Maternal Concentrations of Persistent Organochlorine Pollutants and the Risk of Asthma in Offspring: Results from a Prospective Cohort with 20 Years of Follow-up

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Introduction

Polychlorinated biphenyls (PCBs) are a group of structurally related organic compounds that, because of their inertness and thermal stability, have been extensively used in various industrial and commercial applications. Although manufacturing of PCBs was banned in the late 1970s due to concerns of possible adverse effects in humans, these compounds still persist in the environment (Dyke et al. 2003). Similar concerns in the 1970s also led to ban or severe restrictions on the use of the organochlorine pesticides hexachlorobenzene (HCB) and dichlorodiphenyltrichloroethane (p,p'-DDE). Because of their lipophilic and persistent nature, p,p'-DDT and its metabolite dichlorodiphenylchloroethylene (p,p'-DDE), HCB, and PCBs accumulate through the food chain, with seafood currently being the main route of human exposure (Halldorsson et al. 2007; Thompson and Boekelheide 2013). On entering the human body, these compounds dissolve in lipids but they can also bind to proteins in blood (Mohammed et al. 1990), and during pregnancy they are readily transported across the placenta (Covaci et al. 2002; Park et al. 2008).

There is some evidence to suggest that prenatal exposure to PCBs may adversely affect development and maturation of the immune system (Lundqvist et al. 2006). Studies focusing on background prenatal exposures to PCBs have reported associations with increased respiratory and otitis media infections (Dallaire et al. 2006; Gunn et al. 2008; Weisglas-Kuperus et al. 2000), altered immune cell counts (Gunn et al. 2008; Jusko et al. 2011; Weisglas-Kuperus et al. 2000), and reduced antibody responses to childhood vaccines (Heilmann et al. 2006; Weisglas-Kuperus et al. 2000). Reports on atopic diseases such as asthma and wheeze have been divergent, with two studies reporting positive associations (Grandjean et al. 2010; Stovlak et al. 2011) and another reporting an inverse association (Weisglas-Kuperus et al. 2000, 2004). At least two studies have reported positive associations between prenatal exposure to p,p'-DDE and asthma in offspring at 4–9 years of age (Karmaus et al. 2001; Sunyer et al. 2005), whereas evidence for immunological effects of HCB has mostly been obtained from animal studies (Ezendam et al. 2005; Michielsen et al. 1999).

Divergent findings on associations between prenatal exposures to these persistent organochlorine pollutants (POPs) and asthma may relate to the fact that most studies have not had follow-up beyond 6–7 years of age, which would facilitate more accurate diagnoses of permanent asthma when coughing and wheeze symptoms have stabilized. Divergent findings may also relate to differences in relative and absolute concentrations of different organochlorine compounds across studies due to temporal and regional differences (Longnecker et al. 2003). Furthermore, previous studies have mostly relied on self- or parental report to assess asthma, which may be prone to misclassification (Peat et al. 1992, 2001).

The aim of this study was to investigate the association between maternal serum concentrations of PCBs, HCB, and p,p'-DDE in a cohort of environmentally exposed Danish pregnant women and risk of asthma in offspring after 20 years of follow-up.

Methods

Study population. In Aarhus, Denmark, the Danish Fetal Origins 1988–1989 Cohort was formed and included 965 (80%) of 1,212 eligible women with singleton pregnancies who attended a large prenatal clinic during the study period. The cohort has been described in detail elsewhere (Olsen et al. 1995). Briefly, the data collection included a
Participants were prescribed medication(s) used for the treatment of asthma (p,p′-DDE, HCB, and p,p′-DDE). In our primary analysis we examined the association between maternal PCB, HCB, and p,p′-DDE serum concentrations and offspring risk of asthma (based on asthma medication use) during 20 years of follow-up using Cox regression models. Maternal concentrations of the organochlorine compounds were divided into tertiles, and hazard ratios (HRs) and 95% CIs were calculated using age as the underlying time scale. Participants were thus considered at risk of asthma from their age at the start of follow-up in 1995, until time of becoming an asthma case (based on asthma use) or the defined end of follow-up (end of 2008), whichever came first. None of the participants were censored for other reasons, such as death or emigration. Using this model we assumed that all offspring were free of asthma at the start of follow-up in 1995, when the offspring were around 6 years of age. Any prescription of asthma medication before 1995 was assumed to be related to coughing and wheezing rather than asthma (Henderson et al. 2008). Visual inspection of cumulative residual plots did not indicate violations to the assumption of proportional hazards (data not shown). When examining associations between maternal concentrations of POPs and offspring asthma, we performed trend tests by assigning the median concentration to each exposure level (tertile) and included this in the regression models as a continuous variable.

To test the stability of our findings, both with respect to the asthma definition and the assumption that offspring were disease free until 6 years of age, we also estimated associations of PCB, HCB, and p,p′-DDE with first asthma diagnosis in the DNPR from birth to 20 years of age using Cox regression. Furthermore, we examined the relation between PCB, HCB, and p,p′-DDE, self-reported lifetime diagnosis of asthma, and self-reported current use of asthma medication using logistic regression.

Information on covariates was obtained from questionnaires completed by the mothers during pregnancy and from maternal birth records, and the following covariates were included as adjustment factors in the multivariate models: maternal age (continuous), parity (0, 1, ≥ 2), prepregnancy body mass index (BMI; kilograms per meter squared) (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30), maternal education (elementary school, high school or technical school, university education, higher academic education, other education, or
and $p,p'$-DDE maternal prepregnancy BMI was higher in the third tertiles compared with the first tertile (22.1 kg/m$^2$ vs. 21.0 and 21.8 vs. 20.9 for HCB and $p,p'$-DDE, respectively). Offspring of mothers in the third tertiles of PCB and HCB exposure had slightly shorter gestation (281 days) compared with offspring of mothers in the first (283 days) and second tertile (283 days). This difference was not observed across the $p,p'$-DDE tertiles. There was no difference in birth weight across any of the exposure tertiles. More boys than girls were born to mothers in the third tertile of PCB exposure (58.1% vs. 49.0% in the first tertile). For all four outcomes of asthma, there were higher numbers of asthma cases in the second and third tertiles of maternal PCB and HCB exposures compared to the first tertile.

HCB exposure in the third tertile was significantly associated with asthma classified according to medication use in both unadjusted (HR = 1.78; 95% CI: 1.12, 2.84) and adjusted (HR = 1.92; 95% CI: 1.15, 3.21) models (Table 3). We found that for the dioxin-like PCB-118 and PCB-156 combined, HRs of asthma medication use increased across maternal tertiles of exposure. The association was strongest for maternal concentrations of PCB-118 with offspring asthma medication use after adjustment for covariates (third vs. first tertile 1.90; 95% CI: 1.12–3.23). Although there were no significant associations between maternal concentrations of the sum of all PCBs and the non-dioxin-like PCBs with asthma medication use, HRs were positive and increased with increasing tertiles of maternal exposure. There was no association between maternal concentrations of $p,p'$-DDE and offspring asthma medication. Overall, additional adjustment for gestational age did not alter any of the results (data not shown).

In most cases, maternal concentrations of PCBs and HCB were positively associated with asthma hospital diagnoses, self-reported lifetime diagnoses, and self-reported current medication use (Table 4). The strongest associations were found between maternal concentrations of PCB-118 and PCB-156 combined, HRs of asthma medication use increased across maternal tertiles of exposure. The association was strongest for maternal concentrations of $p,p'$-DDE with offspring asthma medication use after adjustment for covariates (third vs. first tertile 1.90; 95% CI: 1.12–3.23). Although there were no significant associations between maternal concentrations of the sum of all PCBs and the non-dioxin-like PCBs with asthma medication use, HRs were positive and increased with increasing tertiles of maternal exposure. There was no association between maternal concentrations of $p,p'$-DDE and offspring asthma medication. Overall, additional adjustment for gestational age did not alter any of the results (data not shown).

The correlations between the compounds were high (Spearman $r = 0.53–0.99$), which made mutual adjustments problematic. However, when the analyses with PCB-118 and HCB (Spearman $r = 0.77$) were mutually adjusted for each other in addition to the other covariates, we found weakened associations and wider CIs for PCB-118 (HR = 1.47; 95% CI: 0.75, 2.86) and for HCB (HR = 1.58; 95% CI: 0.83, 3.01) with offspring asthma medication use comparing the third tertile to the first tertile of exposure (data not shown).

**Discussion**

In this study with 20 years of follow-up we observed positive associations between maternal serum concentrations of PCBs and HCB and offspring use of asthma medications. For the PCBs, the strongest associations were found for the dioxin-like PCB-118. Similar associations were observed when we used three additional asthma outcomes, including hospital diagnoses and self-reported asthma.

**Table 1. Maternal and offspring characteristics of 872 mother–child pairs.**

| Characteristic | Median (10th, 90th percentiles), mean ± SD, or n(%) |
|---------------|--------------------------------------------------|
| **Maternal**  |                                                  |
| Serum concentration (ng/mL) | 0.17 (0.09, 0.30) |
| PCB-118       | 0.74 (0.41, 1.25) |
| PCB-153       | 1.37 (0.76, 2.26) |
| PCB-156       | 0.10 (0.06, 0.16) |
| PCB-170       | 0.37 (0.21, 0.59) |
| PCB-180       | 0.67 (0.38, 1.10) |
| Sum of PCBs (pmol/mL) | 9.23 (5.32, 15.11) |
| HCB           | 0.54 (0.31, 0.87) |
| $p,p'$-DDE    | 2.47 (1.03, 5.66) |
| Maternal age at birth (years) | 29.0 ± 4.2 |
| Fish intake (g/day) | 19.3 ± 15.6 |
| Alcohol (g/day) | 2.9 ± 3.8 |
| Maternal cholesterol (mmol/L) | 7.3 ± 1.3 |
| Maternal triglycerides (mmol/L) | 2.4 ± 0.8 |
| Previous births | 461 (52.9) |
| 0             | 500 (57.3) |
| 1             | 279 (32.0) |
| ≥ 2           | 93 (10.7) |
| Cigarettes/day during pregnancy | 493 (56.5) |
| 0             | 99 (11.4) |
| 0 to < 5      | 188 (21.6) |
| > 5 to 15     | 41 (4.7) |
| > 15          | 51 (5.9) |
| Maternal education | 103 (11.8) |
| Elementary school | 207 (23.7) |
| High school or technical school | 296 (33.9) |
| University    | 125 (14.3) |
| Higher academic | 89 (10.2) |
| Other education | 52 (6.0) |
| Missing       | 52 (6.0) |
| Prepregnancy BMI (kg/m$^2$) | 89 (10.2) |
| < 18.5        | 676 (77.5) |
| 18.5 to < 25  | 53 (6.1) |
| ≥ 25 to < 30  | 23 (2.6) |
| ≥ 30          | 31 (3.6) |
| **Offspring** |                                                  |
| Registry-based diagnoses ($n = 672$) | 111 (12.7) |
| Asthma medication | 32 (3.7) |
| Self-reported diagnoses ($n = 654$) | 89 (13.5) |
| Lifetime doctor diagnosis | 48 (7.3) |
| Current asthma medication use | 3493.7 ± 579.9 |
| Birth weight (g) | 282.3 ± 11.8 |
| Gestational age (days) | 461 (52.9) |
| Age at follow-up (years) | 19.6 ± 0.49 |
diagnoses. No associations were found for maternal concentrations of \( p,p'\)-DDE and offspring asthma.

To our knowledge, only a few studies have examined developmental exposures to PCBs in relation to wheezing and asthma, and their results have varied, with some reporting positive associations (Grandjean et al. 2010; Stolevik et al. 2011), whereas another reported an inverse association (Weisglas-Kuperus et al. 2000, 2004). In contrast with these studies, we also estimated associations with specific PCB congeners, in addition to the sum of all quantified PCBs. Of the six quantified PCB congeners, only dioxin-like PCB-118 was significantly associated with offspring asthma, and a stronger association was observed for the two dioxin-like congeners combined (PCBs 118 and 156) compared with the non-dioxin-like congeners (PCBs 138, 153, 170, and 180) and the sum of all PCBs.

The suspected influence of the dioxin-like PCBs on immunoregulation is, at least partly, thought to be related to interactions with the aryl hydrocarbon receptor (AhR). AhR-mediated responses with dioxin and dioxin-like compounds are thought to contribute to asthma pathogenesis through increased expression of inflammatory cytokines, including tumor necrosis factor-\( \alpha \) and interleukin-1\( \beta \), which in turn can induce mucin production, cell chemotaxis, and immunoglobulin E (IgE) production (Chiba et al. 2012). Whether AhR-mediated responses are relevant to effects of developmental exposures to dioxin-like compounds remains unknown.

Table 2. Maternal and offspring characteristics of 872 mother–child pairs across tertiles of maternal PCB, HCB, and \( p,p'\)-DDE serum concentrations.

| Characteristic                        | 1st tertile | 2nd tertile | 3rd tertile | \( p \)-Value* |
|---------------------------------------|-------------|-------------|-------------|---------------|
| PCB concentration (pmol/mL) (range)   | 1.4–7.7     | 7.7–11.1    | 11.1–80.6   |               |
| Maternal                              |             |             |             |               |
| Maternal age at birth (years)         | 27.6 ± 4.1  | 29.1 ± 3.9  | 30.4 ± 4.2  | < 0.001       |
| Fish intake (g/day)                   | 18.8 ± 16.3 | 18.4 ± 13.4 | 20.6 ± 16.7 | 0.21          |
| Alcohol (g/day)                       | 2.5 ± 3.7   | 2.9 ± 3.3   | 3.4 ± 4.2   | 0.01          |
| Previous births (% nulliparous)      | 152 (52.4)  | 160 (55.0)  | 188 (64.6)  | 0.02          |
| Smoking during pregnancy (% no)      | 157 (57.5)  | 162 (66.4)  | 154 (56.2)  | 0.09          |
| Maternal education (% higher academic)| 37 (13.6)   | 42 (15.4)   | 46 (16.8)   | 0.02          |
| Prepregnancy BMI (kg/m\(^2\))        | 21.5 ± 3.0  | 21.5 ± 3.1  | 21.3 ± 3.2  | 0.72          |
| Offspring                             |             |             |             |               |
| Birth weight (g)                      | 3514.8 ± 507.7 | 3503.3 ± 563.8 | 3462.7 ± 541.1 | 0.47          |
| Gestational age (days)                | 283 ± 10.8  | 283 ± 12.2  | 281 ± 12.3  | 0.03          |
| Sex (% boys)                          | 142 (49.0)  | 150 (51.6)  | 169 (58.1)  | 0.08          |
| Asthma medication (n cases)           | 33          | 36          | 42          | 0.53          |
| Asthma hospital diagnoses (n cases)   | 8           | 12          | 12          | 0.60          |
| Self-reported diagnoses (n cases)     | 22          | 34          | 33          | 0.26          |
| Current self-reported medication use (n cases) | 11          | 18          | 19          | 0.35          |
| HCB concentrations (ng/mL) (range)    | 0.1–0.5     | 0.5–0.6     | 0.6–2.5     |               |
| Maternal                              |             |             |             |               |
| Maternal age at birth (years)         | 28.0 ± 4.1  | 28.9 ± 3.8  | 30.2 ± 4.2  | < 0.001       |
| Fish intake (g/day)                   | 18.1 ± 14.5 | 19.5 ± 15.7 | 20.2 ± 16.3 | 0.24          |
| Alcohol (g/day)                       | 2.6 ± 3.8   | 3.0 ± 3.5   | 3.2 ± 3.9   | 0.14          |
| Previous births (% nulliparous)      | 140 (48.3)  | 168 (57.7)  | 192 (66.0)  | < 0.001       |
| Smoking during pregnancy (% no)      | 162 (59.6)  | 162 (59.3)  | 169 (61.2)  | 0.64          |
| Maternal education (% higher academic)| 36 (13.2)   | 44 (16.2)   | 45 (16.3)   | 0.22          |
| Prepregnancy BMI (kg/m\(^2\))        | 21.0 ± 2.5  | 21.2 ± 2.4  | 22.1 ± 4.0  | < 0.001       |
| Offspring                             |             |             |             |               |
| Birth weight (g)                      | 3463.2 ± 503.1 | 3534.7 ± 534.8 | 3463.0 ± 572.8 | 0.25          |
| Gestational age (days)                | 283 ± 11.7  | 283 ± 10.9  | 281 ± 12.8  | 0.04          |
| Sex (% boys)                          | 147 (50.7)  | 155 (53.3)  | 159 (54.6)  | 0.63          |
| Asthma medication (n cases)           | 28          | 35          | 48          | 0.04          |
| Asthma hospital diagnoses (n cases)   | 8           | 12          | 12          | 0.60          |
| Self-reported diagnoses (n cases)     | 20          | 34          | 35          | 0.07          |
| Current self-reported medication use (n cases) | 6          | 20          | 22          | 0.01          |
| \( p,p'\)-DDE concentrations (ng/mL) (range) | 0.2–1.9     | 1.9–3.2     | 3.3–38.8    |               |
| Maternal                              |             |             |             |               |
| Maternal age at birth (years)         | 28.0 ± 4.2  | 28.9 ± 4.0  | 30.3 ± 4.1  | < 0.001       |
| Fish intake (g/day)                   | 19.1 ± 14.7 | 17.7 ± 14.4 | 20.9 ± 17.3 | 0.05          |
| Alcohol (g/day)                       | 2.4 ± 3.2   | 3.1 ± 3.9   | 3.4 ± 4.1   | 0.01          |
| Previous births (% nulliparous)      | 148 (51.0)  | 171 (58.8)  | 181 (62.2)  | 0.05          |
| Smoking during pregnancy (% no)      | 162 (58.5)  | 174 (64.4)  | 157 (57.3)  | 0.59          |
| Maternal education (% higher academic)| 35 (12.6)   | 38 (14.1)   | 52 (19.0)   | 0.03          |
| Prepregnancy BMI (kg/m\(^2\))        | 20.9 ± 2.7  | 21.5 ± 2.9  | 21.8 ± 3.6  | 0.003         |
| Offspring                             |             |             |             |               |
| Birth weight (g)                      | 3499.9 ± 533.5 | 3494.7 ± 518.8 | 3486.6 ± 561.1 | 0.96          |
| Gestational age (days)                | 283 ± 11.7  | 282 ± 11.8  | 282 ± 12.0  | 0.49          |
| Sex (% boys)                          | 146 (50.3)  | 159 (54.6)  | 156 (53.6)  | 0.56          |
| Asthma medication (n cases)           | 37          | 34          | 40          | 0.76          |
| Asthma hospital diagnoses (n cases)   | 10          | 11          | 11          | 0.97          |
| Self-reported diagnoses (n cases)     | 30          | 31          | 28          | 0.89          |
| Current self-reported medication use (n cases) | 16          | 16          | 16          | 0.99          |

Values are mean ± SD, n, or n (%).

*\( p \)-Values in maternal age, fish intake, alcohol, prepregnancy BMI, birth weight, gestational age across tertiles of maternal POP concentrations were evaluated using F-test. Differences in previous births, smoking, maternal education, sex, asthma medication, asthma hospital diagnoses, and self-reported diagnoses, self-reported medication across tertiles of maternal POP concentrations were evaluated using chi-square test.
Prenatal exposure to pollutants and the risk of asthma

PCBs is unclear. Stronger associations of PCB-118 with asthma in our study are also indirectly supported by two studies. PCB-118 was positively associated with cord IgE concentrations in a cross-sectional study of children from the Slovak Republic, but no associations were reported for the other quantified PCB congeners (Reichrtova et al. 1999). In an in vitro study, treatment with PCB-118, but not PCB-153, led to a shift in the differentiation of CD4⁺ T lymphocytes toward a T-helper 2-dominated response, which is consistent with allergic disease (Gaspar-Ramirez et al. 2012).

We are not aware of previous studies specifically designed to examine developmental HCB exposures and the risk of offspring asthma. HCB was not associated with wheezing or asthma in a cross-sectional study of 124 Japanese adults (Miyake et al. 2011), but HCB has been found to induce airway hyperreactivity in tissue from HCB-exposed Brown Norway rats (Michielsen C et al. 2002; Michielsen CP et al. 2001). HCB has also been reported to show some agonist activity with the AhR (van Birgelen 1998), which suggests that HCB might affect the immune system and asthma through AhR-mediated mechanisms.

In contrast to two previous studies (Karmaus et al. 2001; Sunyer et al. 2005), we did not find any associations between maternal concentrations of p,p' DDE and offspring asthma. It is worth noting that the children in the previous studies were younger (4–9 years of age) than our study population, and their findings may therefore at least partly reflect associations with wheezing symptoms that often resolve later in childhood (Bel 2004; Henderson et al. 2008; Tausse et al. 2003).

Breastfeeding may play an important role on the development of the infant’s immune system (Belderbos et al. 2012). On the other hand, breastfeeding is also a major source of exposure to PCBs and other lipophilic pollutants during the first year of life, with accumulation that is proportional to maternal concentrations (Wang et al. 2004) and the duration of breastfeeding (Patandin et al. 1997). In a study of prenatal and lactational exposures to PCBs in a relatively highly exposed fishing community (Grandjean et al. 2010), duration of breastfeeding was strongly correlated with offspring IgE concentrations at 7 years of age, whereas only a non-significant positive association was observed for prenatal PCB exposures. Although the focus of that study was on allergic sensitization and not asthma, the results support the potential importance of lactational POP exposures to immunoregulation. Absence of information on breastfeeding in our study is therefore a major limitation. As a result, we therefore cannot determine to which degree the associations observed in our study may be related to in utero exposure, lactational exposures, or a combination of both. Although speculative, previous surveys suggest that most children in Denmark were exclusively breastfed during the study’s time period (Vestergaard et al. 1999), which may possibly reduce potential confounding by breastfeeding.

The long prospective follow-up period and the high inclusion of 90% (872/965) of the offspring of women originally enrolled in the cohort are major strengths of our study. In contrast to previous studies that have mostly relied on self-reported asthma, our outcome measure was based on objective register data, where misclassification of ICD-10 asthma diagnoses has been shown to be low (Østergaard Jensen et al. 2010). A possible limitation of the definition of asthma based on medication data is that medicine may have been prescribed to clarify a diagnosis, and this method may therefore overestimate the true prevalence of disease; however, we used a definition based on medication data that has been validated against medical records with a sensitivity of 63% and specificity of 86% compared with a doctor diagnosis of asthma (Moth et al. 2007). Furthermore, we did not consider prescriptions before 6 years of age, which we believe is a strength because many children are prescribed asthma medications in the first years of life, although they do not necessarily develop clinical asthma (Ingvarsdensen et al. 2000). In most analyses with PCBs and HCB, we observed positive associations with the outcomes. The analyses based on the hospital diagnoses and the self-reported diagnoses of asthma did not always reach statistical significance, possibly due to a small number of cases and fewer subjects in the analyses, respectively. The significant associations observed between PCB-118 and HCB and self-reported current use of asthma medication may suggest that the associations are driven by persistent cases of asthma that require continuous medical treatment at 20 years of age.

### Table 3. Associations between maternal PCBs, HCB, and p,p’-DDE serum concentrations and offspring asthma medication use after 20 years of follow-up (n = 872) [HR* (95% CI)].

| PCBs in tertiles (range) | Raw model | Adjusted model² |
|-------------------------|-----------|-----------------|
| PCB-118 (ng/mL)         |           |                 |
| 1st (0.02–1.14)         | 1.00      | 1.00            |
| 2nd (> 0.14–0.20)       | 1.50 (0.92, 2.45) | 1.60 (0.96, 2.66) |
| 3rd (> 0.20–0.61)       | 1.69 (1.05, 2.73) | 1.90 (1.12, 3.23) |
| p for trend⁻            | 0.04      | 0.02            |
| PCB-156 (ng/mL)         |           |                 |
| 1st (0.01–0.08)         | 1.00      | 1.00            |
| 2nd (> 0.08–0.12)       | 1.33 (0.82, 2.15) | 1.38 (0.84, 2.26) |
| 3rd (> 0.12–0.32)       | 1.43 (0.90, 2.29) | 1.45 (0.85, 2.46) |
| p for trend⁻            | 0.15      | 0.20            |
| Dioxin-like PCBs (pmol/mL) |           |                 |
| 1st (0.13–0.67)         | 1.00      | 1.00            |
| 2nd (> 0.67–0.96)       | 1.45 (0.90, 2.35) | 1.56 (0.95, 2.56) |
| 3rd (> 0.96–4.10)       | 1.59 (0.99, 2.55) | 1.75 (1.02, 2.98) |
| p for trend⁻            | 0.07      | 0.05            |
| Non-dioxin-like PCBs (pmol/mL) |           |                 |
| 1st (1.23–7.09)         | 1.00      | 1.00            |
| 2nd (> 7.10–10.12)      | 1.10 (0.69, 1.77) | 1.15 (0.70, 1.86) |
| 3rd (> 10.12–76.55)     | 1.30 (0.83, 2.08) | 1.30 (0.78, 2.17) |
| p for trend⁻            | 0.24      | 0.32            |
| Sum of all PCBs (pmol/mL) |           |                 |
| 1st (1.43–7.72)         | 1.00      | 1.00            |
| 2nd (> 7.73–11.11)      | 1.10 (0.68, 1.76) | 1.15 (0.70, 1.87) |
| 3rd (> 11.11–80.65)     | 1.30 (0.83, 2.06) | 1.30 (0.78, 2.17) |
| p for trend⁻            | 0.24      | 0.32            |
| HCB (ng/mL)             |           |                 |
| 1st (0.07–0.45)         | 1.00      | 1.00            |
| 2nd (> 0.45–0.63)       | 1.26 (0.77, 2.07) | 1.31 (0.78, 2.17) |
| 3rd (> 0.63–2.40)       | 1.78 (1.12, 2.84) | 1.92 (1.15, 3.21) |
| p for trend⁻            | 0.01      | 0.01            |
| p,p’-DDE (ng/mL)        |           |                 |
| 1st (0.20–1.68)         | 1.00      | 1.00            |
| 2nd (> 1.86–3.24)       | 0.91 (0.57, 1.44) | 0.92 (0.5, 1.47) |
| 3rd (> 3.25–38.77)      | 1.09 (0.70, 1.71) | 1.09 (0.67, 1.77) |
| p for trend⁻            | 0.62      | 0.64            

*Estimated in a Cox regression model with age as the underlying time scale. ²Adjusted for maternal age, prepregnancy BMI, parity, maternal smoking, maternal education, maternal alcohol intake, maternal cholesterol, maternal triglycerides, child birth weight, and sex. ¹Estimated with median concentrations in each tertile entered in the Cox regression model as a continuous variable. ²Sum of PCB congeners 118 and 156. ³Sum of PCB congeners 138, 153, 156, 170, and 180. ⁴Sum of PCB congeners 118, 138, 153, 156, 170, 180.
As in any other observational study, we cannot exclude the possibility that the observed associations were influenced by residual or unmeasured confounding, including breastfeeding. The POPs included in our study were highly correlated, and consequently we could not distinguish the contributions of individual compounds to the observed associations. The potential confounders that we included as adjustment factors in our regression models seemed to influence our results to a minimal degree, suggesting limited residual confounding.

In conclusion, this study provides epidemiologic evidence that maternal concentrations of dioxin-like PCBs and HCB may be associated with the offspring’s risk of developing asthma that persists into adulthood. However, we cannot exclude the possibility that these associations may be mediated through postnatal exposures to POPs. Our results provide support for the hypothesis that early-life exposure to POPs may have immunoregulatory effects. Although the concentrations of these particular environmental contaminants have generally decreased since the late 1980s, industrial reduction in production and usage of one particular class of contaminants has typically been matched with a corresponding rise in the production and usage of other related industrial chemicals (Fangstrom et al. 2008; Haug et al. 2009) that have been less extensively studied with respect to potential health effects. In addition, evidence regarding the potential health effects of POPs will continue to be relevant to populations with high risks of occupational exposures (Schtettgen et al. 2012) and to communities with high consumption of fish and other marine species (Birgisdottir et al. 2012).

Table 4. Associations between maternal PCBs, HCB, and p,p′-DDE serum concentrations and the risk of offspring hospital diagnoses (n = 872), self-reported doctor diagnosis of asthma (n = 654), and self-reported current medication use (n = 654) in the adjusted model.

| PCBs | Asthma hospital diagnosis (HP (% CI)) | Self-reported lifetime diagnosis [Odds ratio (% CI)] | Current self-reported medication use [Odds ratio (% CI)] |
|------|-------------------------------------|------------------------------------------|------------------------------------------|
| 1st (0.07–0.45) | 1.00 | 1.00 | 1.00 |
| 2nd (> 0.45–0.63) | 1.66 (0.66, 4.13) | 1.79 (0.97, 3.31) | 3.38 (1.29, 8.85) |
| 3rd (> 0.63–2.45) | 1.84 (0.70, 4.98) | 1.85 (0.97, 3.51) | 4.10 (1.57, 11.15) |
| p for trend | 0.24 | 0.09 | 0.01 |
| p,p′-DDE (ng/mL) | 1st (0.20–0.86) | 1.00 | 1.00 | 1.00 |
| 2nd (> 1.86–3.24) | 1.17 (0.49, 2.80) | 0.96 (0.55, 1.69) | 0.95 (0.45, 1.98) |
| 3rd (> 3.25–38.77) | 1.14 (0.46, 2.92) | 0.80 (0.44, 1.45) | 0.80 (0.46, 1.58) |

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