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In utero exposure to bisphenols and asthma, wheeze, and lung function in school-age children: a prospective meta-analysis of 8 European birth cohorts

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ABSTRACT

Background: In utero exposure to bisphenols, widely used in consumer products, may alter lung development and increase the risk of respiratory morbidity in the offspring. However, evidence is scarce and mostly focused on bisphenol A (BPA) only.
Objective: To examine the associations of *in utero* exposure to BPA, bisphenol F (BPF), and bisphenol S (BPS) with asthma, wheeze, and lung function in school-age children, and whether these associations differ by sex.

Abbreviations: BMI, body mass index; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; CI, confidence interval; DAG, directed acyclic graph; FEV_1, forced expiratory volume in 1s; $FEF_{25-75\%}$, mid-expiratory flow; FVC, forced vital capacity; GLI, Global Lung Function Initiative; IPD, individual participant data; ISAAC, International Study on Asthma and Allergy in Childhood; LOD, limit of detection; OR, odds ratio.

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Asthma
Wheezing
Lung function
Mother-child cohort

Methods: We included 3,007 mother–child pairs from eight European birth cohorts. Bisphenol concentrations were determined in maternal urine samples collected during pregnancy (1999–2010). Between 7 and 11 years of age, current asthma and wheeze were assessed from questionnaires and lung function by spirometry. Wheezing patterns were constructed from questionnaires from early to mid-childhood. We performed adjusted random-effects *meta*-analysis on individual participant data.
Results: Exposure to BPA was prevalent with 90% of maternal samples containing concentrations above detection limits. BPF and BPS were found in 27% and 49% of samples. *In utero* exposure to BPA was associated with higher odds of current asthma (OR = 1.13, 95% CI = 1.01, 1.27) and wheeze (OR = 1.14, 95% CI = 1.01, 1.30) (p-interaction sex = 0.01) among girls, but not with wheezing patterns nor lung function neither in overall nor among boys. We observed inconsistent associations of BPF and BPS with the respiratory outcomes assessed in overall and sex-stratified analyses.
Conclusion: This study suggests that *in utero* BPA exposure may be associated with higher odds of asthma and wheeze among school-age girls.

1. Introduction

Impaired development of the respiratory and immune systems resulting from adverse environments *in utero* might predispose individuals to respiratory morbidity later in life (Miller and Marty, 2010; Håland et al., 2006; Bui et al., 2018; Drazen and Martinez, 2016; Vardavas et al., 2016; Gehring et al., 2015; Bui et al., 2017). There is growing concern over the role of chemical pollutants on early life origins of respiratory diseases (Gascon et al., 2013; Vrijheid et al., 2016; Casas and Gascon, 2020; Abellan and Casas, 2021), specifically on bisphenols due to their large production worldwide (CHEMTrust, 2018) and its widespread exposure to human populations (Calafat et al., 2008; Haug et al., 2018). Bisphenol A (BPA) is the most commonly used bisphenol. It is present in polycarbonate plastics and epoxy resins, used in many consumer products, and diet is the main source of exposure (Liao and Kannan, 2013). In 2017, the European Chemical Agency considered BPA as a "substance of very high concern" (Calafat et al., 2008; Agency and Bisfenol, 2017). Consequently, BPA production is restricted in some countries, which has resulted in the emergence of substitutes such as bisphenol F (BPF) and bisphenol S (BPS), with suspected similar toxicity (Lehmler et al., 2018; Rochester and Bolden, 2015). Bisphenols can cross the placenta and are also found in breastmilk, which results in exposure to foetuses and newborns (Lee et al., 2018). Individual prospective cohort studies investigated *in utero* exposure to BPA, assessed from maternal urine during pregnancy, in relation to asthma-related symptoms from birth to 12 years of age and lung function from 4 to 12 years of age, but showed inconsistent results (Spanier et al., 2012; Spanier et al., 2014; Vernet et al., 2017; Agier et al., 2019; Berger et al., 2020; Gascon et al., 2015; Zhou et al., 2017; Buckley et al., 2018; Donohue et al., 2013; Berger et al., 2019). Because bisphenols can interfere with sex hormones (Lan et al., 2017), their potential effects may be sex-dependent. However, previous published studies reported an increased risk of wheeze associated with BPA among girls (Zhou et al., 2017), among boys (Buckley et al., 2018), or no sex differences (Spanier et al., 2012; Gascon et al., 2015). Limited sample size of previous studies may have hindered consistent and sex-specific effects. Additionally, no study has investigated the influence of *in utero* exposure to bisphenols other than BPA on asthma-related outcomes and lung function.

Therefore, we aimed to investigate whether *in utero* exposure to bisphenols is associated with current asthma, wheeze, and lung function at school-age, and wheezing patterns from early to mid-childhood. We also investigated whether any of these associations differ by sex.

2. Methods

2.1. Study population

We included 3,007 mother–child pairs from 8 European population-based birth cohorts: Generation R, The Netherlands (Jaddoe et al., 2006); INMA (INfancia y Medio Ambiente) Sabadell, INMA Gipuzkoa, INMA Valencia, Spain (Guxens et al., 2012); BiB (Born in Bradford), UK (Wright et al., 2013); EDEN (Etude des Déterminants pré et post natals du développement et de la santé de l'Enfant), France (Heude et al., 2016); MoBa (Norwegian Mother, Father and Child Cohort Study), Norway (Magnus et al., 2016; Paltiel et al., 2014); and RHEA (Mother-Child Cohort in Crete), Greece (Chatzi et al., 2017). Cohorts recruited the population between 1999 and 2010 (Table 1). Five of these were part of the HELIX (Human Early Life Exposome) Project and followed common standardised protocols, questionnaires and lung function measurements (Maitre et al., 2018). Mother-child pairs that had concentrations of bisphenols measured during pregnancy and information on asthma, wheeze or lung function during childhood were included in the study (Figure S1). All cohorts received approval from the ethics committees of the centres involved and written informed consent was obtained from all participants.

2.2. Bisphenol exposure assessment

Concentrations of BPA, BPF and BPS were determined in maternal urine samples. BPA was measured in all included cohorts; BPF and BPS were measured in Generation R and in the three INMA cohorts. Concentrations were determined in a single spot urine sample collected throughout pregnancy in all cohorts except in the INMA cohorts where two spot urine samples were available (1st and 3rd trimester). In INMA Sabadell and Valencia, bisphenols were quantified in each spot sample and we used the average of both measurements as main exposure variable, whereas in INMA Gipuzkoa bisphenols were quantified in a pool of both urines (Table 2). Bisphenols concentrations were adjusted for creatinine to correct for urine dilution. See Supplementary Methods 1 for complete details.

2.3. Asthma, wheeze, and lung function

We defined current asthma (Hohmann et al., 2014) as having a positive answer to two of the following: i) ever asthma diagnosis; ii) wheezing in the last year; iii) asthma medication in the last year. Ever asthma diagnosis, and wheeze and asthma medication in the last year were assessed from parental-administered questionnaires adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) at school-age (Asher et al., 1995). Information on wheezing was collected from 1 to 11 years (Table S1) and was used to construct wheezing patterns: i) never wheezing; ii) early wheezing, $\leq$4 years; iii) late wheezing, $>$4 years; and iv) persistent wheezing, $\leq$4 and $>$ 4 years. Lung function was assessed by spirometry performed at school-age following the ATS/ERS guidelines (Miller et al., 2005). All children with at least one acceptable manoeuvre were included. Lung function parameters selected for the study were forced vital capacity (FVC), FEV_1, FEV_1/FVC and mid-expiratory flow ($FEF_{25-75\%}$). For comparability between cohorts, we standardised lung function parameters into sex-, age-, height- and ethnicity-adjusted z-scores based on the Global Lung Function

Initiative (GLI) reference values (Quanjer et al., 2012).

2.4. Covariates

Relevant covariates were selected from literature and summarised in a directed acyclic graph (DAG) (Figure S2) to depict the known and hypothesised causal relations between variables and to avoid adjusting for mediators or colliders. Information on maternal and child characteristics was obtained from questionnaires, medical records, antenatal healthcare visits and physical measurements during the cohort's follow-ups. We collected information on maternal age, pre-pregnancy body mass index (BMI), education, smoking during pregnancy, and children's ethnicity, sex, weeks of gestation at birth, birth weight, and age and height at the time of spirometry. Data collection and harmonisation was similar across cohorts. For maternal education, smoking during pregnancy and child ethnicity, cohort-specific categories were harmonised for our analyses (Table S2).

2.5. Statistical analyses

We imputed missing values in covariates and BPA concentrations below the limit of detection (LOD) using multiple imputation by chained equations methods in which 25 complete datasets were generated. Imputation was performed in each cohort separately (Supplementary Methods 2). Since the number of samples with BPF and BPS concentrations below the LOD was very high (>50%), these two compounds were dichotomised (<LOD, ≥LOD) and "<LOD" was set as the reference category. Because distributions of BPA concentrations were skewed, they were $\log_2$ transformed. This means that all estimates referring to BPA are expressed per doubling of BPA concentration.

Main analyses To assess the associations between bisphenols and respiratory outcomes, we first performed a 1-stage *meta*-analysis on individual participant data (IPD) using mixed-effect models to account for the clustering of individuals within cohorts (random intercepts models). For the associations of bisphenols with current asthma and wheeze, we performed multivariable logistic models. For the associations with wheezing patterns, we performed three multivariable logistic regression models; one for each wheezing category (early, late, persistent) and establishing "never wheezing" as the reference category in each model. For the associations of bisphenols with lung function parameters, we performed multivariable linear models. Current asthma and wheeze models were adjusted for covariables selected from the DAG: maternal education, age, pre-pregnancy BMI, smoking during pregnancy, and child's sex, age, and ethnicity. Lung function models were adjusted for the same set as the above models except child's sex and age. Although ethnicity was also accounted for in the z-scores, we additionally adjusted

Table 1
Maternal and child characteristics of participating cohorts (n = 3007).

	Overall	Generation R	INMA Gipuzkoa	INMA Sabadell	INMA Valencia	BiB[a]	EDEN[a]	MoBa[a]	RHEA[a]
	(n = 3007)	(n = 1151)	(n = 280)	(n = 379)	(n = 331)	(n = 204)	(n = 197)	(n = 268)	(n = 197)
Years of recruitment		2002–2006	2006–2008	2004–2006	2004–2005	2007–2010	2003–2006	1999–2009	2007–2008
Maternal characteristics									
Maternal age (years), mean (SD)	31.3 (4.52)	31.0 (4.6)	32.8 (3.1)	32.0 (4.1)	31.9 (3.9)	28.7 (5.8)	30.6 (4.9)	32.7 (3.7)	30.8 (4.8)
Pre-pregnancy BMI, (kg/m^2) mean (SD)	24.0 (4.4)	24.3 (4.3)	23.0 (3.6)	23.7 (4.6)	23.4 (4.1)	28.4 (5.4)	23.3 (4.2)	22.6 (3)	24.0 (4.2)
Maternal education, %									
≤ Primary	13	6.7	11.1	21.5	27.8	47.8	6.2	0	4.6
Secondary	38	39.4	35.8	42.6	40.5	17.8	36.9	20.9	55.9
University	49	53.9	53.1	35.9	31.7	34.4	56.9	79.1	39.5
Smoking during pregnancy, %	15	13.4	13.7	14.4	22.7	13.8	23.4	3.5	21.4
Child characteristics at birth									
Child ethnicity, %									
Caucasian	86	78.2	99.2	94.2	97.3	43.5	99.5	96.5	100
African/American	3	6.9	0	0	0	2.6	0	0	0
Asian	6	6.5	0	0	0	49.7	0.5	2.7	0
Other or Mixed	5	8.4	0.8	5.8	2.7	4.2	0	0.8	0
Child sex, % girls	48	49	50	47	48	47	46	49	43
Preterm birth, % yes	3	2.4	3.2	2.1	2.7	3.9	5.6	4.6	10.2
Low birth weight, % yes	3	2.4	5.0	4.0	3.6	6.9	3.1	3.1	3.1
Child characteristics at respiratory outcomes assessment									
Child age (years), mean (SD)	8.4 (1.4)	9.7 (0.2)	7.9 (0.2)	6.8 (0.4)	7.5 (0.2)	6.6 (0.2)	10.8 (0.6)	8.5 (0.5)	6.5 (0.3)
Child height (cm), mean (SD)	131.8 (10.6)	141.1 (6.4)	127.9 (5.5)	121.6 (5.7)	126 (5.1)	119.8 (5)	143.6 (7.4)	133.4 (6.1)	120.4 (4.8)
Current asthma, % yes	9	6.7	7.9	8.8	7.3	22.1	14.7	7.8	10.2
Wheeze in the last year, % yes	9	4.1	8.7	10.6	11.5	25.5	12.7	7.5	7.6
Wheezing patterns, %									
Never	56	49.7	51.3	43.7	47.9	46.3	69.7	81.8	84.8
Early	32	37.1	39.9	45.9	40.8	23.9	9.5	9.8	7.6
Late	4	2.8	3.4	0.5	1.5	13.4	13.1	5.6	5.6
Persistent	8	10.4	5.4	9.9	9.8	16.4	7.7	2.8	2.0
FVC z-score, mean (SD)	0.19 (1.02)	0.16 (0.94)	0.63 (0.96)	0.32 (0.96)	0.26 (0.91)	0.28 (1.37)	−0.65 (0.82)	0.11 (0.91)	0.15 (1.31)
FEV_1 z-score, mean (SD)	0.01 (1.02)	0.12 (0.99)	0.26 (0.94)	−0.00 (0.97)	0.26 (0.94)	−0.36 (1.22)	−0.79 (0.92)	−0.22 (0.95)	−0.06 (1.03)
FEV_1/FVC z-score, mean (SD)	−0.31 (1.20)	−0.10 (0.98)	−0.61 (0.97)	−0.55 (0.95)	−0.01 (0.93)	−1.07 (1.00)	−0.19 (0.95)	−0.58 (0.83)	−0.51 (0.95)
$FEF_{25-75\%}$ z-score, mean (SD)	−1.84 (3.41)	0.52 (1.08)	−0.24 (1.07)	−0.36 (1.01)	−0.12 (0.90)	−1.19 (1.14)	−0.90 (0.98)	−0.63 (1.07)	−0.62 (0.97)

Abbreviations: BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$: mid expiratory flow; SD: standard deviation.
[a] Subsample included in the HELIX Project.

for it to avoid any residual confounding (Quanjer et al., 2012). We reported all primary analyses stratified by sex, testing for interaction ($p \leq 0.1$), in addition to reporting estimates for boys and girls combined. Sex-stratified models between BPF, BPS and wheezing patterns could not be performed because numbers in each category were too small.

Sensitivity analyses We performed a 2-stage *meta*-analysis to assess the associations between BPA and current asthma, wheeze, and lung function. We did not perform 2-stage *meta*-analysis neither for BPF and BPS, only available in 4 cohorts, nor for wheezing patterns, because of the low number of individuals in each wheezing category. We estimated the effect estimates in each cohort separately and calculated the combined estimate by a random effects *meta*-analysis model. We used multivariable logistic regression models for the associations of BPA with current asthma and wheeze, and multivariable linear regression models for the associations with lung function. All models were adjusted for the same set of covariates as the 1-stage *meta*-analysis. To test whether results were not explained by birth outcomes, we repeated the analyses excluding preterm (<37 weeks) and low weight (<2500 g) births as these children are at higher risk of respiratory symptoms and lower lung function (Sonnenschein-Van Der Voort et al., 2014; Den Dekker et al., 2016). Additionally, we ran the models using the complete case datasets and further repeated them excluding one cohort at a time to determine the influences of any particular cohort in the overall estimates. To account for exposure misclassification due to the high variability of bisphenols, we ran the models correcting for measurement error applying regression calibration methods, a regression method that aims to estimate the true exposure value based on the exposure within-subject temporal variability. We considered a reliability coefficient for BPA of 0.14 (Supplementary Methods 3). We also performed the lung function models including only children with at least two acceptable and reproducible spirometry manoeuvres and excluding children with an asthma diagnosis. All sensitivity analyses were performed in the 1-stage *meta*-analysis models.

3. Results

3.1. Characteristics of study population

Table 1 shows the main maternal and child characteristics in each cohort. EDEN, MoBa, and RHEA showed the lowest percentage of early wheezers and BiB showed the largest percentage of persistent wheezers (Table 1). There were no differences in main characteristics between the observed and imputed datasets (Table S3). Median BPA concentrations ranged from 1.56 (Generation R) to 9.54 (MoBa) μg/g. Overall, BPA was detected in 90% of the samples. BPF and BPS were detected in fewer samples except in Generation R, where 40% and 70% of samples had detectable levels of BPF and BPS, respectively (Table 2).

3.2. Bisphenols and asthma and wheeze

Results from the 1-stage *meta*-analysis showed that overall, *in utero* BPA exposure tended to be associated with higher odds of wheeze at school-age (OR = 1.05, 95 %CI = 0.97, 1.13 per doubling of BPA concentration) but not with current asthma nor with wheezing patterns (Table 3). Associations with asthma and wheeze at school-age were modified by child's sex (p-interaction = 0.01). Stratified analyses showed that, among girls, each doubling in BPA concentration during pregnancy was associated with higher odds of having current asthma (OR = 1.13, 95 %CI = 1.01, 1.27) and wheeze (OR = 1.14, 95 %CI = 1.01, 1.30) (Table 3). We did not observe sex differences with wheezing patterns. We did not observe associations with BPF. *In utero* BPS levels above the LOD seemed to be associated with lower odds of late (OR = 0.43, 95 %CI = 0.19, 1.00) and persistent wheeze (OR = 0.56, 95 %CI = 0.35, 0.90). The 2-stage *meta*-analysis of the association between BPA and current asthma and wheeze showed similar results than the 1-stage *meta*-analysis with some heterogeneity across cohorts (Fig. 1). BPA estimates with asthma and wheeze (in the overall population, in girls and boys) were similar when excluding preterm and low weight births (Table S4), and when using the complete case datasets (Table S5). When excluding cohort by cohort, results did not show notable changes (Table S6). Associations between BPS and wheezing patterns did not change substantially in complete case analysis (Table S5).

3.3. Bisphenols and lung function

The 1-stage *meta*-analysis showed small or no associations of increasing *in utero* BPA concentrations with lung function parameters. In the overall population, each doubling in BPA concentrations was associated with a 0.02 (95% CI = 0.00, 0.04) higher z-score in FEV_1 (Table 3). No associations were observed with FVC and FEV_1/FVC. Associations with FEV_1 were modified by child's sex (p-interaction < 0.10). In sex-stratified analysis, we observed higher FEV_1 associated with BPA exposure among boys (z-score = 0.03, 95 %CI = 0.00, 0.06). BPF levels above the LOD during gestation were associated with higher FEV_1 (z-score = 0.12, 95% CI = 0.01, 0.23) and $FEF_{25-75\%}$ (z-score = 0.13, 95% CI = 0.01, 0.25) (Table 3). Associations of BPF with FVC and FEV_1 were modified by child's sex, observing associations with higher FVC (z-score = 0.17, 95 %CI = 0.02, 0.32) and FEV_1 (z-score = 0.15, 95 %CI = -0.00, 0.29) among girls (p-interaction < 0.10). No associations were observed between BPS and lung function parameters (Table 3). Results from the 2-stage *meta*-analysis showed overall null effects in the associations between *in utero* BPA exposure and lung function with low

Table 2
Maternal urinary bisphenol levels and percentage of bisphenol samples above the LOD.

	Overall	Generation R	INMA Gipuzkoa	INMA Sabadell	INMA Valencia	BiB[a]	EDEN[a]	MoBa[a]	RHEA[a]
Trimester measurement	–	1st	1st and 3rd	1st and 3rd	1st and 3rd	3rd	3rd	2nd	1st
BPA									
LOD BPA (ng/ml)	–	0.15	0.12	0.10	0.03	0.03	0.40	0.03	0.03
BPA, % >LOD	90	78	80	99	100	99	100	100	100
BPA μg/g, median (IQR)	2.50 (3.70)	1.56 (3.03)	2.95 (4.23)	2.51 (2.25)	3.51 (3.99)	1.59 (1.58)	2.50 (2.31)	9.54 (13.22)	1.98 (2.77)
BPA ng/ml, median (IQR)	2.30 (3.37)	1.65 (2.93)	2.74 (3.91)	2.13 (2.28)	2.80 (3.02)	1.50 (1.92)	2.56 (2.71)	5.50 (5.29)	2.44 (3.45)
BPF									
LOD BPF (ng/ml)	–	0.18	0.06	0.07	0.10	–	–	–	–
BPF, % >LOD	27	40	10	8	5	–	–	–	–
BPS									
LOD BPS (ng/ml)	–	0.05	0.05	0.10	0.33	–	–	–	–
BPS, % >LOD	49	71	30	17	10	–	–	–	–

Abbreviations: BPA: bisphenol A; BPS: bisphenol F; BPS: bisphenol S; IQR: interquartile range; LOD: limit of detection.
[a] Subsample included in the HELIX Project.

Table 3
Overall and sex-stratified associations between creatinine adjusted bisphenols and respiratory outcomes from 1-stage *meta*-analysis.

	$N_{Overall}$	Overall	$P_{interaction}$	N_{Girls}	Girls	N_{Boys}	Boys
BPA (μg/g)							
Asthma and wheeze, OR (95% CI)[a]							
Current asthma	2831	1.01 (0.94, 1.09)	0.009	1323	1.13 (1.01, 1.27)	1431	0.95 (0.87, 1.03)
Wheeze in the last year	2846	1.05 (0.97, 1.13)	0.013	1327	1.14 (1.01, 1.30)	1442	0.99 (0.90, 1.09)
Wheezing patterns, OR (95% CI)[a,c]							
Early	2023	0.99 (0.94, 1.04)	0.572	962	0.97 (0.90, 1.04)	1026	1.00 (0.93, 1.08)
Late	1378	1.02 (0.90, 1.15)	0.463	665	1.06 (0.90, 1.25)	658	0.95 (0.80, 1.12)
Persistent	1474	0.97 (0.89, 1.06)	0.288	702	1.00 (0.87, 1.16)	741	0.94 (0.84, 1.05)
Lung function, z-score (95% CI)[b]							
FVC	2677	0.01 (-0.01, 0.03)	0.397	1292	0.01 (-0.01, 0.04)	1385	0.02 (-0.01, 0.04)
FEV_1	2729	0.02 (0.00, 0.04)	0.044	1318	0.01 (-0.01, 0.04)	1411	0.03 (0.00, 0.06)
FEV_1/FVC	2662	0.00 (-0.01, 0.02)	0.111	1288	−0.00 (-0.03, 0.03)	1374	0.01 (-0.02, 0.04)
$FEF_{25-75\%}$	2741	0.01 (-0.01, 0.03)	0.869	1291	0.01 (-0.02, 0.04)	1384	0.02 (-0.01, 0.05)
BPF (≥LOD vs < LOD)							
Asthma and wheeze, OR (95% CI)[a]							
Current asthma	1776	1.09 (0.69, 1.73)	0.029	871	0.44 (0.17, 1.14)	905	1.55 (0.89, 2.67)
Wheeze in the last year	1791	1.12 (0.66, 1.90)	0.024	875	0.46 (0.15, 1.45)	916	1.59 (0.87, 2.94)
Wheezing patterns, OR (95% CI)[a,c]							
Early	1302	0.98 (0.73, 1.31)	0.495	–	–	–	–
Late	757	1.12 (0.48, 2.62)	0.938	–	–	–	–
Persistent	851	0.94 (0.57, 1.56)	0.011	–	–	–	–
Lung function, z-score (95% CI)[b]							
FVC	1808	0.10 (-0.01, 0.20)	0.035	892	0.17 (0.02, 0.32)	916	0.01 (-0.14, 0.16)
FEV_1	1806	0.12 (0.01, 0.23)	0.099	891	0.15 (-0.00, 0.29)	915	0.08 (-0.07, 0.24)
FEV_1/FVC	1806	0.02 (-0.09, 0.13)	0.256	891	−0.09 (-0.24, 0.06)	915	0.13 (-0.03, 0.29)
$FEF_{25-75\%}$	1806	0.13 (0.01, 0.25)	0.934	891	0.14 (-0.02, 0.31)	915	0.14 (-0.03, 0.31)
BPS (≥LOD vs < LOD)							
Asthma and wheeze, OR (95% CI)[a]							
Current asthma	1776	0.73 (0.47, 1.14)	0.405	871	1.08 (0.51, 2.27)	905	0.61 (0.36, 1.05)
Wheeze in the last year	1791	0.64 (0.40, 1.04)	0.382	875	0.66 (0.29, 1.50)	916	0.69 (0.38, 1.25)
Wheezing patterns, OR (95% CI)[a,c]							
Early	1302	1.01 (0.77, 1.32)	0.928	–	–	–	–
Late	757	0.43 (0.19, 1.00)	0.624	–	–	–	–
Persistent	851	0.56 (0.35, 0.90)	0.440	–	–	–	–
Lung function, z-score (95% CI)[b]							
FVC	1808	0.05 (-0.05, 0.16)	0.216	892	0.06 (-0.08, 0.20)	916	0.04 (-0.10, 0.19)
FEV_1	1806	0.09 (-0.02, 0.19)	0.084	891	0.10 (-0.03, 0.23)	915	0.09 (-0.06, 0.24)
FEV_1/FVC	1806	0.06 (-0.05, 0.16)	0.846	891	0.01 (-0.14, 0.15)	915	0.11 (-0.04, 0.26)
$FEF_{25-75\%}$	1806	0.02 (-0.09, 0.14)	0.870	891	0.02 (-0.14, 0.18)	915	0.04 (-0.12, 0.21)

Note: discrepancies between the overall N and sex-stratified N are due to missing values in sex. Overall N in each wheezing pattern includes also never wheezers.
Abbreviations: BPA: bisphenol A; BPF: bisphenol F; BPS: bisphenol S; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$: mid expiratory flow; LOD: limit of detection; OR: odds ratio; CI: confidence interval.

[a] Models adjusted for maternal age, education, pre-pregnancy BMI, smoking during pregnancy, and child's age, sex and ethnicity.

[b] Models adjusted for maternal age, education, pre-pregnancy BMI, smoking during pregnancy, and child's ethnicity.

[c] Reference base category: Never wheezers.

heterogeneity between cohorts (Fig. 1). Results remained similar when excluding preterm and low birth weight babies (Table S4), when using the complete case datasets (Table S5), when including only children with at least two acceptable and reproducible spirometry manoeuvres, and when excluding children with asthma (Table S7). The estimates of the association between BPA and FEV_1 shifted towards the null when we excluded Generation R from the model (Table S6). The association between BPA and FEV_1 (z-score = 0.02 (95% CI: 0.00, 0.04) also disappeared when we repeated the models applying regression calibration (z-score = 0.00 (95 %CI = -0.13, 0.13). Regression calibration could not be applied in logistic regression models for wheezing and asthma. Associations observed for BPF diluted and disappeared when including children with at least two acceptable and reproducible spirometry manoeuvres, and when excluding children with asthma (Table S7).

4. Discussion

Results from this prospective IPD *meta*-analysis of 3,007 mother–child pairs suggest that *in utero* exposure to BPA may be associated with higher odds of asthma and wheeze at school-age among girls. The associations did not seem to be explained by lung function adaptations, as results did not show consistent associations of *in utero* BPA exposure with lung function. Substitute bisphenols were associated with higher FEV_1 and $FEF_{25-75\%}$ (BPF) and lower risk of late and persistent wheezing (BPS).

4.1. Comparison with previous studies

Our findings support the hypothesis that *in utero* BPA may increase the risk of asthma-related symptoms during childhood reported in some (Spanier et al., 2012; Spanier et al., 2014; Vernet et al., 2017; Berger et al., 2020; Gascon et al., 2015; Zhou et al., 2017; Buckley et al., 2018) but not all (Donohue et al., 2013; Berger et al., 2019) previous studies. Our study adds evidence for potential sex-dependent effects of BPA exposure on the risk of asthma-related symptoms, only assessed in few studies that yielded contradicting results (Gascon et al., 2015; Zhou et al., 2017; Buckley et al., 2018). Two studies reported higher risk in girls, one showed higher odds of infant allergic diseases (including wheeze and eczema) at 6 months of age (Zhou et al., 2017), and another reported higher risk of asthma at 7 years (Gascon et al., 2015), but without statistical evidence that BPA effects differed between sexes. One study reported higher odds of asthma diagnosis at 7 years among boys (Buckley et al., 2018). A cohort study that involved only boys also reported a tendency of higher risk of asthma at 5 years, but not with wheeze at the same age, from *in utero* BPA exposure (Vernet et al., 2017). The lack of consistency of sex-specific effects of previous studies might

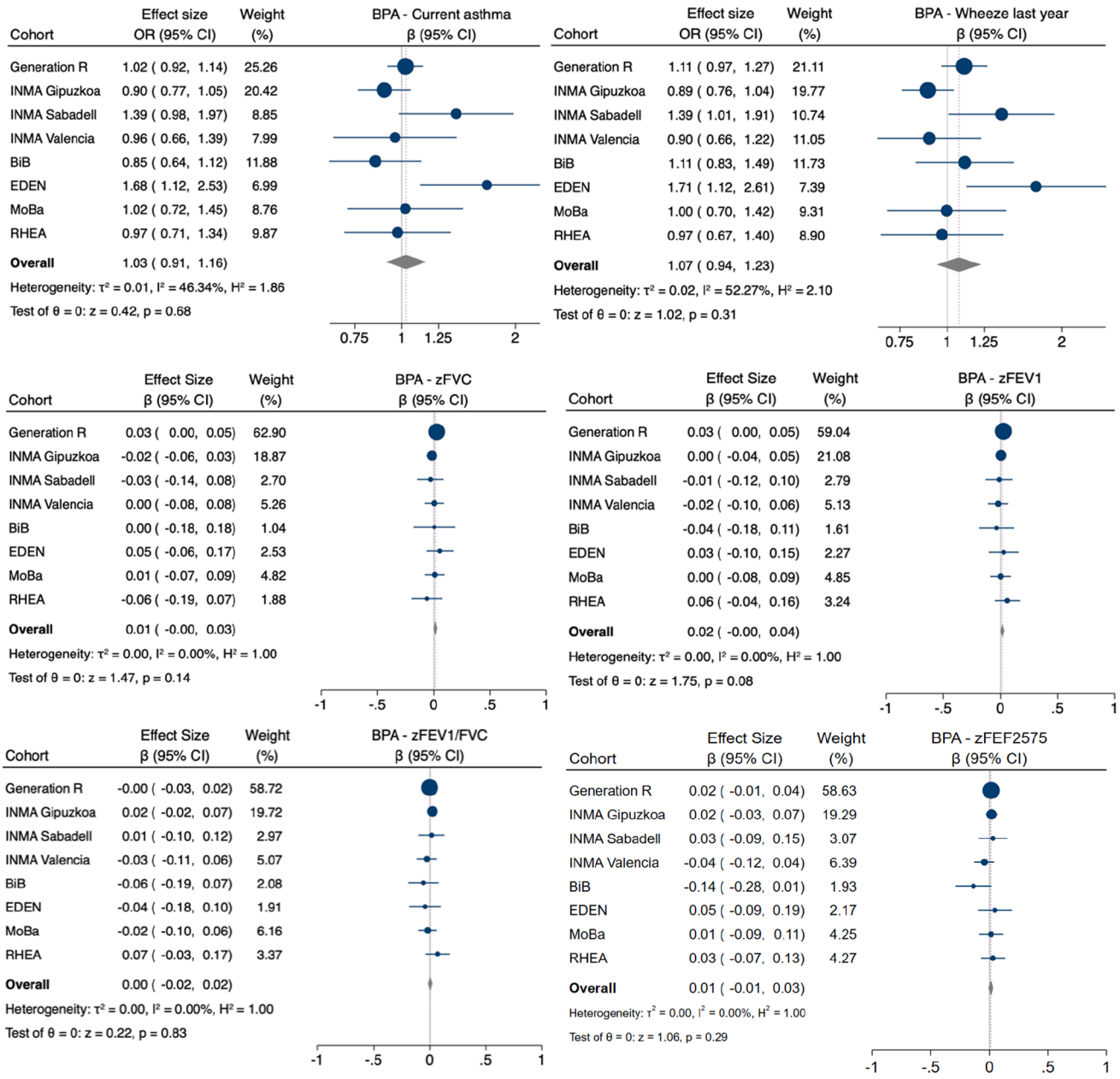

Fig. 1. Overall associations between creatinine adjusted bisphenol A (μg/g) and respiratory outcomes from 2-stage *meta*-analysis [a]. [a]Values represent OR (95 %CI) in associations between bisphenol A and current asthma and wheeze; and z-score (95% CI) in associations between BPA and lung function parameters. Current asthma and wheeze models were adjusted for maternal education, age, pre-pregnancy BMI, smoking during pregnancy, and child's sex, age, and ethnicity. Lung function models were adjusted for maternal education, age, pre-pregnancy BMI, smoking during pregnancy, and child's ethnicity. Abbreviations: BPA: bisphenol A; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; FEF25-75%: mid expiratory flow; OR: odds ratio; CI: confidence interval.

be partly explained by their small sample size. In our study population, with a large sample size after stratification, we observed that *in utero* exposure to BPA was associated with higher odds of current asthma and wheeze at school-age in girls. Further, most previous studies have focused on children of ages ≤ 7 years; only one study (Donohue et al., 2013) assessed current asthma until 12 years of age and reported no associations in relation to *in utero* BPA; in that study sex-dependent effects were not examined. The urinary BPA levels measured during pregnancy in this study are similar to those reported in previous studies that assessed *in utero* BPA exposure in relation to respiratory outcomes in North American (Spanier et al., 2012; Spanier et al., 2014), European (Vernet et al., 2017; Agier et al., 2019), and Chinese (Zhou et al., 2017) cohort studies and higher than those reported in three North American studies (Berger et al., 2020; Buckley et al., 2018; Donohue et al., 2013). To our knowledge, there is no previous study assessing *in utero* exposure to BPA on wheezing patterns across childhood, preventing comparison of our findings of no associations between increasing BPA exposure with any wheezing pattern.

Literature on *in utero* BPA exposure and lung function is scarce. Only one cohort study associated *in utero* BPA exposure with lower %FEV_1 at 4 years but this association disappeared at 5 years of age (Spanier et al., 2014). This association was not observed in three other cohorts that assessed lung function from 5 to 12 years (Vernet et al., 2017; Agier et al., 2019; Berger et al., 2020). In our study, BPA was associated with higher lung function from 6 to 12 years of age only among boys, but estimates were small and generally towards the null. Such associations disappeared in sensitivity analyses when using complete case datasets and when excluding Generation R from the analyses, the cohort with the

largest sample size. Further studies are warranted to study the role of BPA on lung function growth.

To our knowledge, this is the first study to assess the associations of *in utero* BPF and BPS exposure with respiratory health. In our study we observed higher FEV_1 and $FEF_{25-75\%}$ associated with detectable levels of BPF and lower odds of late and persistent wheezing associated with detectable levels of BPS. These associations could have been at least partly explained by exposure misclassification (high temporal variability of BPF and BPS) and residual confounding arisen by the dichotomisation of exposure variables into detected and undetected. Mothers among the detected group tended to smoke less and had a higher educational level compared to those among the undetected group (data not shown). We suspect mothers with higher education and a healthier lifestyle tend to use more BPA-free products which in turn may contain BPA substitute, similar as observed for parabens (Montazeri et al., 2019). Of interest, the Generation R cohort presented the highest proportion of study participants with detectable levels of BPF and BPS. This might indicate that the introduction of BPA substitutes in the Netherlands was earlier than in other countries, as previously reported (Philips et al., 2018). In other countries where these bisphenols were not as present in the market as they are currently, we expect current population's exposure to be higher, which guarantees the need for further investigation.

4.2. Interpretation of findings

Our results suggest that *in utero* exposure to BPA may increase the risk of asthma and wheeze at school-age through immunomodulatory mechanisms without notable lung function adaptations. This could be explained by the ability of bisphenols to cross the placenta (Lee et al., 2018) and interfere with the developing respiratory and immune systems by binding to a number of receptors related to inflammatory and oxidative stress pathways (Welshons et al., 2006; Vandenberg et al., 2007; Rogers et al., 2013; Kim et al., 2020). Immunomodulatory alterations from exposure to BPA have been observed in *in vitro*, animal, and human studies and include the increase in serum immunoglobulin-E, eosinophilic inflammation in the airways, stimulation of pro-inflammatory cytokines, T helper (Th) 1/Th2 cell shifts, and alterations in Th17 and β-cell counts (Rogers et al., 2013; Kim et al., 2020; Luo et al., 2016). Although animal studies have observed deleterious effects on the structural development of the lung after *in utero* exposure to BPA (Van Winkle et al., 2013; Hijazi et al., 2015), we could not confirm that in our study. We did not observe an association with notable lung function adaptations that could relate to the effects observed with asthma and wheeze. However, children with asthma usually present a normal spirometry (Dufetelle et al., 2018; Bacharier et al., 2004). On a population level, children without a current asthma exacerbation or with adequately controlled asthma, might present spirometry results within the healthy standards (Bacharier et al., 2004; Baatenburg de Jong et al., 2006). Additionally, BPA presents obesogenic properties acting through different pathways including the interference with thyroid hormones and its affinity to estrogenic and glucocorticoid receptors (Andrianou et al., 2016; Prasanth et al., 2010). In rodents, *in utero* exposure to BPA has been shown to increase adiposity and circulating lipid levels (Wassenaar et al., 2017). In epidemiological studies, BPA has been associated with increased risk of obesity in children (Kim et al., 2019), which in turn is a risk factor for asthma development in children (Lang et al., 2018), which may partially explain the results observed in our study.

Sexually dimorphic effects of bisphenols on diverse health outcomes have been reported, including asthma and obesity (Braun et al., 2011; Buckley et al., 2016; Doherty et al., 2017; Ilagan et al., 2017; Pu et al., 2017; Harley et al., 2013). Given the endocrine disrupting capacity of bisphenols, they can alter key hormone-signalling pathways and thus induce changes in sex hormones, which may partly explain the results found in this study. Fluctuations of sex hormones and their consequences on immune functions can play a role in asthma pathogenesis. The sexual dimorphism of asthma is especially observed in hormonally changing periods such as puberty, pregnancy, and menopause (Shah and Newcomb, 2018). Observational, clinical, and animal studies have highlighted changes in oestrogen and testosterone levels to influence incidence and severity of asthma (Han et al., 2020; DeBoer et al., 2018; Cephus et al., 2017; Bonds and Midoro-Horiuti, 2013).

4.3. Strengths and limitations

The strengths of this study rely on its prospective IPD *meta*-analysis design with multiple bisphenols, detailed, harmonized, and objective respiratory outcomes, and large sample size, which enabled us to assess the subtle effects usually associated with exposure to environmental hazards (Frey and Usemann, 2019) and potential effect modifiers. By performing prospective IPD *meta*-analyses, we increased the strength of evidence without relying on published data and thus limited potential publication bias, a common limitation of retrospective *meta*-analysis (Seidler et al., 2019). Also, current asthma status was constructed based on having two of three conditions (ever asthma diagnosis, wheeze in the last year, medication in the last year), which may have reduced outcome misclassification.

This study has however several limitations. First, exposure to bisphenols was determined in 1 or 2 spot urine samples, which given the short biological half-life of bisphenols, might have led to exposure misclassification. To overcome this bias, we applied regression calibration. After this correction, the increase in FEV_1 associated with prenatal BPA exposure disappeared, which tells us that it is unlikely that BPA is associated with an increase, although small, in lung function. Regression calibration models could not take into account the clustering of individuals within cohorts (random intercepts) like the main analyses. In addition, regression calibration could not be performed for asthma and wheeze because in logistic models, the bias in the regression calibration corrected analysis is high when the measurement error variance is high (Nab and Groenwold, 2021), as it was in our case. Further studies collecting repeated biospecimens per subject during pregnancy are needed (Casas et al., 2018; Vernet et al., 2018). Second, due to the low number of samples with detectable levels of BPF and BPS, we were not able to consider the exposure as continuous and categorised them into detected and undetected. This may have led to residual confounding since detected and undetected groups differed in socioeconomic and lifestyle characteristics as mentioned before. Third, bisphenols were analysed in different laboratories with some showing poor correlations (Supplementary Methods 2). However, after excluding the cohorts that conducted the analyses in these laboratories from the analyses, results did not change. Fourth, bisphenols were quantified at different trimesters of pregnancy in the cohorts. However, we tested whether trimester of the sampling was an explanatory factor of the heterogeneity, and it did not explain it (data not shown). Fifth, although we were able to construct childhood wheezing phenotypes, the data on wheezing episodes available across ages differed between cohorts (Supplementary Table S1). We were able to create four patterns, which might not be sufficient to capture effects on a specific age. Sixth, although lung function parameters were obtained following the ATS/ERS criteria, these estimates need to be carefully interpreted since the spirometry measurement error might be greater than the estimates, when these estimates are expected to be small. Finally, the included population tended to be of somewhat higher educated and socioeconomic status families. Although our results might not be generalised to the general population, this study encompasses the largest number of participants from different regions of Europe to date, and it is unlikely this might affect the internal validity of the study.

4.4. Conclusions

Our study suggests that *in utero* exposure to BPA may increase the risk of asthma and wheeze among school-age girls but shows no

evidence of an association with lung function at school-age. Identification of early determinants of respiratory health in childhood is of utmost importance, given their long-term effect on disease throughout life. Further research is needed on the assessment of temporal variabilities in exposure in relation to health outcomes, in order to improve current EU chemical legislation. Current regulation is focused on BPA, obviating analogues that are suspected to have similar toxicity (Rosenmai et al., 2014), and needs to move forward by avoiding entire chemical classes instead of individual compounds.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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