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Shareable abstract (@ERSpublications)

This meta-analysis of 150 000 children suggests that mostly lower respiratory tract infections are associated with an increased risk of asthma and lower lung function. This is independent from preceding respiratory tract infections or early-life asthma. https://bit.ly/3weE62I

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Abstract

Background Early-life respiratory tract infections might affect chronic obstructive respiratory diseases, but conclusive studies from general populations are lacking. Our objective was to examine if children with early-life respiratory tract infections had increased risks of lower lung function and asthma at school age.

Methods We used individual participant data of 150 090 children primarily from the EU Child Cohort Network to examine the associations of upper and lower respiratory tract infections from age 6 months to 5 years with forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow at 75% of FVC ($FEF_{75\%}$) and asthma at a median (range) age of 7 (4–15) years.

Results Children with early-life lower, not upper, respiratory tract infections had a lower school-age FEV_1, FEV_1/FVC and $FEF_{75\%}$ (z-score range: −0.09 (95% CI −0.14– −0.04) to −0.30 (95% CI −0.36– −0.24)). Children with early-life lower respiratory tract infections had a higher increased risk of school-age asthma than those with upper respiratory tract infections (OR range: 2.10 (95% CI 1.98–2.22) to 6.30 (95% CI 5.64–7.04) and 1.25 (95% CI 1.18–1.32) to 1.55 (95% CI 1.47–1.65), respectively). Adjustment for preceding respiratory tract infections slightly decreased the strength of the effects. Observed associations were similar for those with and without early-life wheezing as a proxy for early-life asthma.

Conclusions Our findings suggest that early-life respiratory tract infections affect development of chronic obstructive respiratory diseases in later life, with the strongest effects for lower respiratory tract infections.

Introduction

Respiratory tract infections are common in early life [1, 2]. An accumulating body of evidence suggests that early-life respiratory tract infections have short-term consequences, but also affect the development of both the respiratory and immune systems [3–6]. Thus, early-life respiratory infections may predispose individuals to chronic respiratory diseases such as asthma in later life.

Previous individual observational studies have shown inconsistent findings on the associations of respiratory tract infections in early life with the risk of wheezing or asthma in later life, which ranges from a 1.5- to 10-fold increased risk [7–13]. Relatively few observational studies focused on lung function as an outcome, which showed that early-life respiratory tract infections were associated with a lower lung function in childhood or adulthood [14–18]. Most studies considered only severe respiratory infections, *e.g.* requiring hospitalisation, or specific pathogens found in nasal lavage fluids or other biological samples. This, however, might reflect a subset of infections only, which is not representative of mostly less severe upper and lower respiratory tract infections in the general population. Studying the associations of early-life upper and lower respiratory tract infections separately with lung function and asthma using individual participant data from the general European population allows better harmonisation of the data, usage of the same set of confounders and more powerful analyses compared with these separate studies with different definitions of respiratory tract infections and respiratory outcomes, measured at different ages and often with limited power. We hypothesised that mostly lower respiratory tract infections in early life would be associated with lower lung function and an increased risk of asthma.

Therefore, we conducted an individual participant data meta-analysis among 150 090 children from 38 European birth cohorts to examine the associations of early-life upper and lower respiratory tract infections with lung function and asthma at school age.

Methods

General design

We identified 53 European pregnancy and birth cohorts from the EU Child Cohort Network (www.lifecycle-project.eu) and a birth cohort registry (www.birthcohorts.net) [19]. Inclusion criteria were cohorts that had included children born between 1989 and 2013, had available data on early-life respiratory tract infections and childhood lung function and/or asthma, had approval for the study from local institutional review boards, and gave written informed consent for using their data and the possibility to exchange original data. Of the invited cohorts, some did not respond (n=3), were unable to participate due to lack of data (n=10) or had other reasons for nonparticipation (n=2), leading to a total of 38 cohorts (24 from the EU Child Cohort Network) with 150 090 mother–child pairs for the current analyses (supplementary figure S1). Cohorts shared original data, and data harmonisation and analysis was performed within the lead institute (Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands).

Early-life respiratory tract infections

Information on respiratory tract infections was obtained at the ages of 6 months, 1, 2, 3, 4 and 5 years, and reflected any upper or lower respiratory tract infection in the last 6 or 12 months. For most cohorts (74% (n=110 067)), data on respiratory tract infections were obtained by questionnaires (supplementary table S1). Other methods to obtain information on respiratory tract infections included the use of registry data or interviews. Upper respiratory tract infections included croup, whooping cough, ear infection, throat infection, rhinitis and cold. Lower respiratory tract infections included bronchitis, bronchiolitis, pneumonia and chest infections. Infections were preferably doctor-diagnosed in order to limit the possibility that symptoms of asthma were misdiagnosed as infections or due to allergy. Early-life respiratory tract infections were categorised into upper respiratory tract infections (no/yes) and lower respiratory tract infections (no/yes).

School-age lung function and asthma

The main respiratory outcomes used were lung function and asthma (median (range) age 7 (4–15) years). Lung function was measured by spirometry, and comprised forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 75% of FVC ($FEF_{75\%}$). All cohorts performed spirometry according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. Cohorts provided absolute values of all lung function measurements, and these were subsequently converted into sex-, age-, height- and ethnicity-adjusted z-scores based on the Global Lungs Initiative reference values by the primary data analyst [20]. Asthma was defined as ever doctor diagnosis of asthma (no/yes) diagnosed at or after age 5 years, which was preferably obtained by questionnaire (40% (n=60 036)) through questions adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) [21]. Other methods to obtain information on asthma were healthcare registry data, interviews and symptom diary or report. If cohorts had data on lung function or asthma measured at multiple time-points, we only used data from the age closest to the median age of all cohorts (7 years) in the full meta-analysis. If cohorts had both lung function and asthma data available (16% (n=23 955)), we used data obtained at concomitant ages.

Covariates

Information on socioeconomic, lifestyle and growth-related factors was mostly obtained by questionnaire, with diaries or registry data as other methods of data ascertainment (supplementary table S1). Covariates were selected from the literature and were visualised by means of a directed acyclic graph. The final set of confounders included maternal age, education, ethnicity, parity, smoking during pregnancy, history of asthma or atopy and pet keeping, and child's sex, gestational age at birth, birthweight, season of birth, breastfeeding and daycare attendance. We obtained information on early-life wheezing by questions adapted from the ISAAC on wheezing in the past 12 months at the ages of 1, 2, 3 and 4 years [21]. As asthma is difficult to diagnose at young ages and early-life wheezing is a strong predictor of later asthma development, we used wheezing as a proxy for early-life asthma to assess whether the associations between early-life respiratory tract infections and school-age lung function and asthma differed between those with and without early-life wheezing.

Statistical analyses

We conducted a one-stage random effects meta-analysis to study the associations of any upper and lower respiratory tract infections in early life with lung function and asthma at school age. For this analysis,

individual participant data from all cohorts were combined in one analysis and were modelled simultaneously taking into account the clustering of participants within studies by using a random intercept at cohort level. With this, potential differences in cohorts and geographical regions were taken into account. First, we studied any upper and lower respiratory tract infections at all different ages separately, using linear regression models for lung function and logistic regression models for asthma as the outcome. Our first model was unadjusted, our second model was adjusted for socioeconomic, lifestyle and growth-related factors based on their known associations with lung function and asthma from literature, and a third model was additionally adjusted for preceding upper or lower respiratory tract infections, as appropriate, to minimise bias due to vulnerability to these infections. We considered the second model (confounder model) as our main model.

As a sensitivity analysis, we conducted a two-stage random effects meta-analysis to study the associations of early-life respiratory tract infections with the main lung function outcome FEV_1/FVC and asthma (no/yes). For this analysis, we used linear and logistic regression models per cohort, after which pooled regression coefficients (β-values) from the per-cohort effect estimates were calculated. We tested for heterogeneity between effect estimates by using I^2-values [22].

We performed additional analyses on the main models of our one-stage random effects meta-analysis. We additionally stratified for early-life wheezing to examine whether associations of early-life respiratory tract infections with lung function and asthma were different among children with and without symptoms of early-life wheezing. Also, to assess differences in results related to trajectories of post-natal lung growth, we repeated our analyses in strata of children aged <9 and ⩾9 years at the time of outcome assessment. This cut-off was based on both data availability and age of change in FEV_1/FVC trajectories [23]. We performed sensitivity analyses by applying a complete case analysis to explore any differences between complete and noncomplete case analyses, excluding cohorts that used parental report of asthma not according to the ISAAC, excluding cohorts that used other methods to assess respiratory tract infections rather than questionnaire of parental report, or that comprised a large number of participants (>5% of the total), and two cohorts that assessed lung function at age 4 years because reliable and valid measurements of lung function below the age of 4 years in population-based cohorts is difficult. For all analyses, missing values in covariates were used as an additional group in the categorical variables to prevent exclusion of noncomplete cases. Measures of association were z-score differences or odds ratios presented with their 95% confidence intervals. Analyses were performed with SPSS version 25.0 for Windows (IBM, Armonk, NY, USA) and RevMan version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Participant characteristics

The characteristics of asthma, lung function and respiratory tract infections are shown in tables 1 and 2, and supplementary table S2. The prevalence of upper and lower respiratory tract infections was highest at the age of 1 year (mean 62.9% and 23.0%, respectively) and thereafter decreased until the age of 5 years (42.6% and 15.0%, respectively) (table 2). The mean prevalence of asthma across all cohorts was 12.3%. Characteristics of covariates can be found in supplementary table S3.

Respiratory tract infections and lung function

Unadjusted associations of upper and lower respiratory tract infections with lung function are provided in supplementary table S4. After adjustment for socioeconomic, lifestyle and growth-related factors, only upper respiratory tract infections at the age of 6 months were associated with a higher FEV_1/FVC and $FEF_{75\%}$ (z-score difference: 0.05 (95% CI 0.00–0.10) and 0.10 (95% CI 0.03–0.19), respectively), and upper respiratory tract infections at the age of 5 years with a higher FEV_1 (z-score difference: 0.04 (95% CI 0.00–0.08)) (figure 1 and supplementary table S5). After additional adjustment for preceding upper respiratory tract infections, the direction and size of the effect estimates remained similar (figure 1 and supplementary table S6). Lower respiratory tract infections at all ages were associated with a lower FEV_1 and FEV_1/FVC (z-score difference range: −0.09 (95% CI −0.14– −0.04) to −0.30 (95% CI −0.36– −0.23)) (figure 1 and supplementary table S5). Only lower respiratory tract infections at age 1 year were associated with a lower FVC (z-score difference: −0.08 (95% CI −0.12– −0.04)). Additionally, lower respiratory tract infections at all ages, except at the age of 6 months, were associated with a lower $FEF_{75\%}$ (z-score difference range: −0.12 (95% CI −0.21– −0.03) to −0.24 (95% CI −0.39– −0.09)). After additional adjustment for preceding lower respiratory tract infections, the direction of the effect estimates remained, but the sizes attenuated (z-score difference range: −0.08 (95% CI −0.12– −0.04) to −0.21 (95% CI −0.36– −0.06)) (figure 1 and supplementary table S6).

TABLE 1 Characteristics of asthma and lung function in participating cohorts

Cohort name (country)	Age at outcome, years	Participants, n	Asthma, % (n)	FEV_1, z-score	FVC, z-score	FEV_1/FVC, z-score	$FEF_{75\%}$, z-score
ABIS (Sweden)	5	12 618	4.6 (578)	NA	NA	NA	NA
ALSPAC (UK)	8	8376	21.7 (1605)	−0.34±1.01	−0.50±1.02	0.42±1.07	NA
BAMSE (Sweden)	8	3402	12.4 (420)	0.46±0.95	0.65±0.93	−0.36±0.89	NA
BiB (UK)	5	2674	8.3 (223)	NA	NA	NA	NA
BILD (Switzerland)	6	254	5.6 (14)	−0.00±0.95	−0.19±0.97	0.41±0.97	NA
CoNER (Italy)	8	214	6.1 (13)	−1.02±0.87	1.73±0.80	1.80±0.50	NA
COPSAC 2000 (Denmark)	7	290	19.7 (57)	−0.26±1.09	−0.58±1.06	0.78±1.17	2.01±1.14
COPSAC 2010 (Denmark)	5	550	22.4 (123)	−0.11±1.00	−0.18±1.00	0.17±0.98	1.53±0.92
DNBC (Denmark)	7	34 437	15.2 (5250)	NA	NA	NA	NA
EDEN (France)	6	900	18.6 (167)	−1.3±1.65	−1.63±1.65	0.87±1.12	1.33±1.93
FLEHS (Belgium)	10	110	7.3 (8)	NA	NA	NA	NA
GASPII (Italy)	9	464	13.1 (61)	−0.01±0.88	0.05±0.76	−0.15±0.97	NA
Generation R (Netherlands)	10	5441	9.3 (436)	0.15±0.98	0.19±0.93	−0.11±0.96	0.02±0.92
Generation XXI (Portugal)	7	5485	6.1 (331)	0.56±0.96	0.38±0.94	0.29±0.89	1.39±1.93
GINI (Germany)	15	1965	12.9 (217)	−0.58±0.92	−0.53±0.90	−0.11±1.00	−0.13±0.95
HUMIS (Norway)	9	2384	5.3 (127)	NA	NA	NA	NA
INMA Gipuzkoa (Spain)	4	277	NA	−0.60±1.15	−0.54±1.15	−0.05±0.91	−0.16±1.00
INMA Menorca (Spain)	12	422	6.4 (27)	−0.16±1.07	0.01±1.13	−0.24±1.19	−0.06±1.13
INMA Sabadell (Spain)	4	406	NA	−0.57±1.30	−0.48±1.37	−0.08±1.03	−0.25±1.13
INMA Valencia (Spain)	8	455	NA	0.30±1.08	0.30±1.10	−0.04±0.95	0.04±0.90
Isle of Wight (UK)	10	1327	19.9 (264)	NA	NA	NA	NA
KOALA (Netherlands)	7	1875	7.6 (141)	−0.13±0.95	0.16±0.94	−0.55±0.84	NA
LRC (UK)	12	3978	20.3 (809)	−0.11±1.17	−0.16±1.09	0.23±1.05	0.20±0.98
Lifeways Cross-Generation Cohort Study (Ireland)	9	138	6.5 (9)	NA	NA	NA	NA
LISA (Germany)	15	941	9.7 (77)	−0.50±0.93	−0.44±0.97	−0.12±0.98	−0.12±0.90
LucKi (Netherlands)	6	337	15.4 (52)	NA	NA	NA	NA
LUKAS (Finland)	6	374	9.9 (37)	−0.08±1.09	0.30±1.00	−0.73±0.84	−0.48±1.01
MAS-90 (Germany)	7	826	6.6 (44)	0.28±1.09	0.06±0.91	0.41±1.00	NA
Millennium Cohort Study (UK)	11	14 917	15.3 (2284)	NA	NA	NA	NA
MoBa (Norway)	7	34 542	10.6 (3677)	NA	NA	NA	NA
NINFEA (Italy)	7	1072	3.0 (32)	NA	NA	NA	NA
PELAGIE (France)	6	941	11.3 (106)	NA	NA	NA	NA
PIAMA (Netherlands)	11	2810	11.3 (299)	0.52±0.92	0.37±0.87	0.21±1.01	NA
REPRO_PL (Poland)	7	106	2.1 (2)	0.33±1.20	0.23±1.16	0.18±1.15	2.22±1.05
Rhea (Greece)	7	596	9.3 (55)	−0.01±1.16	0.18±1.18	−0.33±1.03	−0.22±1.06
STEPS (Finland)	5	713	8.3 (59)	NA	NA	NA	NA
SWS (UK)	6	2033	14.1 (287)	0.02±0.96	−0.12±1.03	−0.14±1.08	NA
WHISTLER (Netherlands)	5	1438	8.1 (116)	0.43±1.06	−0.38±1.00	1.71±0.87	1.99±0.79
Total	Median 7	150 090	12.3 (18 007)	−0.02±1.10	−0.03±1.11	0.03±1.07	0.35±1.37

z-scores for lung function measurements are presented as mean±SD. NA: not available.

Respiratory tract infection and asthma

Unadjusted associations of upper and lower respiratory tract infections with asthma are provided in supplementary table S4. Upper respiratory tract infections at all ages were associated with an increased risk of asthma (OR range: 1.25 (95% CI 1.18–1.32) to 1.57 (95% CI 1.48–1.67)) (figure 2 and supplementary table S5). Also, lower respiratory tract infections at all ages were associated with an increased risk of asthma (OR range: 2.10 (95% CI 1.98–2.22) to 6.30 (95% CI 5.64–7.04)). After additional adjustment for preceding upper or lower respiratory tract infections (as appropriate), the effect estimates slightly attenuated and this decreasing effect was stronger with increasing age (figure 2 and supplementary table S6).

Additional and sensitivity analyses

The two-stage random effect meta-analyses using combined effects showed similar magnitude and strength of effects as the one-stage random effects meta-analysis, with low to moderate heterogeneity (I^2 range: 0–72%) (supplementary table S8). The associations of upper and lower respiratory tract infections with lung function and asthma did not materially differ for those without and with early-life wheezing at the same

TABLE 2 Prevalence of upper and lower respiratory tract infections among children

	Prevalence, % (n)
Upper respiratory tract infections	
6 months	41.2 (36 564)
1 year	62.9 (58 949)
2 years	46.0 (27 119)
3 years	47.7 (35 641)
4 years	42.8 (11 159)
5 years	42.6 (19 424)
Lower respiratory tract infections	
6 months	6.7 (3587)
1 year	23.0 (13 297)
2 years	16.0 (9045)
3 years	16.0 (11 117)
4 years	11.8 (2354)
5 years	15.0 (5783)

age as the respiratory tract infection or for children aged <9 and ⩾9 years (supplementary table S7, table 3 and supplementary table S9, respectively). Results did not materially change when we restricted our analyses to cohorts that used ISAAC-based questionnaires of asthma, that used parental report of respiratory tract infections with questionnaire, complete cases (supplementary table S9), when leaving out one cohort at a time with a large number of participants (supplementary table S10) or when leaving out the two cohorts that assessed lung function at age 4 years (data not shown).

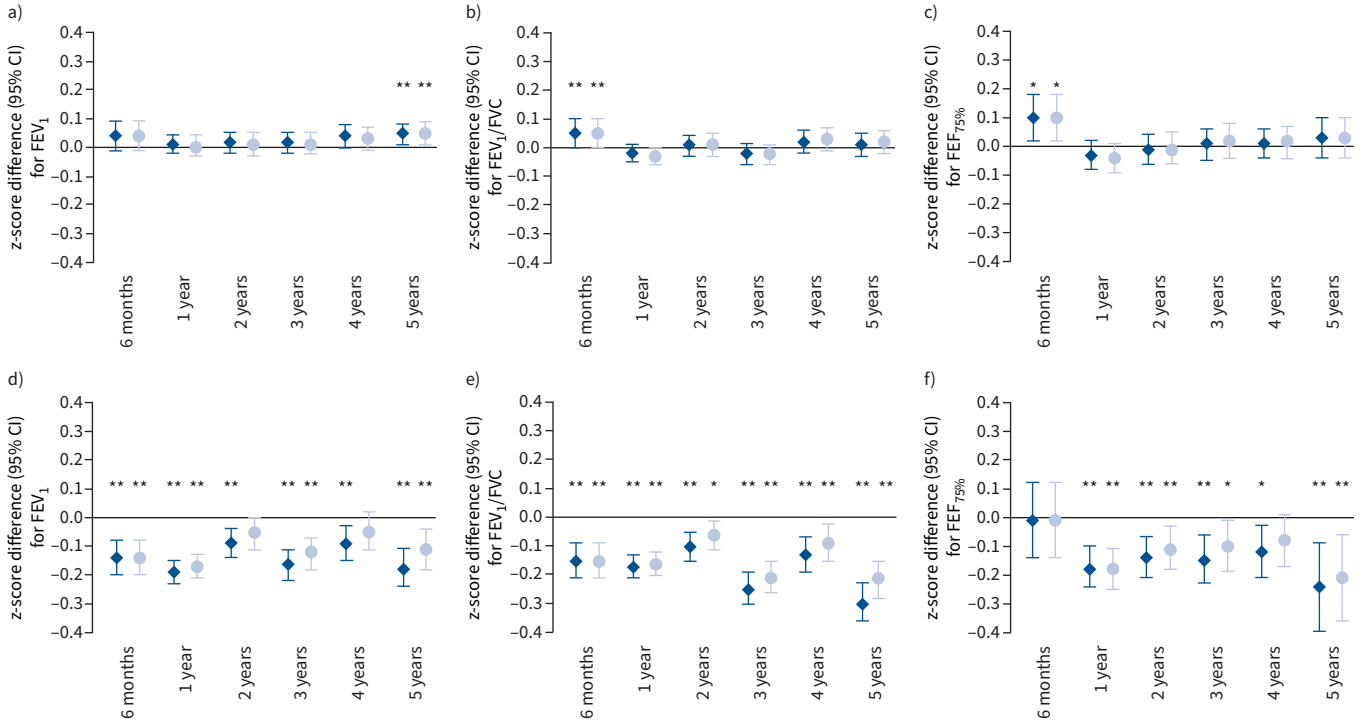

FIGURE 1 Associations of early-life a–c) upper and d–f) lower respiratory tract infections with school age: a, d) forced expiratory volume in 1 s (FEV_1), b, e) FEV_1/forced vital capacity (FVC) and c, f) forced expiratory flow at 75% of FVC ($FEF_{75\%}$). Data are presented as change in z-score (95% confidence interval), derived from multilevel linear regression models. The dark blue diamonds represent models adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birthweight, season of birth, breastfeeding, and daycare attendance. The light blue circles represent models additionally adjusted for preceding a–c) upper or d–f) lower respiratory tract infections. *: p<0.05; **: p<0.01.

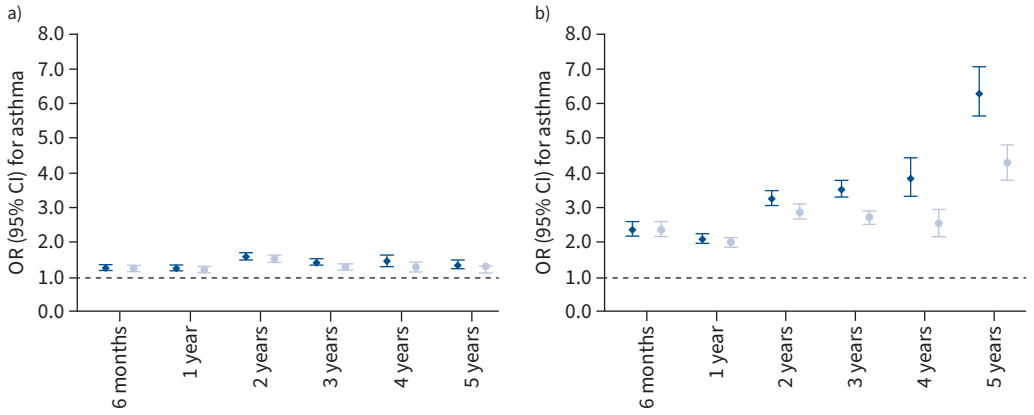

FIGURE 2 Associations of early-life a) upper and b) lower respiratory tract infections with school-age asthma. Data are presented as odds ratio (95% confidence interval), derived from multilevel logistic regression models. The dark blue diamonds represent models adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birthweight, season of birth, breastfeeding and daycare attendance. The light blue circles represent models additionally adjusted for preceding a) upper or b) lower respiratory tract infections. p-values all <0.01.

Discussion

Our results from an individual participant meta-analysis among 150 090 participants from 38 cohorts across Europe demonstrate that 1) early-life upper respiratory tract infections were associated with an increased risk of school-age asthma, not lung function, and 2) early-life lower respiratory tract infections were associated with increased risks of both school-age lower lung function (FEV_1, FEV_1/FVC and $FEF_{75\%}$) and asthma. The effect sizes for the associations of lower respiratory tract infections with asthma were much larger than those for the association of upper respiratory tract infections with asthma. The strength of the effects slightly decreased when adjusting for preceding respiratory tract infections. Results were not modified by wheezing in early-life, suggesting that these associations could in part be present irrespective of possible early-life susceptibility to asthma.

TABLE 3 Associations of any early-life upper and lower respiratory tract infections with school-age asthma, stratified for early-life wheezing

	Asthma, no early-life wheezing OR (95% CI)	Asthma, early-life wheezing OR (95% CI)
Upper respiratory tract infections		
6 months	1.11 (1.03–1.21)**	1.03 (0.87–1.22)
1 year	1.19 (1.08–1.32)**	1.22 (1.06–1.41)**
2 years	1.20 (1.04–1.37)*	1.14 (0.95–1.37)
3 years	1.17 (1.06–1.30)**	1.00 (0.86–1.16)
4 years	1.19 (1.01–1.41)*	1.01 (0.86–1.19)
Lower respiratory tract infections		
6 months	2.09 (1.45–3.01)**	1.40 (1.18–1.66)**
1 year	2.28 (1.97–2.66)**	1.87 (1.63–2.13)**
2 years	2.25 (1.89–2.68)**	1.87 (1.59–2.20)**
3 years	2.67 (2.12–3.35)**	1.43 (1.21–1.69)**
4 years	2.54 (1.98–3.28)**	1.45 (1.17–1.80)**

Data are presented as odds ratio with 95% confidence interval, derived from multilevel logistic regression models. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birthweight, season of birth, breastfeeding and daycare attendance. Early-life wheezing reflects wheezing at the same age as upper or lower respiratory tract infections. *: p<0.05; **: p<0.01.

Comparison with previous studies

We showed that mostly early-life lower respiratory tract infections were associated with increased risks of school-age lower lung function and asthma, both before and after age 9 years. The results are in line with a meta-analysis of 15 studies demonstrating that rhinovirus wheezing illness in the first 3 years of life is associated with a 2-fold increased risk of asthma or wheezing at older childhood ages [24]. These findings were present both before and after the childhood age of 10 years. The large majority of studies have assessed specific pathogens of the respiratory infections, mostly rhinovirus or respiratory syncytial virus in relation to later-life chronic respiratory diseases. Relatively few cohort studies focused on respiratory infections such as pneumonia or bronchiolitis. A birth cohort showed that lower respiratory tract infections were associated with an increased risk of asthma at age 7 years, while repeated upper respiratory tract infections in the first year of life were associated with a decreased risk [25]. One study demonstrated that pneumonia in childhood was associated with a lower FEV_1/FVC at age 7 years, but only in those with current asthma [26]. Another study demonstrated that severe bronchiolitis during infancy was associated with a 2.5-fold increased risk of asthma at age 5 years [13]. Studies assessing the association of early-life respiratory tract infections with lung function in later life are scarce. A systematic review showed that respiratory infections until age 3 years are associated with a lower FEV_1 % pred at the age of 7.5–20 years [27]. The novelty of our study is that it adds to these findings by demonstrating that in the general European population, early-life lower respiratory tract infections, including bronchitis, bronchiolitis, pneumonia and chest infection, are associated with not only lower FEV_1 but also lower FEV_1/FVC and $FEF_{75\%}$, and an increased risk of asthma, which could have persistent and profound effects on later-life respiratory function and health. The use of harmonised data and the same set of confounders, and diagnoses of respiratory tract infections in the general population as opposed to specific pathogens in hospital-based populations, leads to better generalisability of the results.

Possible mechanisms

In this study, we found that both upper and lower respiratory tract infections are associated with an increased risk of asthma, while only lower respiratory tract infections are associated with lower lung function. The effect sizes for the associations of upper respiratory tract infections with asthma were smaller than the effect sizes for the association of lower respiratory tract infections with asthma; upper respiratory tract infections were not associated with lower lung function. Although the effect sizes for the associations of upper respiratory tract infections with asthma remained when additionally adjusted for concomitant lower respiratory tract infections (data not shown), we cannot fully rule out that this observed association is due to misclassifications of infections or concomitant infections. We consider the observed associations of upper respiratory tract infections at age 6 months with higher FEV_1/FVC and $FEF_{75\%}$ most likely as chance findings rather than biologically true observations. Both the immune and respiratory systems are still developing in the first years of life, and any disturbance in this development could be associated with adverse respiratory health in later life [28–31]. It is likely that both upper and lower respiratory tract infections have an effect on the immune system through adapted T-helper 2 and regulatory T-cell responses, which could subsequently lead to an increased risk of asthma [32]. Additionally, lower respiratory tract infections might have a more direct effect on the lungs through disruption of normal lung development and growth, specifically in the smaller airways. This could in turn lead to a lower lung function, predominantly airway obstruction and airflow limitation. This is in line with the findings that lower respiratory tract infections have an adverse effect on FEV_1, FEV_1/FVC and $FEF_{75\%}$, but not FVC. Some have suggested that the association of early-life respiratory tract infections with lung function and asthma might be explained by a pre-existing underlying predisposition [27, 33]. We demonstrated that the association of respiratory tract infections with lung function and asthma does not differ between those with and without concomitant wheezing. This suggests that asthma susceptibility does not modify these associations, although we cannot fully rule out overlap of respiratory symptoms due to respiratory tract infections and asthma if both are present. This is supported by a cohort study demonstrating that lower respiratory tract infections in infancy are associated with a lower lung function at age 1 year, irrespective of lung function at age 6 weeks [16]. In line with the Developmental Origins of Health and Disease hypothesis, studies have suggested that the effect of respiratory tract infections in early life on respiratory health carries on until adulthood [34–36]. Additionally, lung function trajectories, either obstructive or restrictive phenotypes, are shown to persist into adolescence and adulthood [37]. Whether early-life risk factors, altered lung function and diagnosis of asthma in childhood either separately or combined lead to adverse respiratory health such as asthma or chronic obstructive pulmonary disease in adulthood needs to be carefully elucidated. Last, our results could potentially be explained by reverse causation. This suggests that those with lower lung function or asthma in early life have an increased risk of respiratory infections in later life. To minimise this reversed effect, we additionally adjusted for preceding respiratory tract infections, but lacked appropriate statistical methods to fully rule this out on a meta-analysis-based level.

Strengths and limitations

The main strengths of this study include the use of a large dataset with individual participant data from across Europe, with harmonised data and the same set of confounders. The large majority of cohorts used ISAAC-based questionnaires commonly used in epidemiological studies for asthma diagnosis rather than providing medication, with potential side-effects for measuring lung function reversibility for relatively healthy subjects of population-based cohorts, and ATS/ERS criteria for spirometry, leading to homogeneity of data ascertainment. Last, we used various statistical methods and sensitivity analyses to test the robustness of the results. However, some limitations do apply. First, lung function measurements were available in ∼17% of the cohorts, and therefore we were not able to reliably assess mediation of lung function in the association between respiratory tract infections and asthma. Second, we did not have information on lung function in early life and therefore were not able to assess change in lung function due to respiratory tract infections. Further studies should also focus on forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) as a lung function outcome as this measure might be the first declining lung function parameter as a result of small airway impairment obtained in early life. We also did not have information on bronchodilator reversibility, which might have biased the diagnosis of asthma. Additionally, even though we used individual participant data to allow harmonisation of the data, there is heterogeneity both in terms of assessment and prevalence of respiratory tract infections across the cohorts. This could in part reflect true differences in prevalence between different countries, but it is also likely that this is due to differences in data collection, including ascertainment of the diagnoses. Due to nonconsistent data availability we were not able to study a possible mediating effect of antibiotic use. However, in a previous study we found no mediating effect of antibiotic use in the association of respiratory tract infections with lung function and asthma [17].

Conclusions

In conclusion, early-life upper respiratory tract infections are associated with an increased risk of school-age asthma. Early-life lower respiratory tract infections are associated with lower lung function at school age, indicative of airway obstruction and airflow limitation, and even stronger increased risk of asthma. These results suggest that predominantly lower respiratory tract infections could have a direct effect on lung development and subsequent chronic respiratory diseases.

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