

A cohort study of the association between secondary sex ratio and parental exposure to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB)

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Abstract

Background: Polybrominated biphenyl (PBB), a brominated flame retardant, was accidentally mixed into animal feed in Michigan (1973-1974) resulting in human exposure through consumption of contaminated meat, milk and eggs. Beginning in 1976 individuals who consumed contaminated food products were enrolled in the Michigan Long-Term PBB Study. This cohort presents a unique opportunity to study the association between parental exposures to PBB and offspring sex ratio.

Methods: We identified offspring of female PBB cohort participants born between 1975 and 2005 and obtained electronic birth records for those born in the state of Michigan. We linked this information to parental serum PBB and PCB concentrations collected at enrollment into the cohort. We modelled the odds of a male birth with generalized estimating equations accounting for the non-independence of siblings born to the same parents. We explored potential confounders: parental age and education at offspring's birth, parental body mass index at cohort enrollment, birth order and year of offspring's birth. Separate and combined effects of maternal or paternal exposures were modelled in relation to the odds of a male birth.

Results: The overall proportion of male offspring among 1,392 live births to cohort mothers was 0.542. This is significantly higher than the national male proportion of 0.514 (binomial test: $p=0.02$). When both parents were in the cohort ($n=300$), we found increased odds of a male birth with moderate and high maternal and paternal combined PBB exposure (OR=1.5, 95% CI: 1.1-2.2) and with paternal PBB exposure alone (OR=1.6, 95% CI: 0.8-3.1), although this was not significant. Maternal PBB exposure alone was not associated with increased odds of a male birth. In addition, there was no association with parental PCB exposure (parents' exposure modelled separately or combined) on the odds of a male birth.

Conclusions: This study adds to the body of literature on secondary sex ratio and exposure to environmental contaminants. In this population, parental exposure to PBBs was associated with increased odds of a male birth. Further research is needed to corroborate these findings and shed light on the biological mechanisms that influence the secondary sex ratio.

Background

The secondary sex ratio, defined as the ratio of males to females at birth, has generally been held to be about 104 to 106 males to 100 females world-wide. Studies have suggested that this ratio has declined in the United States and abroad [1-5]. A number of factors such as maternal and paternal age and hormone levels, birth order, plurality, race/ethnicity, environmental factors, exposure to endocrine disrupting chemicals, and differential fetal death have been implicated (reviewed in [4, 6, 7]). The Michigan Long-Term PBB Study presents a unique opportunity to study the association of parental exposures to halogenated organics and the secondary sex ratio of their offspring.

Polybrominated biphenyl (PBB), a brominated flame retardant, was used in the United States in the 1970's and added to commercial products such as plastics, textiles, and electronics. The manufacture of PBB was discontinued in the United States in 1976 following a large-scale contamination incident. A company that manufactured two products (FireMaster, a fire retardant mixture of PBBs and NutriMaster, a feed-grade magnesium oxide supplement for cattle) inadvertently delivered FireMaster to Michigan Farm Bureau Services where it was mixed into animal feed that was shipped to feed mills across the state. The PBB-contaminated feed was ingested by animals, and ultimately by the Michigan residents through meat, milk, eggs and other animal products. Most Michigan residents had low but detectable levels of PBB in their serum; however, high PBB levels were detected in families residing on quarantined farms which received the contaminated feed and in neighboring families who purchased food from these farms. Nearly 4,000 of these individuals were enrolled in a cohort study established in 1976 by the Michigan Department of Public (now Community) Health to track the long-term health effects of PBB exposure [8]. This cohort has been followed prospectively since that time, and by design includes

information linking family members. Details of the incident and earlier studies have been described elsewhere [9-11].

PBBs belong to a class of chemicals known as persistent organic pollutants. They are structurally similar to polychlorinated biphenyls (PCBs) [12]. The estimated half-life of PBB in humans is about 10.8 years [13], and ranges from 13-29 years in females [14]. PBBs are lipophilic and can be transferred *in utero* and through breast milk [15, 16]. As a suspected endocrine disruptor, a number of studies have been conducted in this cohort investigating associations between PBB and reproductive health outcomes [17-21]. Studies that have examined the association of environmental pollutants on the secondary sex ratio have had mixed results. A significant decline in male births was found among Seveso, Italy residents accidentally exposed to high levels of dioxins [22]. Multiple studies have reported similar findings with exposures to dioxins, PCBs and related environmental pollutants [23-28], while studies in other populations have suggested increases [27, 29] or little if any associations of environmental pollutants on the sex ratio [30-32]. The present study aims to add to the body of literature on the secondary sex ratio in relation to PBB and PCB exposure.

Methods

Study Population

The participants of the present study are the offspring of female PBB cohort members born during 1975-2005, potentially exposed to maternal PBB *in utero*. Births before 1975 were excluded since these offspring could have directly ingested contaminated food products. Offspring were identified by matching demographic information of first-generation female cohort members (born before July 1973) to maternal information in the Michigan electronic birth files. These matches were verified

using cohort registry records, and additional births were identified from cohort infant enrollment records. We could not obtain electronic birth records for many offspring born outside Michigan so these births were excluded. Paternal information was available in the electronic birth files for offspring born in 1989 or later. For earlier births, father's name and age were determined from a manual search of cohort registry records and checked against paper copies of the birth certificate. The studies from which these data were derived have undergone human subjects review and approval by IRBs at Michigan Department of Community Health and Emory University and informed consent was obtained from all participants.

Exposure assessment

The Michigan cohort was predominately exposed to a mixture of PBBs that contained mostly PBB-153 (60%) [12]. PBB-153, or 2,2',4,4',5,5'-hexabromobiphenyl, was measured in serum samples collected from PBB cohort participants by the Michigan Department of Community Health Bureau of Laboratories. The serum samples were first extracted with 1:1 petroleum ether-ethyl or 1:1 hexane-ether, and then passed through either a Florisil or Florisil and silica gel column. PBBs were detected and quantitated using gas chromatography with electron capture detection. The coefficients of variation ranged from 7.1% to 14.0% [33, 34] and the limit of detection (LOD) was 1.0 micrograms per liter ($\mu\text{g/L}$). PCB determination was based on Aroclor 1254. The coefficients of variation ranged from 12% to 30% [33, 34] and the LOD was 5 $\mu\text{g/L}$. For most of the parents, the serum specimens were collected in 1976-1979 when they were enrolled in the cohort. Around 1979 the Bureau of Laboratories switched to the Double Determination method which measured both total PBB and PCB concentrations in the same serum sample, so both values are available for most cohort participants (85%). All serum samples were collected from non-fasting participants, and lipids were not measured.

As a secondary estimate of PBB exposure, we calculated an estimated maternal PBB at the time of conception of the offspring using a decay model. This estimation of PBB exposure accounts for time since the mother's PBB exposure, along with maternal factors of age, body mass index (BMI), smoking history, parity, and breast-feeding history [35]. However, not all mothers in the present study had their enrollment PBB concentration measured before the birth of their offspring. Thus, the decay model extrapolated backwards for those offspring born before their mother's PBB was taken. We did not estimate paternal PBB at conception because no such decay model has been established for the male participants in the PBB cohort.

Statistical data analysis

Information from the electronic birth file used in this study included: offspring's sex, mother's age at offspring's birth (as a continuous variable and in categories at the 90th percentile of <33 and \geq 33 years), mother's education at offspring's birth (\leq HS and >HS), birth order (categorized as first-born and non first-born), plurality (for exclusion of multiple births) and gestational age (for calculation of conception date); and for births after 1988, father's age at offspring's birth (as a continuous variable and in categories at the 90th percentile of <36 and \geq 36 years), father's education at offspring's birth (\leq HS and >HS), and father's race (for exclusion of non-white fathers), and mother's use of alcohol and tobacco during pregnancy.

Parental information obtained from historic records of the Long-Term PBB Study included: earliest serum PBB and PCB exposure measurements and height and weight at enrollment to calculate body mass index (BMI). Analyses that included BMI were restricted to females at least 16 years old at enrollment in the cohort and males at least 19 years old at enrollment in the cohort, accounting for

later growth spurts that often occur in males. BMI was categorized based on standard classifications from CDC of under ($< 18.5 \text{ kg/m}^2$), normal ($18.5\text{-}24.9 \text{ kg/m}^2$) and overweight ($\geq 25 \text{ kg/m}^2$) and also as two-level variables for underweight versus normal and overweight combined, and overweight versus normal and underweight combined.

Additional maternal information was obtained from structured telephone interviews conducted with female cohort members during 1997-1998 and 2003-2006 which collected detailed reproductive, hormonal, and lifestyle information. From the telephone interviews we obtained data on months of unprotected intercourse (1-3 months and >3 months) and the use of any medical interventions to achieve that pregnancy (no/yes); and when not available in the electronic birth file, maternal information on offspring's gestational age and birth order.

We categorized PBB and PCB concentrations into three groups because of their skewed distributions. For PBB, we grouped exposures as $\leq \text{LOD}$ ($\leq 1 \text{ }\mu\text{g/L}$), $>\text{LOD}$ up to the median and \geq the median of $4 \text{ }\mu\text{g/L}$ for maternal PBB and $6 \text{ }\mu\text{g/L}$ for paternal PBB. In addition, we considered exposure categories of $\leq \text{LOD}$ ($\leq 1 \text{ }\mu\text{g/L}$), $>\text{LOD}$ up to the 90th percentile and $\geq 90^{\text{th}}$ percentile of $14 \text{ }\mu\text{g/L}$ for maternal PBB and $21 \text{ }\mu\text{g/L}$ for paternal PBB. We created similar groupings for PCB exposure where the medians were $8 \text{ }\mu\text{g/L}$ and $9 \text{ }\mu\text{g/L}$ and the 90th percentiles were $9 \text{ }\mu\text{g/L}$ and $13 \text{ }\mu\text{g/L}$ for mothers and fathers, respectively.

The earlier births were more likely from parents who were both enrolled in the cohort. This is because most cohort members were enrolled as part of a household that lived or purchased food from a quarantined farm. Females that were adults at the time of enrollment into the cohort were more likely to be enrolled as the wife and mother of a household. Subsequent offspring of these females

born mostly in the 1970's and 1980's would likely have the enrolled husband as their father. However, for females enrolled in the cohort as children, it was unlikely that they remained on a quarantined farm as adults and had offspring from a father that also grew up on a quarantined farm. Therefore, we could only analyze paternal exposures in offspring born during 1975-1988. To account for this temporal effect of fathers' in the cohort, we restricted the models with maternal exposures to the same time period of births (1975-1988) and adjusted all models for year of offspring's birth.

All bivariate and multivariate analyses were performed using generalized estimating equations (GEE) because our study population included up to five siblings. We first assessed confounding with unadjusted GEE models relating each covariate to the odds of male sex and with PBB or PCB exposure. Then in multivariate analyses, we ran a series of models with potential confounders and maternal or paternal exposure in relation to the odds of a male birth. We also examined the association of maternal estimated PBB at conception, for mothers who participated in the telephone interviews. Covariates were removed sequentially using backward elimination and were retained if the main exposure odds ratios changed by at least ten percent. To examine if there was a combined association of maternal and paternal exposures on the odds of a male birth, we created a dichotomous variable of high parental exposure (with each parent having either moderate or high levels) and compared this combined group to the referent group (including at least one parent with low levels). All analyses were performed using SAS v9.2 [36].

Results

Population characteristics

In total, we identified 1,555 offspring of PBB cohort mothers from linkage with electronic birth records. Of these, 218 had fathers' identified from the electronic birth records who were also cohort participants. An additional 148 offspring had fathers in the PBB cohort who were identified only from cohort registry records, giving a total of 366 offspring with fathers in the PBB cohort.

Offspring were excluded from the study for the following reasons: no maternal PBB measurement (n=116); father's race missing or listed as non-white on the offspring's birth record (n=9); and non-singleton births (n=38). Thus, our final sample included 1,392 Michigan born offspring to PBB cohort mothers during 1975-2005 (n=865 born during 1975-1988). The overall proportion male among these offspring with potential in utero PBB exposure was 0.542 (corresponding sex ratio=1.18). This is significantly higher than the national male proportion [4] of roughly 0.514 (binomial test: p=0.02).

PBB and PCB concentrations

The mean age of mother's during the PBB exposure period (based on age in 1973) was 14 years (range: infancy-38 years). Fathers' mean age during the PBB exposure period was 24 years (range: 13-61 years). In general, fathers had higher PBB and PCB levels than the mothers. The median serum PBB concentration was 4 µg/L for mothers and 6 µg/L for fathers (maternal PBB range : < LOD-1490 µg/L; 16% < LOD; paternal PBB range : < LOD-1744 µg/L; 5% < LOD). The median serum PCB concentration was 8 µg/L for mothers and 9 µg/L for fathers (maternal PCB range : < LOD-78 µg/L; 45% < LOD; paternal PCB range : < LOD-85 µg/L; 16% < LOD). As shown in Figure 1, there is a positive relationship between mothers and fathers log-transformed exposure concentrations of both PBB and PCB. The relationship appears stronger with PBB. In addition, PCB concentrations were lower than PBB, as expected, since the duration of exposure to PCB was over a continuous time period rather than one year time period, like the PBB exposure incident.

Association with sex ratio

Table 1, gives descriptive characteristics and odds ratios for a male birth among offspring born from 1975 through 2005 whose mothers' were in the cohort. The odds of a male birth decreased slightly with older maternal or paternal age, although these effects were not significant (OR=0.8, 95% CI: 0.6-1.1). High paternal BMI at enrollment was associated with an increase in the odds of a male birth (OR=1.4, 95% CI: 1.0-2.1). Tobacco use during pregnancy, which was not collected for pre-1989 births, was associated with a decrease in the odds of a male birth (OR=0.5, 95% CI: 0.3-0.9). Other covariates such as age during the PBB exposure period, maternal BMI at enrollment, maternal or paternal education at offspring's birth, months of unprotected intercourse to achieve the pregnancy, birth order, medical interventions to achieve the pregnancy, and alcohol use during pregnancy showed no association with the odds of a male birth. Among the subset of 865 offspring born to cohort mothers during 1975-1988, the associations of the above variables with the odds of a male birth were similar.

Table 2 presents the proportion of male births among the offspring born during 1975-1988 when both parents were in the cohort (n=300). There was a significant increase in the proportion of males in two combinations of parental exposures: 1) where the mother and father both had high PBB levels (high maternal PBB ≥ 4 $\mu\text{g/L}$, high paternal PBB ≥ 6 $\mu\text{g/L}$; proportion male=0.60); and 2) where one of the parents had moderate PBB levels and the other parent had high PBB levels (moderate maternal PBB $>1-4$ $\mu\text{g/L}$, moderate paternal PBB $>1-6$ $\mu\text{g/L}$; proportion male=0.54 to 0.62). In a multivariate model, this corresponded to an increased odds of a male birth (OR=1.5, 95% CI: 1.1-2.2) among moderate and high combined parental exposure when adjusted for year of offspring's birth, paternal age and paternal BMI at enrollment. Separate models of maternal and paternal PBB

exposure among offspring born during 1975-1988 are presented in Table 3. There was no association between maternal enrollment PBB exposure alone and the odds of a male birth (Table 3, Model 1) or for maternal estimated PBB exposure alone (estimated PBB >1–<4 µg/L OR=1.3; 95% CI: 1.0-1.9; estimated PBB≥4 µg/L OR=1.1, 95% CI: 0.7-1.6) when adjusted for year of offspring's birth. When maternal PBB levels were categorized at the 90th percentile, the odds ratios were not appreciably different. For paternal PBB exposure alone, there was a non-significant increase in the odds of a male birth when adjusted for year of offspring's birth, paternal age and paternal BMI at enrollment (Table 3 Model 2, OR=1.6, 95% CI: 0.8-3.1). For the 90th percentile of paternal PBB levels, the odds of a male birth were similar and did not reach statistical significance (paternal PBB >1–<21 µg/L OR=1.6, 95% CI: 0.9-3.0; paternal PBB ≥21 µg/L OR=1.3, 95% CI: 0.6-2.8). For PCB exposure, the combination of parents' exposure was not associated with the odds of a male birth when categorized similarly as Table 2 for PBB exposure. Further, in separate models of maternal and paternal PCB exposure, there was no association of either parent's exposure with the odds of a male birth (Table 4).

Discussion

Among this Michigan cohort, the overall proportion of male births was 0.542 for offspring with potential *in utero* PBB exposure. This was significantly higher than the national male proportion of 0.514 [4] and higher than that of Michigan births over the same time period (range: 0.510-0.516, Source:1973-2006 Live Birth Files, Vital Records and Health Data Development Section, MDCH). When we considered the small subset of births when both parents were in the cohort, we found significant increased odds of a male birth with combined moderate and high maternal and paternal PBB exposures. Paternal PBB exposure alone was associated with a non-significant increased odd of a male birth. However, there was no association with maternal PBB exposure alone. To our

knowledge, this is the first study to investigate the relationship of secondary sex ratio and PBB exposure.

For PCB exposure, our findings did not support an association between maternal or paternal PCB exposure and the odds of a male birth. Other studies of PCB exposure in relation to the sex ratio have reported with mixed findings. A Michigan Great Lakes study measured PCB levels in sport fish consuming families and found no association with maternal PCB exposure on offspring's sex, but an increase in the sex odds ratio for paternal PCB exposure [29]. Conversely, a study by a consortium of Great Lakes fish consuming populations found a decrease in the sex ratio of offspring with maternal PCB exposure and no association with paternal PCB exposure [24]. A study of women participants in the New York Anglers Cohort attempting pregnancy measured preconception PCB levels and found that while the odds of a male birth decreased with maternal anti-estrogenic PCBs, the odds increased with maternal estrogenic PCBs [27]. However, these results were not significant and the sample size in this study was small. A larger study of participants from the Child Health and Development Study measured PCB levels during pregnancy and reported a decrease in sex ratio with increased maternal PCB levels [23]. In three of the above studies the predominant exposure was via consumption of sport caught Great Lakes fish, whereas Hertz-Picciotto et al. [23] and our study did not involve a population selected for fish consumption. Since different exposure sources may contain different congeners, the PCB congeners these populations were exposed to were likely different [37, 38]. In addition, lower levels of PCB exposure are seen in non-fish consuming populations, as in the Michigan cohort where PCB levels are similar to those in the general population [39].

Comparisons between the above mentioned studies are further complicated by the different time periods of when the births occurred. In the Hertz-Picciotto et al. [23] study and the Karmaus et al. study [29], births spanned from the 1960's to the early 1970's. The Karmaus et al. [29] study also included later births up to the year 2000, while the Weisskopf et al. [24] study included births from 1970-1995. In contrast, the Taylor et al. [27] study included births from women trying to achieve a pregnancy sometime after 1997. For our study population, births ranged from 1975-2005. Since PCB levels have been decreasing over the years [40], it is likely that the earlier births were exposed to higher parental PCB levels than the later births. However, we were unable to adjust for any changes in PCB levels with time because we used maternal and paternal PCB levels collected at enrollment into the PBB cohort.

We considered several covariates and their association with the odds of a male birth. We found a significant association between high paternal BMI at enrollment and increased odds of a male birth. We did not find this same association with maternal BMI at enrollment. However, we cannot rule out the potential for bias, given that weight and height were self-reported by participants. In this population, BMI has been shown to slow the decay of PBB [14, 35]. Thus, it is possible that the heavier fathers at enrollment into the cohort had higher levels of PBB at the time of their offspring's conception. The association between parental weight and sex ratio has been reported in earlier studies. It has been hypothesized that heavier parents are suspected to have males [41]. Cagnacci et al. found mothers with low pre-pregnancy weight to have a reduced sex ratio, although they did not specifically measure BMI [42]. Taylor et al. [27] found a higher proportion of males with higher maternal BMI [27]. For maternal tobacco use during pregnancy, we found increased odds of a female birth. This is consistent with findings in other studies [43, 44]. However, maternal tobacco use during pregnancy was not available for pre-1989 birth records and we did not have any

information on paternal smoking or smoking history around the time of conception for either parent to consider in our analyses.

Our sample included over a thousand offspring born to mothers in the cohort during 1975-2005, but only 300 offspring born to fathers in the cohort. The earlier births (1975-1988) were more likely from parents who were both enrolled in the cohort. In addition, our results may have been biased because among the offspring born to both parents in the cohort, the mothers and fathers PBB levels were higher in comparison to the subset of mothers where the father was not a cohort participant. We were further limited in that we only had fathers' enrollment PBB levels and we did not have a male decay model to estimate paternal PBB concentrations. Thus, we may have overestimated paternal exposure for offspring born farthest from when their father's PBB sample was taken. For maternal PBB exposure, we estimated maternal PBB concentration at conception for 79% (681/865) of the offspring born during 1975-1988, using a decay model that accounted for factors such as maternal BMI and breastfeeding history, which have been shown to affect the mother's body burden of PBB over time [14, 35]. For 116 offspring that were born before their mothers PBB measurement was taken, the decay model was used to estimate exposure backwards. When we repeated our model excluding these offspring, our results did not change (maternal estimated PBB >1- 4 µg/L OR=1.3; 95% CI: 0.9-1.9; maternal estimated PBB ≥ 4 µg/L OR=1.0, 95% CI: 0.7-1.5).

The results of our study were not consistent with the multiple studies that have found decreases in the sex ratio [22-28]. We found an increase in the odds of a male birth for paternal PBB exposure alone which is consistent with several studies that have found associations with fathers exposure but not necessarily mothers exposure in relation to the sex ratio (reviewed in [6]). However, in our study determining the association between a particular parent's exposure and sex ratio was complicated

because the PBB exposure levels of mothers and fathers from the same family were correlated ($r=0.64$, $p<0.001$). This has also been shown in an earlier study of Michigan dairy farmers exposed to PBBs [45]. Additional research is needed to clarify whether a combination of parents' exposure or paternal or maternal exposure alone contributes to a skewed sex ratio.

Conclusions

Our results add to the body of literature on the possible effects of environmental pollutants on the sex ratio. This study includes a well-defined period of PBB exposure, and over 30 years of birth record and cohort registry data from the long-term study. In this population, parental PBB exposure (paternal PBB exposure alone or combined maternal and paternal PBB exposure) was associated with increased odds of a male birth. Further research is needed to corroborate these findings and shed light on the biological mechanisms that influence the secondary sex ratio.

Abbreviations: PBB – polybrominated biphenyl, PCB – polychlorinated biphenyl, BMI – body mass index, µg/L – micrograms per liter, LOD – limit of detection

Competing interests: The authors declare that they have no competing interests for this work.

Author’s contributions: All authors have made substantial contribution to this study and to the writing and editing of this manuscript. Additional contributions are as follows: MM, LC and CS designed the study and provided historical cohort data; JW retrieved and matched cohort records and verified offspring/parental relationships; MT and AB performed statistical analyses.

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Figure Legend

Figure 1. Relationship between parents' serum PBB and PCB concentrations. Spearman Correlation coefficients: PBB, $r=0.64$; PCB, $r=0.19$

Table 1. Characteristics of Michigan births from parents in the Michigan PBB Long-Term Study and unadjusted odds ratios for a male birth (births 1975-2005; n=1392)

Characteristic	N %	Unadjusted OR (95% CI)
Maternal age at offspring's birth (years)		
< 33	1218 (88)	1.00
≥ 33	174 (12)	0.82 (0.60, 1.12)
Paternal age at offspring's birth (years)		
< 36	1172 (87)	1.00
≥ 36	172 (13)	0.82 (0.59, 1.13)
Maternal education at offspring's birth		
≤ HS	711 (51)	1.00
> HS	673 (49)	1.0 (0.82, 1.23)
Paternal education at offspring's birth		
≤ HS	741 (56)	1.00
> HS	590 (44)	1.08 (0.88, 1.33)
Maternal BMI at enrollment (kg/m ²) [^]		
< 18.5	70 (9)	1.02 (0.64, 1.64)
18.5-25	541 (68)	1.00
> 25	183 (23)	0.98 (0.74, 1.30)
Paternal BMI at enrollment (kg/m ²) [^]		
< 18.5	4 (1)	0.82 (0.25, 2.67)
18.5-25	173 (57)	1.00
> 25	129 (42)	1.42 (0.97, 2.09)
Months unprotected intercourse to achieve pregnancy ^ξ		
1-3 months	526 (51)	1.00
>3 months	359 (35)	1.11 (0.85, 1.44)
Birth order		
First-born	489 (35)	1.00
Non first-born	903 (65)	1.09 (0.87, 1.36)
Medical interventions to achieve pregnancy		
No	396 (95)	1.00
Yes	21 (5)	0.91 (0.38, 2.18)
Maternal tobacco use during pregnancy [*]		
No	469 (90)	1.00
Yes	53 (10)	0.52 (0.29, 0.92)

Maternal alcohol use during pregnancy*

No	515 (99)	1.00
Yes	5 (1)	1.34 (0.23, 7.69)

[^] Maternal enrollment BMI restricted to mothers' ages ≥ 16 and fathers' ages > 18 years

^ξ Mothers who reported "doing something to prevent the pregnancy" were not asked the follow-up question of how many months of unprotected intercourse it took to achieve pregnancy (for n=148)

* Information on maternal tobacco and alcohol use during pregnancy was not collected for pre-1989 births

Table 2. Proportion of male births among parents in the Michigan PBB Long-Term Study with serum PBB measurements (births 1975-1988; n=300)

Father's PBB	Mother's PBB						Totals	
	$\leq 1 \mu\text{g/L}$		$> 1 - < 4 \mu\text{g/L}$		$\geq 4 \mu\text{g/L}$		Proportion	
	N	Male	N	Male	N	Male	N	Male
$\leq 1 \mu\text{g/L}$	19	0.53	4	0.50	2	0.00	25	0.48
$> 1 - < 6 \mu\text{g/L}$	69	0.51	45	0.56	21	0.62	135	0.54
$\geq 6 \mu\text{g/L}$	18	0.39	41	0.54	81	0.60	140	0.56
Totals	106	0.49	90	0.54	104	0.60	300	0.54

Table 3. Odds ratios (OR) for a male birth among offspring from parents in the Michigan PBB Long-Term Study with serum PBB measurements (births 1975-1988)

Exposure Variable	Model 1	Model 2
	OR* (95% CI) n=865	OR* (95% CI) N=300
Maternal PBB ($\mu\text{g/L}$)		
≤ 1	1.00	
$>1 - <4$	1.22 (0.89, 1.67)	
≥ 4	1.05 (0.77, 1.43)	
Paternal PBB ($\mu\text{g/L}$)		
≤ 1		1.00
$>1 - <6$		1.58 (0.84, 3.00)
≥ 6		1.58 (0.80, 3.11)

*Maternal model adjusted for year of offspring's birth; paternal model adjusted for year of offspring's birth, paternal age and paternal BMI at enrollment

Table 4. Odds ratios (OR) for a male birth among offspring from parents in the Michigan PBB Long-Term Study with serum PCB measurements (births 1975-1988)

Exposure Variable	Model 1	Model 2
	OR* (95% CI) n=790	OR* (95% CI) N=253
Maternal PCB ($\mu\text{g/L}$)		
≤ 5	1.00	
$>5 - <8$	0.92 (0.65, 1.31)	
≥ 8	1.13 (0.83, 1.54)	
Paternal PCB ($\mu\text{g/L}$)		
≤ 5		1.00
$>5 - <9$		0.69 (0.48, 0.99)
≥ 9		1.04 (0.63, 1.72)

*Maternal model adjusted for year of offspring's birth; paternal model adjusted for year of offspring's birth, paternal age and paternal BMI at enrollment

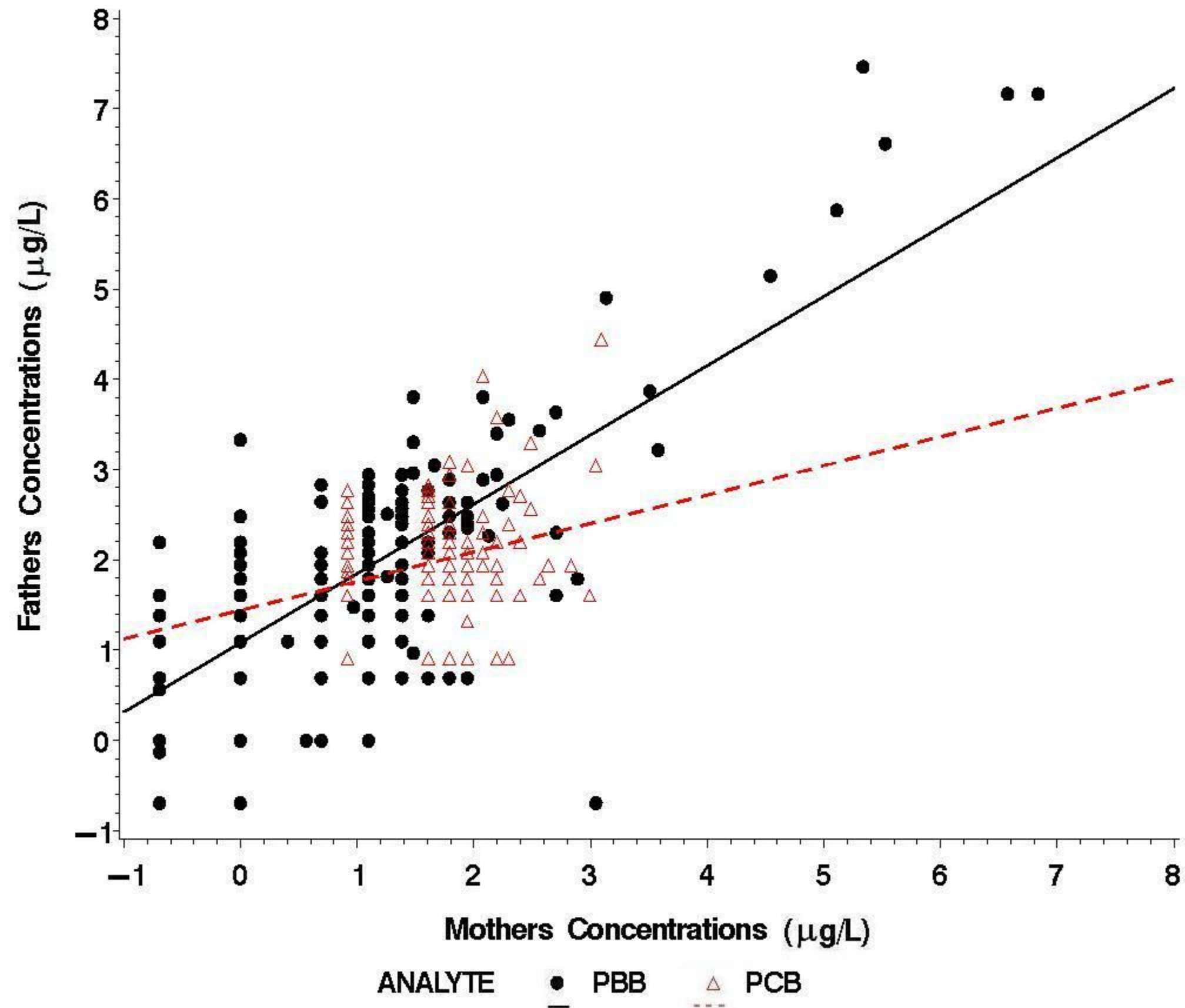


Figure 1