



Prenatal exposure to organochlorine compounds and lung function during childhood



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ABSTRACT

Introduction: Prenatal exposure to organochlorine compounds (OCs) can increase the risk of reported respiratory symptoms in children. It remains unclear whether these compounds can also impact on lung function. We assessed the association between prenatal exposure to OCs and lung function during childhood.

Methods: We included 1308 mother-child pairs enrolled in a prospective cohort study. Prenatal concentrations of *p,p'*-dichlorodiphenyltrichloroethane [*p,p'*-DDT], *p,p'*-dichlorodiphenyldichloroethylene [*p,p'*-DDE], hexachlorobenzene [HCB], and seven polychlorinated biphenyls [PCBs] were measured in cord blood. Spirometry was performed in the offspring at ages 4 (n = 636) and 7 years (n = 1192).

Results: More than 80% of samples presented quantifiable levels of *p,p'*-DDE, HCB, PCB-138, PCB-153, and PCB-180; *p,p'*-DDE was the compound with the highest median concentrations. At 4 years, prenatal *p,p'*-DDE exposure was associated with a decrease in forced expiratory volume in 1 s (FEV₁) in all quartiles of exposure (e.g., third quartile [0.23–0.34 ng/mL]: β for FEV₁ –53.61 mL, 95% CI –89.87, –17.35, vs. the lowest). Prenatal *p,p'*-DDE levels also decreased forced vital capacity (FVC) and FEV₁/FVC, but associations did not reach statistical significance in most exposure quartiles. At 7 years, *p,p'*-DDE was associated with a decrease in FVC and FEV₁ in only the second quartile of exposure (e.g. β for FEV₁ –36.96 mL, 95% CI –66.22, –7.70, vs. the lowest). Prenatal exposure to HCB was associated with decreased FVC and FEV₁, but in only the second quartile and at 7 years (e.g. [0.07–0.14 ng/mL]: β for FEV₁ –25.79 mL, 95% CI –55.98, 4.39, vs. the lowest). PCBs were not consistently associated with lung function.

Conclusion: Prenatal exposure to *p,p'*-DDE may decrease lung function during childhood, especially FEV₁ and at medium levels of exposure. Further and deeper knowledge on the impact of environmental chemicals during pregnancy on lung development is needed.

1. Introduction

Respiratory diseases are among the leading causes of paediatric morbidity worldwide and the aetiology of some of them, such as

asthma, remains unclear (European Respiratory Society, 2017). Adverse environmental exposures such as air pollution and smoking during prenatal life have been associated with respiratory diseases and alterations in the lung development in childhood and adulthood (Gehring

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et al., 2015; Kajekar, 2007; Miller and Marty, 2010). Organochlorine compounds (OCs), synthetic persistent pollutants extensively used as pesticides, electrical insulators, and other industrial products until their ban in 1970s, have also been suspected to influence the development of the lung (Hansen et al., 2016). Exposure to environmental chemicals such as OCs during prenatal life may induce developmental adaptations of the lung and airways, leading to relatively small airways. Such adaptations could lead to a reduction in expiratory flows - reflected by lower lung function values - and consequently increasing the risk of adverse respiratory outcomes (Miller and Marty, 2010). Due to their persistence, OCs are still detectable in current populations' blood (Haug et al., 2018). General population is exposed mainly through diet, whereas fetuses and new-borns can be exposed to OCs through placental transfer and breastfeeding (Sunyer et al., 2005).

Several studies have assessed the effects of prenatal exposure to OCs on adverse respiratory outcomes in the offspring, mainly using parental-reported symptoms (Dallaire et al., 2006; Gascon et al., 2014a, 2014b, 2012; Hansen et al., 2016, 2014; Sunyer et al., 2010, 2006, 2005). These studies showed that prenatal exposure to OCs, particularly *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) but also hexachlorobenzene (HCB) and polychlorinated biphenyls (PCBs), can increase the risk of lower respiratory tract infections, wheeze, and asthma in children (Gascon et al., 2014a, 2014b, 2012; Sunyer et al., 2006, 2005) and asthma medication use in adults (Hansen et al., 2014), even at low exposure levels (Sunyer et al., 2005). Only one study assessed the impact of OCs exposure during prenatal life on lung function (Hansen et al., 2016). Authors observed that prenatal exposure to *p,p'*-DDE, HCB, and PCBs was associated with offspring reduced forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) ratio (increased risk of airway obstruction) at 20 years of age. In this cohort however, the sample size was quite small (n = 414) and the OCs concentrations were determined in the 80's and might not reflect current exposure (Hansen et al., 2016).

Investigating the effects of prenatal exposure to OCs on lung function is relevant because reduced lung function in infancy not only poses a burden of childhood morbidity but is also a risk factor for the development of chronic diseases during adulthood such as bronchial asthma (Antó et al., 2010; Martinez, 2009) and chronic obstructive pulmonary disease (Bui et al., 2017; Martinez, 2016). The present study therefore aims to estimate the association between exposure to OCs during pregnancy and lung function in childhood.

2. Material and methods

2.1. Study population

This study is based in three geographic areas belonging to the Spanish INMA (INfancia y Medio Ambiente - Environment and Childhood) population-based birth cohort: Gipuzkoa, Sabadell, and Valencia. Pregnant women attending for prenatal care visits during the first trimester of their pregnancy who fulfilled the eligibility criteria were invited to participate in the cohort between 2004 and 2008 (Guxens et al., 2012). Eligible women had to be 16 years or older, residing in the study area, willing to deliver in the reference hospital, not have followed assisted reproduction, not to be twin pregnant, and not have any communication problems.

For the present study, population was restricted to children with prenatal OCs concentrations measured in maternal serum drawn during pregnancy or in cord serum that additionally had available and acceptable lung function data at 4 or at 7 years of age. A total of 1308 children had available data on exposure and outcome at 4 or at 7 years (Fig. 1). The study was approved by the ethical committees of the centres involved in the study. Written informed consent was obtained from the parents of all children.

2.2. Prenatal OCs exposure assessment

Quantification of *p,p'*-dichlorodiphenyltrichloroethane (*p,p'*-DDT), *p,p'*-DDE, HCB, and several PCB congeners (PCB-28, -52, -101, -118, -138, -153, and -180) was determined in maternal or cord serum. Maternal serum samples were collected between the 7th and 26th week of pregnancy (median = 13 weeks; interquartile range (IQR) = 1.6) and cord serum samples were extracted at birth. Samples were analysed by gas chromatography methods described elsewhere (Goñi et al., 2007). Limits of detection (LOD) in Gipuzkoa and Sabadell were 0.073 ng/mL for all compounds and in Valencia they ranged between 0.01 and 0.071 ng/mL. *p,p'*-DDT and PCB congeners 28, 52, 101, and 118 presented detectable levels in < 25% of analysed samples and were excluded from the analyses. We therefore calculated the sum of PCBs (Σ PCB) as the sum of PCB-138, PCB-153, and PCB-180. Samples with *p,p'*-DDE, HCB, PCB-138, -153, and -180 concentrations below the LOD were imputed on a defined range between 0 and each corresponding LOD (data not shown). Since cord serum is considered the best proxy of OCs exposure during foetal life (Korrick et al., 2000), we estimated the equivalent concentrations in cord serum from the concentrations measured in maternal serum by applying cohort specific conversion factors using paired cord and maternal measurements available in Gipuzkoa and Valencia (Supplementary Methods 1).

2.3. Lung function assessment

Lung function was assessed from spirometry tests performed at 4 years (mean = 4.4 years, standard deviation (SD) = 0.2) in Gipuzkoa and Sabadell, and at 7 years in Gipuzkoa, Sabadell, and Valencia (mean = 7.4 years, SD = 0.5) following the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines (Miller et al., 2005). Children with at least one acceptable manoeuvre were included. Lung function parameters selected for the analyses were FVC (mL), FEV₁ (mL), and FEV₁/FVC (%).

2.4. Covariates

Information on maternal ethnicity, country of birth, education level, socio-economic status (coded according to the International Standard Classification of Occupations-88 system), smoking during pregnancy, alcohol consumption, history of allergy, rhinitis or eczema, age at delivery, and parity was obtained by questionnaires administered to the mothers at 12th and 32th weeks of pregnancy. Information on maternal diet was obtained from a 100-item semi-quantitative food frequency questionnaire administered to the mothers at 12th and 32th weeks of pregnancy. Measured maternal height and reported weight by the mother at the first trimester visit were used to calculate pre-pregnancy body mass index (BMI) (kg/m²). Gestational age, child's sex, and birth weight and height were obtained from clinical records. Preterm birth and low birth weight were defined as < 37 weeks of gestational age and < 2500 g at birth, respectively. Postnatal questionnaires provided information on number of breastfeeding, day care attendance, and doctor diagnosed asthma. Child's height and weight at 4 and 7 years were measured and age was recorded at the time of the spirometry test.

2.5. Statistical analysis

The analyses were performed separately for children who had outcome data at 4 years (n = 636) and at 7 years (n = 1192) (Fig. 1). The shape of the relationship between OCs and lung function was tested by General Additive Models (GAMs). None of the associations showed linearity (Supplementary Fig. S1) and therefore OCs concentrations were included in the models as exposure categories using age-specific quartiles as cut-offs. To reduce the likelihood of bias due to follow-up losses and missing data, we performed multiple imputations by chained equations of missing values for the covariates where 10 complete

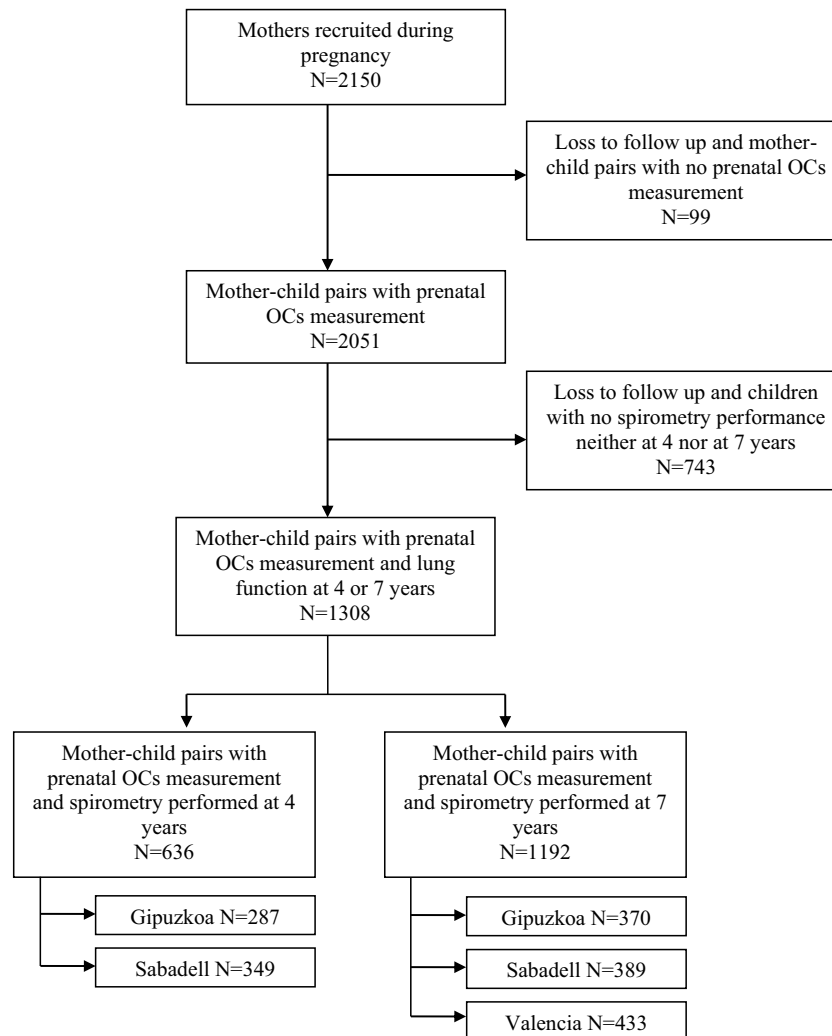


Fig. 1. Flowchart of the included study population.

datasets were generated (Supplementary Methods 2). Distributions among variables from the imputed and the observed datasets did not differ (Supplementary Table S1). Potential confounders, effect modifiers, and mediators of the association of interest were assessed by the construction of a directed acyclic graph (DAG) using DAGitty software (Supplementary Fig. S2) (Textor et al., 2011). Multivariable linear regression models were used to estimate the association between quartiles of OCs concentrations and lung function separately at 4 ($n = 636$) and 7 ($n = 1192$) years of age. Multivariable linear mixed models were used in the population with two lung function measurements available ($n = 520$) with random intercepts for subjects and cohorts. Covariates included in the models were those selected from the DAG: maternal age at delivery, maternal pre-pregnancy BMI, maternal educational level, maternal social class, maternal country of birth, parity, maternal lifestyle (smoking and alcohol consumption during pregnancy), and maternal diet (specifically fish, meat, vegetables and fruits). Additionally, models were adjusted for region of residence and child's sex, age, and height at the time of the lung function assessment because these child characteristics are the most important predictors of pulmonary function (Quanjer et al., 2012). Effect modification by preterm birth, low birth weight, maternal history of asthma, rhinitis or eczema, and child's sex was assessed through inclusion of the interaction terms in the models (p -value < 0.10) and stratified analyses, when possible. OCs can influence height of the child and hence potentially mediate the association of OCs and lung function (Balte et al., 2017). We therefore, tested whether height met the conditions to act as mediator: i) it was

associated with OCs; ii) it was associated with lung function and iii) after including it in the models as confounder the association was no longer significant. In case all these conditions were fulfilled we then performed mediation analysis. To assess the robustness of our results, various sensitivity analyses were performed. We performed all models again by using the complete case dataset, the lipid-adjusted OCs concentrations, the maternal serum concentrations, and the lung function parameters expressed as sex, height, age, and ethnicity -adjusted z-scores according to the Global Lung Function Initiative reference values (Quanjer et al., 2012). Models were also repeated by excluding children who were unable to perform reproducible spirometry tests and children with asthma. Finally, to differentiate the role of each OC, we performed a multipollutant model in which all main exposure variables (p,p' -DDE, HCB, and Σ PCB) were included.

3. Results

3.1. Study population

Children from the study population were representative of the total sample in terms of sex, gestational age, and birth weight, among other characteristics. Mothers included in the analyses were slightly older, had higher education levels but lower social class, and were more likely to be European in comparison to the total sample (Supplementary Table S2). Complete details of the characteristics of the study populations at 4 and 7 years are shown in Table 1. p,p' -DDE was the compound with the

Table 1
Maternal and child characteristics of the study populations at 4 and 7 years of age^a.

	4 years (n = 636)	7 years (n = 1192)
Maternal characteristics		
Age at delivery (years), mean (SD)	32.3 (3.8)	32.1 (3.9)
Pre-pregnancy BMI (kg/m ²), mean (SD)	23.3 (4.3)	23.5 (4.3)
Educational level, %		
Less than primary or primary	18.3	21.2
Secondary	37.4	40.4
University	44.2	38.3
Social class, %		
Low	27.5	25.3
Medium	32.4	29.2
High	40.1	45.5
Country of birth, %		
European	96.5	96.4
Non-European	3.5	3.6
Parity, %		
Nulliparous	57.6	56.6
Multiparous	42.4	43.4
Smoking during pregnancy, %		
Never smoker	49.8	46.2
Smoker before pregnancy	36.4	37
Smoker during pregnancy	13.9	16.8
History of asthma, rhinitis, or eczema, % yes	28.8	28
Diet (servings/day), mean (SD)		
Vegetables	4.9 (1.8)	4.9 (1.9)
Fish	0.7 (0.3)	0.7 (0.3)
Meat	1.1 (0.4)	1.1 (0.4)
Alcohol consumption (g/day), mean (SD)	0.3 (0.9)	0.3 (1.0)
Child characteristics		
Sex, % female	48.3	49.3
Gestational age (weeks), mean (SD)	39.9 (1.8)	39.9 (1.8)
Preterm, yes (< 37 weeks), mean (SD)	2.7	3.9
Birth weight (g), mean (SD)	3266 (423)	3257 (456)
Low birth weight, % < 2500 g	4.4	5.1
Breastfeeding, % yes	93	89.6
Day care attendance, % yes	87.8	83.1
Height at follow-up (cm), mean (SD)	106.3 (4.3)	125.3 (6)
Weight at follow-up (kg), mean (SD)	18.4 (2.7)	27.4 (5.6)
Ever asthma, % yes	2.9	6.2
FVC (L), mean (SD)	1.0 (0.2)	1.8 (0.3)
FEV ₁ (L), mean (SD)	0.9 (0.2)	1.5 (0.2)
FEV ₁ /FVC (%), mean (SD)	92.9 (6.7)	86.7 (6.7)
≥ 2 acceptable and reproducible manoeuvres, %	61.2	63.6

BMI: body mass index; SD: standard deviation; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s.

^a Values come from the observed dataset.

Table 2
Concentrations (ng/mL) of *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE), hexachlorobenzene (HCB), polychlorinated biphenyl congeners (PCB-138, PCB-153, PCB-180), and the sum of polychlorinated biphenyls (ΣPCB) in the study population^a.

	% < LOD	Minimum	p25	Median	p75	Maximum
<i>p,p'</i> -DDE	1.6	0.00	0.18	0.28	0.48	43.39
HCB	13.6	0.00	0.07	0.13	0.23	4.64
PCB-138	20.3	0.00	0.05	0.08	0.11	1.61
PCB-153	12.8	0.00	0.07	0.11	0.16	1.44
PCB-180	20.6	0.00	0.05	0.08	0.12	1.33
ΣPCB	–	0.01	0.18	0.28	0.39	4.02

LOD: limit of detection; p: percentile.

^a Cord serum concentrations (ng/mL) from mother-child pairs with prenatal OCs measurement and lung function assessment at 4 or 7 years of age (n = 1308). LODs in Gipuzkoa and Sabadell were 0.071 ng/mL and in Valencia ranged between 0.01 and 0.071 ng/mL.

highest median concentrations in cord blood (0.28 ng/mL; IQR = 0.3 ng/mL) (Table 2). HCB and the ΣPCB presented median concentrations of 0.13 ng/mL and 0.28 ng/mL, respectively. Among the three study regions, the highest median levels of OCs were observed in Valencia (Supplementary Table S3).

3.2. *p,p'*-DDE and lung function

At 4 years, prenatal exposure to *p,p'*-DDE seemed to be associated with a decrease in FVC in all quartiles of exposure compared to the lowest quartile, but associations did not reach statistical significance (e.g. fourth quartile [> 0.35 ng/mL] $\beta -37.56$ mL, 95% CI $-80.58, 5.46$) (Fig. 2a and Supplementary Table S4). Prenatal exposure to *p,p'*-DDE was associated with a decrease in FEV₁ in all quartiles of exposure compared to the lowest quartile (e.g. fourth quartile $\beta -42.82$ mL, 95% CI $-80.65, -4.99$) (Fig. 2a and Supplementary Table S4). Being exposed to the second and third quartiles of *p,p'*-DDE concentrations were also associated with decreased FEV₁/FVC, compared to the lowest quartile; however only the third quartile showed statistical significance (e.g. third quartile [0.23–0.34 ng/mL] $\beta -2\%$, 95% CI $-3.5, -0.5$) (Fig. 2a and Supplementary Table S4). At 7 years, children exposed to the second quartile of *p,p'*-DDE concentrations (0.17–0.28 ng/mL), had a decreased FVC and FEV₁ (β for FVC -39.45 mL, 95% CI $-71.23, -7.66$; and FEV₁ -36.07 mL, 95% CI $-65.21, -6.92$) compared to the lowest quartile of exposure; such associations were not observed in children exposed to the third and fourth quartiles (Fig. 2a and Supplementary Table S4). No association was observed for FEV₁/FVC at 7 years. In children with two available lung function measurements (n = 520), we observed an overall association between prenatal exposure to the second and third quartiles of *p,p'*-DDE and reduced FEV₁ (e.g. third quartile [23–34 ng/mL] $\beta -37.17$ mL, 95% CI $-71.92, -2.42$), although results on the second quartile were borderline statistically significant ([0.14–0.23 ng/mL] $\beta -33.82$ mL, 95% CI $-68.22, 0.59$) (Table 3). We did not observe any associations with FVC nor FEV₁/FVC (Table 3).

3.3. HCB and lung function

At 4 years, cord blood HCB seemed to be related to reduced FVC and FEV₁, particularly in the third and fourth quartiles, when compared to the lowest exposed group, although associations did not reach statistical significance (Fig. 2b and Supplementary Table S4). HCB was not associated with FEV₁/FVC at 4 years. At 7 years, only children exposed to the second quartile of HCB concentrations (0.07–0.14 ng/mL) had reduced FVC and FEV₁ (e.g. β for FVC -56.68 mL, 95% CI $-89.87, -23.49$) and increased FEV₁/FVC ($\beta 1.24\%$, 95% CI 0.14, 2.34) (Fig. 2b and Supplementary Table S4) but no associations were observed among the third and fourth quartiles of exposure. In the multivariate linear mixed models we did not observe any association between HCB and lung function (Table 3).

3.4. PCBs and lung function

Regarding PCBs, no consistent associations were observed between any of the analysed PCBs, including the ΣPCB, and lung function parameters neither at 4 nor at 7 years (Fig. 2c and d, and Supplementary Fig. S3 and Table S4). We only observed an increase in FEV₁/FVC ratio at 7 years ($\beta 1.2\%$, 95% CI 0.1, 2.3) associated with being exposed to the second quartile of PCB-153 concentrations (0.08–0.12 ng/mL) compared to the lowest quartile (Fig. 2c and Supplementary Table S4). No associations were observed in the analysis considering those children with two available lung function measurements (Table 3).

3.5. Additional analyses

Interaction and stratification analyses could only be performed for

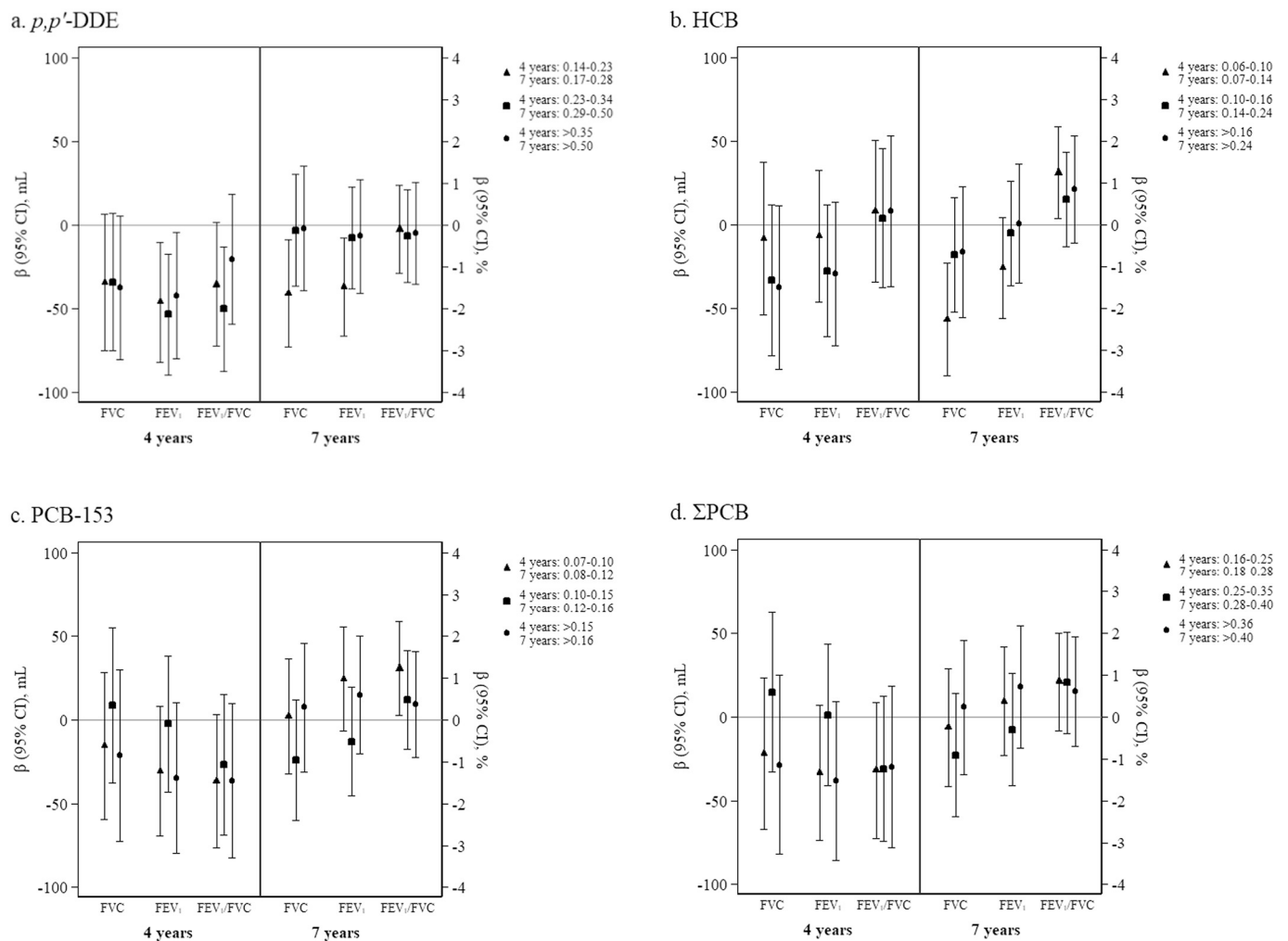


Fig. 2. Associations (β (95% CI)) between cord serum p,p' -DDE (a), HCB (b), PCB-153 (c), and Σ PCB (d), in quartile ranges (ng/mL), and lung function at 4 ($n = 636$) and 7 ($n = 1192$) years of age^a.

^aModels adjusted for children's region of residence, sex, age and height at the time of the lung function assessment, maternal age at delivery, maternal pre-pregnancy BMI, maternal educational level, maternal social class, maternal country of birth, parity, maternal smoking during pregnancy, maternal diet, and maternal alcohol consumption. Values represent mL for FVC and FEV₁ and % for FEV₁/FVC.

child's sex due to the low number of preterm, low birth weight babies, and mothers with history of asthma, rhinitis or eczema in each quartile of exposure. Child's sex did not show any interaction in our associations of interest (data not shown). Height was not associated with any quartile of OCs and hence we did not perform subsequent mediation analysis.

Overall, effect estimates did not change in complete case analyses (Supplementary Table S5), using the lipid-adjusted OCs concentrations (data not shown), the maternal serum concentrations (Supplementary Table S5), and the lung function standardised z-scores (Supplementary Fig. S4). Results were similar after excluding those children who were not able to perform reproducible spirometry tests (Supplementary Table S6) and children with asthma (data not shown). Finally, results remained robust when models were adjusted for all main OCs together (data not shown).

4. Discussion

In this prospective study, we observed that prenatal exposure to p,p' -DDE was associated with reduced FEV₁ and also with reduced FVC and FEV₁/FVC at 4 years, although most of the associations with FVC and FEV₁/FVC did not reach statistical significance. Prenatal p,p' -DDE levels also reduced FVC and FEV₁ at 7 years but only at medium levels of

exposure. Additionally, HCB seemed to be associated with reduced FVC and FEV₁ at certain exposure levels at both ages, but most of the associations were borderline statistically significant. Inconsistent results were observed among analysed PCBs.

To our knowledge, only one study has assessed the effects of prenatal exposure to OCs and lung function in the offspring (Hansen et al., 2016). In a Danish birth cohort of 414 participants established in the 80s, they observed an increased risk of airway obstruction (FEV₁/FVC < 75%) at 20 years of age associated with exposure to very high concentrations of p,p' -DDE, HCB, and PCBs (e.g. p,p' -DDE = 3.2–38.8 ng/mL). They did not find any association with reduced FEV₁ (% predicted value < 90%). Two other studies have assessed postnatal exposure to p,p' -DDE in relation to lung function and found decreases in FVC and FEV₁ with increasing blood concentrations of p,p' -DDE in adults ($n = 1696$; median = 152 ng/g lipid; IQR = 213.1) (Ye et al., 2015) and in school-aged children ($n = 328$; median = 0.30 ng/mL, IQR = 0.2) (Balte et al., 2017). These two studies did not assess neither HCB nor PCBs (Balte et al., 2017; Ye et al., 2015). In our study we observed a reduction in lung function, especially in FEV₁, at pre-school and school ages in relation to prenatal p,p' -DDE concentrations around 0.30 ng/mL, at similar concentrations and even lower than these previous studies. These associations were not seen at higher p,p' -DDE exposure levels in the case of 7-year-old children. We

Table 3

Associations (β (95% CI)) between cord serum p,p' -DDE (a), HCB (b), PCB-153 (c), and Σ PCB (d), in quartile range (ng/mL), and lung function during childhood in children with repeated measurements (n = 520)^a.

	FVC (mL)	FEV ₁ (mL)	FEV ₁ /FVC (%)
ng/mL	β (95% CI)	β (95% CI)	β (95% CI)
<i>p,p'</i> -DDE			
< 0.14	Ref	Ref	Ref
0.14–0.23	–16.71 (–55.43, 22.01)	–33.82 (–68.22, 0.59)	–1.21 (–2.54, 0.12)
0.23–0.34	–25.03 (–64.15, 14.09)	–37.17 (–71.92, –2.42)	–1.12 (–2.46, 0.22)
> 0.35	–7.83 (–48.61, 32.95)	–19.84 (–56.07, 16.39)	–0.70 (–2.09, 0.70)
HCB			
< 0.06	Ref	Ref	Ref
0.06–0.10	–14.78 (–57.91, 28.36)	–11.68 (–48.60, 25.25)	0.35 (–1.19, 1.88)
0.10–0.16	–29.65 (–72.58, 13.27)	–12.52 (–50.23, 25.18)	0.76 (–0.74, 2.27)
> 0.16	–29.01 (–76.37, 18.35)	–22.43 (–64.00, 19.15)	0.47 (–1.18, 2.12)
PCB-138			
< 0.04	Ref	Ref	Ref
0.04–0.07	–6.94 (–50.47, 36.59)	–9.22 (–47.78, 29.34)	–0.28 (–1.76, 1.19)
0.07–0.10	–16.58 (–60.84, 27.68)	–30.07 (–69.41, 9.27)	–1.02 (–2.55, 0.51)
> 0.10	–6.69 (–54.19, 40.81)	4.95 (–37.28, 47.18)	0.73 (–0.86, 2.32)
PCB-153			
< 0.07	Ref	Ref	Ref
0.07–0.10	–16.28 (–57.33, 24.77)	–16.23 (–53.06, 20.59)	–0.38 (–1.82, 1.06)
0.10–0.15	6.07 (–36.98, 49.13)	2.13 (–36.35, 40.61)	–0.31 (–1.80, 1.18)
> 0.15	–4.76 (–52.50, 42.99)	–5.05 (–47.71, 37.61)	–0.27 (–1.90, 1.37)
PCB-180			
< 0.05	Ref	Ref	Ref
0.05–0.07	–5.11 (–51.95, 41.73)	–12.07 (–54.06, 29.91)	–0.71 (–2.28, 0.86)
0.07–0.11	13.79 (–34.88, 62.46)	18.49 (–24.91, 61.89)	0.14 (–1.51, 1.78)
> 0.11	2.21 (–52.70, 57.11)	7.67 (–41.37, 56.71)	0.08 (–1.76, 1.91)
Σ PCBs			
< 0.16	Ref	Ref	Ref
0.16–0.25	–31.43 (–74.09, 11.24)	–28.20 (–67.30, 10.91)	–0.29 (–1.77, 1.20)
0.25–0.35	0.46 (–44.56, 45.48)	–7.72 (–48.48, 33.05)	–0.61 (–2.14, 0.93)
> 0.36	–13.91 (–64.24, 36.42)	–7.73 (–53.19, 37.72)	0.17 (–1.54, 1.88)

^a Models adjusted for children's region of residence, sex, age and height at the time of the lung function assessment, maternal age at delivery, maternal pre-pregnancy BMI, maternal educational level, maternal social class, maternal country of birth, parity, maternal smoking during pregnancy, maternal diet, and maternal alcohol consumption.

observed a similar exposure-response relationship in relation to prenatal HCB exposure and lung function at school-age, where associations were not seen at higher HCB exposure levels.

Similarly to previous studies on OCs and respiratory health, for p,p' -DDE and HCB we only observed associations at certain exposure concentrations but not at higher levels (Dallaire et al., 2004; Dewailly et al., 2000; Glynn et al., 2008; Karmaus et al., 2003). It is well established that endocrine disrupting chemicals, including OCs, can have a non-monotonic exposure-response having effects at low doses that are not predicted by effects at higher doses (Vandenberg et al., 2012). This means that increasing concentrations not necessarily have greater effects on the complete exposure range. This exposure-response pattern is very common in natural hormones and endocrine disruptors since they act at extremely low concentrations. Biological mechanisms involved in this pattern are related to cytotoxicity and cellular or tissue specific receptors including negative feedback, down-regulation and desensitization, receptor selectivity, and receptor competition (Vandenberg et al., 2012).

Reduced lung function in early life can predispose to asthma-related symptoms in childhood (Martinez, 2009). In recent years, many studies have reported associations between prenatal exposure to OCs, mainly p,p' -DDE, and low respiratory tract infections, wheezing, asthma, and asthma medication use during childhood and early adulthood assessed through parental-reported symptoms (Dallaire et al., 2006; Gascon et al., 2014a, 2014b, 2012; Hansen et al., 2016, 2014; Sunyer et al., 2010, 2006, 2005). These findings are in accordance with our results since we observed a decrease in FEV₁, FVC and/or FEV₁/FVC, which reflect decreased airway patency in obstructive lung diseases such as

asthma, associated with exposure to p,p' -DDE during foetal life. These associations did not change after excluding children with asthma diagnosis, probably because these children often perform spirometry tests within the normal range (Bacharier et al., 2004).

We suspect OCs may interact with cellular receptors and alter signalling pathways which are associated with lung morphogenesis and inflammation. The development of the lung starts at around 4 weeks of gestation and continues postnatally with alveolarisation and lung growth and expansion (Kajekar, 2007). Lung development is the result of a complex interaction between growth factors, hormones, genetic factors, and environmental factors, among others (Frey and Gerritsen, 2006). Estrogenic and androgenic receptors are expressed in the lung and their modulation plays an important role on the development and functioning of the lungs during foetal development (Carey et al., 2007). OCs are endocrine disruptors able to interfere with hormonal activities due to their estrogenic and anti-androgenic properties. They can interact with the estrogenic receptor (ER) signalling pathway directly and indirectly through the aryl hydrocarbon receptor (AhR) (Shanle and Xu, 2011), and consequently alter the development and the correct functioning of the airways. p,p' -DDE, HCB, and PCB-153 have been shown to induce AhR expression in vitro (Gaspar-Ramírez et al., 2015). Activation of AhR has been associated to delayed lung development in rats and to adverse immunological effects through different mechanisms such as inflammation (Kransler et al., 2009). In children, OCs have been associated with increased inflammatory markers such as interleukins and immunoglobulins (Brooks et al., 2007; Gascon et al., 2014b; Karmaus et al., 2005). Induction of AhR expression and activity modulation by exposure to OCs might be crucial in the developing lung and

immune system.

The importance for the study of OCs relies on the widespread human exposure to these compounds and their adverse health effects. Even though OCs have been banned since the 1970s, detectable levels of *p,p'*-DDE, HCB, and some PCBs have been found in > 80% of pregnant women included in our study, even the recruitment started after 2004. Indeed, OCs concentrations have been detected in almost all children aged 6–11 years participating in the HELIX cohort between 2013 and 2016 including INMA (Haug et al., 2018); showing that current populations, and consequently the future generations, are still exposed to these compounds.

The main strengths of the present study are its population-based prospective design, the relatively large sample size, and the objective assessment of lung function. The present study, however, has some limitations. First, differences were observed between mothers of included children and those from the total sample: included mothers tended to be older, more educated, and European. This might have biased the obtained estimates, but we would not expect the estimates to change since such variables did not affect the associations (data not shown). Although our results may not be generalisable to the general population, it is not likely to affect internal validity, i.e. the association estimates between exposure to OCs and lung function in the offspring. Second, the acceptability criteria of the lung function tests were similar in all INMA regions of residence but were not identical. This could have led to a differential lung function parameter selection between the studied regions. We took this into account by adjusting the models for region of residence. Third, the reliability of spirometry results in children, particularly FVC and in 4 year-olds, might be arguable. Thus, results obtained need to be interpreted carefully. Nonetheless, to ensure the optimal reliability achievable, tests were performed by pulmonologists or trained nurses and each obtained manoeuvre was thoroughly examined to be considered acceptable and reproducible for the analyses following the ATS/ERS guidelines. Furthermore, the estimates did not substantially change when analyses were restricted to children who performed reproducible manoeuvres. Fourth, in our study population we did not measure postnatal exposure to OCs, which may be relevant since the lung mainly develops until 2 years of age (Kajekar, 2007). Further studies assessing the childhood exposure to OCs in relation to lung function, and preferable using physiologically based pharmacokinetic models to estimate lactational exposure to OCs are needed to elucidate which is the most susceptible period of exposure to OCs for lung development. Fifth, we could not perform stratified analysis for most of the effect modifiers due to the small sample size. Studies pooling information from different birth cohorts would allow an appropriate analysis of effect modification to detect susceptible groups of the population to these exposures. Sixth, we only considered OCs exposure although the foetus is exposed to a wide range of environmental chemicals including perfluoroalkyl compounds (PFASs), phenols, phthalates, and organophosphate pesticides that can also potentially affect lung development (Gascon et al., 2015; Qin et al., 2017; Raanan et al., 2016). Nonetheless, recent exposome studies reveal that correlations between exposures in different exposure groups (e.g. between OCs and PFASs) are much lower than among exposures in the same group (e.g. within OCs) (Tamayo-Uria et al., 2019). Therefore, we do not expect our estimates to be largely affected by other exposure groups not considered in the present study. Finally, we did not correct for multiple comparisons which may have led to false-positive findings (type I error). However, statistical correction for multiple comparisons increases the chances of false negative findings (type II error), which in the context of public health research might have worse consequences. Also, it assumes that the tested hypotheses are independent, which may not be the case in this study since the exposures tested, as well as the outcomes, are related.

5. Conclusion

In conclusion, our results suggest that prenatal exposure to *p,p'*-DDE may decrease lung function during childhood, especially FEV₁ and at medium levels of exposure. Since lung function in infancy predicts pulmonary function throughout life, further and deeper knowledge on the impact of environmental chemicals during pregnancy on lung development is needed for the development of public health policies targeted at the prevention of chronic respiratory diseases.

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Declaration of Competing Interest

All authors declare they do not have any conflict of interest in the presented work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.105049>.

References

- Antó, J.M., Sunyer, J., Basagaña, X., Garcia-Esteban, R., Cerveri, I., De Marco, R., Heinrich, J., Janson, C., Jarvis, D., Kogevinas, M., Kuenzli, N., Leynaert, B., Svanes, C., Wjst, M., Gislason, T., Burney, P., 2010. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy* 65, 1021–1030. <https://doi.org/10.1111/j.1398-9995.2009.02301.x>.
- Bacharier, L.B., Strunk, R.C., Mauger, D., White, D., Lemanske, R.F., Sorkness, C.A., 2004. Classifying asthma severity in children. *Am. J. Respir. Crit. Care Med.* 170, 426–432. <https://doi.org/10.1164/rccm.200308-1178OC>.
- Balte, P.P., Kühn, J., Kruse, H., Karmaus, W.J.J., 2017. Body burden of dichlorodiphenyl dichloroethene (DDE) and childhood pulmonary function. *Int. J. Environ. Res. Public Health* 14. <https://doi.org/10.3390/ijerph14111376>.
- Brooks, K., Hasan, H., Samineni, S., Gangur, V., Karmaus, W., 2007. Placental *p,p'*-dichlorodiphenyldichloroethylene and cord blood immune markers. *Pediatr. Allergy Immunol.* 18, 621–624. <https://doi.org/10.1111/j.1399-3038.2007.00546.x>.
- Bui, D.S., Burgess, J.A., Lowe, A.J., Perret, J.L., Lodge, C.J., Bui, M., Morrison, S.,

- Thompson, B.R., Thomas, P.S., Giles, G.G., Garcia-Aymerich, J., Jarvis, D., Abramson, M.J., Walters, E.H., Matheson, M.C., Dharmage, S.C., 2017. Childhood lung function predicts adult chronic obstructive pulmonary disease and asthma–chronic obstructive pulmonary disease overlap syndrome. *Am. J. Respir. Crit. Care Med.* 196, 39–46. <https://doi.org/10.1164/rccm.201606-1272OC>.
- Carey, M.A., Card, J.W., Voltz, J.W., Arbes, S.J., Germolec, D.R., Korach, K.S., Zeldin, D.C., Zeldin, D.C., 2007. It's all about sex: gender, lung development and lung disease. *Trends Endocrinol. Metab.* 18, 308–313. <https://doi.org/10.1016/j.tem.2007.08.003>.
- Dallaire, F., Dewailly, É., Muckle, G., Vézina, C., Jacobson, S.W., Jacobson, J.L., Ayotte, P., 2004. Acute infections and environmental exposure to organochlorines in Inuit infants from Nunavik. *Environ. Health Perspect.* 112, 1359–1364. <https://doi.org/10.1289/ehp.7255>.
- Dallaire, F., Dewailly, E., Vézina, C., Muckle, G., Weber, J.-P., Bruneau, S., Ayotte, P., 2006. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. *Environ. Health Perspect.* 114, 1301–1305. <https://doi.org/10.1289/EHP.8683>.
- Dewailly, E., Ayotte, P., Bruneau, S., Gingras, S., Belles-Isles, M., Roy, R., 2000. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. *Environ. Health Perspect.* 108, 205–211. <https://doi.org/10.1289/ehp.00108205>.
- European Respiratory Society, 2017. *Forum of International Respiratory Societies the Global Impact of Respiratory Disease, Second edition.* (Sheffield).
- Frey, U., Gerritsen, J., 2006. *Respiratory Diseases in Infants and Children.* European Respiratory Society <https://doi.org/10.1183/1025448x.erm3706>.
- Gascon, M., Vrijheid, M., Martínez, D., Ballester, F., Basterrechea, M., Blarduni, E., Esplugues, A., Vizcaino, E., Grimalt, J.O., Morales, E., Sunyer, J., 2012. Pre-natal exposure to dichlorodiphenyldichloroethylene and infant lower respiratory tract infections and wheeze. *Eur. Respir. J.* 39, 1188–1196. <https://doi.org/10.1183/09031936.00011711>.
- Gascon, M., Sunyer, J., Casas, M., Martínez, D., Ballester, F., Basterrechea, M., Bonde, J.P., Chatzi, L., Chevrier, C., Eggesbø, M., Esplugues, A., Govarts, E., Hannu, K., Ibarluzea, J., Kasper-Sonnenberg, M., Klümper, C., Koppen, G., Nieuwenhuijsen, M.J., Palkovicova, L., Pelé, F., Polder, A., Schoeters, G., Torrent, M., Trnovec, T., Vassilaki, M., Vrijheid, M., 2014a. Prenatal exposure to DDE and PCB 153 and respiratory health in early childhood: a meta-analysis. *Epidemiology* 25, 544–553. <https://doi.org/10.1097/EDE.0000000000000097>.
- Gascon, M., Sunyer, J., Martínez, D., Guerra, S., Lavi, L., Torrent, M., Vrijheid, M., 2014b. Persistent organic pollutants and children's respiratory health: the role of cytokines and inflammatory biomarkers. *Environ. Int.* 69, 133–140. <https://doi.org/10.1016/j.envint.2014.04.021>.
- Gascon, M., Casas, M., Morales, E., Valvi, D., Ballesteros-Gómez, A., Luque, N., Rubio, S., Monfort, N., Ventura, R., Mthalath, D., Sunyer, J., Vrijheid, M., 2015. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. *J. Allergy Clin. Immunol.* 135, 370–378. <https://doi.org/10.1016/j.jaci.2014.09.030>.
- Gaspar-Ramírez, O., Pérez-Vázquez, F.J., Salgado-Bustamante, M., González-Amaro, R., Hernández-Castro, B., Pérez-Maldonado, I.N., 2015. DDE and PCB 153 independently induce aryl hydrocarbon receptor (AhR) expression in peripheral blood mononuclear cells. *J. Immunotoxicol.* 12, 266–272. <https://doi.org/10.3109/1547691X.2014.961018>.
- Gehring, U., Wijga, A.H., Hoek, G., Bellander, T., Berdel, D., Brüske, I., Fuentes, E., Gruzieva, O., Heinrich, J., Hoffmann, B., de Jongste, J.C., Klümper, C., Koppelman, G.H., Korek, M., Krämer, U., Maier, D., Melén, E., Pershagen, G., Postma, D.S., Standl, M., von Berg, A., Anto, J.M., Bousquet, J., Keil, T., Smit, H.A., Brunekreef, B., 2015. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. *Lancet Respir. Med.* 3, 933–942. [https://doi.org/10.1016/S2213-2600\(15\)00426-9](https://doi.org/10.1016/S2213-2600(15)00426-9).
- Glynn, A., Thuvander, A., Aune, M., Johansson, A., Darnerud, P.O., Ronquist, G., Cnattingius, S., 2008. Immune cell counts and risks of respiratory infections among infants exposed pre- and postnatally to organochlorine compounds: a prospective study. *Environ. Health* 7, 62. <https://doi.org/10.1186/1476-069X-7-62>.
- Goñi, F., López, R., Etxeandia, A., Millán, E., Amiano, P., 2007. High throughput method for the determination of organochlorine pesticides and polychlorinated biphenyls in human serum. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 852, 15–21. <https://doi.org/10.1016/j.jchromb.2006.12.049>.
- Guxens, M., Ballester, F., Espada, M., Fernández, M.F., Grimalt, J.O., Ibarluzea, J., Olea, N., Rebaglato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., Sunyer, J., 2012. Cohort profile: the INMA-Infancia y Medio Ambiente-(environment and childhood) project. *Int. J. Epidemiol.* 41, 930–940. <https://doi.org/10.1093/ije/dyr054>.
- Hansen, S., Strøm, M., Olsen, S.F., Maslova, E., Rantakokko, P., Kiviranta, H., Rytter, D., Bech, B.H., Hansen, L.V., Halldorsson, T.I., 2014. Maternal concentrations of persistent organochlorine pollutants and the risk of asthma in offspring: results from a prospective cohort with 20 years of follow-up. *Environ. Health Perspect.* 122, 93–99. <https://doi.org/10.1289/ehp.1206397>.
- Hansen, S., Strøm, M., Olsen, S.F., Dahl, R., Hoffmann, H.J., Granström, C., Rytter, D., Bech, B.H., Linneberg, A., Maslova, E., Kiviranta, H., Rantakokko, P., Halldorsson, T.I., 2016. Prenatal exposure to persistent organic pollutants and offspring allergic sensitization and lung function at 20 years of age. *Clin. Exp. Allergy* 46, 329–336. <https://doi.org/10.1111/cea.12631>.
- Haug, L.S., Sakhi, A.K., Cequier, E., Casas, M., Maitre, L., Basagana, X., Andrusaityte, S., Chalkiadaki, G., Chatzi, L., Coen, M., de Bont, J., Dedele, A., Ferrand, J., Grazuleviciene, R., Gonzalez, J.R., Bjerve Gutzkow, K., Keun, H., McEachan, R., Meltzer, H.M., Petravičienė, I., Robinson, O., Saulnier, P.-J., Slama, R., Sunyer, J., Urquiza, J., Vafeiadi, M., Wright, J., Vrijheid, M., Thomsen, C., 2018. In-utero and childhood chemical exposure in six European mother-child cohorts. *Environ. Int.* 751–763. <https://doi.org/10.1016/j.envint.2018.09.056>. in press.
- Kajekar, R., 2007. Environmental factors and developmental outcomes in the lung. *Pharmacol. Ther.* 114, 129–145. <https://doi.org/10.1016/j.pharmthera.2007.01.011>.
- Karmaus, W., Davis, S., Chen, Q., Kuehr, J., Kruse, H., 2003. Atopic manifestations, breast-feeding protection and the adverse effect of DDE. *Paediatr. Perinat. Epidemiol.* 17, 212–220. <https://doi.org/10.1046/J.1365-3016.2003.00488.X>.
- Karmaus, W., Brooks, K.R., Nebe, T., Witten, J., Obi-Osius, N., Kruse, H., 2005. Immune function biomarkers in children exposed to lead and organochlorine compounds: a cross-sectional study. *Environ. Health* 4, 5. <https://doi.org/10.1186/1476-069X-4-5>.
- Korrick, S.A., Altshul, L.M., Tolbert, P.E., Burse, V.W., Needham, L.L., Monson, R.R., 2000. Measurement of PCBs, DDE, and hexachlorobenzene in cord blood from infants born in towns adjacent to a PCB-contaminated waste site. *J. Expo. Anal. Environ. Epidemiol.* 10, 743–754.
- Kransler, K.M., McGarrigle, B.P., Swartz, D.D., Olson, J.R., 2009. Lung development in the Holtzman rat is adversely affected by gestational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol. Sci.* 107, 498–511. <https://doi.org/10.1093/toxsci/kfn235>.
- Martinez, F.D., 2009. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc. Am. Thorac. Soc.* 6, 272–277. <https://doi.org/10.1513/pats.200808-092RM>.
- Martinez, F.D., 2016. Early-life origins of chronic obstructive pulmonary disease. *N. Engl. J. Med.* 375, 871–878. <https://doi.org/10.1056/NEJMra1603287>.
- Miller, M.D., Marty, M.A., 2010. Impact of environmental chemicals on lung development. *Environ. Health Perspect.* 118, 1155–1164. <https://doi.org/10.1289/ehp.0901856>.
- Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P.M., Gustafsson, P., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J., ATS/ERS Task Force, 2005. Standardisation of spirometry. *Eur. Respir. J.* 26, 319–338. <https://doi.org/10.1183/09031936.05.00034805>.
- Qin, X.-D., Qian, Z. (Min), Dharmage, S.C., Perret, J., Geiger, S.D., Rigdon, S.E., Howard, S., Zeng, X.-W., Hu, L.-W., Yang, B.-Y., Zhou, Y., Li, M., Xu, S.-L., Bao, W.-W., Zhang, Y.-Z., Yuan, P., Wang, J., Zhang, C., Tian, Y.-P., Nian, M., Xiao, X., Chen, W., Lee, Y. L., Dong, G.-H., 2017. Association of perfluoroalkyl substances exposure with impaired lung function in children. *Environ. Res.* 155, 15–21. doi:<https://doi.org/10.1016/j.envres.2017.01.025>.
- Quanjer, P.H., Stanojevic, S., Cole, T.J., Baur, X., Hall, G.L., Culver, B.H., Enright, P.L., Hankinson, J.L., Ip, M.S.M., Zheng, J., Stocks, J., Schindler, C., 2012. Multi-ethnic reference values for spirometry for the 3–95 yr age range: the global lung function 2012 equations. *Eur. Respir. J.* 40, 1324–1343. <https://doi.org/10.1183/09031936.00080312>.
- Raanan, R., Balmes, J.R., Harley, K.G., Gunier, R.B., Mazgamen, S., Bradman, A., Eskenazi, B., 2016. Decreased lung function in 7-year-old children with early-life organophosphate exposure. *Thorax* 71, 148–153. <https://doi.org/10.1136/thoraxjnl-2014-206622>.
- Shanley, E.K., Xu, W., 2011. Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. *Chem. Res. Toxicol.* 24, 6–19. <https://doi.org/10.1021/tx100231n>.
- Sunyer, J., Torrent, M., Muñoz-Ortiz, L., Ribas-Fitó, N., Carrizo, D., Grimalt, J., Antó, J.M., Cullinan, P., 2005. Prenatal dichlorodiphenyldichloroethylene (DDE) and asthma in children. *Environ. Health Perspect.* 113, 1787–1790. <https://doi.org/10.1289/ehp.8127>.
- Sunyer, J., Torrent, M., Garcia-Esteban, R., Ribas-Fitó, N., Carrizo, D., Romieu, I., Antó, J.M., Grimalt, J.O., 2006. Early exposure to dichlorodiphenyldichloroethylene, breastfeeding and asthma at age six. *Clin. Exp. Allergy* 36, 1236–1241. <https://doi.org/10.1111/j.1365-2222.2006.02560.x>.
- Sunyer, J., Garcia-Esteban, R., Alvarez, M., Guxens, M., Goñi, F., Basterrechea, M., Vrijheid, M., Guerra, S., Antó, J.M., 2010. DDE in mothers' blood during pregnancy and lower respiratory tract infections in their infants. *Epidemiology* 21, 729–735. <https://doi.org/10.1097/EDE.0b013e3181e5ea96>.
- Tamayo-Uria, I., Maitre, L., Thomsen, C., Nieuwenhuijsen, M.J., Chatzi, L., Siroux, V., Aasvang, G.M., Agier, L., Andrusaityte, S., Casas, M., de Castro, M., Dedele, A., Haug, L.S., Heude, B., Grazuleviciene, R., Gutzkow, K.B., Krog, N.H., Mason, D., McEachan, R.R.C., Meltzer, H.M., Petravičienė, I., Robinson, O., Roumeliotaki, T., Sakhi, A.K., Urquiza, J., Vafeiadi, M., Waiblinger, D., Warembourg, C., Wright, J., Slama, R., Vrijheid, M., Basagaña, X., 2019. The early-life exposome: description and patterns in six European countries. *Environ. Int.* 123, 189–200. <https://doi.org/10.1016/j.envint.2018.11.067>.
- Textor, J., Hardt, J., Knüppel, S., 2011. DAGitty. *Epidemiology* 22, 745. <https://doi.org/10.1097/EDE.0b013e318225c2be>.
- Vandenbergh, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R., Lee, D.-H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T., Myers, J.P., Myers, J.P., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and non-monotonic dose responses. *Endocr. Rev.* 33, 378–455. <https://doi.org/10.1210/er.2011-1050>.
- Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2015. Association between lung function in adults and plasma DDT and DDE levels: results from the Canadian Health Measures Survey. *Environ. Health Perspect.* 123, 422–427. <https://doi.org/10.1289/ehp.1408217>.