical analysis

Sons ages 5–17 years presented a cross-sectional view of growth and development; therefore, their data was analyzed separately from sons age 18 years or older, who contributed retrospective information on growth and development. Using maternal PBB at the time of enrollment, PBB concentration was categorized into three groups based on the limit of detection (LOD) and the median of detectable values. Among sons younger than age 18 the resulting categories were: <=1 ppb, 1–3.0 ppb, >3.0 ppb. Among older sons the resulting categories were: <=1 ppb, 1–3.5 ppb, and >3.5 ppb. For estimated PBB exposure at the time of the son’s conception, the cutpoints were <=1 ppb, 1–2.4 ppb, >2.4 ppb for the younger sons and <=1 ppb, 1–3.1 ppb, >3.1 ppb for the older sons.

The distribution of population characteristics for both age groups was stratified by PBB level, and Chi Square or Fisher exact tests were used in initial assessments of associations between PBB and covariates. Current height and weight were reported as percentiles adjusted for age based on CDC growth charts. Similarly, an age-adjusted BMI percentile was calculated and categorized according to CDC guidelines for healthy children and teens (<5%= underweight; 5–85%=healthy weight; 85–95% =risk of overweight; and >95% =overweight) (24).

Among 5–17 year olds, for whom we have a cross-sectional view of development, we modeled the odds of having more advanced development and adjusted for current age, for each characteristic examined. Development outcomes with more than one level, such as Tanner stages, were modeled with ordinal regression. Odds ratios and 95% confidence intervals were calculated comparing the middle and highly exposed PBB groups with those less than or equal to the limit of detection. For example, we modeled the odds of having a later Tanner stage of genital development among boys with maternal PBB in the highest category (>3.0 ppb) compared to boys in the lowest category of maternal PBB (<= 1 ppb). Where indicated, a test of the statistical significance of a trend was computed.

Among sons 18–30 years of age, for whom we have a retrospective view of development, we calculated mean values of continuous outcomes (current height, weight, and BMI, and age when current height was reached, and age when pubic hair appeared) for each PBB category and adjusted for relatedness of siblings. Score test p values and tests of trends assessed differences between means. For ordinal outcomes (taller compared to peers at age 11 years, heavier compared to peers at age 11 years, later growth spurt relative to peers), we modeled the odds of having more advanced development using ordinal regression. Odds ratios and 95% confidence intervals were calculated comparing the middle and high exposed PBB groups with those less than or equal to the limit of detection.

Throughout modeling, we assessed two surrogates for in utero exposure: maternal enrollment PBB and maternal PBB estimated at conception, and examined the effects of potential confounding variables. Calculations were performed using SAS Version 9.2 (Cary, NC).

Results

Maternal enrollment PBB concentration differed by son’s age. Among sons younger than 18 the median of detectable PBB was 3.0 ppb (range: <1 – 423 ppb). Among sons 18 years and older, the median detectable concentration was 3.5 ppb (range: <1 – 361 ppb). Tables 1 and 2 show the characteristics of the sons who participated in the parent-son questionnaire (age 5–17 years) and telephone interview (18 years and older), respectively. The birth weight (range: 964–5216 g) and gestational age (range: 26–46 weeks) for the sons participating in the parent-son questionnaire did not differ by PBB level (see table 1). The birth weight (range: 1928–5868 g) and gestational age (range: 34–45 weeks) for the sons participating in the telephone interview did not differ by PBB level (see table 2).

Among sons younger than 18 years, both height and weight was high relative to national averages. Whereas we would expect 25% of these sons to fall in the categories of >75% percentile of height for age or weight for age, nearly 50% of sons fell into these categories (see table 1). Average height for age was at the 75%ile among participants in the lowest PBB category compared to the 63%ile for those in the highest PBB category.

Average weight for age was at the 76%ile among participants in the lowest PBB category compared to the 70%ile those in the highest PBB category. Neither of these differences was statistically significant.

This same trend is seen among sons older than 18 where 34% of the participants are over six feet tall (see table 2).

Among sons 5–17 years, those in the highest exposure group were less likely to report advanced Tanner stage genital development (OR=0.4, 95% CI: 0.2–0.9) and they were less likely to report advanced pubic hair development (OR=0.5; 95% CI: 0.2–1.0) after adjusting for current age (see table 3). Estimates were similar when estimated PBB at conception was modeled. No differences were seen in growth spurt status, voice change, arm or face hair development between the exposure groups. Neither height for age or weight for age differed by PBB exposure (data not shown).

Among sons 18–30 years, those with higher exposure were more likely to weigh less and have lower BMI (test of trend p=0.01, and =0.04 respectively). Comparing those most highly exposed to those with lowest exposure, weight differed on average by 15.4 lbs. The weight trend was seen whether maternal enrollment PBB or estimated PBB at conception were used. Similarly, when these participants were asked to retrospectively assess their growth, they were less likely to report being tall (OR=0.5; 95% CI 0.2–0.9) or heavy (OR=0.6; 95% CI 0.3–1.1) compared to their peers at age 11 (Table 5).

Self-reported age when pubic hair appeared and age when current height was reached did not appear related to PBB. Whether or not a participant reported having a growth spurt during adolescence was not related to PBB exposure (see table 5). Furthermore, self reported age at growth spurt and inches grown during growth spurt were not related to PBB exposure (data not shown).

The analyses were not confounded by either birth weight or gestational age. Whether or not a son was breast-fed as an infant did not change the relationship between PBB and the outcomes. Other covariates which might affect growth or development including medications use, dietary supplementation, health problems, and sports participation did not alter our findings.

Discussion

These results suggest that sons with higher in utero PBB exposure may have slower development than those with less exposure. Sons age 5–17 years self reported less advanced Tanner stages for both genital and pubic hair development (after adjusting for age). In addition, adult sons appear to weigh less and have lower BMI. This is consistent with their recall of being smaller and lighter than their peers at age 11 years. However, among the younger sons, there did not appear to be an association of PBB exposure with height and weight.

Several studies have examined the effects of structurally related compounds on puberty and found conflicting results. Den Hond and colleagues (20) found an increase in PBB congeners 138 and 153 was associated with a delay in puberty. The Firemaster mixture, which was the source of exposure in the present study, had a PBB component that was 60% PBB 153 (25). A study of sons from the Yucheng cohort suggested an association between in utero PCB and PCDFs exposure and decreased penile length during puberty (18). Another

study of the Yucheng cohort found no effect on Tanner status, but increased serum estradiol concentrations among sons with higher in utero exposure (19). No association was seen between umbilical cord PCB concentration and Tanner stages among boys born in the Faroe Islands (26). While in utero DEE was associated with height of boys it appeared to have no affect on Tanner staging (27).

An association between PBBs (or related compounds) and development may be mediated through a hormonal mechanism. Fetal testes are susceptible to alterations in hormonal exposure and abnormal development of testes can affect adult reproductive health (28). Cao and colleagues (15) reported lower levels of estrogen among newborns exposed to PBBs and PCDD/Fs. Early disruption of the hypothalamic-pituitary-gonadal axis may result in long term consequences as endocrine disruption during critical periods of fetal development may be irreversible (29).

Our findings were robust through a series of analyses. Whether enrollment PBB or estimated PBB at the time of conception was treated as the exposure, the results were similar. Our findings were not altered when we stratified by whether or not the sons had been breastfed. In addition, we had similar findings (among the younger sons) when we included only the subset of sons who were younger than 12 years old. We had a discrepant finding in the association with growth among the older sons as compared to the younger sons. Among the older sons, those with increased exposure appeared to weigh less. We did not find this same association among younger sons. There are at least two possible explanations for this discrepancy. Older sons were born closer to the PBB contamination incident and had higher exposure levels in utero. Further, it is possible that the difference in adult weight may not be manifested until after puberty and will be seen among these younger sons when they reach their adult heights.

Participants in the PBB Long Term Study were informed of their serum PBB level shortly after enrollment. In theory, we cannot exclude the possibility of reporting bias. However, it seems unlikely for two reasons. First, sons who completed the questionnaires themselves may be unaware of their parent’s PBB levels. Second, the conditions being reported are not diseases or disorders. It is difficult to imagine that sons would consistently and differentially recall puberty as early or later based on their knowledge of exposure. It is likely that some misclassification exists within the Tanner Stage reporting. As reviewed by Coleman, the correlation between self-reported/parental-reported Tanner stage and physician reported (specifically of boys) ranges from 0.59–0.88 (30). However, it is unlikely that misclassification of Tanner stages in the present study would be systematically associated with PBB exposure and bias results away from the null.

Our results add to the body of literature on the possible effects of environmental pollutants on puberty and development. This study provided a uniquely well-defined period of exposure to the brominated flame retardant, PBB, and over 30 years follow up allowing for an examination of cross-generational effects. Our results suggest that sons exposed to PBBs in utero are more likely to have delayed puberty. Further research is needed to corroborate these findings among structurally related compounds and shed light on the biological mechanisms that may be disrupted during puberty and development. Furthermore, additional

prospective research is needed to consider more carefully differences in both the timing and pace of development among children exposed to endocrine disruptors.

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Abbreviations

PBB	polybrominated biphenyls
GU	genitourinary
OR	odds ratio
CI	confidence interval
ppb	parts per billion
MDCH	Michigan Department of Community Health
LOD	limit of detection

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Table 1.

Characteristics of males (ages 5–17), stratified by maternal PBB concentration at enrollment (N=248)

		PBB concentration (ppb)			
Characteristic	**N (%)**	**≤1 N (%)**	**1–3.0 N (%)**	**>3.0 N (%)**	***p* value***
Age (years)					0.25
5–10	84 (33.9)	21 (30.4)	26 (28.9)	37 (41.6)	
11–13	67 (27.0)	16 (23.2)	26 (28.9)	25 (28.1)	
14–16	66 (26.6)	19 (27.5)	28 (31.1)	19 (21.4)	
17–18	31 (12.5)	13 (18.8)	10 (11.1)	8 (9.0)	
Height for age (%)					0.84
1–25	30 (12.3)	333	13 (14.8)	10 (11.4)	
26–50	49 (20.1)	15 (22.1)	17 (19.3)	17 (19.3)	
51–75	43 (17.6)	9 (13.2)	18 (20.5)	16 (18.2)	
76–100	122 (50.0)	37 (54.4)	40 (45.5)	45 (51.1)	
Weight for age (%)					0.69
1 – 25	26 (11.1)	9 (13.9)	9 (10.7)	8 (9.3)	
26 – 50	39 (16.6)	6 (9.2)	16 (19.1)	17 (19.8)	
51 – 75	55 (23.4)	16 (24.6)	19 (22.6)	20 (23.3)	
76 – 100	115 (48.9)	34 (52.3)	40 (47.6)	41 (47.7)	
BMI Percentile					0.76
Underweight	14 (6.0)	5 (7.7)	4 (4.8)	5 (5.9)	
Healthy weight	138 (59.0)	35 (53.9)	52 (61.9)	51 (60.0)	
Risk of overweight	41 (17.5)	12 (18.5)	17 (20.2)	12 (14.1)	
Overweight	41 (17.5)	13 (20.0)	11 (13.1)	17 (20.0)	
Birthweight (g)					
964 – 2499	5 (2.0)	1 (1.5)	2 (2.2)	2 (2.3)	0.59*
2500 – 4500	208 (83.9)	62 (89.9)	76 (84.4)	70 (78.7)	
4501 – 5216	10 (4.0)	2 (2.9)	2 (2.2)	6 (6.7)	
Missing	25 (10.1)	4 (5.8)	10 (11.1)	11 (12.4)	
Gestational age (wks)					
26 – 37	29 (11.7)	9 (13.0)	8 (8.9)	12 (13.5)	0.15*
38 – 42	215 (86.7)	60 (87.0)	78 (86.7)	77 (86.5)	
43 – 46	4 (1.6)	0	4 (4.4)	0	

Missing values are not shown when they comprise less than 5% of the data.

*Chi Square p value shown, except where indicated by superscript. Superscript indicates Fisher's Exact Test.

Table 2.

Characteristics of males (ages 18–30), stratified by maternal PBB concentration at enrollment (N=216)

		PBB concentration (ppb)			
Characteristic	**N (%)**	**≤1 N (%)**	**1–3.5 N (%)**	**>3.5 N (%)**	**P-value***
Age (years)					0.77*
18 – 19	30 (13.9)	11 (14.3)	8 (11.4)	11 (15.9)	
20 – 24	98 (45.4)	34 (44.2)	37 (52.9)	27 (39.1)	
25 – 29	74 (34.3)	27 (35.1)	22 (31.4)	25 (36.2)	
30 – 31	14 (6.5)	5 (6.5)	3 (4.3)	6 (8.7)	
Birthweight (g)					0.36
1928 – 2499	7 (3.3)	1 (1.3)	1 (1.5)	5 (7.3)	
2500 – 4500	196 (91.2)	71 (92.2)	64 (92.8)	61 (88.4)	
4501 – 5868	12 (5.6)	5 (6.5)	4 (5.8)	3 (4.4)	
Gestational age (wks)					0.63
34 – 37	22 (10.2)	11 (14.3)	6 (8.6)	5 (7.3)	
38 – 42	173 (80.1)	59 (76.6)	56 (80.0)	58 (84.1)	
43 – 45	21 (9.7)	7 (9.1)	8 (11.4)	6 (8.7)	
Current height					0.38
4’5” – 5 ‘ 7”	18 (8.3)	3 (3.9)	9 (12.9)	6 (8.7)	
5’ 8” – 6’	125 (57.9)	45 (58.4)	40 (57.1)	40 (58.0)	
6’1” – 6’10”	73 (33.8)	29 (37.7)	21 (30.0)	23 (33.3)	
Current Weight (lbs) (quartiles)					0.02
110 – 175	82 (38.1)	27 (35.1)	26 (37.1)	29 (42.7)	
176 – 215	82 (38.1)	23 (29.9)	28 (40.0)	31 (45.6)	
216 – 300	51 (23.7)	27 (35.1)	16 (22.9)	8 (11.8)	
BMI (kg/m^2)					0.07*
17.6 –18.5	6 (2.8)	2 (2.6)	1 (1.4)	3 (4.4)	
18.6 – 24.9	79 (36.7)	27 (35.1)	24 (34.3)	28 (41.2)	
25 – 29.9	86 (40.0)	24 (31.2)	33 (47.1)	29 (42.7)	
30 – 44.4	44 (20.5)	24 (31.2)	12 (17.1)	8 (11.8)	
Height compared to peers at age 11					0.13
Shorter	34 (15.7)	8 (10.4)	12 (17.1)	14 (20.3)	
About average	122 (56.5)	43 (55.8)	36 (51.4)	43 (62.3)	
Taller	60 (27.8)	26 (33.8)	22 (31.4)	12 (17.4)	
Weight compared to peers at age 11					0.17
Thinner	45 (20.8)	16 (20.8)	10 (14.3)	19 (27.5)	
About average	111 (51.4)	36 (46.8)	38 (54.3)	37 (53.6)	
Heavier	60 (27.8)	25 (32.5)	22 (31.4)	13 (18.8)	

Missing values not shown when they comprise less than 5% of the data.

* Chi Square p value shown, except where indicated by superscript. Superscript indicates Fisher’s Exact Test.

Table 3.

PBB exposure and the odds of more advanced development among sons age 5 to 17 years, adjusting for current age

		Maternal PBB at enrollment (ppb)				Estimated PBB at conception			
Later stage of development*	**N**	**≤1**	**1 – 3.0**	**>3.0**	**P value†**	**≤1**	**1 – 2.4**	**>2.4**	**P value**
Tanner Stage: Genital development	201	REF	0.88 (0.43–1.82)	0.43 (0.20–0.91)	0.05 Trend *p*=0.02	REF	0.79 (0.38–1.63)	0.46 (0.22–0.95)	0.10 Trend *p*=0.04
Tanner stage: Pubic hair	206	REF	0.79 (0.37–1.69)	0.47 (0.21–1.04)	0.15 Trend *p*=0.06	REF	0.75 (0.35–1.62)	0.53 (0.24–1.15)	0.27 Trend *p*=0.09
Growth Spurt	248	REF	0.69 (0.34–1.34)	1.14 (0.57–2.28)	0.26	REF	0.63 (0.31–1.26)	1.25 (0.63–2.48)	0.12
Voice Change	247	REF	1.26 (0.56–2.85)	1.25 (0.53–3.00)	0.28	REF	1.29 (0.56–2,93)	1.24 (0.53–2.89)	0.82
Arm Hair	245	REF	0.83 (0.38–1.82)	0.71 (0.31–1.63)	0.72	REF	0.86 (0.39–1.91)	0.70 (0.31–1.58)	0.69
Face Hair	247	REF	1.06 (0.50–2.25)	1.02 (0.45–2.29)	0.99	REF	1.00 (0.47–2.16)	1.08 (0.49–2.39)	0.97

*Ordinal regression models adjust for current age.

†Wald Chi Square p value for the joint effect of all PBB levels. Test of trend shown where indicated.

Table 4.

Mean value of developmental outcomes stratified by PBB concentration, among sons age 18–30 years old

		Mean stratified by maternal enrollment PBB*				Mean stratified by estimated PBB at conception*			
Developmental Outcome	**N**	**≤1 ppb**	**1 – 3.5 ppb**	**>3.5 ppb**	***P* value†**	**≤1 ppb**	**1 – 3.1 ppb**	**>3.1 ppb**	**P value†**
Current Height (in)	216	71.7	70.9	71.2	0.17	71.9	70.9	71.2	0.06
Current Weight (lbs)	215	201.7	190.7	186.3	0.05, Trend *p*= 0 .01	200.4	193.6	186.8	0.11, Trend *p*= 0 .04
Current BMI (kg/m^2)	215	27.6	26.5	25.8	0.14, Trend *p*= 0.04	27.2	27.0	25.9	0.21, Trend *p*= 0 .12
Age when current height reached (years)	215	17.4	17.4	17.1	0.64	17.5	17.2	17.3	0.65
Age when pubic hair appeared (years)	195	12.7	12.2	12.5	0.07	12.7	12.2	12.5	0.08

*The mean values are adjusted for the relatedness of siblings.

†Score Test *p* values shown first. Test of trend shown where indicated.

Table 5.

PBB exposure and the odds of more advanced development among sons age 18–30

		Maternal PBB at enrollment (ppb)				Estimated PBB at conception (ppb)			
Developmental Outcome*	**N**	**≤1**	**1 – 3.5**	**>3.5**	**P value**	**≤1**	**1 – 3.1**	**>3.1**	**P value**
Taller compared to peers at age 11	212	REF	0.78 (0.40–1.46)	0.45 (0.24–0.86)	0.05	REF	1.33 (0.71–2.49)	0.70 (0.37–1.31)	0.12
Heavier compared to peers at age 11	212	REF	1.14 (0.62–2.11)	0.56 (0.30–1.05)	0.07	REF	1.04 (0.56–1.95)	0.49 (0.26–0.93)	0.04
Reported a growth spurt (yes/no)	205	REF	0.89 (0.38–2.10)	0.56 (0.25–1.25)	0.32	REF	0.97 (0.40–2.36)	0.53 (0.23–1.21)	0.20
Relative to peers, later growth spurt	167	REF	0.82 (0.40–1.67)	1.07 (0.51–2.23)	0.77	REF	0.65 (0.31–1.35)	0.99 (0.47–2.11)	0.42

*These developmental outcomes were modeled with ordinal regression