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Birth Outcomes Associated with Paternal Polybrominated and Polychlorinated Biphenyl Exposure

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Abstract

In 1973-74, a polybrominated biphenyl (PBB) flame retardant mixture was shipped to Michigan livestock feed mills in place of a nutritional supplement and contaminated the food supply. Following the accident, the Michigan PBB Registry was established to study the long-term health effects of halogenated compounds and is now led by a community-academic partnership. PBB exposure is associated with altered DNA methylation in sperm, which may lead to adverse birth outcomes in children whose fathers have increased levels of serum PBB or polychlorinated biphenyl (PCB). Paternal PBB and PCB levels of men enrolled in the Michigan PBB Registry (n=155) were analyzed against matched offspring birthweight and gestational age (n=336). Birthweight and gestational age were dichotomized at the 25th percentile and 37 weeks, respectively, and paternal PBB and PCB levels were examined as continuous measures and divided into tertiles. Associations of offspring birthweight and gestational age with paternal PBB and PCB serum concentrations were modeled using multivariable linear spline and log-risk regression, adjusting for family clustering, paternal health and lifestyle factors, maternal PBB, and PCB serum concentrations, sex, and offspring gestational age (for birthweight). Fathers in the middle and upper PBB and PCB tertiles had increased risks for lowest quartile birthweight compared to the first tertile, with adjusted risk ratios (aRR) =1.67 (95% CI: 0.93, 2.99) and aRR=2.06 (95% CI: 1.12, 3.79) for PBB, and aRR=1.47 (95% CI: 0.79, 2.75) and aRR=1.34 (95% CI: 0.70, 2.54) for PCB, respectively. Elevated paternal PBB levels were not associated with an increased risk for preterm birth, while PCB levels were associated with a small, but not significant, decrease in gestational age, β=−0.37 (95% CI: −0.76, 0.03) weeks per log unit increase PCB. The findings

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Competing Interests

The authors declare that they have no competing interests

suggest that increased paternal PBB and PCB levels negatively impact offspring birthweight, and paternal PCB levels may negatively impact gestational age.

Keywords

Birth Outcome; Polybrominated Biphenyl; Polychlorinated Biphenyl; Endocrine Disrupting Chemical; Paternal Exposure; Infant Health

1. Introduction

Polybrominated biphenyls (PBBs) have not been manufactured in the United States since 1978 following a large-scale industrial accident; however, today, many Michigan residents still have PBB levels above the national average (Chang et al. 2020). In early 1973, the Velsicol Chemical Company accidentally sent PBB, a flame retardant used in plastics, textiles, and electronics, to the Michigan Farm Bureau Service in place of magnesium oxide, a commonly used feed-grade nutrient supplement. The PBB was unknowingly mixed with animal feed across Michigan and entered the food chain through ingestion by farm animals and subsequently by Michigan residents via contaminated eggs, milk, meat, or other animal-based food products. In the spring of 1974, because of the persistent efforts of an individual farmer, the mistake was discovered (Fries and Kimbrough, 1985). In 1976, the Michigan Department of Public Health (now the Michigan Department of Health and Human Services, MDHHS) enrolled individuals into the Michigan Long-Term PBB Study to track the long-term effects of exposure to PBB and other halogenated compounds (Landrigan et al., 1979, Kreiss et al. 1982). This cohort, now known as the Michigan PBB Registry and led by a community-academic partnership, has been continually maintained since 1976 and includes three generations, individuals in the parent generation who were exposed directly by the Michigan PBB Disaster and two subsequent generations of family offspring.

PBBs and polychlorinated biphenyls (PCBs) are halogenated organic compounds manufactured from the 1930s until the 1970s in the United States. Both chemicals were added to numerous products, including plastics, textiles, and electronics, as flame retardants, insulators, and lubricants (Faroon and Olson, 2002, Pohl et al., 2002). While PBB and PCB production has been discontinued both in the United States and worldwide following the Stockholm Convention in 2001, neither readily decomposes, and both are environmentally persistent (Lallas, 2001). PCB and PBB exposure has been identified in areas with background contamination via environmental matrices and biota; however, PBB levels within the Michigan PBB Registry are primarily due to direct exposure following the Michigan PBB disaster and PBB's slow elimination time (Hedgeman et al., 2009, Prince et al., 2020, Xu et al., 2019, Hesse and Powers, 1978, Zhihua et al., 2018, Chang et al. 2020) The estimated median half-life for PBB samples whose primary congener is PBB-153 is 10 years for men and between 13 and 13.5 years for women (Rosen et al., 1995, Blanck et al., 2000). PCB in women has an estimated mean half-life between 6.6 and 90.1 years and between 4.2 and 33.3 years for PCB in men depending on the PCB congener (Seegal et al., 2011).

PBB and PCB exposure and reproductive health and birth outcomes have been investigated with notable results. Maternal PBB exposure has been linked to lower offspring Apgar scores, earlier menarche and subsequent increased miscarriages among female offspring, and low offspring birthweight in mothers with high exposure, while maternal PCB exposure has been associated with altered ages at menarche of female offspring, low offspring birthweight, and lower IQ and reading comprehension scores in offspring of mothers with elevated PCB levels (Terrell et al. 2015, Small et al., 2011, Givens et al., 2007, Marks et al., 2021, Baibergenova et al., 2003, Jacobson and Jacobson, 1996). Paternal PCB exposure has also been associated with altered offspring sex ratios, reduced paternal fertility, and reduced offspring birthweight (del Rio Gomez et al., 2002, Louis et al., 2016, Robledo et al., 2015). Furthermore, PBB exposure has been linked to decreased DNA methylation patterns of imprint control regions and differentially methylated regions in genes essential for fetal growth in male gametes (Greeson et al., 2020). While DNA methylation is essential in regulating gene expression, altered sperm methylation could negatively impact the expression of genes required for early development (Carroll, 2016). Persistent multigenerational DNA methylation patterns have also been documented in mice models and human oocytes, suggesting altered methylation could impact multiple generations (Tuscher and Day, 2019, Gold et al., 2018). Importantly, in addition to the biological plausibility that paternal PBB exposure could impact birth outcomes, based on their personal and familial experiences, PBB Registry members have asked the research team to investigate whether a man's PBB exposure could influence his children's and grandchildren's health. This paper reports an analysis of paternal PBB exposure and birthweight and gestational age and expands research on paternal PCB exposure and these birth outcomes to understand the effects and potential mechanisms of halogenated compounds on fetal development.

2. Material and methods

2.1 Study Population

The analysis utilized primary data collected from PBB registry members who lived on PBB contaminated farms, consumed food from contaminated farms, or were exposed to PBB from employment at the chemical plant and were enrolled in the Michigan PBB Registry (first generation). Data were queried from interviews and self-completed questionnaires that included demographic, lifestyle, and health information, and blood samples tested for PBB and PCB at enrollment in 1976-78.

Data on the offspring of Registry participants (second generation) born after the PBB disaster were obtained from electronic birth records and matched to mothers and fathers enrolled in the Michigan PBB Registry. Fathers were considered a match to offspring if they met one of the two following criteria: (1) offspring birth certificate data matched the following variables from the paternal enrollment questionnaire: last name, first name, date of birth, year of birth, and SSN; or (2) data from the offspring's enrollment questionnaires matched paternal information including the father's name as identified on the enrollment form. We identified 1961 offspring as having parents in the PBB cohort. 383 offspring were paternally matched, of which 337 offspring were selected as they had the following: a paternal ID number, available measured paternal PBB levels, and a completed paternal

health and lifestyle questionnaire when the father was ≥ 18 years old. One observation was removed from this subset due to extreme preterm birth (22 weeks). The study was approved by the Institutional Review Board at Emory University in Atlanta, GA, and MDHHS. MDHHS designed the matching protocol and compiled data from vital records and state health department records from yearly parental updates. Emory received de-identified data from MDHHS. The results of this study have been shared and discussed with the Michigan PBB Leadership Team, which includes representatives from the PBB Citizens Advisory Board, Pine River Superfund Citizen Task Force, Mid-Michigan District Health Department, Central Michigan University, and Alma College. This community-academic partnership works together to understand the long-term health outcomes of exposure to PBB.

2.2 Exposures

Participants enrolled in the PBB Registry have slightly elevated background levels of PCB and were tested for PCB and PBB (Kreiss et al., 1982, Kreiss, 1985). The MDHHS Bureau of Laboratories analyzed serum samples collected from participants at enrollment. Details on the analytical methods are reported elsewhere (Burse et al., 1980, Needham et al., 1981). PBB determination was based on Firemaster BP-6 and FF-1 (PBB-153 was the primary congener, representing 60% of the commercial mixtures), and PCB determination was based on Aroclor 1254. The limit of detection (LOD) for maternal and paternal serum samples was 1 part per billion (ppb) for PBB and 5 ppb for PCB (Needham et al., 1981). Blood samples were collected from non-fasting participants, and lipids were not measured.

2.3 Covariates

Paternal risk factors for low birthweight and altered gestational age were captured in the cohort's enrollment questionnaires administered to fathers. We considered paternal health, lifestyle, and demographic factors, including age, race, cancer diagnosis, diabetes, BMI, smoking, and education, as potential confounders based on previous findings (Reichman and Teitler 2006, Khandwala et al. 2018, Meng and Groth 2018, McCowan et al. 2011). The population of fathers was 99.9% white, 98.5% diabetes-free, and had no cancer diagnoses. Paternal smoking habits were underreported but assessed, given the potential effect on birth outcomes. Smoking had no association with either variable, and inclusion as a covariate led to unstable models due to sample size. Therefore, race, diabetes status, smoking, and cancer status were excluded from the models. Previous research identified an altered sex ratio among offspring of fathers younger than 20 at the time of exposure to PBBs, making age at exposure an important effect modifier to assess and include in the models (del Rio Gomez et al., 2002). Lastly, maternal PBB and PCB levels were included as covariates to help isolate the potential effect of paternal exposures (Givens et al., 2007, Terrell et al., 2015, Terrell et al., 2009). Covariates were added to the adjusted models, a priori, based on associations with birthweight or gestational age identified in the literature.

2.4 Analysis of Covariates

Paternal and maternal PBB and PCB levels were heavily right-skewed, and natural log transformation was performed to help normalize the distribution. For samples in which PBB or PCB were not detected, levels were imputed with LOD/2. Serum samples from the mothers and fathers in the Michigan PBB Registry and paternal and maternal variables

from enrollment questionnaires were categorized and defined as follows: (1) paternal PBB level (as a continuous variable and categorized into tertiles at <=3ppb, 3-8ppb, or >8ppb), (2) paternal PCB level (as a continuous variable and categorized into tertiles at <=5ppb, 6-8ppb, or >8ppb), (3) education (≤high school diploma or >high school diploma), (4) age at offspring birth (<34 years old or ≥34 years old). For analyses that included body mass index (BMI), BMIs were calculated from self-reported height and weight at enrollment and categorized based on NIH standards (overweight at ≥25 or normal/underweight at <25) (Weir and Jan, 2020).

Offspring variables were obtained from electronic birth records and maternal questionnaire data from mothers in the Michigan PBB Registry. This included offspring sex, offspring birthweight in grams and dichotomized at the 25th percentile (3232 grams in this sample) to capture lower birth weights while maintaining adequate cell sizes, and offspring gestational age categorized based on World Health Organization standards (≥37 weeks, full-term and <37 weeks, preterm) (World Health Organization, 2012).

2.5 Statistical Analyses

Continuous and categorical outcome variables were compared across tertiles of exposure using Kruskal-Wallis rank sum and Pearson's Chi-squared tests, respectively. Pearson correlation coefficients were conducted to analyze potential relationships between paternal and maternal PBB serum levels, paternal and maternal PCB serum levels, and paternal PBB and PCB serum levels. Mixed models and generalized estimating equations (GEE) were considered, due to their ability to adjust for clustering of fathers with multiple children in the study, but the latter was selected to model continuous, binary, and categorical birth outcomes. Linear GEE models were generated to estimate beta coefficients for the association of PBB and PCB with continuous birthweight and continuous gestational age. Quadratic spline GEE models were evaluated when non-linear dose response curves were present. Unadjusted and adjusted log-binomial models were produced to estimate risk ratios for the association of PBB and PCB with birthweight below the 25th percentile and gestational age dichotomized at 37 weeks. BMI had an inverse correlation with PBB and PCB levels in the data, and this pattern has been reported elsewhere (Wolff et al., 2000). Therefore, sensitivity analyses adjusting for BMI as a confounder in the models were performed to independently analyze BMI's effect on PBB and PCB levels and birthweight. All statistical analyses were performed using SAS v9.4 (Cary, NC).

3. Results

3.1 Summary Characteristics of Study Population

A total of 336 children born between 1975 and 2003 were matched with 155 fathers in the Michigan Long-Term PBB Study. Demographic, lifestyle, and health variables differed among father-offspring pairs across tertiles of PBB (Table 1) or PCB (Table 2). Compared to the lower and middle tertiles, fathers in the highest PBB tertile were younger at the time of exposure, had a higher percentage of healthy or underweight BMIs, and were younger at offspring birth. Maternal PBB levels were also significantly higher in the highest paternal PBB tertile. Fathers in the lowest PCB tertile had a lower percentage of healthy or

underweight BMIs than the middle and upper tertiles and had a higher percentage of fathers older than 34 at offspring birth.

Offspring were comparable in distributions of sex and gestational age for PBB and sex for PCB. Offspring from fathers in the middle and upper PBB and PCB tertiles had a higher proportion of lower birthweights than the lower tertile, and the middle and upper PCB tertiles had a lower average gestational age compared to the lower tertile.

3.2 Paternal and Maternal PBB and PCB Concentrations

Fathers had a geometric mean of 6.1 ppb of PBB in serum and 6.9 ppb of PCB in serum at the time of enrollment, while mothers had a geometric mean of 2.5 ppb of PBB in serum and 4.9 ppb of PCB in serum. Fathers had higher PBB and PCB concentrations compared to mothers and fewer concentrations less than LOD (paternal PBB range: <LOD-1744 ppb; 4.2% <LOD; paternal PCB range: <LOD-85 ppb; 15.2% <LOD; maternal PBB range: <LOD-933 ppb; 17.8% <LOD; maternal PCB range: <LOD-22 ppb; 32.5% <LOD). Log-adjusted paternal and maternal PBB serum levels were strongly correlated ($r = 0.764$ $p = 0.001$) and log-adjusted paternal and maternal PCB serum levels were weakly correlated ($r = 0.252$ $p = 0.001$). Log adjusted paternal PBB and PCB levels were significantly but minimally correlated ($r = 0.155$ $p = 0.007$).

3.3 Offspring Birthweight and Gestational Age

Lowest quartile offspring birthweight was associated with increased paternal PBB levels in bivariate analyses. The middle and upper paternal PBB tertiles demonstrated an increased percentage of babies born in the lower birthweight class, 19.2% vs. 28.6% and 32.2% (Pearson's Chi-squared test, p=0.06) for the lower, middle, and upper tertiles, respectively. Lowest quartile offspring birthweight was associated with monotonic increased adjusted risk ratios (aRR) in the middle (aRR=1.67, 95% CI: 0.93, 2.99) and upper tertiles (aRR=2.06, 95% CI = 1.12, 3.79) for PBB (Table 3). There were elevated but not significant aRRs for the middle and upper PCB tertiles (aRR=1.47, 95% CI: 0.79, 2.76) and (aRR=1.34, 95% CI = 0.70, 2.54) PCB tertiles. Preterm gestational age was not associated with increasing paternal PBB or PCB levels in the log-risk models (Table 4).

Birthweight illustrated a U-shaped curve with PBB levels (Table 5), while birthweight was inversely associated with continuous paternal PCB (Table 6) levels. The multivariable spline model for PBB illustrated a U-shaped curve with a negative trend from <LOD to 4 log-PBB ($\beta = -57.48$, 95% CI: −136.07, 21.11 grams per log unit increase in PBB), and a positive trend above 4 log-PBB ($\beta = 370.25$, 95% CI: 220.27, 520.23 grams per log unit increase in PBB), due to a small cluster of 12 offspring with high birthweight among fathers with high PBB levels. The multivariable linear model for PCB was also negatively associated with birthweight ($\beta = -101.01$, 95% CI: −212.93, 10.91 grams per log unit increase in PCB). Preterm gestational age was not associated with increasing paternal PBB levels but was negatively associated with PCB ($\beta = -0.37$, 95% CI: −0.76, 0.03 weeks per log unit increase in PCB) in the continuous models (Tables 7 and 8).

3.4 Sensitivity Analysis for Paternal BMI and Offspring Birthweight and Gestational Age

The inclusion of paternal BMI in the log-risk PBB model produced decreased risk ratios and shifted the 95% confidence intervals to include null values in the middle (aRR=1.50, 95% CI: 0.86-2.65) and upper (aRR=1.69, 95% CI: 0.94, 3.05) PBB tertiles, respectively, though the apparent monotonic dose-response across tertiles remained (Table 3). The continuous spline PBB model including BMI followed a similar trend producing estimates with decreased significance from <LOD to 4 log-PBB (β= −31.42, 95% CI: −116.15, 53.32 grams per log unit increase in PBB), and above 4 log-PBB (β=316.62, 95% CI: 157.79, 475.45 grams per log unit increase in PBB) (Table 5). However, the continuous PCB model, including BMI, produced a more significant trend for birthweight (β= −117.41, 95% CI: −223.61, −11.22 grams per log unit increase PCB) while the results of the log-risk PCB model remained unchanged (Tables 6 and 4). Preterm gestational age was not associated with increasing paternal PBB adjusting for BMI (Tables 3 and 7), while gestational age was negatively associated with PCB levels (β= −0.48, 95% CI: −0.85, −0.11 weeks per log unit increase in PCB) in the continuous models adjusting for BMI (Table 8).

4. Discussion

4.1 Interpretation of Results

This study expands the understanding of the relationship between paternal body burdens of halogenated chemicals and birth outcomes. Higher paternal PBB and PCB levels were associated with lower birthweight, but PBB levels were not associated with earlier birth, while PCB levels were weakly associated with earlier birth.

We also note the U-shaped dose-response curve illustrated by paternal PBB levels and offspring birthweight, evident at very high levels of paternal PBB. Similar U-shaped and non-linear curves have been noted for PCBs and other halogenated compounds and adverse health outcomes; however, these curves are often present at much lower doses (Lee et al., 2007, Lim et al., 2008). Additionally, non-linear trends have been noted in maternally matched multigenerational studies for dioxin-like compounds and altered offspring thyroid hormone levels, along with paternally matched multigenerational studies for DDT and offspring birth defects (Warner et al., 2020, Salazar-Garcia et al., 2004). However, paternally matched multigenerational PBB studies have not found similar non-linear patterns which may be due to their much lower exposure ranges (Robledo et al., 2015).

These results indicate a concerning trend as gestational age and birthweight are correlated in prenatal development. Variance in this development trend resulting from high paternal PBB or PCB exposure may negatively affect neonatal development (Oken et al., 2003). The PBB results showing decreasing birthweight with no change in gestational age suggest PBB may negatively impact prenatal growth. Furthermore, while the PCB results showed decreasing birthweight with decreasing gestational age, the birthweight models were adjusted for the decreasing gestational age pattern and illustrate a divergence from the normal birthweight for gestational age. We note that a previous study in a population with much lower paternal PBB and PCB levels did not find an association between paternal PBB and

offspring birthweight but did find a negative association between paternal PCB exposure and birthweight that was consistent with our findings (Robledo et al., 2015).

4.2 Paternal BMI and Halogenated Compound Burden

The sensitivity analysis adjusting for BMI as a confounder showed a decreased risk of lowest quartile birthweight associated with PBB but increased risk of lowest quartile birthweight associated with PCB. These findings may be explained by the nature of PBB and PCB exposure. PCB levels reflect long-term low-level chronic exposures and would be less affected by BMI, while PBB levels were taken shortly after the Michigan PBB disaster and may not have reached equilibrium through sequestration in adipose tissue (Wolff et al., 2000). In addition, higher BMI is associated with a slower elimination rate of halogenated compounds in serum, elevating the potential long-term impact of persistent PBB and PCB levels on sperm (Chevrier et al., 2000, Blanck et at., 2000). However, the confidence intervals of the sensitivity analysis overlapped with non-BMI adjusted models, and a recent meta-analysis has reported conflicting results between paternal BMI and offspring birthweight, making it hard to support a precise mechanism by which paternal BMI and halogenated compound levels may impact offspring birthweight, and further research is required (Oldereid et al., 2018).

4.3 Strengths and Limitations

The study's strengths are the large sample size, PBB and PCB levels measured before the offspring births, and the large number of covariates identified in survey data. The study had limitations, however. Paternal education, height, and weight were collected via self-reporting questionnaires that may be subject to recall or response bias. Maternal PBB and PCB levels were based on enrollment levels and were not adjusted for giving birth and breastfeeding, which are routes of maternal POP elimination (Chang et al., 2020). Additionally, paternal and maternal PBB and PCB levels were based on enrollment levels and not adjusted for the time between measurement and offspring birth, which may have led to potential misclassification. The sample size of preterm newborns was small, which led to unstable estimates and wide confidence intervals with multiple covariates, including maternal PCB levels and paternal health and lifestyle factors in the PCB log-binomial models and did not allow BMI to be tested with effect modification. Lastly, we dichotomized the lowest quartile birthweight at the 25th percentile rather than at the WHO definition of 2500 grams due to our population's small sample size of newborns <2500 grams, which may reduce the public health implications of the findings given that many of these infants are considered to be a healthy weight.

5. Conclusion

These findings suggest paternal PBB and PCB exposure may negatively affect offspring birthweight. With respect to other findings, including sperm methylation of key imprinted regions and BMI association with halogenated compound burden that supports the transgenerational impact of these compounds, relevant mechanisms of action for PBB, PCB, and other halogenated compounds and persistent organic pollutants must be further studied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

PBB	Polybrominated Biphenyl
PCB	Polychlorinated Biphenyl
MDHHS	Michigan Department of Health and Human Services
LOD	Limit of Detection
aRR	Adjusted Risk Ratio
CI	Confidence Interval
ppb	Parts per Billion
GEE	Generalized Estimating Equation
NIH	National Institutes of Health
EPA	Environmental Protection Agency

References

Blanck HM, Marcus M, Hertzberg V, et al. Determinants of polybrominated biphenyl serum decay among women in the Michigan PBB cohort. Environ Health Perspect. 2000;108(2):147–152. [PubMed: 10656855]

Burse VW, Needham LL, Liddle JA, Bayse DD, Price HA. Interlaboratory comparison for results of analyses for polybrominated biphenyls in human serum. J Anal Toxicol. 1980;4(1):22–26. doi:10.1093/jat/4.1.22 [PubMed: 6098783]

Carroll M Sperm DNA Methylation, Infertility and Transgenerational Epigenetics. GGS. 2016;1(1):1–9. doi:10.24966/GGS-2485/100004

Chang CJ, Terrell ML, Marcus M, et al. Serum concentrations of polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in the Michigan PBB Registry 40 years after the PBB contamination incident. Environ Int. 2020;137:105526. doi:10.1016/j.envint.2020.105526 [PubMed: 32062441]

Chevrier J, Dewailly E, Ayotte P, Mauriège P, Després JP, Tremblay A. Body weight loss increases plasma and adipose tissue concentrations of potentially toxic pollutants in obese individuals. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2000;24:1272–1278. doi:10.1038/sj.ijo.0801380 [PubMed: 11093288]

del Rio Gomez I, Marshall T, Tsai P, Shao Y, Guo Y. Number of boys born to men exposed to polychlorinated byphenyls. Lancet (London, England). doi:10.1016/s0140-6736(02)09386-8

Faroon O, Olson J. ATSDR's Toxicological Profiles: Web Version. CRC Press; 2002. doi:10.1201/9781420061888

Fries GF, Kimbrough RD. The Pbb Episode in Michigan: An Overall Appraisal. CRC Critical Reviews in Toxicology. 1985;16(2):105–156. doi:10.3109/10408448509056268 [PubMed: 3002722]

Givens ML, Small CM, Terrell ML, et al. Maternal exposure to polybrominated and polychlorinated biphenyls: Infant birth weight and gestational age. Chemosphere. 2007;69(8):1295–1304. doi:10.1016/j.chemosphere.2007.05.031 [PubMed: 17617441]

Gold HB, Jung YH, Corces VG. Not just heads and tails: The complexity of the sperm epigenome. Journal of Biological Chemistry. 2018;293(36):13815–13820. doi:10.1074/jbc.R117.001561 [PubMed: 29507096]

Greeson KW, Fowler KL, Estave PM, et al. Detrimental effects of flame retardant, PBB153, exposure on sperm and future generations. Scientific Reports. 2020;10(1):8567. doi:10.1038/s41598-020-65593-x [PubMed: 32444626]

Hedgeman E, Chen Q, Hong B, et al. The University of Michigan Dioxin Exposure Study: Population Survey Results and Serum Concentrations for Polychlorinated Dioxins, Furans, and Biphenyls. Environ Health Perspect. 2009;117(5):811–817. doi:10.1289/ehp.11780 [PubMed: 19479026]

Hesse JL, Powers RA. Polybrominated biphenyl (PBB) contamination of the Pine River, Gratiot, and Midland Counties, Michigan. Environmental Health Perspectives. 1978;23:19–25. doi:10.1289/ehp.782319 [PubMed: 209975]

Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med. 1996;335(11):783–789. doi:10.1056/NEJM199609123351104 [PubMed: 8703183]

Khandwala YS, Baker VL, Shaw GM, Stevenson DK, Lu Y, Eisenberg ML. Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study. BMJ. Published online October 31, 2018:k4372. doi:10.1136/bmj.k4372 [PubMed: 30381468]

Kreiss K, Roberts C, Humphrey HE. Serial PBB levels, PCB levels, and clinical chemistries in Michigan's PBB cohort. Arch Environ Health. 1982;37(3):141–147. doi:10.1080/00039896.1982.10667553 [PubMed: 6284069]

Kreiss K Studies on populations exposed to polychlorinated biphenyls. Environ Health Perspect. 1985;60:193–199. [PubMed: 3928345]

Lallas PL. The Stockholm Convention on Persistent Organic Pollutants. Am j int law. 2001;95(3):692–708. doi:10.2307/2668517

Landrigan PJ, Wilcox KR, Silva J, Humphrey HEB, Kauffman C, Heath CW. Cohort Study of Michigan Residents Exposed to Polybrominated Biphenyls: Epidemiologic and Immunologic Findings. Annals of the New York Academy of Sciences. 1979;320(1):284–294. doi:10.1111/j.1749-6632.1979.tb56611.x [PubMed: 222186]

Lee DH, Lee IK, Porta M, Steffes M, Jacobs DR. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. Diabetologia. 2007;50(9):1841–1851. doi:10.1007/s00125-007-0755-4 [PubMed: 17624515]

Lim JS, Lee DH, Jacobs DR Jr. Association of Brominated Flame Retardants With Diabetes and Metabolic Syndrome in the U.S. Population, 2003–2004. Diabetes Care. 2008;31(9):1802. doi:10.2337/dc08-0850 [PubMed: 18559655]

Louis GMB, Barr DB, Kannan K, Chen Z, Kim S, Sundaram R. Paternal exposures to environmental chemicals and time-to-pregnancy: overview of results from the LIFE study. Andrology. 2016;4(4):639–647. doi:10.1111/andr.12171 [PubMed: 27061873]

Marks KJ, Howards PP, Smarr MM, et al. Prenatal exposure to mixtures of persistent endocrine disrupting chemicals and early menarche in a population-based cohort of British girls. Environmental Pollution. 2021;276:116705. doi:10.1016/j.envpol.2021.116705 [PubMed: 33592441]

McCowan LM, North RA, Kho EM, et al. Paternal Contribution to Small for Gestational Age Babies: A Multicenter Prospective Study. Obesity. 2011;19(5):1035–1039. doi:10.1038/oby.2010.279 [PubMed: 21127471]

Meng Y, Groth S. Fathers Count: the Impact of Paternal Risk Factors on Birth Outcomes. Matern Child Health J. 2018;22(3):401–408. doi:10.1007/s10995-017-2407-8 [PubMed: 29218490]

Needham LL, Burse VW, Price HA. Temperature-programmed gas chromatographic determination of polychlorinated and polybrominated biphenyls in serum. J Assoc Off Anal Chem. 1981;64(5):1131–1137. [PubMed: 6270054]

Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr. 2003;3:6. doi:10.1186/1471-2431-3-6 [PubMed: 12848901]

Oldereid NB, Wennerholm UB, Pinborg A, et al. The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. Human Reproduction Update. 2018;24(3):320–389. doi:10.1093/humupd/dmy005 [PubMed: 29471389]

Pohl H, Bosch S, Amata R, Eisenmann C. Toxicological Profile for Polybrominated Biphenyls. Published online 2002:366.

Prince KD, Taylor SD, Angelini C. A Global, Cross-System Meta-Analysis of Polychlorinated Biphenyl Biomagnification. Environ Sci Technol. 2020;54(18):10989–11001. doi:10.1021/acs.est.9b07693 [PubMed: 32786558]

Reichman NE, Teitler JO. Paternal Age as a Risk Factor for Low Birthweight. Am J Public Health. 2006;96(5):862–866. doi:10.2105/AJPH.2005.066324 [PubMed: 16571696]

Robledo CA, Yeung E, Mendola P, et al. Preconception Maternal and Paternal Exposure to Persistent Organic Pollutants and Birth Size: The LIFE Study. Environ Health Perspect. 2015;123(1):88–94. doi:10.1289/ehp.1308016 [PubMed: 25095280]

Rosen DH, Flanders WD, Friede A, Humphrey HE, Sinks TH. Half-life of polybrominated biphenyl in human sera. Environ Health Perspect. 1995;103(3):272–274. doi:10.1289/ehp.95103272 [PubMed: 7768229]

Salazar-García F, Gallardo-Díaz E, Cerón-Mireles P, Loomis D, Borja-Aburto VH. Reproductive effects of occupational DDT exposure among male malaria control workers. Environmental Health Perspectives. 2004;112(5):542–547. doi:10.1289/ehp.112-1241918 [PubMed: 15064158]

Seegal RF, Fitzgerald EF, Hills EA, et al. Estimating the half-lives of PCB congeners in former capacitor workers measured over a 28-year interval. Journal of Exposure Science & Environmental Epidemiology. 2011;21(3):234–246. doi:10.1038/jes.2010.3 [PubMed: 20216575]

Small CM, Murray D, Terrell ML, Marcus M. Reproductive Outcomes Among Women Exposed to a Brominated Flame Retardant In Utero. Arch Environ Occup Health. 2011;66(4):201–208. doi:10.1080/19338244.2010.539640 [PubMed: 22014192]

Terrell ML, Berzen AK, Small CM, Cameron LL, Wirth JJ, Marcus M. A cohort study of the association between secondary sex ratio and parental exposure to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB). Environ Health. 2009;8:35. doi:10.1186/1476-069X-8-35 [PubMed: 19682390]

Terrell ML, Hartnett KP, Lim H, Wirth J, Marcus M. Maternal exposure to brominated flame retardants and infant Apgar scores. Chemosphere. 2015;118:178–186. doi:10.1016/j.chemosphere.2014.08.007 [PubMed: 25203650]

Tuscher JJ, Day JJ. Multigenerational epigenetic inheritance: One step forward, two generations back. Neurobiology of Disease. 2019;132:104591. doi:10.1016/j.nbd.2019.104591 [PubMed: 31470104]

Warner M, Rauch S, Ames J, et al. Prenatal dioxin exposure and thyroid hormone levels in the Seveso second generation study. Environmental Research. 2020;183:109280. doi:10.1016/j.envres.2020.109280 [PubMed: 32311913]

Weir CB, Jan A. BMI Classification Percentile And Cut Off Points. In: StatPearls. StatPearls Publishing; 2020. Accessed November 22, 2020. http://www.ncbi.nlm.nih.gov/books/NBK541070/

Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P. Risk of Breast Cancer and Organochlorine Exposure. Cancer Epidemiol Biomarkers Prev. 2000;9(3):271–277. [PubMed: 10750665]

World Health Organization. Born too soon: the global action report on preterm birth. Published online 2012:112.

Xu C, Niu L, Zou D, Zhu S, Liu W. Congener-specific composition of polychlorinated biphenyls (PCBs) in soil-air partitioning and the associated health risks. Science of The Total Environment. 2019;684:486–495. doi:10.1016/j.scitotenv.2019.05.334 [PubMed: 31154221]

Zhihua L, Panton S, Marshall L, et al. Spatial analysis of polybrominated diphenylethers (PBDEs) and polybrominated biphenyls (PBBs) in fish collected from UK and proximate marine waters. Chemosphere. 2018;195:727–734. doi:10.1016/j.chemosphere.2017.11.114 [PubMed: 29289018]

Table 1:

Population characteristics of parents and children divided into paternal PBB tertiles

	Lowest PBB Tertile (N=120)	Middle PBB Tertile (N=98)	Highest PBB Tertile(N=118)	Total (N=336)	p-value
Paternal Characteristics					
Paternal PBB Level (ppb)					0.001
Geometric Mean (SD)	1.8 (1.8)	5.3 (1.3)	23.4 (3.3)	6.1 (3.8)	
Range	<LOD - 3.0	4.0 - 8.0	9.0 - 1744.0	<LOD - 1744.0	
Maternal PBB Level (ppb)					0.001
Geometric Mean (SD)	1.1 (2.4)	2.0 (2.2)	6.6 (4.2)	2.5 (3.8)	
Range	<LOD - 21.1	<LOD - 18.0	<LOD - 933.0	<LOD - 933.0	
Missing	0	9	2	11	
Paternal Age at Offspring Birth					0.045
<=34 years old	98 (81.7%)	76 (77.6%)	106 (89.8%)	280 (83.3%)	
>34 years old	22 (18.3%)	22 (22.4%)	12 (10.2%)	56 (16.7%)	
Missing	0	0	0	0	
Paternal age at the time of PBB Exposure Accident					0.013
Mean (SD)	25.0 (7.2)	24.4 (5.4)	22.8 (4.2)	24.1 (5.8)	
Range	16.0 - 61.0	11.0 - 40.0	17.0 - 38.0	11.0 - 61.0	
Missing	0	0	1	1	
Paternal Education					0.229
<=High School Level of Education	67 (57.8%)	66 (68.8%)	77 (65.3%)	210 (63.6%)	
>High School Level of Education	49 (42.2%)	30 (31.2%)	41 (34.7%)	120 (36.4%)	
Missing	4	2	0	6	
Paternal BMI					0.001
Healthy or Underweight	45 (39.1%)	48 (49.5%)	92 (81.4%)	185 (56.9%)	
Overweight	70 (60.9%)	49 (50.5%)	21 (18.6%)	140 (43.1%)	
Missing	5	1	5	11	
Offspring Characteristics					
Sex					0.941
Male	63 (52.5%)	51 (52.0%)	64 (54.2%)	178 (53.0%)	
Female	57 (47.5%)	47 (48.0%)	54 (45.8%)	158 (47.0%)	
Offspring Birthweight					0.193
Mean (SD)	3654.9 (576.2)	3563.1 (602.2)	3521.9 (554.2)	3581.4 (577.5)	
Range	2041.0 - 5868.0	992.0 - 4933.0	2126.0 - 5557.0	992.0 - 5868.0	
Offspring Birthweight					0.064
Upper Weight (>=3232 grams)	97 (80.8%)	70 (71.4%)	80 (67.8%)	247 (73.5%)	
Lower Weight (< 3232 grams)	23 (19.2%)	28 (28.6%)	38 (32.2%)	89 (26.5%)	
Offspring Gestational Age					0.538
Mean (SD)	40.3 (1.9)	40.1 (2.0)	40.3 (1.7)	40.2 (1.8)	
Range	36.0 - 45.0	32.0 - 45.0	36.0 - 44.0	32.0 - 45.0	
Missing	4	2	3	9	
Offspring Gestational Age					0.325

Full-Term	109 (94.0%)	87 (90.6%)	110 (95.7%)	306 (93.6%)
Preterm	7 (6.0%)	9 (9.4%)	5 (4.3%)	21 (6.4%)
Missing	4	2	3	9

Table 2:

Population characteristics of parents and children divided into paternal PCB tertiles

	Lowest PCB Tertile (N=91)	Middle PCB Tertile (N=108)	Highest PCB Tertile (N=97)	Total (N=296)	p-value
Paternal Characteristics					
Paternal PCB Level (ppb)					0.001
Geometric Mean (SD)	3.5 (1.4)	6.8 (1.1)	13.4 (1.6)	6.9 (1.9)	
Range	<LOD - 5.0	6.0 - 8.0	9.0 - 85.0	<LOD - 85.0	
Maternal PCB Level (ppb)					0.145
Geometric Mean (SD)	4.5 (1.7)	5.0 (1.7)	5.1 (1.8)	4.9 (1.7)	
Range	<LOD - 20.0	<LOD - 17.0	<LOD - 22.0	<LOD - 22.0	
Missing	8	7	3	18	
Paternal Age at Offspring Birth					0.001
<=34 years old	85 (93.4%)	96 (88.9%)	71 (73.2%)	252 (85.1%)	
>34	6 (6.6%)	12 (11.1%)	26 (26.8%)	44 (14.9%)	
Paternal Education					0.426
<=High School Level of Education	59 (67.0%)	65 (60.7%)	67 (69.1%)	191 (65.4%)	
>High School Level of Education	29 (33.0%)	42 (39.3%)	30 (30.9%)	101 (34.6%)	
Missing	3	1	0	4	
Paternal BMI					0.084
Healthy or Underweight	42 (49.4%)	70 (64.8%)	57 (61.3%)	169 (59.1%)	
Overweight	43 (50.6%)	38 (35.2%)	36 (38.7%)	117 (40.9%)	
Missing	6	0	4	10	
Offspring Characteristics					
Sex					
Male	48 (52.7%)	57 (52.8%)	54 (55.7%)	159 (53.7%)	0.895
Female	43 (47.3%)	51 (47.2%)	43 (44.3%)	137 (46.3%)	
Offspring Birthweight					
Mean (SD)	3661.0 (521.1)	3554.2 (593.2)	3483.0 (529.4)	3563.7 (553.9)	0.086
Range	2126.0 - 5557.0	992.0 - 5000.0	2126.0 - 4933.0	992.0 - 5557.0	
Offspring Birthweight					
Upper Weight (>=3232 grams)	72 (79.1%)	74 (68.5%)	68 (70.1%)	214 (72.3%)	0.21
Lower Weight (< 3232 grams)	19 (20.9%)	34 (31.5%)	29 (29.9%)	82 (27.7%)	
Missing	0	0	1	1	
Offspring Gestational Age					
Mean (SD)	40.7 (1.8)	40.0 (1.9)	39.9 (1.8)	40.2 (1.9)	0.005
Range	36.0 - 45.0	32.0 - 45.0	36.0 - 44.0	32.0 - 45.0	
Missing	5	1	1	7	
Offspring Gestational Age					
Full Term	83 (96.5%)	100 (93.5%)	86 (89.6%)	269 (93.1%)	0.181
Preterm	3 (3.5%)	7 (6.5%)	10 (10.4%)	20 (6.9%)	
Missing	5	1	1	7	

Table 3:

Risk ratio estimates for low birthweight by paternal PBB/PCB tertiles, dichotomized at 25th percentile for birthweight (<3232 grams)

PBB exposure level (range in ppb) (n=below/above cut point and total)	**Unadjusted RR (95% CI) for birthweight <3232 grams[1]**	**Adjusted RR (95% CI) for birthweight <3232 grams[2]**	**Adjusted RR (95% CI) for birthweight <3232 grams including BMI[4]**
PBB Tertile 1 (<LOD-3.0) (n=23/97, 120)	1.00 (referent)	1.00 (referent)	1.00 (referent)
PBB Tertile 2 (4.0-8.0) (n=28/70, 98)	1.62 (0.86, 3.03)	1.67 (0.93, 2.99) *	1.50 (0.86, 2.65)
PBB Tertile 3 (9.0-1744.0) (n=38/80, 118)	1.76 (1.00, 3.10) **	2.06 (1.12, 3.79) **	1.69 (0.94, 3.05) *
PCB exposure level (range in ppb) (n=below/above cut point and total)	**Unadjusted RR (95% CI) for birthweight <3232 grams[1]**	**Adjusted RR (95% CI) for birthweight <3232 grams[3]**	**Adjusted RR (95% CI) for birthweight <3232 grams including BMI[5]**
PCB Tertile 1 (<LOD-5.0) (n=19/72, 91)	1.00 (referent)	1.00 (referent)	1.00 (referent)
PCB Tertile 2 (6.0-8.0) (n=34/74, 108)	1.73 (0.94, 3.18) *	1.47 (0.79, 2.75)	1.24 (0.68, 2.25)
PCB Tertile 3 (9.0-85.0) (n=29/68, 97)	1.68 (0.92, 3.09) *	1.34 (0.70, 2.54)	1.21 (0.66, 2.24)

RR=risk ratio, CI=confidence interval

[1]Model adjusted for offspring born to the same father

[2]Model adjusted for offspring born to the same father, maternal PBB concentration, offspring gestational age and sex, paternal age at offspring birth, paternal age at PBB exposure, and paternal education

[3]Model adjusted for offspring born to the same father, maternal PCB concentration, offspring gestational age and sex, paternal age at offspring birth, and paternal education

[4]Sensitivity analysis adjusted for offspring born to the same father, maternal PBB concentration, offspring gestational age and sex, paternal age at offspring birth, paternal age at PBB exposure, paternal education, and paternal BMI

[5]Sensitivity analysis adjusted for offspring born to the same father, maternal PCB concentration, offspring gestational age and sex, paternal age at offspring birth, paternal education, and paternal BMI

*p<0.1

**p<0.05

Table 4:

Risk ratio estimates for preterm birth by paternal PBB/PCB tertiles preterm gestational age (<37 weeks)

PBB exposure level (range in ppb) (n=below/above cut point and total)	**Unadjusted RR (95% CI) for gestational age <37 weeks[1]**	**Adjusted RR (95% CI) for gestational age <37 weeks[2]**	**Adjusted RR (95% CI) for gestational age <37 weeks including BMI[4]**
PBB Tertile 1 (<LOD-3.0) (n=7/109, 116)	1.00 (referent)	1.00 (referent)	1.00 (referent)
PBB Tertile 2 (4.0-8.0) (n=9/87, 96)	0.97 (0.88, 1.07)	0.99 (0.91, 1.08)	0.99 (0.91, 1.09)
PBB Tertile 3 (9.0-1744.0) (n=5/110, 115)	1.02 (0.96, 1.09)	1.02 (0.95, 1.09)	1.02 (0.94, 1.11)
PCB exposure level (range in ppb) (n=below/above cut point and total)	**Unadjusted RR (95% CI) for gestational age <37 weeks[1]**	**Adjusted RR (95% CI) for gestational age <37 weeks[3]**	**Adjusted RR (95% CI) for gestational age <37 weeks including BMI[5]**
PCB Tertile 1 (<LOD-5.0) (n=3/83, 86)	1.00 (referent)	1.00 (referent)	-
PCB Tertile 2 (6.0-8.0) (n=7/100, 107)	0.97 (0.89, 1.05)	0.97 (0.90, 1.05)	-
PCB Tertile 3 (9.0-85.0) (n=10/86, 96)	0.93 (0.85, 1.01)	0.93 (0.84, 1.01)	-

RR=risk ratio, CI=confidence interval

[1] Model adjusted for offspring born to the same father

[2] Model adjusted for offspring born to the same father, maternal PBB concentration, offspring sex, paternal age at offspring birth, paternal age at PBB exposure, and paternal education

[3] Model adjusted for offspring born to the same father, offspring sex

[4] Model adjusted for offspring born to the same father, maternal PBB concentration, offspring sex, paternal age at offspring birth, paternal age at PBB exposure, paternal education, and paternal BMI

[5] Model did not converge due to small sample size

* p<0.1

** p<0.05

Table 5:

Beta coefficients for change in birthweight by paternal PBB with covariates and BMI sensitivity analysis

	Birthweight (g)				Birthweight (g)			
	Coefficient	**95% C.I.**		**p-value**	**Coefficient**	**95% C.I.**		**p-value**
Log Paternal PBB (<54.6 ppb) (n=324)	−57.48	−136.07	21.11	0.15	−31.42	−116.15	53.32	0.47
Log Paternal PBB (>54.6 ppb) (n=12)	370.25	220.27	520.23	<0.001	316.62	157.79	475.45	<0.001
Gestational Age (Weeks)	65.32	32.32	98.31	<0.001	65.86	32.36	99.36	<0.001
Log Maternal PBB (ppb)	−39.55	−110.21	31.11	0.27	−40.67	−112.67	31.32	0.27
Offspring Sex[1]								
Male	191.12	80.70	301.53	<0.001	197.73	84.57	310.89	<0.001
Paternal Age at Offspring Birth[2]								
>34 Years Old	−21.19	−268.45	226.08	0.87	−47.68	−305.58	210.21	0.72
Age at PBB Exposure (years)	10.57	−11.53	32.67	0.35	10.68	−12.12	33.48	0.36
Paternal Education[3]								
>High School Level of Education	112.60	−11.27	236.47	0.07	109.71	−15.18	234.60	0.09
Paternal BMI[4]								
Overweight	-	-	-	-	103.55	−46.74	253.84	0.18

[1] Referent category - Female

[2] Referent category <= 34 years old

[3] Referent category <= High School Level of Education

[4] Referent category – Healthy or Underweight BMI

Table 6:

Beta coefficients for change in birthweight by paternal PCB level with covariates and BMI sensitivity analysis

	Birthweight (g)				Birthweight (g)			
	Coefficient	**95% C.I.**		**p-value**	**Coefficient**	**95% C.I.**		**p-value**
Log Paternal PCB (ppb)	−101.01	−212.93	10.91	0.08	−117.41	−223.61	−11.22	0.03
Gestational Age (Weeks)	43.80	8.64	78.97	0.01	46.28	11.45	81.11	0.01
Log Maternal PCB (ppb)	−19.44	−160.50	121.61	0.79	−35.30	−170.54	99.94	0.61
Offspring Sex[1]								
Male	145.94	34.27	257.61	0.01	159.14	47.47	270.82	0.01
Paternal Age at Offspring Birth[2]								
>34 Years Old	25.63	−190.80	242.06	0.82	−24.89	−233.86	184.09	0.82
Paternal Education[3]								
>High School Level of Education	90.28	−36.52	217.09	0.16	58.02	−66.06	182.09	0.36
Paternal BMI[4]								
Overweight	-	-	-	-	241.06	102.42	379.69	<0.001

[1]Referent category - Female

[2]Referent category <= 34 years old

[3]Referent category <= High School

[4]Referent category – Healthy or Underweight BMI

Table 7:

Beta coefficients for change in gestational age by paternal PBB level with covariates and BMI sensitivity analysis

	Gestational age (weeks)				Gestational age (weeks)			
	Coefficient	**95% C.I.**		**p-value**	**Coefficient**	**95% C.I.**		**p-value**
Log Paternal PBB (<54.6 ppb)	0.04	−0.20	0.28	0.74	0.03	−0.24	0.31	0.81
Log Paternal PBB (>54.6 ppb)	−0.07	−0.55	0.41	0.77	−0.03	−0.53	0.47	0.91
Log Maternal PBB (ppb)	−0.02	−0.27	0.23	0.87	−0.03	−0.29	0.23	0.82
Offspring Sex[1]								
Male	−0.09	−0.45	0.28	0.65	−0.01	−0.38	0.37	0.97
Paternal Age at Offspring Birth[2]								
>34 Years Old	−0.39	−1.12	0.32	0.28	−0.42	−1.16	0.33	0.56
Age at PBB Exposure (years)	−0.01	−0.06	0.03	0.58	0.20	−0.25	0.65	0.39
Paternal Education[3]	0.20	−0.25	0.65	0.38	0.20	−0.25	0.65	0.39
>High School Level of Education								
Paternal BMI[4]								
Overweight	-	-	-	-	−0.06	−0.54	0.43	0.82

[1] Referent category - Female

[2] Referent category <= 34 years old

[3] Referent category <= High School Level of Education

[4] Referent category – Healthy or Underweight BMI

Table 8:

Beta coefficients for change in gestational age by paternal PCB level with covariates and BMI sensitivity analysis

	Gestational age (weeks)				Gestational age (weeks)			
	Coefficient	**95% C.I.**		**p-value**	**Coefficient**	**95% C.I.**		**p-value**
Log Paternal PCB (ppb)	−0.37	−0.76	0.03	0.07	−0.48	−0.85	−0.11	0.01
Log Maternal PCB (ppb)	−0.06	−0.46	0.35	0.79	−0.06	−0.47	0.35	0.77
Offspring Sex[1]								
Male	−0.12	−0.52	0.27	0.54	−0.03	−0.42	0.37	0.90
Paternal Age at Offspring Birth[2]								
>34 Years Old	−0.46	−1.09	0.17	0.15	−0.49	−1.13	0.14	0.13
Paternal Education[3]								
>High School Level of Education	0.04	−0.41	0.49	0.86	0.00	−0.44	0.44	1.00
Paternal BMI[4]								
Overweight	-	-	-	-	−0.08	−0.52	0.35	0.71

[1] Referent category - Female

[2] Referent category <= 34 years old

[3] Referent category <= High School Level of Education

[4] Referent category – Healthy or Underweight BMI