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Maternal insecticide levels are associated with autism in offspring from a national birth cohort

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Abstract

Objective: Autism is a complex neurodevelopmental disorder with a largely unknown etiology. To date, few studies have investigated exposure to prenatal toxins and risk of the disorder using maternal biomarkers of exposure. Persistent organic pollutants (POPs) are lipophilic halogenated organic compounds including the insecticide dichlorodiphenyl trichloroethane (DDT), its metabolite p,p'-dichlorodiphenyl dichloroethylene (p,p'-DDE) and polychlorinated biphenyls (PCBs). We tested whether elevated levels of maternal POPs are associated with autism among offspring.

Method: The investigation was conducted in the Finnish Prenatal Study of Autism (FiPS-A), a national birth cohort study based on a nested case-control design. Cases of childhood autism born from 1987 to 2005 were ascertained by national registry linkages. Maternal serum specimens from early pregnancy were assayed for p,p'-DDE and total PCBs in pregnancies of cases of childhood autism and matched controls (778 matched case-control pairs).

Results: The odds of autism among offspring were significantly increased for maternal p,p'-DDE levels in the highest 75th percentile, adjusting for maternal age, parity, and psychiatric history (OR=1.32, 95% CI=1.02–1.71, p=0.03). The odds of autism with intellectual disability were increased by greater than twofold for maternal p,p'-DDE levels above this threshold (OR=2.21, 95% CI=1.32–3.69, p=0.002). There was no association between maternal total PCBs and autism.

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Conflict of Interest: The authors report no competing interests.

Conclusions: These findings provide the first biomarker-based evidence to date that maternal exposure to an insecticide is associated with autism among offspring.

Introduction:

Autism is a complex neurodevelopmental disorder with a largely unknown etiology. It is characterized by impaired language, disrupted reciprocal social interactions, and stereotyped behaviors and interests(1). Both genetic and environmental factors have been associated with this disorder(2–4). To date, few studies have investigated prenatal toxins and autism, and most have been based on ecologically rather than serologically documented exposures. For example, specific associations were reported for residential proximity to sites contaminated with pesticides(5, 6) and traffic-related air pollution(7). However, a Swedish twin study(8) and a large collaborative European study(9) did not show associations between prenatal exposure to air pollution and risk of ASD.

Persistent organic pollutants (POPs) are lipophilic halogenated organic compounds including dichlorodiphenyl trichloroethane (DDT), its metabolite p,p'-dichlorodiphenyl dichloroethylene (p,p'-DDE) and polychlorinated biphenyls (PCBs)(10). Prior to the late 1970s, these compounds were in widespread use in developed countries, i.e. as insecticides (DDT) and in transformers and electrical equipment (PCBs). Although these chemicals were widely banned in many nations over 30 years ago, they became ubiquitous in these countries, including the USA(11) and Finland(12). Due to their lipophilic nature and chemical half-lives ranging as long as several decades(13), they persist in the food chain, particularly through fatty food sources resulting in continuing exposure to populations. POPs are transferred across the placenta resulting in lipid-adjusted cord blood concentrations 1.3 times those found in maternal plasma(14).

Thus, there is ongoing prenatal exposure potential for nearly all children, due to existing maternal body burdens(11). This was demonstrated in a nationally representative sample of U.S. women in 2003–4(11).

Maternal exposure to POPs has been associated with aberrant perinatal and childhood neurocognitive outcomes. Increasing maternal levels of p,p'-DDE were related to an elevated risk of preterm birth in a large study(15), and reductions in indices of psychomotor development and other cognitive functions(16, 17) and processing speed (18) in exposed offspring have been observed. Maternal PCBs have also been associated with aberrant neurocognitive outcomes, though the findings are mixed [for review see(19)].

Although several studies that used interview and ecologic data on maternal POP exposure reported associations with autism-related behaviors(5, 6, 20, 21), few studies have investigated biomarker-based measures of maternal POP exposure and ASD in offspring(22, 23). In a small pilot study from our group in the Finnish Prenatal Study of Autism (FiPS-A), we found that maternal levels of p,p'-DDE and PCBs were related to autism in childhood, though the findings were not statistically significant(22). In the Early Markers of Autism study, Lyall et al(23) found increased mean levels of several PCB congeners, including PCB 138/158 and PCB 153, in mothers of ASD cases.

We therefore hypothesized the following: 1) maternal p,p'-DDE levels, and 2) total PCB levels, each in the highest quartile of the distribution, would be related to risk of autism among offspring. Supplementary analyses were conducted to investigate whether offspring sex and co-morbid intellectual disability (ID) modified the relationship between these maternal POPs and autism. Strengths of the present study include a larger sample than the previous studies mentioned(22), high detection rates, and a national population-based sample.

Method:

Study population.

The methods are described in detail in Lampi et al(24), and will be summarized here. The FiPS-A is based on a nested case-control design. The sampling frame was defined such that all members of this national birth cohort were within the age of risk of autism. Toward this end, the subjects consisted of all offspring born in Finland from 1987–2005, and subjects were followed up until 2007 (see "Case and comparison subject identification").

Description of the birth cohort, biobank, and national registries.

All offspring in the FiPS-A were derived from the Finnish Maternity Cohort (FMC), which consists of greater than 1 million pregnancies with archived prenatal serum specimens drawn beginning in 1983(24). Sera were obtained during the first and early second trimesters (months 2–4 of pregnancy) from over 98% of pregnant women in Finland. One maternal serum sample was acquired for each pregnancy. Following the screening, serum samples were stored as one aliquot at minus 25°C in a single biorepository at THL in Oulu, Finland. All samples in the FMC can be linked with offspring using a unique personal identification number (PIN), which has been assigned to all residents of Finland since 1971.

Case and comparison subject identification.

The Finnish Hospital and Outpatient Discharge Registry (FHDR) was utilized to identify all recorded diagnoses from psychiatric hospital admissions and outpatient visits for childhood autism (ICD-10 F84.0) among members of the FMC. Registry diagnoses of childhood autism were validated with the Autism Diagnostic Interview-Revised (ADI-R)(24). Computerized data are available from January 1, 1987 to the present. Only singleton births were included. Cases diagnosed over the sampling frame were identified from registry linkages between the FMC and the FHDR from January 1, 1987 to December 31, 2007. The total number of childhood autism cases in the FiPS-A study sample was 1,132.

The cases were matched 1:1 to comparison subjects (singleton births only) drawn from the birth cohort who were without ASD (no F84 diagnosis) on date of birth, sex, birthplace, and residence in Finland. The analytic sample consisted of 778 cases from the 1,132 total autism cases, and 778 matched controls.

Laboratory analyses and methods.

All assays were performed blind to case/control status. Matched cases and controls were analyzed in the same run to minimize variation between runs. In the analysis of POPs, we

tested two primary hypotheses: autism in offspring will be associated with 1) increased maternal concentration of p,p'-DDE; 2) increased maternal concentration of total PCBs. The analytical method used has been published previously(25). In brief, ethanol and ^{13}C-labelled internal standards of each POP compound were added to the serum samples. Dichloromethane-hexane was added for extraction of POPs followed by activated silica to bind the sample water, ethanol, and protein precipitate. The upper dichloromethane-hexane layer was poured into a multilayer silica column for the removal of co-extracted compounds that interfere with the GC-MS/MS quantitation. POPs were eluted from the cleanup column with additional dichloromethane-hexane; the recovery standard ^{13}C-PCB-128 was added and the eluate was concentrated for gas chromatography tandem mass spectrometry (GC-MS/MS) analysis for quantification of POPs. In each batch of samples a control serum sample from the National Institute of Standards and Technology, SRM 1958, was included. Recoveries of p,p'-DDE and PCBs varied from 86% to 106% (CV% 1.6–6.5%) of the certified concentrations for SRM 1589 and from 83% to 101% (CV% 2.0–6.6%) of the calculated concentrations for diluted SRM 1589, respectively. The limits of quantification (LOQ) were 5 pg/ml for each PCB congener and 40 pg/ml for p,p'-DDE. Fresh weight serum concentrations of POPs, which have shown very high correlation with lipid-based concentrations in a prior study (overall r=0.95)(26), are reported.

Classification of POP variables.

In order to limit the number of analyses of these compounds, we focused on two hypothesized primary measures of maternal POP exposure: 1) maternal p,p'-DDE levels in the highest 75th percentile of the distribution, and 2) maternal total PCBs, quantified as the sum of concentrations of the 10 measured congeners (PCB-74, PCB-99, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, and PCB-187), in the highest 75th percentile of the distribution. These PCBs were selected as they represent approximately 85–90% of all PCBs on a mass basis.

The study was approved by the ethical committees of the hospital district of Southwest Finland, THL, and the Institutional Review Board of the New York State Psychiatric Institute. Informed consent was obtained at the time of donation of all maternal serum specimens after the nature and possible consequences of the procedure and data derived from serum analyses were explained.

Statistical analysis plan.

We first computed descriptive statistics and correlations between POP levels. These were analyzed separately for cases and controls. Potential confounders were selected based either on previous relationships with POP exposure or autism(27) and were compared between cases and controls using chi-squared and t-tests. They include maternal age, number of previous births (0, ≥1), socioeconomic status (upper white collar, lower white collar, blue collar, other), maternal/parental history of psychiatric disorders (see Table 1 for definition), and gestational week of the blood draw. Data on maternal age, maternal socioeconomic status, and previous births were acquired from the FMBR. Data on maternal/paternal history of psychiatric disorders were acquired from the FHDR and data on paternal age from the

Finnish Population Registry. Data on gestational week of the blood draw were obtained from the FMC.

Appropriate to the case-control study design, point and interval estimates of odds ratios for the association of maternal levels of p,p'-DDE and total PCBs with autism were obtained by fitting conditional logistic regression models for matched sets. Statistical significance was judged at $P < 0.05$. Covariates were included in the adjusted models based on associations with the outcome. We did not match on these covariates given well-described disadvantages in overmatching(28) and the fact that they can be controlled effectively in the multivariable analyses.

For the primary POP analyses (p,p'-DDE, total PCBs) the exposures were analyzed as dichotomous variables, with cut-points at the 75th percentile. Exploratory analyses were conducted following stratification by sex and intellectual disability (ID) of the case, given well-known sex differences in autism(29); and extensive evidence of co-morbid ID in autism(30) [ICD-10/9 codes for ID are: F70/317, F71/318.0, F72/318.1, F73/318.2, F78 (no ICD-9 code), and F79/319]. Prior studies indicate that some risk factors may be distinct for autism with(31) versus without ID(32); these include our prior finding in this population that accelerated growth velocity of head circumference at 3 months of age was associated with autism with ID, but not autism without ID(31). We examined effect modification of p,p'-DDE and total PCBs by adding product terms to models for each variable x p,p'-DDE or PCB levels >75th percentile. The evidence for heterogeneity of the odds ratios between strata of each potential effect modifier was assessed based on the p-values for the product terms. In order to evaluate whether maternal levels of PCB 138/158 and PCB 153 were associated with autism, we conducted supplementary analyses of these maternal PCBs and autism.

Statistical analyses were performed with SAS software (SAS 9.4, SAS Institute, Cary, NC, USA). Given that the study tested only two primary hypothesized variables (maternal p,p'-DDE levels >75th percentile, maternal total PCB levels > 75th percentile), as noted above, Bonferroni correction was not performed.

Results:

Covariates.

Older maternal age, increased maternal parity, and maternal/parental psychiatric history were significantly associated with odds of autism in offspring (Table 1). There were no relationships between maternal socioeconomic status and odds of autism. Earlier birth year, older maternal age, lower maternal parity, and higher maternal socioeconomic status were associated with higher maternal levels of total PCBs and of p,p'-DDE among the controls (data available on request). Offspring sex and maternal or parental history of psychiatric disorder were not associated with maternal levels of these POPs.

Main findings.

The mean (SD) and median maternal POP levels among cases and controls are shown in Table 2. p,p'-DDE was measured above the level of quantitation (LOQ) in almost all samples (775/778 among both cases and controls). The individual PCB congeners were

measured above the LOQ in 95–100% of samples. The mean (SD) maternal p,p'-DDE level among pregnancies giving rise to cases was 1,032 (2176) pg/ml versus 811 (1660) pg/ml among corresponding controls. The median levels of maternal p,p'-DDE were also higher among cases [median (IQR)=512 pg/ml (263–948)] than among controls [median (IQR)=469 pg/ml (249–806)]. The mean (SD) level of total maternal PCBs was 1,022 (649) pg/ml among cases versus 999 (660) pg/ml among controls, and the median (IQR) levels of total maternal PCBs were 884 (583–1282) versus 865 (570–1258) pg/ml in cases versus controls. We also report mean (SD) and median levels of individual PCB congeners for descriptive purposes.

The odds of autism in offspring were significantly increased, by 32%, for maternal p,p'-DDE levels in the top 75th percentile of the control distribution (OR=1.32, 95% CI=1.02–1.71, p=0.03), adjusting for maternal age, parity, and maternal psychiatric history (Table 3). For total maternal PCB levels, there was no increase in the adjusted odds of offspring autism for exposure above the 75th percentile (OR=0.95, 95% CI=0.73–1.24, p=0.69). Adjusting models for maternal age and parity only; or for maternal age, parity, and parental psychiatric history had minimal impact on the results (available on request).

Stratum-specific estimates for the associations between maternal p,p'-DDE and total PCBs and autism are shown in Table 4. The association between maternal p,p'-DDE > 75th percentile and odds of autism was significant among males [OR (95% CI)=1.35 (1.02–1.80), p=0.04] but not among females [OR (95% CI)=1.19 (0.67–2.13), p=0.55], although the estimates for males versus females did not differ significantly (p-value for interaction=0.70). The increase in odds of autism associated with maternal p,p'-DDE > 75th percentile was greater among cases with ID [OR (95% CI)= 2.21 (1.32–3.69), p=0.002] than among cases without ID [OR (95% CI)=1.22 (0.88–1.69), p=0.18], and these ORs were significantly different from one another (p-value for interaction=0.04). There were no associations between maternal total PCBs and autism among males or females and among autism cases with or without ID.

We also examined whether maternal PCB 138 and PCB 153 levels were associated with autism, given the findings of Lyall et al(23). No associations were observed for PCB 138 (OR=0.90, 95% CI=0.60–1.18, p=0.44) or PCB 153 (OR=0.97, 95% CI=0.74–1.26, p=0.80). There were also no associations between any of the other individual PCB congeners and autism (results available on request).

Correlations between POPs.

The correlation between maternal p,p'-DDE and total PCBs was 0.4. Total PCBs were correlated with the levels of individual PCB congeners with r values ranging from 0.74–0.99 (Supplemental Table 1).

Discussion:

There were two principal findings from this large, national birth cohort study of maternal POPs and autism among offspring. First, maternal levels of p,p'-DDE were significantly increased in pregnancies giving rise to autism, compared to control subjects without autism.

The findings persisted following adjustment for covariates related to autism. To our knowledge, this is the first biomarker-based evidence of this association. Second, maternal levels of total PCBs, and other PCBs variously defined, were unrelated to autism risk, and thus we did not replicate the associations between maternal PCBs and autism in our prior pilot study of the FiPS-A birth cohort, despite the similar source population and method. However, the sample size in the pilot study was small and none of those findings reached statistical significance(22).

We propose two reasons for the observation that maternal exposure to p,p'-DDE was related to autism while maternal PCB exposure was not. First, maternal exposure to DDT/DDE is associated with both premature birth and with small for gestational age status; both of these exposures have been well-replicated as risk factors for ASD (15, 33). In contrast, maternal PCB exposure has not been related to prematurity or small for gestational age status(34). Second, p,p'-DDE inhibits androgen receptor binding, androgen-induced transcriptional activity, and androgen action including in developing rats(35). Offspring of rats injected with valproic acid (VPA), an in utero risk factor for autism(36), exhibited reduced androgen receptor expression in most cerebellar lobules in both male and female offspring(37); cerebellar abnormalities including Purkinje cell numbers have been demonstrated in the brains of cases of autism(38) and in rat offspring exposed to prenatal VPA(39). In contrast, PCBs increase androgen receptor transcription(40).

One possible reason for inconsistent findings of POPs and autism across studies include differences in the chemical mixtures and contexts of exposure between populations. A study that examined PCB-153 and p,p'-DDE levels in adults from four different geographic populations found that the correlation between the levels of these two POPs varied considerably, as did the associated covariates, likely reflecting differences in primary routes of exposure(41). Animal studies have demonstrated interactive effects on behavior and learning between different neurotoxicant chemicals including PCBs and methylmercury(42). Therefore, it is possible that the differences in findings for p,p'-DDE and PCBs in the studies of POPs and autism were due to differences between populations in the exposure profiles to other chemicals which interact with these POPs. Moreover, Schmidt et al(43) observed that folic acid intake during pregnancy attenuated the relationship between maternal insecticide exposure (determined based on interviews and ecologically defined exposures to pesticide amounts); conceivably, substances that might protect against developmental pathology from insecticides and other POPs differ between populations(43).

Our findings are not in agreement with those of Lyall et al(23), who demonstrated that maternal levels of PCB 138/158 and 153 in the highest 75th percentile of the distribution were significantly associated with offspring ASD. In one other study of maternal POP levels relevant to autism, based on a different cohort, a relatively small sample was utilized, and autistic behaviors rather than clinical diagnoses of ASD were included; thus, those results may not be comparable with the results of the present study(44). The authors of that study found that maternal PCB-178 levels were associated with *fewer* autistic behaviors in offspring and maternal p,p'-DDE and DDT did not show associations with the outcome.

The association between maternal p,p'-DDE and autism was isolated to cases with comorbid ID. This might suggest that the relationship between maternal p,p'-DDE and autism is related to ID in general and not to autism specifically. Previous studies showed associations between maternal p,p'-DDE and cognitive dysfunction, including reduced psychomotor development(16), general cognitive function, verbal and memory ability (17), and processing speed and verbal comprehension(18) in offspring; however, other studies did not show these associations. For example, transplacental exposure to p,p'-DDE was associated with higher scores on the Bayley Scales of Infant Development at 6 months; the relationship disappeared at 12 months(45); no associations were observed for maternal p,p'-DDE concentrations and scores on the Bayley Scales of Infant Development at age 8 months and IQ at age 7(46). If maternal exposure to DDT or p,p'-DDE has no effect on childhood neurocognition in general population samples, this might suggest that this exposure is related to a subgroup of autism cases characterized by co-morbid ID, rather than to ID itself.

While the association between maternal p,p'-DDE levels and autism was significant among male but not female offspring, the estimates of association themselves did not differ significantly between males and females. It is possible that the lower number of female subjects hindered our ability to detect differences between the sexes, if present.

Limitations.

First, we did not have a comparison group of individuals with ID but without autism; hence, we cannot rule out the possibility that our finding of an association between maternal p,p'-DDE and autism was accounted for by ID. However, in addition to the preceding discussion on maternal p,p'-DDE and neurocognition, we note that Lyall et al(23) reported similar associations in subgroup analyses of autism with versus without co-morbid ID. In their analysis of ID without ASD, they found a numerically increased risk for ID among subjects in the second and fourth quartiles of PCB-138/158, and in the third quartile of p,p'-DDE, although the tests for trend were not significant for these associations. Second, though the majority of mothers of cases in our birth cohort had serum samples tested, a significant proportion were not included. The included subjects were born in later years ($p<0.0001$) and were more likely to be positive for maternal ($p=0.01$) or parental ($p=0.04$) psychiatric history than were those not included (Supplemental Table 2); however, this should not have biased our results given that we accounted for these characteristics in the design and analyses. Third, we presented fresh weight serum concentrations of POPs, rather than lipid-adjusted concentrations. However, the unadjusted measures were found to have a low degree of bias under a range of causal scenarios(47) and to be highly correlated with lipidad-justed concentrations ($r=0.95$)(26). Nonetheless, we cannot entirely rule out bias due to uncontrolled confounding by serum lipids. Fourth, we did not adjust for multiple comparisons; if we had, the association of maternal p,p'-DDE with autism would have narrowly missed the Bonferonni-corrected traditional threshold for statistical significance (alpha=0.025 given that two POPs were tested). However, the Bonferroni method is concerned with situations in which multiple statistical tests are being conducted without *a priori* hypotheses or when testing for whether all null hypotheses are true simultaneously(48). These situations did not apply to our primary statistical tests, which were restricted to a priori hypotheses, and these were evaluated separately. Finally, although

potential confounders were adjusted in the analyses, there is always the possibility, as in any observational study, of residual confounding. However, given the selectivity of our finding for p,p'-DDE, this does not appear likely, unless the potential for residual confounding is greater for p,p'-DDE as compared to PCBs.

Conclusion:

In the present study, we demonstrated an association between maternal p,p'-DDE levels and odds of autism in offspring. To our knowledge, this is the first time this relationship has been reported. There was no association between maternal PCB exposure and autism. Further research is necessary to replicate this finding and evaluate a potential role for maternal PCBs in autism. This work has potential implications for the prevention of autism and a better understanding of its pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Although further research is necessary to replicate this finding, this work has implications for the prevention of autism and a better understanding of its pathogenesis.

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Table 1:

Comparison of covariate distributions among cases with autism and matched controls

	Cases (N=778)		Controls (N=778)		
Covariate	**N**	**%**	**N**	**%**	**P-value[1]**
Birth year					1.0
1987–1990	68	8.7	68	8.7	
1991–1993	209	26.9	209	26.9	
1994–1996	208	26.7	208	26.7	
1997–2005	293	37.7	293	37.7	
Infant sex					1.0
Male	606	77.9	606	77.9	
Female	172	22.1	172	22.1	
Maternal age					0.01
≤19	9	1.2	21	2.7	
20–24	107	13.8	134	17.2	
25–29	257	33.0	254	32.7	
30–34	228	29.3	233	30.0	
35–39	141	18.1	116	14.9	
≥40	36	4.6	20	2.6	
Maternal parity[3]					0.001
0	189	24.3	254	32.9	
1	266	34.2	241	31.2	
2	177	22.8	134	17.3	
3+	145	18.7	144	18.6	
Maternal socioeconomic status[4]					0.46
Upper white collar	89	13.5	106	16.6	
Lower white collar	305	46.3	284	44.4	
Blue collar	134	20.3	131	20.5	
Other	131	19.9	119	18.6	
Maternal psychiatric history[5]					0.0003
No	650	83.6	699	89.9	
Yes	128	16.5	79	10.2	
Parental psychiatric history[5]					0.02
No	586	75.3	624	80.2	
Yes	192	24.7	154	19.8	
	Mean	SD	Mean	SD	P-value[2]
Gestational weeks at blood draw	10.9	3.47	10.8	3.4	0.49

[1] P-value from chi-squared test for difference in proportion of cases and controls across all strata of the covariate

[2] P-value from t-test for difference between cases and controls

[3] N missing = 1 Case, 5 Controls

[4] N missing = 119 Cases, 138 Controls

[5] ICD-10 codes F20–25, F28–29, F30–34, F38–39, F84, F40–45, F48, F50–53, F55, F59–66, F68–69, F99, F10–19; ICD-9 codes 295, 296, 297, 298.8A, 298.9X, 300.4, 301.2C, 299, 300–300.3, 300.5–301.1, 301.2 excluding 301.2C, 301.3–301.9, 302, 307.1A, 307.4A, 307.4F, 307.4H, 307.5A–C and 307.5E, 307.8A, 307.9X, 309–309.1, 309.2 excluding 309.2A and 309.2B, 309.2D–309.2F, 309.3–309.9 excluding 309.3A and 309.4A, 312.0A, 312.1–312.2, 312.3 excluding 312.3D, 312.4–312.9, 291–292, 303–305; ICD-8 codes 295, 296, 297, 298.00, 298.10, 298.20, 298.30, 298.99, 299, 300.41, 308, 300.0–300.3, 300.4, 300.5–302.9, 305, 306.40, 306.50, 306.98, 307.99, 291, 303–304.

Table 2:

Mean (SD) and median maternal persistent organic pollutant (POP) levels (pg/ml) by autism case-control status among offspring

	Cases (N=778)			Controls (N=778)		
Variable	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
p,p'-DDE	1032.0	2175.5	512.0	811.2	1659.8	469.4
Total PCBs[1]	1022.4	649.4	883.6	998.6	659.7	864.8
Individual PCB congeners						
PCB 74	23.9	26.2	18.7	22.2	20.2	17.8
PCB 99	28.1	21.0	23.4	28.2	27.1	22.3
PCB 118	57.4	42.6	46.9	54.5	43.7	44.4
PCB 153	293.8	185.5	258.9	289.6	198.7	249.5
PCB 138	198.2	127.4	174.6	195.8	134.6	168.8
PCB 156	29.8	20.1	25.5	29.0	20.6	24.8
PCB 187	55.7	41.1	46.4	53.9	40.1	45.1
PCB 183	24.6	17.4	21.6	24.1	17.1	20.9
PCB 180	211.2	140.5	181.2	204.2	132.0	176.6
PCB 170	99.8	65.8	88.2	96.9	60.8	84.8

[1]Sum of the concentrations of 10 measured congeners (PCB-74, PCB-99, PCB-118, PCB-138, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, and PCB-187), selected as they represent approximately 85–90% of all PCBs on a mass basis

Table 3:

Association between maternal persistent organic pollutant (POP) levels and autism among offspring

			Unadjusted		Adjusted[2]	
Persistent organic pollutants (POPs)	**Cases N (%)**	**Controls N (%)**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
p,p'-DDE						
>75th percentile	239 (30.7)	194 (24.9)	1.41 (1.11–1.80)	0.01	1.32 (1.02–1.71)	0.03
Total PCBs[1]						
>75th percentile	202 (26.0)	194 (24.9)	1.06 (0.84–1.35)	0.62	0.95 (0.73–1.24)	0.69

[1] Sum of concentrations of 10 congeners measured (see Table 2)

[2] Adjusted for maternal age, maternal parity, and maternal history of psychiatric disorder (see definition in Table 1)

Table 4:

Stratum-specific associations between maternal persistent organic pollutant levels (>75th percentile) and autism among offspring

	N Cases[1]	N Controls[1]	OR (95% CI)[2]	P	P-Int[3]
p,p'-DDE					
Sex					
Male	605	601	1.35 (1.02–1.80)	0.04	0.70
Female	172	172	1.19 (0.67–2.13)	0.55	
Intellectual disability in the case					
Yes	218	216	2.21 (1.32–3.69)	0.002	0.04
No	559	557	1.22 (0.88–1.69)	0.18	
Total PCBs					
Sex					
Male	605	601	0.95 (0.70–1.27)	0.72	1.0
Female	172	172	0.95 (0.54–1.67)	0.85	
Intellectual disability in the case					
Yes	218	216	0.97 (0.60–1.56)	0.88	0.93
No	559	557	0.94 (0.69–1.28)	0.70	

[1] Number of subjects in each group with complete information for covariates (information on maternal parity was missing for 6 subjects)

[2] Adjusted for maternal age, parity, and maternal history of psychiatric disorder (see definition in Table 1)

[3] P-value for the difference in odds ratios between strata