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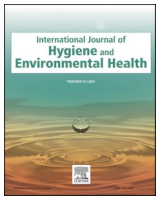

Maternal exposure to polychlorinated biphenyls in indoor air and asthma, allergic rhinitis, atopic eczema, and respiratory tract infections in childhood

Laura Deen [a,*], Karin Sørig Hougaard [b,c], Harald William Meyer [a], Camilla Sandal Sejbæk [a], Kajsa Ugelvig Petersen [a], Marie Frederiksen [c], Jens Peter Bonde [a,b], Marie Standl [d,e,f], Claudia Flexeder [d,e,g], Sandra Søgaard Tøttenborg [a,b]

[a] Department of Occupational and Environmental Medicine, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Denmark
[b] Department of Public Health, The Faculty of Health Sciences, University of Copenhagen, Denmark
[c] National Research Centre for the Working Environment, Denmark
[d] Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany
[e] Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research (DZL), Munich, Germany
[f] German Center for Child and Adolescent Health (DZKJ), Partner Site Munich, Munich, Germany
[g] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany

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ABSTRACT

Polychlorinated biphenyls (PCBs) are industrial chemicals commonly found in food and building materials. PCBs are immunotoxic and may disturb the fetal programming of the immune and respiratory systems. We evaluated the association between maternal PCB exposure in indoor air and asthma, allergic rhinitis, atopic eczema, and respiratory infections in the offspring in the Health Effects of PCBs in Indoor Air (HESPAIR) cohort. This register-based study examined 7982 children born to mothers residing in two partially PCB contaminated residential areas in Greater Copenhagen before and/or during pregnancy. Children were included if their mothers at any point had lived in a contaminated or uncontaminated apartment in the period from 3.6 years prior to conception until the date of birth. PCB exposure was defined as mothers' number of years in an apartment prior to birth of the child multiplied with the PCB concentration in indoor air based on air measurements. Information on the outcomes was retrieved from the Danish health registers from 1977 to 2018. We estimated adjusted hazard ratios using Cox regression. Our main analyses revealed no association between maternal exposure to PCBs in indoor air and any of the studied allergic and respiratory outcomes. Findings of sensitivity analyses were consistent with main analyses. While these findings may appear reassuring for the considerable number of people living or working in PCB contaminated indoor environments, they should be interpreted with caution due to the indirect measure of exposure, incomplete registration of diagnoses, and lack of supporting evidence from comparable studies.

1. Background

In the early 2000s, it became evident that individuals living or working in buildings constructed with materials containing polychlorinated biphenyls (PCBs) were exposed to elevated levels of lower-chlorinated PCBs (LC-PCBs), i.e., containing four or fewer chlorine atoms, in the indoor air (Herrick et al., 2011; Meyer et al., 2013; Frederiksen et al., 2020). This raised concerns about the potential health implications of living and working in such PCB contaminated buildings. However, a comprehensive risk assessment of PCBs in indoor air was not possible since the available literature at the time focussed on PCBs ingested through food. These PCBs primarily consist of higher-chlorinated PCBs (HC-PCBs), containing five or more chlorine atoms and with potential different mechanisms of action compared to the LC-PCBs (Grimm et al., 2015; Pěnčíková et al., 2018). To address this critical gap, we established the Health Effects of PCBs in Indoor Air

* Corresponding author. Department of Occupational and Environmental Medicine, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Bispebjerg Bakke 23, Building 20F, 2400, Copenhagen, NW, Denmark.
E-mail address: Laura.deen@regionh.dk (L. Deen).

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(HESPAIR) cohort comprising all residents of two partially PCB contaminated residential areas in Denmark (Deen et al., 2022).

Using this cohort, we have previously reported higher risk of liver cancer and meningioma, type 2 diabetes, and acute myocardial infarction among residents in private homes contaminated with LC-PCBs in indoor air (Deen et al., 2022, 2023a, 2023b). We also investigated birth outcomes after exposure during pregnancy and found a higher risk of cryptorchidism indicative of disrupted fetal programming (Kofoed et al., 2021). The fetal stage represents a critical period for the development and maturation of the immune and respiratory systems, and some findings indicate that these systems may also be susceptible to programming by PCBs (West, 2002; Hertz-Picciotto et al., 2008). Several epidemiological studies have assessed the impact of prenatal exposure to HC-PCBs on respiratory and allergic outcomes (Berlin et al., 2022; Abellan et al., 2019; Dallaire et al., 2004; Hansen et al., 2014; Gascon et al., 2013). Prenatal exposure to HC-PCBs has been associated with higher levels of lymphocytes and T cells in Dutch children (Weisglas-Kuperus et al., 2000), immunoglobulin E antibodies in cord serum of Slovakian infants (Reichrtová et al., 1999), and interleukin-10 in Spanish children (Gascon et al., 2014a), and lower vaccine response in Dutch children and children in the Faroe Islands (Weisglas-Kuperus et al., 2000; Heilmann et al., 2006). Yet, results are inconsistent for associations between prenatal HC-PCB exposure and clinical diseases. While some studies have reported positive associations with respiratory infections, bronchitis, asthma, and wheezing (Dallaire et al., 2004; Hansen et al., 2014; Stølevik et al., 2011; Gascon et al., 2014b), others did not detect associations with asthma, allergic rhinitis, atopic dermatitis, wheezing, and lung function (Berlin et al., 2022; Abellan et al., 2019; Gascon et al., 2014b). In contrast, limited research has been conducted on exposure to LC-PCBs relative to immune system function. Prenatal exposure to the LC-PCBs, PCB-28 and PCB-52, has been linked to a higher risk of respiratory infections among Swedish infants (Glynn et al., 2008). Occupational exposure during pregnancy has also been associated with higher odds for asthma, eczema/hay fever, and frequent ear infections in the offspring (Parker-Lalomio et al., 2018). Two Chinese studies investigated the association between PCB exposure in indoor environment at 3–6 years of age and childhood asthma (Meng et al., 2016a, 2016b). While no association was found for LC-PCB levels in indoor dust (Meng et al., 2016b), positive associations were observed for LC-PCB blood levels and asthma in the children (Meng et al., 2016a). To increase the knowledge base, we aimed to examine if maternal exposure to LC-PCBs in indoor air is linked to development of asthma, allergic rhinitis, atopic eczema, and respiratory infections among children in the HESPAIR cohort.

2. Methods

2.1. Setting

The study was nested in the HESPAIR cohort comprising 51,921 residents of two residential areas in the Copenhagen area: Farum Midtpunkt (Farum) and Brøndby Strand Parkerne (Brøndby) (Deen et al., 2022). Both residential areas were built during 1969–1974, and the sections built first were erected with PCB containing building materials while the remaining sections were erected without PCB. Consequently, around one third of the apartments are contaminated with PCB in indoor air (Deen et al., 2022; Frederiksen et al., 2012; Andersen et al., 2020). Large contrasts in LC-PCB concentrations between contaminated and reference apartments have previously been documented (Deen et al., 2022; Frederiksen et al., 2012; Andersen et al., 2020). This was also reflected in measurements in subsets of residents, that showed blood levels of PCBs containing 3–4 chlorine atoms to be over 50 times higher among exposed residents than residents in reference apartments (Meyer et al., 2013; Frederiksen et al., 2020).

2.2. Study population

For this study, we identified all live-born children born of female residents in the HESPAIR cohort after the woman's first relocation to one of the residential areas (N = 20,323). We retrieved information on dates of relocation to specific addresses from the Danish Civil Registration System (Pedersen, 2011). This enabled calculation of timing of residence in the residential areas and was used for defining inclusion in the study. Exposed children were included if their mother at any time had lived in the residential areas in the period between 3.6 years prior to conception until the date of birth (Fig. 1). The time window of 3.6 years is the average of estimated half-life of PCB-28, ranging between 0.5 and 6.7 years, in a review from 2023 (Idowu et al., 2023), which would result in *in utero* exposure regardless of timing for the mother's exposure. For children to be included as prenatally unexposed, the same criteria were applied for reference apartments, with the additional criterion that mothers could not have lived in contaminated apartments in the two residential areas at any point previously or during the period of interest for this study.

2.3. Maternal PCB exposure

Concentrations of the seven indicator PCBs (PCB−28, −52, −101, −118, −138, −153, −180) have been measured in indoor air in subsets of apartments in both Brøndby and Farum (Deen et al., 2022; Frederiksen et al., 2012; Golder Associates, 2015). In Farum, indoor air measurements were performed in 83 contaminated and 20 reference apartments in March and April 2011 (Frederiksen et al., 2012). In Brøndby, indoor air measurements were performed in 117 contaminated and 18 reference apartments from 2011 to 2017 (Golder Associates, 2015). The PCB measurements are reported in Table 1. We summarised PCB concentrations in indoor air as PCB_{total}, defined as the sum of the seven indicator PCBs times a factor of five, which is commonly used in research in Europe, to account for unmeasured PCBs in air (Verein et al., 2009). Using the indoor PCB measurements combined with relocation dates from the Civil Registration System, we assigned each mother-child pair an exposure based on PCB_{year} defined as the mothers' number of years of living in an apartment prior to birth of her child multiplied with PCB_{total}. Thus, this PCB exposure measure reflected the entire history of maternal residence in Brøndby and Farum prior to the birth of the child. Since the PCB measurements were only available in subsets of apartments, we used the mean of the measurements in the specific building or, if no measurements were available, the mean of the neighbouring building. We assumed a stabile PCB concentration over time.

2.4. Outcomes

Information on childhood asthma, allergic rhinitis, atopic eczema, and respiratory infections was extracted from the National Patient Register (NPR) and the Danish National Prescription Registry (DNPR) (Wallach Kildemoes et al., 2011; Lynge et al., 2011). Information on relevant hospital diagnoses was obtained from the NPR from 1977 based on the International Classification of Disease (ICD) (ICD-8 from 1977 and ICD-10 from 1994). NPR holds information on all inpatient hospital admissions in Denmark since 1977 and outpatient and emergency contacts since 1995 (Lynge et al., 2011). Diseases treated in general practice are not registered and were instead approximated by redeemed prescriptions using Anatomical Therapeutic Chemical (ATC) Classification codes in the DNPR, where information on all redeemed drug prescriptions from Danish pharmacies from 1994 and onwards is available (Wallach Kildemoes et al., 2011). Asthma was defined based on a diagnosis of asthma and status asthmaticus from the NPR or claims of at least two prescriptions of any anti-asthmatic medication within one year obtained from DNPR (Table S1). Allergic rhinitis was identified using a modified version of an algorithm developed in previous studies based on hospital diagnoses from NPR or claims of prescribed medication from

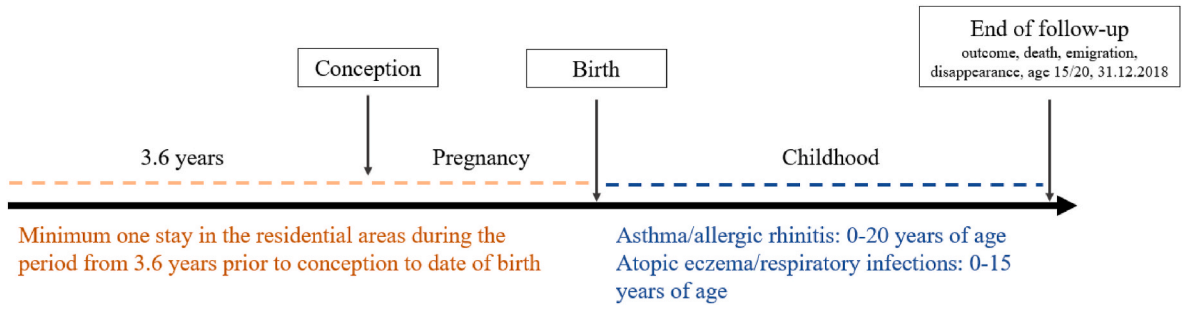

Fig. 1. Inclusion criteria and follow-up period for the selected outcomes.

Table 1
PCB concentrations in indoor air in contaminated and reference apartments of Farum and Brøndby.

	Farum		Brøndby	
	Median ng/m^3 (p_5; p_{25}; p_{75}; p_{95})		Median ng/m^3 (p_5; p_{25}; p_{75}; p_{95})	
	Contaminated apartments	Reference apartments	Contaminated apartments	Reference apartments[a]
Number of measurements	83	20	117	18
Lower-chlorinated-PCBs (tri-tetra chlorinated)				
PCB-28	61 (28; 42; 105; 211)	<LOQ (<LOQ; <LOQ; <LOQ; 2.3)	120 (26; 74; 180; 330)	–
PCB-52	95 (33; 56; 137; 294)	<LOQ (<LOQ; <LOQ; 1.6; 3.1)	130 (24; 73; 210; 330)	–
Higher-chlorinated PCBs (penta chlorinated)				
PCB-101	9 (3; 6; 17; 34)	<LOQ (<LOQ)	7 (1; 4; 13; 26)	–
PCB-118	1.2 (<LOQ; 0.7; 2;6)	<LOQ (<LOQ)	<LOQ (<LOQ; <LOQ; 1.3; 3,1)	–
PCB-138	<LOQ (<LOQ)	<LOQ (<LOQ)	<LOQ (<LOQ; <LOQ; <LOQ; 1.8)	–
PCB-153	<LOQ (<LOQ)	<LOQ (<LOQ)	<LOQ (<LOQ; <LOQ; <LOQ; 2.1)	–
PCB-180	<LOQ (<LOQ)	<LOQ (<LOQ)	<LOQ (<LOQ)	–
Summary measures				
PCB_7[b]	174 (67; 109; 270; 559)	4 (3; 4; 6; 8)	259 (57; 152; 392; 683)	–
PCB_{total}[c]	871 (334; 545; 1352; 2794)	20 (16; 19; 29; 40)	1298 (287; 759; 1958; 3414)	32 (2; 8; 87; 139)

[a] No data on individual congeners available in Brøndby.
[b] Sum of PCB-28, 52, 101, 118, 138, 153, 180.
[c] 5 × (PCB-28, 52, 101, 118, 138, 153, 180); Abbreviations: LOQ, limit of quantification; P, percentile; PCB, polychlorinated biphenyls; Values below the LOQ were replaced by LOQ/2.

DNPR (Stensballe et al., 2017; Henriksen et al., 2015): At least one of the following criteria needed to be fulfilled for a child to be identified as having allergic rhinitis: (1) a hospital diagnosis of allergic rhinitis or chronic rhinitis, (2) at least two prescriptions of intranasal corticosteroids within one year, (3) at least two prescriptions of oral antihistamines within one year, (4) at least one prescription of ophthalmic antihistamine (Table S1 for specification). Atopic eczema and respiratory infections were identified based on hospital diagnoses (ICD-8 and ICD-10) from the NPR (Table S1).

2.5. Covariates

From the Danish registers, we obtained the following information: maternal age at birth (continuous); maternal highest attained educational level at birth (short [7–10 years], medium [11–12 years], long [>12 years], vocational training); maternal ethnicity (Danish, Western, non-Western); parity (1, ≥2), and maternal atopy (asthma, allergic rhinitis, and atopic eczema identified in NPR and DNPR using the same criteria as for the children). Information on maternal smoking in the first trimester was available from the Danish Medical Birth Register (MBR) since 1991 and maternal pre-pregnancy Body Mass Index (BMI) from 2003 (Bliddal et al., 2018). Information on the children's date of birth, sex, death, disappearance (individuals whose residence is unknown to Danish authorities), and emigration was retrieved from the Danish Civil Registration System (Pedersen, 2011).

2.6. Statistical approach

Characteristics of the children are presented according to maternal exposure status. We calculated pseudo-percentiles for PCB exposure and maternal age based on the mean of the five values nearest to the actual value, according to local regulations (GDPR, Regulation EU, 2016/679 of May 25, 2018). To take into account differences in time to disease and right censoring, associations between maternal PCB exposure and asthma, allergic rhinitis, atopic eczema, and respiratory infections, respectively, were analysed using Cox regression with age as the underlying timescale. Follow-up started at the date of birth and continued until the date of the first diagnosis of the outcome in question, age 20 years (asthma and allergic rhinitis) or 15 years (atopic eczema and respiratory infections), death, emigration, disappearance, or end of follow-up on December 31, 2018, whichever occurred first. We estimated hazard ratios (HR) and corresponding 95 % confidence intervals (CI) per interquartile range (IQR) increase of maternal PCB_{year} accumulated prior to birth of the child. As this approach assumed a linear relation between PCB_{year} and outcome, we also assessed PCB_{year} as a continuous variable using a restricted cubic spline with four equal knots. Correlations between siblings were accounted for in all analyses by applying robust standard errors when calculating confidence intervals. The assumption of proportional hazards was tested using scaled Schoenfeld residuals. Prior to analyses, potential confounders were identified through review of the literature, and assessed using Directed Acyclic Graphs (Fig. S1) (Greenland et al., 1999). Factors predictive of both exposure and outcome were considered possible confounders. Consequently, all analyses were adjusted for child age (timescale), maternal age at time of birth, ethnicity, atopy status, parity, and calendar period. Due to the relatively high proportions of missing data on maternal educational attainment (19 %), which did not become available in the registers until 1981, maternal education at time of birth was

included in a separate step.

We also performed several sensitivity analyses to test the robustness of our findings. To take potential confounding by maternal smoking in the first trimester into account, we further adjusted all analyses for maternal smoking for children born after 1991, where smoking information (no/yes) became available in the MBR (Bliddal et al., 2018). Similarly, to account for confounding by body fat composition, which can be related to blood levels of PCB due to the lipophilicity of PCBs (Koh et al., 2016), we restricted our analyses to children born after 2003 when the information on pre-pregnancy BMI became available in the MBR (Bliddal et al., 2018), and adjusted for pre-pregnancy BMI ($\leq$18.5, 18.6–24.9, and $\geq$25 kg/m^2). Due to PCBs' endocrine disrupting properties and reports that prenatal PCB exposure interferes with sex hormone levels in both boys and girls, and hence potentially the children's immune response (Eskenazi et al., 2017; Tang et al., 2018; Warembourg et al., 2016; Bonds and Midoro-Horiuti, 2013), we repeated all analyses stratified by the sex of the child. As it is challenging to diagnose children with asthma before the age of three years (Martinez et al., 1995), we conducted sensitivity analyses only including asthma in children three years and above, where diagnoses are considered more valid. To mitigate any potential contribution from PCB exposure in early life, we excluded children who resided in contaminated apartments during the first five years of their life. Lastly, to assess the impact of the less comprehensive identification of asthma and allergic rhinitis prior to 1995 (diagnoses only available from the NPR and only as inpatients), we restricted analyses to individuals born from 1995, from when we began identification of cases based on diagnoses in the NPR and redeemed prescriptions from the DNPR. All analyses were conducted using SAS Institute version 9.4.

3. Results

Of the 20,232 children born after their mothers' first relocation to the residential areas, 8357 children fulfilled the inclusion criteria of being exposed or unexposed during the defined observation window. We further excluded 375 children with missing information on maternal ethnicity or born before 1977, the year the NPR was established. The final study population consisted of 7982 children. Characteristics of the children and their mothers are summarised according to maternal exposure in Table 2. A total of 20 % of the children had mothers residing in contaminated apartments prior to birth and half of the children were girls. Exposed and unexposed children were similar with respect to maternal age, education, and parity. There was a small difference in maternal ethnicity, since more exposed compared to unexposed children had mothers of Danish origin.

3.1. Maternal PCB exposure and asthma, allergic rhinitis, atopic eczema, and respiratory infections

We identified 1092 cases of asthma (14 %), 1310 cases of allergic rhinitis (16 %), 69 cases of atopic eczema (1 %), and 2547 cases of respiratory infections (32 %) (Table 3). The median PCB_{year} ranged from 0 to 30,162 ng/m^3 $\times$ year, with a median of 55 ng/m^3 $\times$ year. Other key percentiles were 5th: 3, 25th: 17, 75th: 225, 95th: 4493 ng/m^3 $\times$ year. We found no association between maternal exposure to PCB in indoor air and any of the studied allergic and respiratory outcomes: adjusted HR per IQR increase (208 ng/m^3 $\times$ year) in PCB_{year} for asthma: 1.00 (95 % CI: 1.00–1.01); allergic rhinitis: 1.00 (95 % CI: 1.00–1.01); atopic eczema: 0.99 (95 % CI 0.97–1.01); respiratory infections: 1.00 (95 % CI: 1.00–1.00) (Table 3). Cubic splines revealed no departure from linearity (Fig. 2). Results from the sensitivity analyses were similar to those from the main analyses, except for the sex stratified analyses where we observed a slightly lower risk of atopic eczema in boys (HR per IQR increase (203 ng/m^3 $\times$ year) in PCB_{year}: 0.94 (95 % CI: 0.88–1.00)) (Tables S2–S7).

Table 2
Characteristics of the 7982 children born by mothers residing in Farum Midtpunkt and Brøndby Strand Parkerne, overall and according to maternal PCB exposure status.

	Total population	Children with mothers in contaminated apartments	Children with mothers in reference apartments
Children, N (%)	7982	1619 (20)	6363 (80)
Child sex, % girls	49	49	49
Maternal age at birth[a]	27 (20; 37)	27 (20; 37)	27 (20; 37)
Maternal education at birth, n (%)			
Short (7–10 years)	2723 (42)	550 (43)	2173 (42)
Medium (11–12 years)	738 (11)	133 (10)	605 (12)
Long (13+ years)	1409 (22)	258 (20)	1151 (22)
Vocational training	1599 (25)	339 (26)	1260 (24)
Missing	1513	339	1174
Maternal ethnicity, n (%)			
Danish	5297 (66)	1157 (71)	4140 (65)
Western	387 (5)	48 (3)	339 (5)
Non-western	2298 (29)	414 (26)	1884 (30)
Parity, n (%)			
1	4396 (55)	900 (56)	3496 (55)
$\geq$2	3586 (45)	719 (44)	2867 (45)
Calendar year of birth, n (%)			
1977–1979	728 (9)	186 (11)	542 (9)
1980–1989	2310 (29)	475 (29)	1835 (29)
1990–1999	2139 (27)	458 (28)	1681 (26)
2000–2009	1584 (20)	331 (20)	1253 (20)
2010–2018	1221 (15)	169 (10)	1052 (17)

Abbreviations: PCB, polychlorinated biphenyls; N, Numbers.
[a] Pseudo-percentiles calculated as the mean of the five values nearest to the actual percentile.

4. Discussion

In this first study to examine maternal PCB exposure in indoor air during pregnancy and offspring immunological outcomes, we found no associations between maternal PCB exposure and offspring development of asthma, allergic rhinitis, atopic eczema, and respiratory infections during childhood.

4.1. Comparison with previous studies

Few studies have previously explored the association between prenatal exposure to LC-PCBs and immunological outcomes. Our null findings contrast that of a Swedish study of 190 infants that found prenatal exposure to the LC-PCBs, PCB-28 and -52, measured in maternal serum during pregnancy, to be positively associated with respiratory infections reported by the mothers and higher levels of total white blood cells, lymphocytes, and monocytes in the children's blood (Glynn et al., 2008). Our use of an indirect measure rather than a measure of the internal burden of exposure may have resulted in misclassification and thus have caused us to underestimate the true association. Alternatively, LC-PCBs might induce only subtle changes in immune system components and mainly increase the incidence of less severe infections, e.g., as observed in the Swedish study, changes which would not manifest in the present study where outcomes are based on hospital registrations, and hence, the more severe cases of disease. Our findings also contrast those of an American study showing increased

Table 3
Maternal exposure to PCB_{year} [a] in indoor air and hazard ratio of developing childhood asthma, allergic rhinitis, atopic eczema, and respiratory infections among 7982 children.

	Cases, n (%)	Crude HR[b] (95 % CI)	Adjusted[c] HR[b] (95 % CI)	Cases[d], n (%)	Adjusted[d] HR[e] (95 % CI) + education
Asthma	1092 (14)	1.00 (1.00–1.01)	1.00 (1.00–1.01)	974 (15)	1.00 (1.00–1.01)
Allergic rhinitis	1310 (16)	1.00 (1.00–1.01)	1.00 (1.00–1.01)	1117 (17)	1.00 (1.00–1.01)
Atopic eczema	69 (1)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	59 (1)	1.00 (0.98–1.01)
Respiratory infections	2547 (32)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	2126 (33)	1.00 (0.99–1.00)

Abbreviations: PCB, Polychlorinated Biphenyls; HR, Hazard Ratios; CI, Confidence Intervals.
[a] PCB_{year} = PCB_{total} ng/m^3 × year (PCB_{total} = 5 × (PCB28, 52, 101, 118, 138, 153, 180)).
[b] HR and 95 % CI per interquartile range increase (208 PCB_{total} ng/m^3 × year) in PCB_{year}.
[c] Adjusted for child age (timescale), maternal age at birth, ethnicity, atopy status, parity, and calendar period.
[d] Additional adjusted for maternal education only available from 1981 (N = 6469).
[e] HR and 95 % CI per interquartile range increase (218 PCB_{total} ng/m^3 × year) in PCB_{year}.

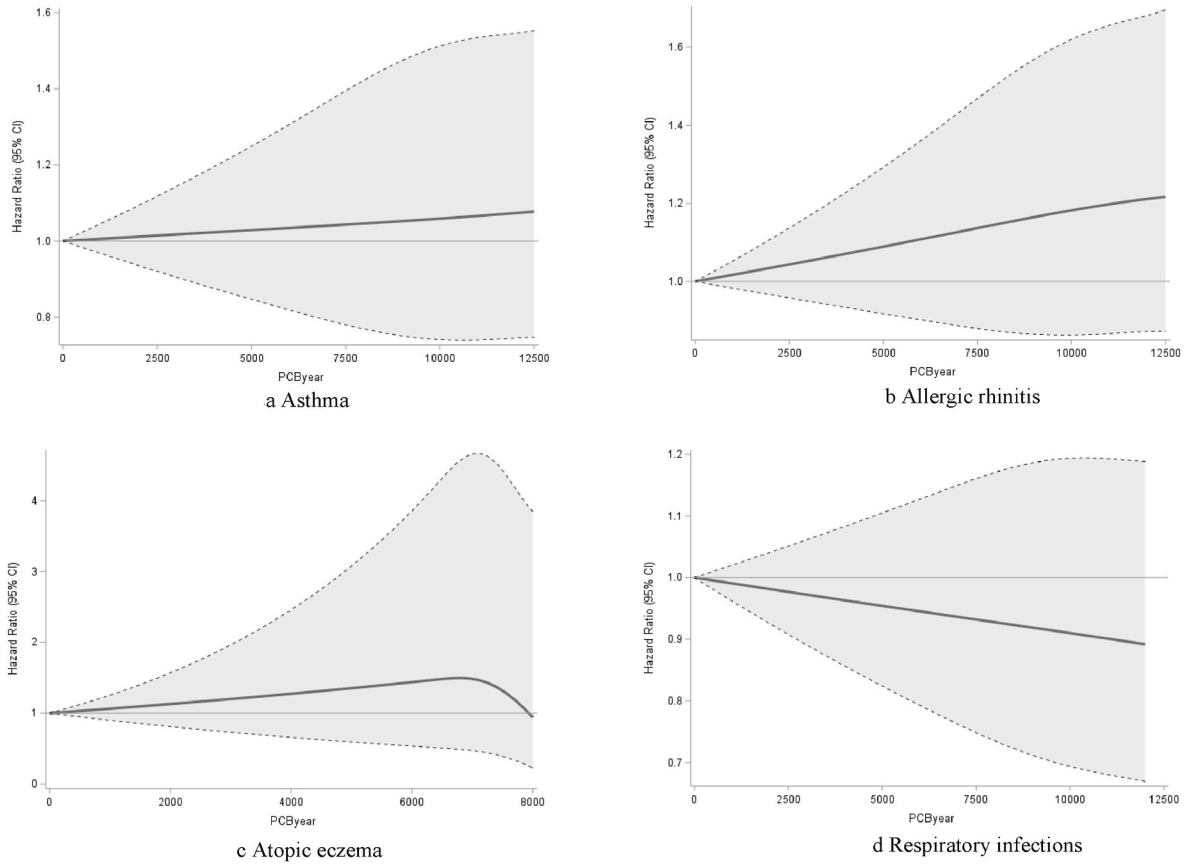

Fig. 2. Risk of asthma, allergic rhinitis, atopic eczema, and respiratory infections according to PCB^{a}_{year} in the HESPAIR cohort. Hazard ratios (HR) (black line) with 95 % confidence intervals (CI) (grey shaded area) estimated using restricted cubic splines with four equally placed knots. Adjusted for child age (timescale), maternal age at birth, ethnicity, atopy status, parity, and calendar period. Individuals with exposure >12,500 ng/m^3 (>8000 ng/m^3 for atopic eczema) were excluded in visualisation of splines due to small numbers. [a]PCB_{year} = PCB_{total} ng/m^3 × year (PCB_{total} = 5 × (PCB28, 52, 101, 118, 138, 153, 180)).

odds of self-reported asthma, eczema/hay fever, and ear infections in offspring of women employed at a capacitor manufacturing plant (Parker-Lalomio et al., 2018). However, this study was unable to isolate the effect of PCBs from concurrent exposure to potentially interacting heavy metals and chlorinated naphthalenes (Parker-Lalomio et al., 2018). Also, while it is assumed that occupational exposure occurs predominantly through the inhalation and dermal routes, this latter study did not measure the exposure's composition of PCB congeners. The mothers' exposure may therefore not have been attributable solely to LC-PCBs. Lastly, our findings differ from those of a Chinese case-control study of 855 children that reported positive associations between levels of several LC-PCBs (PCB−8, −44, −49, −52, −60, −66, −70, −77, −82, −87) in the blood of the 3- to 6-year-old children and childhood asthma (Meng et al., 2016a). However, when PCB levels in indoor dust were examined in homes of a subsample of the children from the Chinese study, no associations between PCB-8 and -49 and childhood asthma were identified (Meng et al., 2016b). While not directly comparable, as the Chinese studies examined childhood and not prenatal exposure, the difference in findings in the biologically verified versus the indirectly estimated exposure further indicate that misclassification may explain the absence of observed effects in the present study. On the other hand, since PCB levels measured in biological samples not only reflect external exposure, but also factors like metabolization and body composition (Christensen et al., 2021), results based on serum measurements may, however, not be directly comparable with results from studies based on air measurements.

In sensitivity analyses, we observed a slightly lower risk of atopic eczema for boys but not for girls. As some PCB congeners have been suggested to exert immunosuppressive effects (Crinnion, 2011), exposure could be hypothesised to lower the risk of immune hyperactivity diseases, such as atopic eczema. Whether this should only be the case for boys is not supported in the literature. A recent study from Greece found a higher risk of eczema at 4 years of age among girls prenatally exposed to HC-PCBs, while no association was found among boys (Margetaki et al., 2022). Since we did not observe this pattern for the other immune hyperactivity diseases of asthma and allergic rhinitis, we interpret the observed sex difference with caution.

Another challenge in comparison between studies investigating PCB, is that PCBs constitute a large group of congeners, which can be divided into separate groups based on, e.g., their toxicological properties (dioxin-like vs. non-dioxin-like) or degree of chlorination (e.g., HC-PCBs vs. LC-PCBs) (Klocke and Lein, 2020). Depending on their chemical properties, individual congeners may exert differential biological effects. This may hamper the comparability of our findings to those of others in case the congener profiles differed in composition between studies and may explain why our results differ from that of studies of HC-PCBs. The dioxin-like PCBs, of which 10 out of 12 are HC-PCBs, exert their main effects through interaction with the aryl hydrocarbon receptor (AhR), potentially triggering immune reactions with relevance for, e.g., development of allergy and inflammatory processes (Chiba et al., 2012). In contrast, the immunotoxic mechanisms and effects of the non-dioxin-like PCBs, which constitute most of the LC-PCBs in indoor air, remain poorly understood. One *in vitro* study demonstrated PCB-28 and PCB-52, but not the dioxin-like PCB-77, to cause rapid cell death among rat thymocytes in a dose-dependent manner, which may represent AhR-independent immunosuppression of non-dioxin-like PCBs (Tan et al., 2004).

4.2. Methodological considerations

The main methodological concerns of the HESPAIR cohort have been thoroughly addressed in previous studies (Deen et al., 2022, 2023a, 2023b; Kofoed et al., 2021; Tøttenborg et al., 2022). In brief, these include potential non-differential misclassification of the PCB exposure and inadequate adjustment for important confounders that cannot be retrieved from the registers.

We tried to account for potential confounding from maternal smoking and BMI in sensitivity analyses of a subset of children for whom this information was available in the MBR, which showed no influence of these two factors. Residual confounding could still be present in these analyses though, since the information is based on a rather restricted subsample and the information may be inadequate as there is a stigma related to given information on smoking to health care providers. The cohort's unique natural design where residents unknowingly relocated to apartments constructed with or without PCB containing building materials, also minimizes the impact of potential unmeasured confounders. Previous analyses of subsamples of the cohort support this assumption, showing that factors such as socioeconomic characteristics and health behaviours are likely similar between exposure groups (Meyer et al., 2013; Frederiksen et al., 2020). Further, adjustment for maternal education, which is considered the most appropriate measure of socioeconomic status for young individuals (Galobardes et al., 2006), also minimized influence of residual confounding from health behaviours like smoking and diet since they are closely related.

We used strict inclusion criteria based on the half-lives of the LC-PCB, PCB-28, to ensure that the mothers had circulating PCB concentrations while carrying the child. Nonetheless, given that we extrapolated PCB air measurements to the individual level, it would have been optimal (although not feasible) to have access to maternal blood samples collected during pregnancy for quantifying PCB body burden, since maternal activities outside of the residential areas could have influenced their exposure to PCBs up to and during pregnancy. For instance, residents could have visited each other, worked in a PCB contaminated building, or may have lived or spent much time elsewhere, which could have affected their PCB body burden. Since we only have data on the mothers' addresses while residing at the estates, it is not possible to account for reference mothers' previous or subsequent residence in housing with higher levels of PCB. If mothers classified as unexposed had previously lived in a contaminated building, their exposure would be misclassified, since they would, in fact, have been exposed. Consequently, if PCB truly increases the risk of immune related diseases, such misclassification would likely attenuate the effect estimates. However, due to the natural experimental design, residents of contaminated and reference apartments are expected to have similar probabilities of prior and future residence in PCB contaminated homes and of occupational PCB exposure. This is supported by a previous study of a subsample of residents from Farum, where hours spent away from home showed equal distributions in the two groups (Frederiksen et al., 2012). PCB measurements were taken at a single time point and extrapolated to several years, which may have introduced some misclassification, since the temporal development of PCB concentration in indoor air is not fully uncovered. A Danish study using indoor air measurements from the Brøndby estates, found some variation in concentration over time, but no general trend was observed, and the variation may be related to maintenance activities rather than temporal development (Andersen et al., 2021). This misclassification is assumed to be unrelated to the outcomes of interest and may have led to an underestimation of the differences between exposure groups.

Sensitivity analyses excluding postnatally exposed children, did not reveal any potential impact of early life exposure to LC-PCB. However, this analysis only considered exposure within the residential areas and did not account for potential exposure in daycare and schools, and other indoor environments. Nevertheless, given that less than 1.5 % of all Danish buildings have indoor air PCB levels exceeding the Danish Health Authority's action level of 300 ng/m^3 (Langeland and Jensen, 2013), we consider this to have minimal impact on the findings.

We used valid and objective register-based information for all outcomes, which reduced bias related to self-report and recall as well as reflected more certain and severe cases than would have been obtained from self-reported information (Laugesen et al., 2021). For asthma and allergic rhinitis, hospital diagnosed cases were supplemented with cases identified by redeemed prescriptions of relevant medication to capture those treated in general practice. Hence, we may have higher sensitivity, but lower specificity compared to use of hospital diagnoses only. Information on prescribed medication did, however, not become available until 1995. Sensitivity analyses of asthma and allergic rhinitis restricted to children born from 1995 suggested no substantial impact of the less comprehensive identification of asthma and allergic rhinitis prior to 1995. The algorithm for identifying allergic rhinitis has been validated against a gold standard (positive serum specific IgE ($\geq$0.35)) among Danish adults (18–69 year) (Leth-Møller et al., 2020). They found a sensitivity of 25 % (95 % CI: 0.23–0.27) and a specificity of 93 % (95 % CI: 0.92–0.94). This study is, however, based on adults during the years 2006–2008 and 2012–2015 and may therefore not be directly comparable to our study based on children with allergic rhinitis identified already from 1977. For respiratory infections and atopic eczema, cases were based solely on hospital diagnoses, capturing only a subset of more severe disease while not considering milder cases. This definition likely led to a considerable underestimation, as these milder cases would typically be treated by general practitioners or practicing dermatologist. Nevertheless, the positive predictive value of hospital diagnoses of atopic eczema in the Danish registers is 98 % according to a study of 52 children (Andersen et al., 2019). Our inclusion of asthma cases already from birth may have identified cases of asthmatic bronchitis during the first years of life that may not necessarily lead to asthma disease later in childhood. This was addressed in a sensitivity analysis restricted to asthma cases in children three years and above. This did not alter the results from the main analyses, indicating only minimal potential

influence from misclassified asthma diagnoses during the first years of life.

4.3. Public health implications

While the findings of this paper may appear reassuring for the many individuals living or working in PCB contaminated indoor environments, they should be interpreted with caution due to the indirect measure of exposure and incomplete registration of diagnoses. These limitations may have introduced bias, potentially attenuating the results. As the dietary exposure to PCB is expected to decline, exposure through inhalation will constitute an even larger proportion of the total PCB exposure in the future (Weitekamp et al., 2021), emphasising the importance to specifically study airborne LC-PCBs. This study is part of a broader investigation of the health effects of LC-PCBs in indoor air. Their findings should be considered alongside the growing evidence from experimental LC-PCB studies when reevaluating the current action limits for PCB in indoor air, as these are currently based on studies of HC-PCBs in food. Recently, Germany lowered action levels for PCB in indoor air from 300 (precautionary value) and 3000 ng/m^3 (health hazard value) to 80 and 800 ng/m^3 respectively, based on research on airborne PCBs from animal, epidemiological, and exposure studies (Richtwerte für Polychlorierte Biphenyle, 2025).

5. Conclusion

In conclusion, we did not find evidence to support an impact of maternal exposure to PCBs from indoor air on childhood asthma, allergic rhinitis, atopic eczema, and respiratory infections in offspring. While these findings may appear reassuring for the considerable number of people living or working in PCB contaminated indoor environments, they should be interpreted with caution due to the indirect measure of exposure, incomplete registration of diagnoses, and lack of comparable literature.

CRediT authorship contribution statement

Laura Deen: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Karin Sørig Hougaard:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Harald William Meyer:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Camilla Sandal Sejbæk:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Kajsa Ugelvig Petersen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Marie Frederiksen:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Jens Peter Bonde:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Marie Standl:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Claudia Flexeder:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sandra Søgaard Tøttenborg:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2025.114567.

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