Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring

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ABSTRACT

Objectives: To investigate the effect of prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyl-dichloroethylene (DDE) on weight, height and body mass index (BMI) in adult female offspring of the Michigan fisheater cohort examined between 1973 and 1991.

Methods: 259 mothers from the Michigan fisheater cohort were studied. Prenatal exposure to PCBs and DDE was estimated by extrapolating maternal measurements to the time that the women gave birth. 213 daughters aged 20–50 years in 2000 were identified and 83% of them participated in at least one of two repeated investigations in 2001/02 (n = 151) and 2006/07 (n = 129). To assess the effect of prenatal PCB and DDE exposure on anthropometric measurements, generalised estimating equations nested for repeated measurements (2001/02 and 2006/07) and for sharing the same mother were used. We controlled for maternal height and BMI and for daughters' age, birth weight, having been breastfed and number of pregnancies.

Results: Maternal height and BMI were significant predictors of the daughters' height, weight and BMI. Low birth weight (<2500 g) was significantly associated with reduced adult offspring weight and BMI. The weight and BMI of adult offspring were statistically significantly associated with the extrapolated prenatal DDE levels of their mothers. Controlling for confounders and compared to maternal DDE levels of <1.503 μg/l, offspring BMI was increased by 1.65 when prenatal DDE levels were 1.503–2.9 μg/l and by 2.88 if levels were >2.9 μg/l. Prenatal PCB levels showed no effect.

Conclusion: Prenatal exposure to the oestrogenic endocrine-disrupting chemical DDE may contribute to the obesity epidemic in women.

1Obesity has been identified as an escalating problem worldwide and is associated with a significant disease burden.[1] Until recently, investigations into the causes of obesity have focused on overeating, unhealthy dietary choices and lack of physical activity.[2 3] Increasingly, however, prenatal exposure to toxicants is suspected of contributing to obesity.[4–6] One new line of inquiry suggests that organochlorines such as polychlorinated biphenyls (PCBs) and dichlorodiphenyl-dichloroethylene (DDE) may exert endocrine disruptive effects.[7–10] Recently, it has been proposed that endocrine disruptors increase bodyweight.[4 5] Another line of inquiry has determined that organochlorines have been linked to the occurrence of type 2 diabetes,[11–13] a disease which is also strongly related to increased bodyweight.[11] However, to the best of our knowledge, no study has investigated the association between prenatal PCB and DDE exposure in humans and subsequent adult obesity.

The Great Lakes have been polluted with industrial wastes since the 1920s.[14] Two of the most significant pollutants in Lake Michigan's waters are the organochlorine compounds dichlorodiphenyl trichloroethane (DDT) and PCBs. The former was widely used as an insecticide after the end of World War II (1945). It was banned in the United States in 1973 but is still used in other parts of the world.[15] DDT has a biological half-life of about 7 years, but its metabolite, DDE, has a much longer half-life, accounting for its greater concentrations in humans.[16] PCBs and DDE are lipophilic. The half-life of PCBs is approximately 7 years,[17 18] so although the production and use of PCBs has been discontinued in most countries, large amounts remain in the environment. DDE and PCBs from water and sediments tend to bioaccumulate in marine life, and their concentration increases as they extend throughout the food web.[17] Humans, at the end of the food chain, thus experience higher exposures, especially those whose diets include sport-caught fish.

Many residents in the area around Lake Michigan practice fishing as a sport and consume three times as much fish as the average American.[19] Previous studies have shown that Michigan anglers and fisheaters have higher serum levels of PCBs and DDE than population controls.[20 21] Contamination of fish in the Great Lakes led to three successive investigations between 1973 and 1991 to assess the PCB and DDE burden in Michigan anglers and fisheaters. In each survey, PCB and DDE serum levels were measured. To test the hypothesis that prenatal exposure to PCBs and DDE is a risk factor for subsequent obesity in women, we contacted the female offspring of this cohort.

METHODS

Population and overview of study design

The Michigan Department of Community Health (MDCH) recruited fisheaters and their spouses in 11 Lake Michigan shoreline communities and determined their organochlorine levels in three investigations (1973–1974, 1979–1982 and 1989–1991); organochlorine levels were measured at least twice in the majority of participants. In 2000, we approached this Michigan fisheater cohort (parental generation) again to identify any daughters aged 20–50 years. We contacted

these offspring in 2001/02 and in 2006/07. During the second investigation, anthropometric measurements of the adult offspring were taken in their homes. The Michigan State University (2001 and 2006) and the MDCH institutional review boards approved the study protocols for both periods of the study.

Determination of serum DDE and PCBs in the parental generation cohort

In each of the three investigations conducted between 1973 and 1991, participants of the parental generation were asked to provide non-fasting blood samples for analyses of serum PCBs and other organochlorines. DDE was not determined during the first investigation (in 1973–1974). Samples were analysed at the Health Risk Assessment Laboratory of the MDCH. Serum PCB and DDE levels were determined using a modification of the Association of the Official Analytical Chemists' approved Webb-McCall packed column gas chromatography technique. The laboratory analytical methods used are described in detail elsewhere.[22 23] We used the Aroclor 1260 standard to determine PCBs, as it was available for all samples. Laboratory values reported as less than the detectable limit for Aroclor 1260 (3 μg/l) were assigned a value of 1.5 μg/l. Less than 5% of the samples were below the threshold in all three analyses. The technical detection limit for DDE was 1 μg/l. The methodology for organochlorine determination remained the same during all three periods of analyses.

Extrapolation of maternal serum PCB and DDE at the time of pregnancy

We devised formulas to extrapolate the maternal serum PCB and DDE concentrations at the time of pregnancy between 1950 and 1980.[24] Briefly, we used repeated serum measurements and survey information (1973–1974, 1979–1982 and 1989–1991) to estimate two regression models covering two separate periods (from 1991 to 1979 and from 1982 to 1973).[25] We identified two formulas that predicted past values with high validity (intra-class correlation coefficients (ICC) 0.77 for the period 1991–1979, and 0.89 for the period 1982–1973). Our estimations mirrored the trends that were detected for PCB concentrations in fish, which peaked around 1970.[24] Finally, these equations were used to extrapolate maternal organochlorine levels at the time of each pregnancy.

Interviews and anthropometric measurements

Information on birth date, birth weight and breastfeeding of offspring was obtained from parents in 2000. We retrieved maternal height and weight from the 1989–1991 survey of Michigan fisheaters (parents).

In 2001–2002, we conducted telephone interviews with the female offspring regarding their reproductive health, and asked them about their weight, height and number of pregnancies. The interviews were repeated in 2006/07 when a trained kinesiology graduate student also measured each participant's height and weight. All measurements were taken three times, recorded sequentially by a second investigator and then averaged. Standing height was measured with a calibrated portable standiometer. To perform the measurements, each woman stood with the heels of her bare feet flat on a hard surface against a wall and looked straight ahead. Weight was measured with a calibrated portable electronic scales to the nearest tenth of a pound.

Data analysis

Outcome variables

Outcome variables included offspring height, weight and body mass index (BMI). BMI is defined as weight/height^2 (kg/m^2). Each was analysed as a continuous variable.

Independent variables

Maternal variables explored included age, height and BMI. Variables of the daughter included prenatal DDE and PCB serum levels, age, birth weight, whether she was breastfed as a child, and her number of pregnancies. We linked each female offspring with her maternal data and her extrapolated prenatal DDE and PCB serum levels. To determine whether serum DDE and PCB values were linearly associated with the offspring's anthropometric measurements, we divided the DDE and PCB levels into quintiles. We used maternal height and BMI, as well as age and height of offspring, as continuous variables. We defined two indicator variables for the birth weight of the offspring: low birth weight (<2500 g) and high birth weight (>4000 g). Breastfeeding (yes or no) and the number of pregnancies of each offspring (1, 2 or 3 and more) were treated as categorical variables.

Statistical models

The observations represent both repeated information (2001/02 and 2006/07) and, in some cases, information nested for having the same mother. The two offspring measurements for each participant are correlated over time; in addition, the data of daughters of the same mother are correlated. Taking these correlations into consideration, we estimated the effect of the extrapolated prenatal DDE and PCB exposures on offspring height, weight and BMI using generalised estimating equations. Analyses used repeated measurement models (GENMOD) in SAS v 9.[26] We controlled for maternal height in the explanatory model for offspring height and for maternal BMI in the explanatory models for offspring weight and BMI. Other confounders included in all analyses were as follows: age of the offspring at the time of the interview, birth weight, breastfed status, and the number of pregnancies of the adult female offspring. We checked the multivariate normal distribution of the residuals for the three linear models (height, weight and BMI).

RESULTS

Since this is a two-generation study, we will begin with a description of the parental generation cohort (fig 1). As existing data of the Michigan fisheater cohort (1973–1991) did not identify which women bore children, we contacted all the women and then selected the 391 who had measured organochlorine levels and were of childbearing age (15–45 years of age) at any time between 1950 and 1980. We identified and contacted 276 (70.6%) of these women and 259 (66.2% of 391) agreed to participate (seven were deceased and 10 did not give consent).

We then identified 213 daughters born to the 259 women participants between 1950 and 1980. A total of 176 (82.6%) daughters participated in at least one of two repeated investigations (151 female offspring in 2001/02 and 129 in 2006/07). One daughter did not have a maternal DDE measurement. In addition, other missing maternal values such as maternal height and weight restricted the sample used in the repeated analyses to 169 women (79.3%). The mothers and their

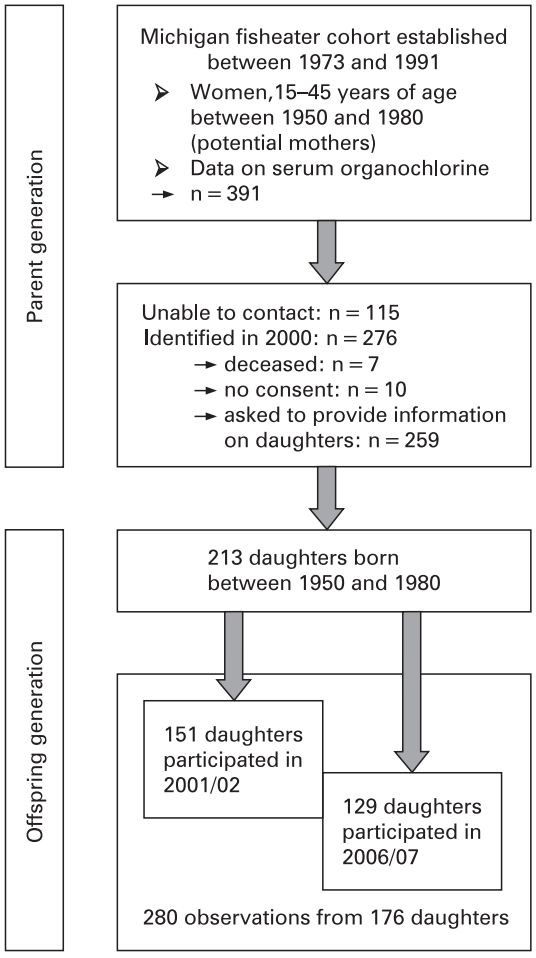

Figure 1 Cohort and participation over two generations.

offspring were almost all non-Hispanic Caucasian women (99%).

To investigate whether there was a selection bias in this two-generation study, we compared age and PCB and DDE measurements in participating and non-participating women from the parental cohort who met the inclusion criteria (table 1). In addition we investigated whether maternal age and serum concentrations were different in daughters who participated and those who did not (table 1). Women of the parent generation who agreed to participate were approximately 5 years younger than those who did not agree to participate. The maternal PCB and DDE values determined in 1973–74, 1979–82 and 1989–91 in daughters who participated in the 2001/02 or 2006/07 investigation were compared to maternal values for daughters who did not participate (table 1). No significant differences were found.

In 2001/02, 17% of the 151 offspring had a BMI of 30 or higher (obese) and 20.5% had a BMI between 25 and 30 (overweight). In 2006/07, 30.5% were obese and 25.8% were overweight. In the 2001/02 investigation, data on weight and height were ascertained by interview and in the 2006/07 investigation by interview and anthropometric measurements. Comparing the 2006/07 interview data with the actual measurements shows excellent agreement. The data for both height and weight were highly correlated (height: $r_{Spearman} = 0.97$, $p<0.001$, $n = 140$; weight: $r_{Spearman} = 0.97$, $p<0.001$, $n = 140$). In addition, the information on weight gathered in 2001/02 by interview and that based on measurements in 2006/07 were highly rank-correlated ($r_{Spearman} = 0.92$, $p<0.001$, $n = 96$), as were the data on height ($r_{Spearman} = 0.97$, $p<0.001$, $n = 96$) and BMI ($r_{Spearman} = 0.89$, $p<0.001$, $n = 96$). In regression analysis, we used interview data from the 2001/02 investigation and anthropometric measurements from the 2006/07 investigation.

The extrapolated prenatal DDE and PCB levels were correlated ($r_{Spearman} = 0.57$, $p<0.001$), which can also be seen when comparing the geometric mean PCB values for the different DDE groups (table 2). The median prenatal DDE value at birth was 4.46 μg/l in offspring who participated in 2001/02, and 3.67 μg/l in offspring who participated in 2006/07. In 2001/02, the median prenatal DDE value at birth of the offspring was 5.58 μg/l in obese, 5.15 μg/l in overweight and 4.18 μg/l in normal weight offspring. In 2006/07, the values were 6.29 μg/l, 3.12 μg/l and 2.8 μg/l for obese, overweight and normal weight offspring, respectively. To determine whether there was a linear trend, prenatal DDE and PCB exposures for the adult offspring who participated in 2001/02 and 2006/07 were divided into quintiles (table 2). In both investigations, compared to the lowest DDE quintile, geometric means for weight and BMI were higher in the third, fourth and fifth quintiles, but without further trend among these upper three groups. The measurements in 2006/07 show a mean weight of 79.2 kg in the third, 78.8 kg in the fourth and 79.9 kg in the fifth quintile group (table 2). The second quintile had an intermediate position. For instance, for the weight data in 2001/02, the mean was 67.6 kg in the first quintile, 69.9 kg in the second and 71.3 kg in the third. In 2006/07, the mean weight was 72.2 kg in the first quintile, 71.9 kg in the second and 79.2 kg in the third. To address this non-linear association, we therefore used quintiles 1 and 2 as separate groups, and combined quintiles 3–5 into one group. The geometric means for weight across the maternal PCB quintiles showed a similar non-linear relationship but a less obvious pattern (table 3). Therefore, we also grouped the PCB quintiles into three categories.

Regarding maternal height, weight and birth weight, there were no statistically significant differences between the DDE quintiles (table 2).

The generalised estimating equation nested for repeated measures and for sharing the same mother showed no significant effect of DDE or PCB on offspring height. Maternal PCB concentrations during pregnancy were not statistically significantly related to any of the anthropometric measurements in the offspring. Compared to maternal DDE concentrations of <1.503 μg/l, the weight of the offspring was 5.93 kg greater when the prenatal DDE concentration was between 1.503 and 2.9 μg/l (table 4, $p = 0.001$) and increased by 9.22 kg when the maternal serum DDE level was higher than 2.9 μg/l ($p = 0.001$). Maternal BMI and age of the offspring were also significantly related to offspring weight.

Compared to the reference (prenatal DDE <1.503 μg/l), the BMI of the offspring was 1.65 higher when the prenatal DDE concentration was between 1.503 and 2.9 μg/l (table 3, $p<0.001$) and 2.88 higher when the maternal serum DDE level was greater than 2.9 μg/l ($p<0.001$). Offspring BMI was also significantly predicted by maternal BMI. Low birth weight (<2500 g) was significantly associated with reduced adult weight and BMI. Offspring BMI also increased with offspring age.

Table 1 Median age, height, weight and organochlorine values of women of the parental generation by participation status and parental and offspring cohorts

Characteristics	Parental generation: women of childbearing age (15–45 years old between 1950 and 1980) (n = 391)		Offspring generation: adult women (n = 213)		
	Non-participating women, n = 132	Participating women, n = 259	Non-participating offspring, n = 37	Participating offspring in 2001/02, n = 151	Participating offspring in 2006/07, n = 129
Maternal age in 2000 (years)	67	62*	62.5 (n = 34)	61.6 (n = 150)	61.6 (n = 129)
Maternal height in 1979–82 (cm)	162.6 (n = 122)	165.1 (n = 252)	172.7 (n = 34)	165.1 (n = 148)	165.1 (n = 128)
Maternal weight in 1979–82 (kg)	62.6 (n = 121)	63.5 (n = 249)	77.6 (n = 33)	63.5 (n = 148)	63.5 (n = 128)
Determinations in 1973–74					
PCB (μg/l)	6.0 (n = 19)	5.0 (n = 24)	1.5 (n = 2)	7.0 (n = 18)	6.0 (n = 14)
Determinations in 1979–82					
PCB (μg/l)	8.1 (n = 122)	8.5 (n = 255)	8.8 (n = 33)	9.35 (n = 150)	9.0 (n = 128)
DDE (μg/l)	13.1 (n = 122)	11.1 (n = 255)	10.0 (n = 33)	12.2 (n = 150)	11.5 (n = 128)
Determinations in 1989–91					
PCB (μg/l)	6.75 (n = 44)	6.85 (n = 118)	8.35 (n = 26)	8.4 (n = 106)	8.2 (n = 95)
DDE (μg/l)	8.05 (n = 44)	6.85 (n = 118)	8.7 (n = 26)	6.9 (n = 115)	6.9 (n = 101)

*$p \leqslant 0.05$, Kruskal–Wallis test.
DDE, dichlorodiphenyl-dichloroethylene; PCB, polychlorinated biphenyl.

DISCUSSION

Our results suggest that higher prenatal exposure to DDE, but not to PCBs, is statistically significantly associated with increased weight and BMI in adult female offspring. To the best of our knowledge, this is the first study to report an association between maternal DDE and anthropometric measurements in adult offspring.

The generalisability of this study may be influenced by the selection of our study population (fig 1). Although only 66.2% of the women from the original cohort participated in this study, we found no differences other than a 5-year age difference between participants (younger) and non-participants. This may be related to the finding that 23.8% of the women in the parental generation cohort were aged 75 years or older in 2000. We were able to determine whether they were alive only if they lived in Michigan. Hence, any women of the parental generation who died in other locations would have contributed to non-participation and could have helped increase the average age of the non-participants by 5 years compared to that of the participants (table 1). Because there are no differences in serum DDE and PCB levels or in anthropomorphic measurements between those who participated and those who did not, selection bias is not a concern in our study's conclusions. Overall, 83% of the daughters participated in the study and no differences were found between participants and non-participants.

Some anthropometric data were obtained by self-report. Mothers were asked for this information in the 1979–1981

Table 2 Characteristics of the offspring sample across quintiles of prenatal DDE exposure (mean or percentages)

	Participation in 2001/02					Participation in 2006/07					
	DDE concentration (μg/l) during pregnancy					DDE concentration (μg/l) during pregnancy					
	0–1.502, n = 28	1.503–2.9, n = 26	2.9–6.1, n = 32	6.1–9.4, n = 31	>9.4, n = 33	0–1.502, n = 28	1.503–2.9, n = 29	2.9–6.1, n = 24	6.1–9.4, n = 25	>9.4, n = 22	Total, n = 176
Height in cm (SD)	166.1 (7.7)	168.6 (8.0)	166.1 (5.7)	167.3 (7.4)	167.6 (6.8)	166.7 (8.2)	166.3 (6.3)	167.6 (6.4)	167.5 (6.9)	166.3 (7.4)	167.0 (6.6) n = 175
Weight in kg (SD)	67.6 (15.9)	69.9 (17.5)	71.3 (14.9)	69.8 (12.1)	72.8 (17.9)	72.2 (17.8)	71.9 (16.2)	79.2 (23.6)	78.8 (16.1)	79.9 (24.1)	74.2 (18.5) n = 175
BMI in kg/m^2 (SD)	24.4 (5.2)	24.4 (4.4)	25.7 (4.7)	24.9 (4.1)	25.8 (5.2)	25.8 (4.9)	26.0 (5.8)	28.1 (7.7)	28.0 (5.4)	28.8 (8.1)	26.5 (6.0) n = 175
PCB at birth in μg/l (SD)	1.9 (2.6)	1.5 (2.1)	3.4 (3.5)	5.6 (3.8)	8.5 (6.1)	1.6 (2.6)	1.6 (2.0)	4.4 (3.5)	4.5 (3.8)	7.3 (5.3)	3.8 (4.4) n = 176
Maternal height in cm (SD)	164.3 (6.1)	164.9 (5.8)	162.7 (7.6)	165.2 (6.6)	163.9 (6.2)	163.8 (5.0)	164.7 (5.1)	162.7 (8.0)	164.5 (6.8)	165.6 (6.2)	164.0 (6.2) n = 173
Maternal BMI in kg/m^2 (SD)	22.6 (3.3)	23.4 (3.3)	24.5 (4.2)	24.1 (3.2)	23.7 (3.2)	22.4 (3.2)	23.6 (3.8)	25.3 (4.3)	23.7 (3.5)	24.5 (3.5)	23.6 (3.5) n = 173
Breastfed as a child	75.0%	53.9%	50.0%	46.7%	42.4%	71.4%	55.2%	45.8%	33.3%	40.9%	49.1% n = 175
Birth weight of the offspring in grams (SD)	3293 (569)	3399 (473)	3309 (436)	3338 (549)	3352 (486)	3402 (489)	3281 (480)	3338 (436)	3271 (633)	3384 (451)	3323 (503) n = 172
Age of the adult female offspring in years (SD)	37.3 (8.5)	36.4 (7.2)	35.3 (8.2)	35.0 (7.6)	39.1 (8.6)	40.5 (10.9)	39.2 (8.9)	39.1 (9.3)	41.6 (7.2)	44.4 (8.1)	n = 176 39.9 (8.9)
Number of pregnancies of the offspring (SD)	1.8 (1.4)	2.8 (3.0)	2.0 (1.9)	1.5 (1.4)	1.8 (1.6)	2.0 (1.5)	2.5 (2.9)	1.9 (1.6)	2.3 (2.0)	2.5 (2.2)	n = 176 2.1 (2.0)

BMI, body mass index; DDE, dichlorodiphenyl-dichloroethylene; PCB, polychlorinated biphenyl.

Table 3 Height, weight and body mass index in the female offspring sample across quintiles of prenatal PCB exposure (mean or percentages)

	Participation in 2001/02					Participation in 2006/07					
	PCB concentration (μg/l) during pregnancy					PCB concentration (μg/l) during pregnancy					
	0–0.05, n = 28	0.05–1.94, n = 31	1.95–3.45, n = 25	3.45–7.08, n = 33	>7.1, n = 34	0–0.05, n = 28	0.05–1.94, n = 25	1.95–3.45, n = 31	3.45–7.08, n = 23	>7.1, n = 22	Total, n = 176
Height in cm (SD)	166.2	166.0	167.2	168.3	167.6	165.1	166.4	167.5	169.1	166.4	167.0 (6.6)
	(6.8)	(7.9)	(7.5)	(7.6)	(5.6)	(6.2)	(8.4)	(6.9)	(7.1)	(7.7)	n = 175
Weight in kg (SD)	70.2	67.4	70.2	72.0	71.8	76.9	70.2	75.1	85.4	73.2	74.2 (18.5)
	(18.2)	(17.4)	(11.6)	(14.6)	(15.5)	(22.4)	(18.0)	(16.2)	(23.3)	(14.6)	n = 175
BMI in kg/m^2 (SD)	25.2	24.2	25.1	25.4	25.5	28.0	25.1	26.8	30.0	26.4	26.5 (6.0)
	(5.3)	(4.4)	(4.0)	(4.7)	(5.0)	(7.1)	(4.5)	(5.7)	(8.6)	(4.7)	n = 175

BMI, body mass index; PCB, polychlorinated biphenyl.

survey and daughters in the telephone interviews conducted between 2001 and 2002. Prior studies have assessed self-report of anthropometric measurements as accurate.[27 28] As regards the 2006/07 anthropometric measurements, there were excellent correlations between measurements and interviews in 2006/07 and measurements in 2006/07 and interview data in 2001/02. We do not believe that this was a source of bias for the association between maternal DDE and offspring body mass since the daughters were unlikely to report a different weight or height even if they were aware of their maternal DDE or PCB concentrations. Individual errors in anthropometric reports may have, however, contributed to non-differential misclassification (random error), which typically leads to an underestimation of the reported effects.

A strength of this study was the availability of the maternal serum DDE and PCB measurements taken during three investigations using consistent laboratory methods. This information allowed us to estimate exposure levels for a given pregnancy with high validity (ICC 0.77 and 0.89).[24] It has been demonstrated that DDE and PCBs cross the placenta and directly expose the fetus.[27 28] A limitation is the lack of information about individual PCB congeners. We used the total PCB concentration based on the Aroclor 1260 standard, which is a mixture of PCB congeners[29] that were utilised to quantify PCBs before specific congeners could be measured. This may pose a problem because various PCB congeners have different, sometimes antagonistic, effects[25 26] which may have obscured a significant association between total PCB levels and BMI. Additionally, there is no information about specific DDE concentrations (p,p′-DDE or o,p′-DDE), nor do we have information on actual organochlorine exposures during the childhood or adulthood of the offspring. Recently, the results of a Spanish cohort study in children showed that prenatal exposure to hexachlorobenzene, but not to DDE or PCBs, was associated with increased BMI at age 6 years.[30] Hence, DDE may not be the only obesogenic halogenated organic compound.

The sample size of the study is small (n = 176) and the numbers cannot be increased as this is a second-generation study. This

Table 4 Regression coefficients for predictors of adult female offspring height, weight and body mass index (repeated measurements in 2001/02 and 2006/07) derived from repeated measurement models adjusting for having the same mother (within-family effect)†

	Height (cm)		Weight (kg)		BMI (kg/m^2)	
	Number of mothers = 101, number of participants = 169, number of observations = 267		Number of mothers = 101, number of participants = 169, number of observations = 267		Number of mothers = 101, number of participants = 169, number of observations = 267	
	Estimate	Standard error	Estimate	Standard error	Estimate	Standard error
Maternal DDE (μg/l)						
1.503–2.9‡	1.17	0.82	5.93*	1.79	1.65*	0.33
>2.9	1.29	1.05	9.22*	3.06	2.88*	0.92
Maternal PCB (μg/l)						
0.05–1.94§	−0.10	0.88	0.93	2.35	−0.39	0.74
>1.94	−1.51	1.50	2.29	3.43	1.28	1.18
Maternal height (cm)	0.07	0.26	–	–	–	–
Maternal BMI (kg/m^2)	–	–	1.59*	0.73	0.56*	0.25
Breastfed as a child (%)	−0.30	0.54	2.73	2.44	1.21	0.95
Birth weight of the offspring¶						
<2500 g	−0.01	0.01	−5.47*	0.98	−2.07*	0.37
>4000 g	4.89	2.47	5.30	6.30	0.29	1.78
Height of the offspring (cm)	–	–	0.055	0.34	–	–
Age of the adult female offspring (years)	–	–	1.02*	0.18	0.39*	0.07
Number of offspring's pregnancies**						
1	–	–	2.44	2.74	1.13	0.93
2	–	–	0.31	3.28	0.14	1.20
3 or more	–	–	0.40	3.26	0.29	1.12

*$p \leqslant 0.05$.
†Each outcome is adjusted for all other variables in the model; ‡maternal DDE at birth of the offspring of 0 to <1.5 μg/l is the reference; §maternal PCB at birth of the offspring of <0.05 μg/l is the reference; ¶birth weight of 2500–4000 g is the reference; **female offspring without pregnancies serve as the reference.
BMI, body mass index; DDE, dichlorodiphenyl-dichloroethylene; PCB, polychlorinated biphenyl.

restriction does not allow us to detect weak associations between intrauterine exposures and anthropometric measurements in offspring. However, the increase in weight of 5.93 kg in female adult offspring with elevated prenatal DDE levels of between 1.503 and 2.9 μg/l and the increase of 9.22 kg if the maternal serum DDE level was greater than 2.9 μg/l indicate a strong effect. Maternal DDE concentrations found in this study between 1973 and 1991 still represent relevant exposures. For instance, a study from Spain reported that DDE levels in cord blood collected in 1997 had a 75th percentile of 1.94 μg/l.[31] A Mexican study conducted between 2001 and 2005 found maternal DDE values of 1.7–21.8 μg/l (10–90th percentile).[32] The National Health Examination Survey (1999–2002) showed that 50% of their sample (n = 2298) had DDE serum concentrations greater than 1.57 μg/l and 25% had concentrations greater than 3.97 μg/l.

Due to the suspicion that maternal DDE levels may be associated with a higher percentage of maternal body fat, we also investigated maternal anthropometric data. We detected a weak association between maternal DDE serum level and maternal BMI ($r_{Spearman} = 0.16$, $p = 0.06$), but no correlation between maternal height and DDE ($r_{Spearman} = 0.02$, $p = 0.80$) (data not shown). To exclude the potential confounding of maternal DDE effects via its correlation with maternal BMI, we adjusted for maternal BMI in the regression models (table 3). In addition, by adjusting for maternal BMI and height, we also took potential genetic effects into account.

Sorensen *et al* reported an increase in adult BMI with birth weight.[33] We also showed that low birth weight is associated with a lower female adult weight and BMI (table 3). In agreement with previous studies, we found a strong association between maternal and offspring weight and BMI.[30–32] Maternal smoking during pregnancy did not confound the association between maternal DDE levels and offspring anthropometric measurements, and thus was not included in the model. We also found no confounding related to maternal and offspring education. The finding that the proportion of breastfed offspring decreased with increasing DDE levels (table 2) has been reported before.[34]

It has been suggested that obesity may be due to oestrogen insufficiency.[35] Evidence for this comes from studies showing that ovariectomised rats and α-estrogen receptor knockout (αERKO) mice have increased weight and fat deposition,[35–37] and that oestrogen treatment of aromatase knockout (ArKO) mice normalises body fat. The environmental pollutant DDE is considered to exert oestrogenic effects. Proposed mechanisms include androgen blocking, a weak oestrogen mimicry,[9 38] or aromatase induction.[36] Chen *et al* reported that DDT isomers and metabolites downregulate the oestrogen receptors in MCF-7 breast cancer cells.[37]

The finding that intrauterine DDE exposure may effect the weight and BMI of adult offspring relies on the assumption of early programming, a mechanism wherein endocrine disruption or metabolic programming leads to a stable metabolic change with a lasting effect.[6 39] To the best of our knowledge, no animal study has investigated whether prenatal DDE exposure is associated with higher weight in adult offspring. However, previous studies have explored the effect on animal weight gain of other oestrogenic endocrine-disruption chemicals. Howdeshell *et al* showed that mice treated with bisphenol A, a toxicant that mimics oestrogen actions, were heavier on postnatal day 22 than controls.[38] This finding was not confirmed in rats at 21 and 33 days of age.[40] Newbold and coworkers demonstrated that mice exposed to diethylstilbestrol manifested increased weight after puberty.[39 41] Wright *et al* reported that exposure to octylphenol during fetal and postnatal life in female lambs led to increased weight at puberty.[42] Additionally, in vitro experiments have shown that bisphenol A stimulates the conversion of fibroblasts to adipocytes,[43] thus increasing adipose tissue. There are various modes of action of endocrine-disrupting chemicals.[44] Thus, it is plausible to speculate that prenatal exposure to DDE may result in increased weight and BMI.

There is evidence that organochlorine exposure may be associated with diabetes.[11–13] In addition, increased BMI is considered a risk factor for diabetes. Our sample is not large enough to assess the effect of PCBs and DDE on diabetes. Two of the 176 female offspring had insulin-dependent diabetes and six had non-insulin-dependent diabetes (data not shown). The association between halogenated compounds and diabetes, obesity and diabetes, and the current finding of an association between DDE and obesity provides compelling evidence to support the need for further investigation on whether halogenated compounds share a common mechanism in the triggering of obesity and diabetes.

In conclusion, our findings suggest that maternal exposure to DDE during pregnancy is linked to overweight in adult female offspring. Environmental epidemiology has suggested several possible endocrine effects of DDE that include a higher rate of preterm delivery,[45] reduced growth in girls,[46] a reduction in breastfeeding,[24 47] earlier age at menarche,[48] higher fecundity,[47] earlier age at menopause,[49] and an elevated relative risk for diabetes.[11] Increased weight may be part of a "DDE health syndrome". In addition, it is also possible that prenatal exposure to DDE partly explains the obesity epidemic in women in different regions of the world. The effects of endocrine disruption on body weight is an important, yet poorly developed, area of obesity research.[5]

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Main messages

- As maternal DDE exposure may be associated with overweight and obesity in adult female offspring, prenatal DDE exposure may partly explain the obesity epidemic.
- Our findings support the hypothesis that the fetus may be vulnerable to prenatal chemical disruption, resulting a tendency later in life to increased body weight.
- The association between prenatal DDE levels and offspring overweight adds to the body of evidence that DDE may have adverse developmental effects.

Policy implications

In order to assess the impact of endocrine-disrupting chemicals on obesity, there is an urgent need to determine the importance of second-generation health effects.

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