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Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: a cohort study

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Abstract

Background: Studies on maternal exposure to polychlorinated biphenyls (PCBs) reported inconsistent findings regarding birth weight: some studies showed no effect, some reported decreased birth weight, and one study found an increase in weights. These studies used different markers of exposure, such as measurement of PCBs in maternal serum or questionnaire data on fish consumption. Additionally maternal exposures, such as dichlorodiphenyl-dichloroethylene (DDE), which are related to PCB exposure and may interfere with the PCB effect, were rarely taken into account.

Methods: Between 1973 and 1991, the Michigan Department of Community Health conducted three surveys to assess PCB and DDE serum concentrations in Michigan anglers. Through telephone interviews with parents, we gathered information on the birth characteristics of their offspring, focusing on deliveries that occurred after 1968. We used the maternal organochlorine (OC) measurement closest to the date of delivery as the exposure. Although one mother may have contributed more than one child, serum concentrations derived from measurements in different surveys could vary for different children from the same mother. The maternal DDE and PCB serum concentrations were categorized as follows: 0 -< 5 microg / L, 5 -< 15 microg / L, 15 -< 25 microg / L, ≥25 microg / L. Using repeated measurement models (Generalized Estimation Equation), we estimated the adjusted mean birth weight controlling for gender, birth order, gestational age, date of delivery as well as maternal age, height, education, and smoking status.

Results: We identified 168 offspring who were born after 1968 and had maternal exposure information. We found a reduced birth weight for the offspring of mothers who had a PCB concentration ≥25 microg / L (adjusted birth weight = 2,958 g, p = 0.022). This group, however, was comprised of only seven observations. The association was not reduced when we excluded preterm deliveries. The birth weight of offspring was increased in women with higher DDE concentrations when controlling for PCBs; however, this association was not statistically significant.

Conclusion: Our results contribute to the body of evidence that high maternal serum PCB concentration may reduce the birth weight in offspring. However, only a small proportion of mothers may actually be exposed to PCB concentrations ≥25 microg / L.

Background

Polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) are ubiquitously distributed environmental contaminants. Due to their lipophilic properties and the low rate at which they are metabolized, organochlorine compounds (OC), such as PCBs and DDE, are biomagnified in the food chain and bioaccumulated within individuals [1]. Both PCBs and DDE have long half-lives; for DDE it is longer than seven years; for different PCB congeners their half-live range between 1 and 71 years [2-5]. PCBs and DDE are capable of crossing the placenta; hence, the developing human fetus of an exposed mother is considered to be at a high risk of being exposed to these compounds [6,7].

Birth weight is considered to be a predictor of a variety of adverse developments in childhood and beyond, including poor school performance, high blood pressure, cardiovascular disease, and depression [8-12]. Thus, it is important to assess whether exposure to PCBs and DDE may contribute to reduced birth weight. Investigations of PCB and DDE exposure and birth weight have produced inconsistent results. However, these studies measured exposure differently: some studies determined PCB or DDE concentrations from maternal blood [13-18], cord blood [13,14], placenta [19], or human milk samples [20-25]. Others measured exposure using consumption of contaminated fish or cooking oil [13,26-29], place of residence [30-32], or type of occupation, as an indicator of toxicant body burden [31,33].

Of the four studies that investigated regional or occupational exposure categories and PCB exposure, two were based on the frequency of low birth weight (LBW) as the outcome [31,32] and two compared mean birth weight [30,33]. Three of these four reports indicated an adverse effect of PCB exposure. Of the five research projects that employed fish consumption or contaminated cooking oil as an indicator of PCB exposure, two found a decreased mean birth weight [13,29], one a higher frequency of LBW [27], one no association [28], and one an increase in birth weight [26]. A limitation of projects that used aggregative categories to indicate exposure, such as region, occupation, and fish or contaminated cooking oil consumption, is that they cannot disentangle the effects of different organochlorine compounds such as PCBs and DDE. Of the six studies that analyzed breast milk as an approximation of intrauterine exposure to either DDE or PCBs, two found no effects of exposure to DDE or PCBs [21,24], one no association with PCBs [22], one a higher incidence of low birth weight with PCBs in girls only [20], and two a decreased birth weight related to DDE exposure [23,25]. In summary, the five exposure approximations above (region, occupation, fish or contaminated cooking oil consumption, and breast milk) reveal conflicting evidence for PCBs: seven studies found an adverse effect, whereas five did not.

Studies that assessed PCB or DDE exposure from maternal, cord blood or placentas have more consistent findings. Four out of five studies on PCBs reported an adverse effect on birth weight [13-15,19]; one did not[16]. Two other studies focused on DDE and reported a decrease in birth weight [17,18,23]. In some investigations of organochlorine contaminations, a limitation is focusing solely on one or a group of chemicals (for instance DDE or PCBs). Since we know that in humans the concentrations of different organochlorine compounds are correlated [34,35], it is possible, that the negative effect attributed to DDE is in fact due to PCBs, or vice versa.

Another line of inquiry has suggested that DDE exerts estrogenic effects, in particular p, p'-DDE [36-38]. Maternal estrogens during pregnancy have been shown to increase birth weight [39]. Hence, it is plausible that DDE may increase birth weight. The DDE effect, however, may be missed or masked by a possible opposite effect of PCBs if exposures are not separated in the analysis.

Taking the above considerations into account, we will focus on maternal serum levels and exposures to DDE and PCBs, separately. Our hypotheses are: PCBs decrease birth weight; DDE increases birth weight.

People who consume a diet with a high percentage of fish, such as sport fishermen and their families, are considered to be at greater risk of PCB and DDE exposure compared to the general population for example, people living in the Great Lakes region [40-42]. For this reason, fish eaters and their families have been the focus of many environmental and epidemiological studies. For this study we used the Michigan fish eater cohort to test our hypotheses.

Methods

Study Sample

Between 1973 and 1991, the Michigan Department of Community Health conducted three surveys to assess the serum concentration of PCBs and DDE in Michigan anglers (Great Lakes Fish Eater Study, GLFS) as described in several reports [41,43,44]. We were interested in potential effects of these toxicants in offspring. It turned out that this cohort of anglers was diverse, including a wide age range and women who never were at risk of child bearing (e.g. nuns). In this work we focus on births that occurred after 1968 in this cohort of anglers. A total of 310 female cohort members were of reproductive age after 1968 (maximum age of 45 years) and had serum organochlorine concentrations determined between 1973 and 1991. In the year 2000, we approached this cohort again. Through telephone interviews, we gathered information

on birth characteristics of their offspring, including birth weight. When interviews were scheduled, the subjects were encouraged to have their documents (birth certificates, hospital address, etc.) on hand for the appointed interview.

Additionally, in order to check the reliability of the birth weight information, we compared these parental reports with birth registry data in a subsample of female offspring who participated in an additional follow-up study. In the second generation follow-up (proportion of participation: 75%), we had 49 female offspring born after 1968, among them 42 allowed us to access their vital statistic records. The study was approved by the boards reviewing research on human subjects at Michigan State University and the Michigan Department of Community Health.

PCB and DDE determination

PCB was determined in all three surveys (1973 – 1974, 1979 – 1982, 1989 – 1991), while DDE was determined in the second and third. To compare exposures, we used those PCBs measurements based on the Aroclor 1260 standard, which measured the more highly PCB chlorinated congeners. Analyses of serum specimens were performed by the Michigan Department of Community Health (Webb-McCall packed column gas chromatography technique). The technical detection limit for PCBs was 3 μg / L and 1 μg / L for DDE.

Statistical analysis

Birth weight was the primary outcome in our study. Although one mother may have more than one child, exposure could vary for different children from the same mother. We used the measurement that was closest to the date of delivery as the maternal exposure. When investigating exposure-response relationships, there are several choices how to deal with exposure data. One is to rely on a continuous exposure. This is appropriate if there is a simple linear exposure-response relationship. A second choice is to group exposure according to their frequency into quartiles, quintiles, etc. The risk of this approach, however, is that having a skewed distribution may result in fewer higher exposures being pooled with medium levels, increasing the likelihood that adverse effects of higher exposure are masked. Another problem with using quartiles is the lack of equidistant categories. A third option is to categorize exposure levels into equidistant groups that can also facilitate addressing a potential adverse effect of higher level and a threshold effect. Since prior data showed a threshold effect for higher organochlorine levels [17,18,23], we decided to categorized maternal DDE and PCB serum concentrations as follows: 0 -< 5 μg / L, 5 -< 15 μg / L, 15 -< 25 μg / L, ≥25 μg / L. Since linearity between gestational age (in weeks) and birth weight was confirmed, we chose to use gestational age as a continuous variable. For descriptive purposes, we divided it into three categories: < 37 weeks, 37 -< 40 weeks, and ≥40 weeks. Three maternal-age groups represent women 15 – 24, 25 – 29 and > 29 years of age at the time of delivery. Educational level of the women, collected from the 1989 – 1991 GLFS questionnaires, was divided into three categories: high school or less, some college, and college graduate or higher. Since maternal height may explain birth weight [45], we also included maternal height as a confounder in the analysis. We obtained smoking status from the 1989 – 1991 GLFS questionnaire. If pregnancy occurred within the time a woman reported having smoked, we recorded smoking status as affirmative. We also included the child's year of birth to assess whether a birth cohort effect might explain different birth weight (categories were 1968 – 1972, 1973 – 1983, and after 1983).

We applied a repeated measurements model to adjust for the autocorrelation of birth weight between siblings from the same mother. Using Generalized Estimation Equations (GEE, SAS PROC MIXED) [46], we estimated the adjusted mean birth weight controlling for gender, birth order, gestational age, date of delivery as well as maternal age, height, education, and smoking status. In our repeated measurements model we treated gender, birth order, date of delivery as well as maternal age, education, and smoking status as categorical variables, while both gestational age and maternal height were treated as continuous variables.

Results

Of the Great Lakes Fish Eater Study cohort, 310 women were 45 years or younger in 1968 and could potentially give birth to a child. In the year 2000, of the 310 women, three were deceased, 73 could not be contacted, and eight did not consent to participate. With 226 women who give their consent, the proportion of participation is 72.9% (226/310). Of the 226 women, 99 gave birth between 1969 and 1995, resulting in a total of 195 offspring. Since twins usually have lower birth weight than singletons, we excluded four pairs of twins (n = 8) from our data, as well as 19 newborns with missing values for birth weight (n = 10) or educational status of the mother (n = 9). Hence, our analysis is based on 168 offspring who came from 89 mothers. Among the 168 offspring, 47.6% were boys; 28.6% were born between 1968 and 1972; 58.3% were born between 1973 and 1983; and 13.1% after 1983 (Table 1). A maternal DDE exposure equal to or larger than 25 μg / L or PCB exposure equal to or larger than 25 μg / L occurred only in a few observations (eight and seven offspring, respectively).

The proportion of boys increased with increasing organochlorine levels (Table 2), which has been reported before for this sample regarding paternal exposure [47]. Maternal

Table 1: Description of the study population

Characteristic		n = 168	%
Gender	Male	80	47.6
	Female	88	52.4
Maternal DDE (μg / L)	< 5	46	27.4
	5 -< 15	89	53.0
	15 -< 25	25	14.9
	≥25	8	4.7
Maternal PCB (μg / L)	< 5	84	50.0
	5 -< 15	66	39.3
	15 -< 25	11	6.5
	≥25	7	4.2
Parity	0	57	33.9
	1	65	38.7
	2	31	18.5
	≥3	15	8.9
Gestational age (weeks)	< 37	5	3.0
	37 -< 40	23	13.7
	≥40	140	83.3
Maternal age (years)	15 – 24	41	24.4
	25 – 29	70	41.7
	30 and older	57	33.9
Maternal height (cm)	<155	14	8.3
	155 -< 170	122	72.6
	≥170	32	19.1
Maternal education	High school	71	42.3
	College	44	26.2
	College plus	53	31.5
Maternal smoking status during pregnancy	Yes	22	13.1
	No	146	86.9
Child birth year	1968 – 1972	48	28.6
	1973 – 1982	98	58.3
	>1983	22	13.1

Table 2: Relationship between PCB, DDE, and potential confounders

	Exposure category	n	Boys (%)	Parity at before delivery (mean)	Gestational age (mean)	Maternal age at delivery (mean)	Maternal Height (mean)	Maternal education (%)			Maternal smoking during pregnancy (%)	Child birth year (%)		
								High school	College	College and higher		69-<73	73-< 83	> 83
Maternal DDE (μg / L)	< 5	46	39.1	0.9	39.8	27.6	163.4	34.8	32.6	32.6	2.2	17.4	58.7	23.9
	5 -< 15	89	48.3	1.0	39.9	28.0	163.9	45.0	15.7	39.3	15.7	24.7	62.9	12.4
	15 -< 25	25	56.0	1.3	40.2	27.6	165.6	44.0	44.0	12.0	20.0	60.0	40.0	0
	≥ 25	8	62.5	0.9	40.5	29.0	166.4	50.0	50.0	0	25.0	37.5	62.5	0
Maternal PCB (μg / L)	< 5	84	45.2	1.0	40.1	28.0	163.6	32.2	33.3	34.5	13.1	16.7	61.9	21.4
	5 -< 15	66	48.5	0.9	39.9	27.9	163.9	51.5	13.6	34.9	16.7	30.3	63.6	6.1
	15 -< 25	11	36.4	1.3	39.6	27.3	166.3	72.7	27.3	0	0	63.6	36.4	0
	≥ 25	7	85.7	1.9	40.0	27.9	169.1	28.6	57.1	14.3	0	100	0	0

age at delivery was not significantly different between exposure groups. We found that maternal PCB levels were significantly higher in children born at an earlier calendar period (between 1969 – 1972, Table 2). A higher DDE exposure was obvious for children born between 1973 and 1982.

Crude birth weight and adjusted birth weight estimated through linear regression analyses are presented in Table 3. The results show that boys were heavier at birth; birth weight increased with gestational age; and there was a significant increase in birth weight with birth order. We did not detect a statistically significant difference in birth weight for different level of exposure to DDE (Table 3). However, the birth weight of the offspring of mothers who had the highest PCB levels (≥ 25 μg / L) significantly reduced by approximately 500 g (p = 0.022) (Table 3). When stratified for gender, PCB exposure was associated with a reduced birth weight in males only. The reduction in boys in the highest PCB exposure level was 561 g (p = 0.02) and 241 g in girls (p = 0.66), however, there was only one girl and six boys in the highest PCB exposure group (≥ 25 μg / L serum).

In addition to controlling for gestational age in the analysis, we determined the percentages of newborns who were considered to be small for gestational age using 10%-reference values [48]. We did not find an association of DDE nor PCB with the prevalence of small for gestational age (average proportion: 8.3%). Finally, when we excluded neonates born before the 37th week of gestation the PCB estimate did not change substantially (reduction of 578 g, p = 0.023). Thus, the association between PCB and birth weight cannot be attributed to preterm delivery.

Table 3: Birth weight in grams in different subgroups

Characteristic		n = 168	Crude birth weight in g (5 – 95% values)	Adjusted ψ birth weight in g (5 – 95% values)
Gender	Male	80	3536 (2679 – 4380)	3491 (3283 – 3698)*
	Female	88	3385 (2693 – 4167)	3272 (3062 – 3481)
Maternal DDE (μg / L)	< 5	46	3411 (2693 – 4139)	3278 (2979 – 3577)
	5 -< 15	89	2456 (2637 – 4253)	3365 (3130 – 3600)
	15 -< 25	25	3504 (2722 – 4253)	3440 (3198 – 3685)
	≥ 25	8	3572 (2807 – 4338)	3278 (3065 – 3815)
Maternal PCB (μg / L)	< 5	84	3470 (2693 – 4338)	3520 (3318 – 3723)
	5 -< 15	66	3428 (2608 – 4167)	3509 (3312 – 3707)
	15 -< 25	11	3647 (3033 – 4167)	3537 (3137 – 3937)
	≥ 25	7	3268 (2722 – 4338)	2958 (2519 – 3397)*
Parity	0	57	3345 (2552 – 4139)	3211 (2999 – 3423)*
	1	65	3474 (2722 – 4253)	3378 (3169 – 3587)
	2	31	3523 (2722 – 4763)	3401 (3168 – 3633)
	≥ 3	15	3668 (3289 – 4338)	3535 (3246 – 3824)
Gestational age	< 37	5	2427 (1361 – 3033)	Continuous variable*
	37 -< 40	23	3279 (2693 – 3941)	
	≥ 40	140	3522 (2792 – 4309)	
Maternal age (years)	15 – 24	41	3388 (2892 – 4082)	3414 (3158 – 3669)
	25 – 29	70	3517 (2693 – 4309)	3396 (3181 – 3610)
	30 and older	57	3432 (2580 – 4536)	3334 (3128 – 3541)
Maternal height (cm)	< 155	14	3112 (2552 – 3714)	Continuous variable
	155 -< 170	122	3470 (2693 – 4167)	
	≥ 170	32	3555 (2722 – 4536)	
Maternal education	High school	71	3379 (2693 – 4139)	3303 (3083 – 3523)
	College	44	3569 (2722 – 4423)	3433 (3196 – 3670)
	College plus	53	3467 (2608 – 4309)	3407 (3152 – 3662)
Maternal smoking status during pregnancy	Yes	22	3175 (2552 – 3969)	3294 (3007 – 3581)
	No	146	3499 (2722 – 4253)	3468 (3300 – 3636)
Child birth year	1968 – 1972	48	3554 (2722 – 4253)	3406 (3200 – 3612)
	1973 – 1982	98	3420 (2693 – 4253)	3333 (3125 – 3540)
	> 1983	22	3405 (2608 – 4536)	3405 (3120 – 3689)

* p-value < 0.05 ψ Adjusted for all other variables in Table 3

As these findings include repeated pregnancies from the same women (168 offspring of 89 mothers), we used Generalized Estimation Equations and adjusted for the within-mother effect. To additionally investigate whether the PCB-related reduction in birth weight is also detected when only considering one offspring per mother, we analyzed data for the first offspring born after 1968 (n = 89). The birth weight was reduced in women with PCB serum concentration of 15 -< 25 μg / L by 220 g (p = 0.38) and for PCB ≥ 25 μg / L by 351 g (p = 0.16).

From the 168 offspring, we selected a subsample of 42 adult daughters and obtained permission to access their birth registry data. To check reliability, we compared this information with maternal recall data. For birth weight, agreement between maternal reports and registry information was nearly perfect: the Spearman correlation coefficient (r_S) is 0.97 (p = 0.0001).

Discussion

Our study found no significant increase in birth weight associated with maternal DDE exposure, but a significant reduction in birth weight of approximately 500 g in offspring of mothers with PCB levels of ≥ 25 μg / L. However, the group with the highest PCB exposure comprised only seven infants. The association was not reduced when we excluded preterm deliveries.

Of the 310 women in the fish eater cohort who were of childbearing age (maximum age of 45 years), 72.9% participated in the study (n = 226). Since the participation proportion is high, we do not suspect that a selection bias can explain our findings. The fact that only 99 of the participating women gave birth after 1968 is likely to be a reflection of chance and not selection.

Regarding a potential information bias, we had a long recall period between births occurring after 1968 and parental reports on birth weight from interviews in the year 2000. The median recall was 24 years. To check reliability, we compared parental information with birth registry data. For birth weight, the agreement between maternal reports and registry information was nearly perfect (r_S = 0.97). We believe that this agreement was achieved primarily due to the fact that most subjects had relevant documents on hand for their interviews. Hence, in accordance with other studies the long recall did not weaken the reliability of the birth weight information [49-51].

Regarding smoking during pregnancy as a potential confounder, we cannot exclude the possibility that some women stopped or reduced smoking during pregnancy. However, the crude smoking effect resulted in an expected reduction of approximately 300 g (3,175 g vs. 3499 g, Table 3). To exclude a misclassification of the smoking status differential with regard to exposure, we investigated non-smoking mothers. This group consisted of 22 women who never smoked or stopped smoking in the year prior to conception. The PCB exposure levels for this group were low as documented in Table 2. Eleven women were in the PCB < 5 μg / L class and 11 women were in the 5 -< 15 μg / L PCB exposure class. The respective average birth weights were 3,348 g and 3003 g. Hence, we also see a reduction in birth weight in the non-smoking group associated with the PCB exposure, which makes differential confounding unlikely.

PCB serum concentrations in other studies that focused on maternal blood, cord blood, or placentas overall ranges between 0.08 – 47.73 μg / L: Fein et al. 1984: 5 – 13 μ/L; Sunahara et al. 1987: 2.29 – 47.73 μg / L; Patandin et al. 1998: 0.59 – 7.35 μg / L; Rylander et al. 1998: 0.08 – 4.3 μg / L; a higher exposed group having a serum concentration of more than 11.7 μg / L (assuming a lipid concentration of 9 g / L), Grandjean et al. 2001 [13-16,19]. The serum concentrations of PCBs determined in our study were between 0 and 29 μg / L and exceeded the concentrations found in four of the five previous studies that used maternal or cord blood serum concentrations.

Fein et al. and Patandin et al. have demonstrated a dose-effect relationship for birth weight with consumption of PCB contaminated fish and with PCB concentrations in cord serum, respectively [13,14]. Our results may indicate a threshold effect, since there is no discernible decrease in birth weight below a maternal PCB concentration of less than 25 μg / L. Assuming an endocrine mode of interference of PCB, a threshold effect is plausible since PCB may hamper the binding of hormones to their receptors [52]. It is possible that the location of the threshold level depends upon smoking, nutrients in fish, and other confounders. Regarding fatty acid intake due to fish consumption, Grandjean et al. reported that some fatty acids, in particular docosapentaenoic acid (DPA), increases birth weight [16]. However, this scenario seems to be even more complex, since the level of DPA also decreases with higher PCB concentrations [16].

Most previous studies that determined organochlorine concentrations in human specimens focused on one compound, for instance PCBs, without considering other correlated toxicants, such as DDE, which might have a confounding effect. In our sample of neonates, maternal PCB and DDE values are correlated (r_S = 0.69, p = 0.0001). Thus, we investigated whether the PCB-birth weight association would change if we do not control for DDE. Without having DDE in the regression model, the highest PCB level still has a diminishing effect on birth weight (p = 0.027, 470 g).

One strength of our study is that we used the maternal blood PCB and DDE concentrations, representing direct measurement of organochlorine compounds (OC) and not approximations, such as fish consumptions, as the indicator of intrauterine exposure. Secondly, we included both PCBs and DDE in our final model, which allowed us to explore the effects of PCBs and DDE on birth weight. A limitation, however, is that the OC measurements between 1973 and 1991 do not coincide with the dates of the pregnancies under consideration (> 1968 to 1995). The median difference is five years. Therefore, these values do not directly reflect the OC concentrations to which these offspring were exposed *in utero*. As expected with persistent chemicals, on average these OC concentrations did not vary much in women when repeated measurements were compared. He et al. analyzed the Michigan fish eater data and reported no substantial decline in the median PCB serum concentration in female fish eaters over three cross-sections (11.0 μg / L in 1973/74; 14.5 μg / L in 1979/82; 13.5 μg / L in 1989/93) [44]. We suppose that chronic consumption of PCB contaminated fish and the long half-lives of PCBs are likely to explain the stability of the serum concentrations. Additionally, we investigated whether PCBs and DDE values were lower, when the spacing between phlebotomy and birth of the child were longer; we found no large differences. For instance PCB levels were higher in both ends of the spacing distribution: 0 – 1 year: 5.4 μg / L, n = 39; 2 – 4 years: 4.0 μg / L, n = 41; 5 – 9 years: 5.2 μg / L, n = 47; > 9 years: 6.1 μg / L, n = 41.

To estimate maternal levels of organochlorine compounds (OC) at the times of pregnancy between 1950 and 1980, we used three repeated serum measurements and additional survey information (1973 – 1974, 1979 – 1982, and 1989 – 1991) [Karmaus W. et al. Unpublished data]. Two linear regression analyses were conducted and their results used to backward extrapolate serum levels. Each of the two regression models covers one period between two of the three survey measurements. We estimated regression coefficients for the most parsimonious models, and tested how well the two equations predicted the actual serum OC concentrations measured in the past. By means of intraclass correlation coefficients (ICC), we compared estimated and measured past concentrations [53]. We identified two formulas that predicted past values with high reliability (ICC = 0.77 for the period of 1991 to 1979, and ICC = 0.89 for the period of 1982 to 1973). The first formula used the PCB values determined in 1989/91, the years that passed between the 1989/91 and 1979/82 determinations, and the number of births in that interval. Of note is that the predicted values were higher in the 1979/82 measurements, as indicated by a positive sign for the years that passed between 1989/91 and 1979/82. The second formula estimates the PCB values in 1973/74 using the 1979/82 determination, the years between 1973/74 and 1979/82, and the years of fish consumption. This formula has a negative sign for the years passed between the two determinations, which indicates lower PCB values for 1979/1982 and before. We applied these formulas to backward-estimate both the maternal serum PCB and DDE concentrations at the time of each pregnancy. When using the values derived from backward extrapolations, our results did not change substantially. The reason is that the ranking of the exposure concentrations changed only marginally when these estimates were used.

A limitation is the lack of information about individual PCB congeners and the lack of information about hydroxylated PCBs. We had to use the total PCB concentration based on the Aroclor 1260 standard. This may be a problem because various PCB congeners may have different, sometimes antagonistic endocrine effects [54,55]. It has also been reported that hydroxylated PCBs are estrogenic while non-hydroxylated PCBs are not [36-38]. An additional limitation is that OC determinations used in our study were determined on a whole serum basis without determination of serum lipids. Thus, we could not determine lipid-based PCB concentrations. However, another strength of the Michigan cohort is that the analytical procedure to determine DDE and PCB (Webb-McCall packed column gas chromatography technique) has not been changed between 1973 and 1991 [43]. These stable analytical techniques facilitated comparisons between PCB and DDE assessment in the three surveys as recently emphasized by Longnecker et al., when comparing different techniques [56].

Several studies have investigated a potential association between PCB and/or DDE exposure and birth weight. However, there is inconsistency when comparing results of studies with varying exposure measurements, which may lead to exposure misclassification. For instance, studies which rely on measurements in breast milk may be plagued by declining OC concentrations with increasing duration of breastfeeding [57], particularly, if the concentration was derived at different times for different participants. However, there is little uncertainty when exposure is determined from maternal or cord blood. Four out of five studies reported an adverse effect on birth weights [13-15,19], one did not [16]. Our study adds to the evidence that high maternal PCB serum concentrations are associated with reduced birth weight. We assume that the apparent inconsistencies in earlier studies can be reduced if the exposure is assessed without major impact of misclassification; for instance, by using maternal or cord blood concentrations. Although we have found that PCBs may be associated with reduced birth weight, the underlying mechanisms remain unknown. We did not

have any information on fatty acid in fish or in the female fish eaters. We believe that future studies should also determine phospholipid fatty acids in fish eating populations. Phospholipid fatty acids are provided by seafood and may be beneficial for the pregnancy and offspring [16]. Since both phospholipid fatty acids and OCs have the same origin and thus are highly likely to be correlated, these substances may confound the PCB – birth weight association. However, since the concentrations of some fatty acids are altered by PCBs [16], it may not be the confounding but the intervening effects of phospholipid fatty acids that need to be considered in structural equation models to appropriately estimate the direct and indirect effect (via fatty acid) of PCBs.

Conclusion

Our study adds to existing evidence that *in utero* exposure to PCB may reduce birth weight when exposure was determined from maternal or cord blood samples. Birth weight is a marker of adverse effects *in utero*, and/or a predictor of a series of adverse developments in childhood. Future studies are warranted to investigate the potential adverse effects of historic organochlorine compounds such as PCBs and DDE, as well as newly emerging toxicants such as polybrominated diphenylethers on birth weight. We recommend designing future studies in a way that would allow for the discovery of the underlying mechanism.

Abbreviations

PCBs: Polychlorinated Biphenyls

DDE: Dichlorodiphenyl Dichloroethylene

OC: Organochlorine compounds

LBW: Low Birth Weight

GLFS: Great Lakes Fish Eater Study

GEE: Generalized Estimation Equations

ICC: Intra class correlation coefficient

r_S: Spearman correlation coefficient

Competing Interests

None of the authors have any competing interests, financial or otherwise.

Authors' contributions

WK designed the study, developed the analytical approach. WK and XBZ analyzed the data and drafted the manuscript. Both authors have read and approved the final manuscript.

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