

**Early View** 

Original research article

# Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150000 European children

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## Early-life respiratory tract infections and the risk of school-age

## lower lung function and asthma: a meta-analysis of 150,000 European children

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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.

**Objective** 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 second (FEV<sub>1</sub>), forced vital capacity (FVC), FEV<sub>1</sub>/FVC, forced expiratory flow at 75% of FVC (FEF<sub>75</sub>), and asthma at a median age of 7 (range 4 to 15) years.

**Results** Children with early-life lower, not upper, respiratory tract infections had a lower school-age FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FEF<sub>75</sub> (Z-score (95% CI): ranging from -0.09 (-0.14, -0.04) to -0.30 (-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 (95%CI): ranging from 2.10 (1.98, 2.22) to 6.30 (5.64, 7.04)), and from 1.25 (1.18, 1.32) to 1.55 (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 proxy for early-life asthma.

**Conclusion** 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 upper respiratory tract infections.

#### Take home message

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.

## INTRODUCTION

Respiratory tract infections are common in early life<sup>1,2</sup>. 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 system<sup>3-6</sup>. 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<sup>7-13</sup>. 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<sup>14-18</sup>. Most studies considered only severe respiratory infections for example requiring hospitalization, 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 harmonization of the data, usage of the same set of confounders and more powerful analyses, as compared to these separate studies with different definitions of respiratory tract infections and respiratory outcomes, measured at different ages and often with limited power. We hypothesized 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)<sup>19</sup>. 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 of 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 non-participation (n=2), leading to a total of 38 cohorts (24 from the EU Child Cohort network) with 150,090 motherchild pairs for the current analyses (Supplementary Figure S1). Cohorts shared original data, and data harmonization and analysis was performed within the lead institute.

**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 was 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 categorized into upper (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 age 7 years, range 4-15 years). Lung function was measured by spirometry and comprised forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital

capacity (FVC), FEV<sub>1</sub>/FVC and forced expiratory flow after 75% of the FVC is exhaled (FEF<sub>75</sub>). All cohorts performed spirometry according to ATS/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 Lung Initiative reference values by the primary data analyst<sup>20</sup>. 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)<sup>21</sup>. Other methods to obtain information on asthma were health care 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 socio-economic, 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 literature, and were visualized by means of a directed acyclic graph (DAG). 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, birth weight, season of birth, breastfeeding and daycare attendance. We obtained information on early-life wheezing by questions adapted from ISAAC on wheezing in the past 12 months at the ages of 1, 2, 3 and 4 years<sup>21</sup>. 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 1-stage random-effect 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 modeled 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 socio-economic, 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 appropriately, to minimize 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 2-stage random effects meta-analysis to study the associations of early-life respiratory tract infections with the main lung function outcome FEV<sub>1</sub>/FVC and asthma (no/yes). For this analysis, we used linear and logistic regression models per cohort, after which pooled regression coefficients (b values) from the per-cohort effect estimates were calculated. We tested for heterogeneity between effect estimates by using I<sup>2</sup> values<sup>22</sup>.

We performed additional analyses on the main models of our 1-stage random-effect 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 postnatal lung growth, we repeated our analyses in strata of children aged less than 9 years and 9 years or older at time of outcome assessment. This cut-off was based on both data availability and age of change in FEV<sub>1</sub>/FVC trajectories<sup>23</sup>. We performed sensitivity analyses by applying a complete case analysis to

explore any differences between complete and non-complete case analyses, excluding cohorts that used parental report of asthma not according to 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 non-complete cases. Measures of association were Z-score differences or Odds Ratio's (OR) presented with their 95% confidence interval (95% CI). Analyses were performed with SPSS version 25.0 for Windows software (IBM Corp) and RevMan version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

## RESULTS

**Participant characteristics** The characteristics of children of the cohorts are shown in Table 1 and Supplementary Table 2. The prevalence of upper and lower respiratory tract infections was highest at the age of 1 year (mean 63.0 and 23.0%, respectively) and thereafter decreased until the age of 5 years (42.6 and 15.0%, respectively). 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 socio-economic, lifestyle and growth-related factors, only upper respiratory tract infections at the age of 6 months were associated with a higher FEV<sub>1</sub>/FVC and FEF<sub>75</sub> (Z-score difference (95% confidence interval): 0.05 (0.00, 0.10) and 0.10 (0.02, 0.18)), and upper respiratory tract infections at the age of 5 years with a higher FEV<sub>1</sub> (0.05 (0.01, 0.08)), respectively (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<sub>1</sub> and FEV<sub>1</sub>/FVC (range Z-score difference (95% confidence interval): -0.09 (-0.14, -0.04) to -0.30 (-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 (-0.08 (-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<sub>75</sub> (range: -0.12 (-0..21, -0.03) to -0.24 (-0.39, -0.09)). After additional adjustment for preceding lower respiratory tract infections, the direction of the effect estimates remained, but the sizes attenuated (range Z-score difference (95% confidence interval) -0.08 (-0.12, -0.04) to -0.21 (-0.36, -0.06) (Figure 1 and Supplementary Table S6).

**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 (range Odds Ratio (95% confidence interval) 1.25 (1.18, 1.32) to 1.57 (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 (range Odds Ratio (95% confidence interval) 2.10 (1.98, 2.22) to 6.30 (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 2-stage random effect meta-analyses using combined effects showed similar magnitude and strength of effects as the 1-stage random effect meta-analysis, with low to moderate heterogeneity (range l<sup>2</sup>: 0 to 72%) (Supplementary Tables S7). 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 age as the respiratory tract infection or for children aged less than 9 years and 9 years or older (Supplementary Table S8 and Table 3, and Supplementary Tables S9 and S10, 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).

## DISCUSSION

Our results from an individual participant meta-analysis among 150,090 participants from 38 cohorts across Europe demonstrate that early-life upper respiratory tract infections were associated with an increased risk of school-age asthma, not lung function and early-life lower respiratory tract infections with increased risks of both school-age lower FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FEF<sub>75</sub> 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.

**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 below and after age 9 years. 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<sup>24</sup>. 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<sup>25</sup>. One study demonstrated that pneumonia in childhood was associated with a lower FEV<sub>1</sub>/FVC at age 7 years, but only in those with current asthma<sup>26</sup>. Another study demonstrated that severe bronchiolitis during infancy was associated with a 2.5-fold increased risk of asthma at age 5 years<sup>13</sup>. 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 percentage predicted FEV<sub>1</sub> at the age of 7.5 to 20 years<sup>27</sup>. 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<sub>1</sub> but also lower FEV<sub>1</sub>/FVC and FEF<sub>75</sub>, and an increased risk of asthma, which could have persistent and profound effects on later life respiratory function and health. The use of harmonized 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 generalizability of 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, and upper respiratory tract infections were not associate 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 a higher FEV<sub>1</sub>/FVC and FEF<sub>75</sub> most likely as chance findings rather than biologically true observations. Both the immune and respiratory system 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<sup>28-31</sup>. It is likely that both upper and lower respiratory tract infections have an effect on the immune system through adapted Thelper-2 and regulatory T-cell responses, which could subsequently lead to an increased risk of asthma<sup>32</sup>. Additionally, lower respiratory tract infections might have a more direct effect on

the lungs through disruption of the normal lung development and growth, specifically in the smaller airways. This could in its 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<sub>1</sub>, FEV<sub>1</sub>/FVC and FEF<sub>75</sub>, 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<sup>27,33</sup>. We demonstrated that the association of respiratory tract infections with lung function and asthma do 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<sup>16</sup>. In line with the Developmental Origins of Health and Disease (DOHaD) hypothesis, studies have suggested that the effect of respiratory tract infections in early life on respiratory health carries on until adulthood<sup>34-36</sup>. Additionally, lung function trajectories, either obstructive of restrictive phenotypes, are shown to persist into adolescence and adulthood<sup>37</sup>. Whether early-life risk factors, altered lung function, and diagnosis of asthma in childhood either separately of combined lead to adverse respiratory health such as asthma or COPD in adulthood need 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 minimize 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** Main strengths of this study include the use of a large dataset with individual participant data from across Europe, with harmonized 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 to 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 around 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 FEF<sub>25-75</sub> 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 harmonization 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 non-consistent 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<sup>17</sup>

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.

#### CONTRIBUTORS

EM, SM-B, HD, JJ, VJ, and LD contributed to the study design, data analysis plan, data collection, data analysis, data interpretation, writing, reviewing the manuscript critically and gave consent for submission.

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## DATA SHARING

Individual participant data will not be available for sharing

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	Prevalence
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 (3,587)
1 year	23.0 (13,297)
2 years	16.0 (9,045)
3 years	16.0 (11,117)
4 years	11.8 (2,354)
5 years	15.0 (5,783)

**Table 1.** Prevalence of upper and lower respiratory tract infections among children.

Values are valid percentages (absolute numbers).

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Cohort name (Country)	Age	Ν	Asthma,	FEV <sub>1</sub>	FVC	FEV <sub>1</sub> /FVC	FEF <sub>75</sub>
	outcome		% (N)	z-score (SD)	z-score (SD)	z-score (SD)	z-score (SD)
ABIS (Sweden)	5 years	12,618	4.6 (578)	N/A	N/A	N/A	N/A
ALSPAC (UK)	8 years	8,376	21.7 (1,605)	-0.34 (1.01)	-0.50 (1.02)	0.42 (1.07)	N/A
BAMSE (Sweden)	8 years	3,402	12.4 (420)	0.46 (0.95)	0.65 (0.93)	-0.36 (0.89)	N/A
BiB (UK)	5 years	2,674	8.3 (223)	N/A	N/A	N/A	N/A
BILD (Swiss)	6 years	254	5.6 (14)	-0.00 (0.95)	-0.19 (0.97)	0.41 (0.97)	N/A
CoNER (Italy)	8 years	214	6.1 (13)	-1.02 (0.87)	1.73 (0.80)	1.80 (0.50)	N/A
COPSAC 2000 (Denmark)	7 years	290	19.7 (57)	-0.26 (1.09)	-0.58 (1.06)	0.78 (1.17)	2.01 (1.14)
COPSAC 2010 (Denmark)	5 years	550	22.4 (123)	-0.11 (1.00)	-0.18 (1.00)	0.17 (0.98)	1.53 (0.92)
DNBC (Denmark)	7 years	34,437	15.2 (5,250)	N/A	N/A	N/A	N/A
EDEN (France)	6 years	900	18.6 (167)	-1.3 (1.65)	-1.63 (1.65)	0.87 (1.12)	1.33 (1.93)
FLEHS (Belgium)	10 years	110	7.3 (8)	N/A	N/A	N/A	N/A
GASPII (Italy)	9 years	464	13.1 (61)	-0.01 (0.88)	0.05 (0.76)	-0.15 (0.97)	N/A
Generation R (Netherlands)	10 years	5,441	9.3 (436)	0.15 (0.98)	0.19 (0.93)	-0.11 (0.96)	0.02 (0.92)
Generation XXI (Portugal)	7 years	5,485	6.1 (331)	0.56 (0.96)	0.38 (0.94)	0.29 (0.89)	1.39 (1.93)
GINI (Germany)	15 years	1,965	12.9 (217)	-0.58 (0.92)	-0.53 (0.90)	-0.11 (1.00)	-0.13 (0.95)
HUMIS (Norway)	9 years	2,384	5.3 (127)	N/A	N/A	N/A	N/A

 Table 2. Characteristics of asthma and lung function in participating cohorts

IMNA Gipuzkoa (Spain)	4 years	277	N/A	-0.60 (1.15)	-0.54 (1.15)	-0.05 (0.91)	-0.16 (1.00)
INMA Menorca (Spain)	12 years	422	6.4 (27)	-0.16 (1.07)	0.01 (1.13)	-0.24 (1.19)	-0.06 (1.13)
INMA Sabadell (Spain)	4 years	406	N/A	-0.57 (1.30)	-0.48 (1.37)	-0.08 (1.03)	-0.25 (1.13)
INMA Valencia (Spain)	8 years	455	N/A	0.30 (1.08)	0.30 (1.10)	-0.04 (0.95)	0.04 (0.90)
Isle of Wight (UK)	10 years	1,327	19.9 (264)	N/A	N/A	N/A	N/A
KOALA (Netherlands)	7 years	1,875	7.6 (141)	-0.13 (0.95)	0.16 (0.94)	-0.55 (0.84)	N/A
LRC (UK)	12 years	3,978	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 years	138	6.5 (9)	N/A	N/A	N/A	N/A
LISA (Germany)	15 years	941	9.7 (77)	-0.50 (0.93)	-0.44 (0.97)	-0.12 (0.98)	-0.12 (0.90)
LucKi (Netherlands)	6 years	337	15.4 (52)	N/A	N/A	N/A	N/A
LUKAS (Finland)	6 years	374	9.9 (37)	-0.08 (1.09)	0.30 (1.00)	-0.73 (0.84)	-0.48 (1.01)
MAS-90 (Germany)	7 years	826	6.6 (44)	0.28 (1.09)	0.06 (0.91)	0.41 (1.00)	N/A
Millennium Cohort Study (UK)	11 years	14,917	15.3 (2,284)	N/A	N/A	N/A	N/A
MoBa (Norway)	7 years	34,542	10.6 (3,677)	N/A	N/A	N/A	N/A
NINFEA (Italy)	7 years	1,072	3,0 (32)	N/A	N/A	N/A	N/A
Pelagie (France)	6 years	941	11.3 (106)	N/A	N/A	N/A	N/A
PIAMA (Netherlands)	11 years	2,810	11.3 (299)	0.52 (0.92)	0.37 (0.87)	0.21 (1.01)	N/A
REPRO_PL (Poland)	7 years	106	2.1 (2)	0.33 (1.20)	0.23 (1.16)	0.18 (1.15)	2.22 (1.05)

Rhea (Greece)	7 years	596	9.3 (55)	-0.01 (1.16)	0.18 (1.18)	-0.33 (1.03)	-0.22 (1.06)
STEPS (Finland)	5 years	713	8.3 (59)	N/A	N/A	N/A	N/A
SWS (UK)	6 years	2,033	14.1 (287)	0.02 (0.96)	-0.12 (1.03)	-0.14 (1.08)	N/A
Whistler (Netherlands)	5 years	1,438	8.1 (116)	0.43 (1.06)	-0.38 (1.00)	1.71 (0.87)	1.99 (0.79)
Total	Median 7 years	150,090	12.3 (18,007)	-0.02 (1.10)	-0.03 (1.11)	0.03 (1.07)	0.35 (1.37)

Values are valid percentages (absolute numbers) for asthma, or Z-scores (SD) for lung function measurements. N/A: not available. United Kingdom (UK).

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

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

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic regression models. \*p-value <0.05, \*\*p-value <0.01. 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, birth weight, season of birth, breastfeeding and daycare attendance. Early-life wheezing reflects wheezing at the same age as upper or lower respiratory tract infections.

**Figure 1.** Associations of early-life upper **(A-C)** and lower **(D-F)** respiratory tract infections with school-age FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FEF<sub>75</sub>, respectively. Values are changes in Z-score with 95% confidence interval, derived from multilevel linear regression models. \*p-value <0.05, \*\*p-value <0.01. The black 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, birth weight, season of birth, breastfeeding, and daycare attendance. The grey circles represent models additionally adjusted for preceding upper (A-C) or lower (D-F) respiratory tract infections. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).



Lower respiratory tract infections

Lower respiratory tract infections

Lower respiratory tract infections

Figure 2. Associations of early-life upper (A) and lower (B) respiratory tract infections with school-age asthma. Values are Odds

Ratio's with 95% confidence interval, derived from multilevel logistic regression models. The black 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, birth weight, season of birth, breastfeeding and daycare attendance. The grey circles represent models additionally adjusted for preceding upper **(A)** or lower **(B)** respiratory tract infections.



# Supplementary tables and figures

## Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150,000 European children.

### Supplementary methods

ALSPAC recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. 14,541 is the initial number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper: <http://ije.oxfordjournals.org/content/early/2012/04/14/ije.dys064.full.pdf+html>. The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 were alive at 1 year of age. A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at

least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.

Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool" and reference the following webpage:

http://www.bristol.ac.uk/alspac/researchers/our-data/

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

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	Respiratory tract inf	fections	Respiratory of	outcomes	Covariates
Cohort name	Method of	Available at	Spirometry	School-age	
(country)	useesement	ugeo	protocol	asthma	
ABIS	Questionnaire,	1, 3, 5 years	N/A	Confirmed doctor	Questionnaires and register
(Sweden)	parental report			diagnosis, derived from the national health care register, at age 5 years	data
ALSPAC	Questionnaire, 6 months, 1, 3, 5 AT		ATS/ERS	Questionnaire,	Questionnaires and register
(United Kingdom)	parental report	years		parental report of doctor diagnosis at age 8 years	data
BAMSE	Questionnaire,	Questionnaire, 1, 2, 4 years AT	ATS/ERS	Questionnaire,	Questionnaires and register
(Sweden)	parental report			parental report of doctor diagnosis (ISAAC based), at age 8 years	data
BiB	Questionnaire,	6 months, 1, 2, 3,	N/A	Confirmed doctor	Questionnaire and register
(United Kingdom)	parental report	4 years		diagnosis, derived from health care registry data, at age 5 years	data
BILD	Questionnaire and interview by study	2, 3, 4 years	ATS/ERS	Questionnaire, parental report at	Questionnaire

Supplementary Table S1. Data collection on respiratory tract infections, lung function and asthma among children per cohort.

(Swiss)	team member, parental report			age 6 years (ISAAC based)		
CoNER	Questionnaire,	6 months, 1, 3	Other	Questionnaire,	Questionnaire and parental	
(Italy)	parental report	years		parental report of doctor diagnosis at age 8 years	report	
COPSAC 2000	Parental report of	3 years	ATS/ERS	Diagnosed by	Interview questionnaire	
(Denmark)	symptoms			physicians in the research clinic according to symptom algorithm, at age 7 years		
COPSAC 2010	Parental report of	ntal report of 1, 2, 3 years ptoms	ATS/ERS	Diagnosed by	Interview questionnaire	
(Denmark)	symptoms			physicians in the research clinic according to symptom algorithm, at age 5 years		
DNBC	Questionnaire,	6 months, 1 year	N/A	Questionnaire,	Questionnaire and register	
(Denmark)	parental report			ISAAC based, at age 7 years	data	
EDEN	Questionnaire,	6 months, 1, 2, 3	ATS/ERS	Questionnaire,	Questionnaire	
(France)	parental report	years		ISAAC based, at age 6 years		
FLEHS	Questionnaire, parental report	6 months, 1, 2, 3, 4, 5 years	N/A	Questionnaire, parental report of doctor diagnosis, at	Questionnaire	

(Belgium)				age 10 years	
GASPII	Questionnaire,	6 months, 1, 4, 5	ATS/ERS	Questionnaire,	Questionnaire
(Italy)	parental report	years		parental report of doctor diagnosis at age 9 years	
Generation R	Questionnaire,	6 months, 1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire,	Questionnaire
(Netherlands)	doctor diagnosis	4, J years		doctor diagnosis (ISAAC based), at age 10 years	nosis sed), at ars
Generation XXI	Questionnaire,	6 months, 2, 4	ATS/ERS	Questionnaire,	Questionnaire
(Portugal)	parental report of doctor diagnosis	rental report of years otor diagnosis		parental report of doctor diagnosis (ISAAC based), at age 7 years	
GINI	Questionnaire,	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire,	Questionnaire
(Germany)	parental report of doctor diagnosis	parental report of doctor diagnosis (ISAAC based), at age 15 years	parental report of doctor diagnosis (ISAAC based), at age 15 years		
HUMIS	Questionnaire,	6 months, 1, 2, 3	N/A	Registry data,	Questionnaire and register
(Norway)	doctor diagnosis	years		visit for asthma at age 9 years	uala
IMNA Gipuzkoa	Questionnaire, parental report	1, 4 years	ATS/ERS	N/A	Questionnaire

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INMA Menorca	Questionnaire,	1, 2, 3, 4 years	ATS/ERS	Questionnaire,	Questionnaire	
(Spain)	parental report			doctor diagnosis (ISAAC based), at age 12 years		
INMA Sabadell	Questionnaire,	6 months, 1, 2, 4	ATS/ERS	N/A	Questionnaire	
(Spain)	parental report	years				
INMA Valencia	Questionnaire,	1, 2, 4 years	ATS/ERS	N/A	Questionnaire	
(Spain)	parental report					
Isle of Wight	Questionnaire,	1, 2, 4 years AT	ATS/ERS	Questionnaire,	Questionnaire	
(United Kingdom)	parental report			parental report of doctor diagnosis (ISAAC based), at age 10 years		
KOALA	Questionnaire,	6 months, 1, 2	ATS/ERS	Questionnaire,	Questionnaire	
(Netherlands)	parental report	years		parental report of doctor diagnosis (ISAAC based), at age 7 years		
LRC	Questionnaire,	1, 2-3, 3-5 years	ATS/ERS	Questionnaire,	Questionnaire and register	
(United Kingdom)	parental report	arental report		parental report of doctor diagnosis at age 12 years	data	

Lifeways Cross- Generation Cohort Study	Parental record of health care visit	1, 2, 3, 4 years	N/A	Health care record, at age 9 years	Questionnaire and register data
(Ireland)					
LISA (Germany)	Questionnaire, parental report	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis, at	Questionnaire
LucKi	Questionnaire	6 months 1 3	N/A	age 15 years	Questionnaire and register
(Netherlands)	parental report	years		ISAAC based, at age 6 years	data
LUKAS (Finland)	Questionnaire, parental report of doctor diagnosis	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis, at age 6 years	Questionnaire
MAS-90	Questionnaire, ICD-	6 months, 1, 2, 3,	Other	Questionnaire,	Interview and questionnaire
(Germany)	9 coding	4, 5 years		age 7 years	
MCS	Questionnaire,	1, 3, 5 years	N/A	Questionnaire,	Questionnaire
(United Kingdom)	parental report			age 11 years	
MoBa (Norway)	Questionnaire, parental report of doctor diagnosis	6 months, 2, 3 years	N/A	Questionnaire, parental report of doctor diagnosis, at	Questionnaire and register data

				age 7 years	
NINFEA (Italy)	Questionnaire, parental report of doctor diagnosis	6 months, 1 year	N/A	Questionnaire, parental report of doctor diagnosis, at age 7 years	Questionnaire
Pelagie (France)	Questionnaire, parental report of doctor diagnosis	2 years	N/A	Questionnaire, ISAAC based, parental report of doctor diagnosis, at age 6 years	Questionnaire
PIAMA (Netherlands)	Questionnaire, parental report of doctor diagnosis	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report, at age 11 years	Questionnaire
REPRO_PL (Poland)	Questionnaire, parental report of doctor diagnosis	1, 2 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis at age 7 years	Questionnaire and registry data
Rhea (Greece)	Questionnaire, parental report of doctor diagnosis	1, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis, at age 7 years	Questionnaire
STEPS (Finland)	Symptom diary, doctor diagnosis	6 months, 1, 2 years	N/A	Questionnaire, ISAAC based, at age 5 years	Questionnaire, diary and registry data

SWS (United Kingdom)	Questionnaire, parental report of doctor diagnosis	6 months, 1, 2, 3 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 6 years	Questionnaire
Whistler (Netherlands)	Registry data	6 months, 1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 5 years	Questionnaire

ATS/ERS: American Thoracic Society/European Respiratory Society; N/A: not available.

	Upper resp	iratory trac	t infections	6			Lower respiratory tract infections						
Cohort name	6 months	1 year	2 years	3 years	4 years	5 years	6 months	1 year	2 years	3 years	4 years	5 years	
ABIS	N/A	98.3 (10,303)	N/A	99.1 (8,722)	N/A	99.3 (7,346)	N/A	40.9 (3,942)	N/A	58.8 (4,849)	N/A	60.4 (4,314)	
ALSPAC	9.7 (778)	30.4 (2,403)	N/A	25.0 (1,928)	N/A	32.2 (2,426)	10.5 (825)	12.2 (929)	N/A	8.8 (674)	N/A	9.4 (678)	
BAMSE	N/A	30.8 (1,032)	43.7 (1,451)	N/A	9.4 (319)	N/A	N/A	10.4 (347)	14.2 (473)	N/A	14.1 (475)	N/A	
BiB	13.0 (166)	22.4 (440)	18.3 (314)	20.7 (253)	35.0 (422)	N/A	8.2 (105)	18.1 (356)	14.0 (240)	14.9 (183)	19.9 (240)	N/A	
BILD	N/A	N/A	45.3 (115)	40.7 (103)	41.1 (104)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
CoNER	71.1 (150)	95.5 (191)	N/A	46.2 (92)	N/A	N/A	12.8 (27)	22.5 (45)	N/A	6.9 (8)	N/A	N/A	
COPSAC 2000	N/A	N/A	N/A	99.7 (289)	N/A	N/A	N/A	N/A	N/A	55.9 (162)	N/A	N/A	
COPSAC 2010	N/A	35.0 (192)	48.2 (261)	27.6 (147)	N/A	N/A	N/A	15.7 (86)	25.1 (136)	13.5 (72)	N/A	N/A	
DNBC	81.5 (24,450)	98.6 (28,903)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
EDEN	55.1 (496)	94.7 (852)	46.8 (421)	48.3 (435)	N/A	N/A	10.2 (92)	41.7 (375)	35.8 (322)	33.4 (301)	N/A	N/A	

Supplementary Table S2. Characteristics of respiratory tract infections among children in participating cohorts

FLEHS	59.6 (65)	81.3 (87)	77.4 (82)	75.2 (79)	85.0 (85)	82.1 (78)	14.2 (15)	24.3 (26)	14.3 (15)	16.3 (17)	13.0 (13)	11.6 (11)
GASPII	6.0 (28)	19.1 (88)	N/A	N/A	30.8 (137)	N/A	13.8 (64)	24.7 (114)	N/A	N/A	N/A	16.8 (78)
Generation R	11.8 (368)	27.0 (1,009)	32.2 (1,259)	25.4 (960)	22.1 (841)	21.66 (1,055)	7.5 (234)	6.9 (261)	11.1 (442)	6.5 (248)	4.4 (167)	4.8 (232)
Generation XXI	14.3 (158)	N/A	49.4 (257)	N/A	60.6 (3,285)	N/A	N/A	N/A	17.7 (116)	N/A	2.4 (129)	N/A
GINI	N/A	69.2 (1,298)	80.9 (1,509)	80.6 (1,502)	83.1 (1,524)	87.2 (1,653)	N/A	N/A	N/A	N/A	N/A	N/A
HUMIS	18.8 (390)	33.3 (682)	35.8 (742)	N/A	N/A	N/A	3.6 (74)	9.0 (184)	11.8 (244)	N/A	N/A	N/A
IMNA Gipuzkoa	N/A	4.01 (111)	N/A	N/A	23.2 (63)	N/A	N/A	52.0 (144)	N/A	N/A	33.3 (90)	N/A
INMA Menorca	N/A	33.9 (122)	38.4 (162)	33.2 (140)	28.7 (121)	N/A	N/A	49.3 (183)	61.6 (260)	47.4 (200)	33.2 (140)	N/A
INMA Sabadell	11.1 (43)	22.9 (104)	26.9 (121)	N/A	29.7 (121)	N/A	22.1 (87)	65.4 (267)	66.1 (281)	N/A	49.9 (203)	N/A
INMA Valencia	N/A	31.6 (129)	32.1 (127)	N/A	30.5 (135)	N/A	N/A	47.7 (217)	66.2 (301)	N/A	41.0 (181)	N/A
Isle of Wight	N/A	15.8 (198)	15.7 (178)	N/A	17.0 (198)	N/A	N/A	7.4 (101)	12.8 (144)	N/A	N/A	N/A
KOALA	85.0 (1,535)	88.3 (2.241)	93.7 (1,726)	N/A	N/A	N/A	N/A	13.0 (224)	17.4 (311)	N/A	N/A	N/A

LRC	N/A	98.8 (3,930)	N/A	99.1 (2,210)	N/A	97.3 (2,684)	N/A	19.0 (721)	N/A	N/A	N/A	N/A
Lifeways	N/A	20.3 (28)	13.0 (18)	1.4 (2)	0.0 (0)	N/A	N/A	20.3 (28)	13.0 (18)	1.4 (2)	0.0 (0)	N/A
LISA	43.2 (402)	69.9 (644)	87.5 (819)	84.6 (766)	82.5 (741)	87.7 (782)	N/A	N/A	N/A	N/A	N/A	N/A
LucKi	88.1 (273)	93.3 (277)	N/A	97.7 (292)	N/A	N/A	7.0 (21)	11.7 (33)	N/A	14.7 (42)	N/A	N/A
LUKAS	N/A	44.6 (165)	96.0 (333)	99.4 (335)	87.7 (314)	82.5 (292)	N/A	8.1 (30)	9.0 (31)	10.4 (35)	5.3 (19)	7.9 (28)
MAS-90	49.8 (381)	71.2 (532)	63.2 (504)	48.8 (392)	50.7 (409)	78.4 (625)	6.3 (48)	13.7 (102)	16.4 (131)	10.8 (87)	11.4 (92)	16.7 (133)
MCS	N/A	11.7 (1,679)	N/A	7.7 (1,030)	N/A	2.4 (351)	N/A	28.0 (4,020)	N/A	0.2 (30)	N/A	0.7 (101)
MoBa	15.1 (4,964)	N/A	43.5 (13,693)	53.0 (13,969)	N/A	N/A	5.1 (1,661)	N/A	13.4 (4,192)	13.7 (3,619)	N/A	N/A
NINFEA	21.0 (210)	N/A	N/A	N/A	N/A	N/A	7.0 (70)	20.0 (206)	N/A	N/A	N/A	N/A
Pelagie	N/A	N/A	64.4 (580)	N/A	N/A	N/A	N/A	N/A	61.3 (576)	N/A	N/A	N/A
PIAMA	N/A	22.1 (605)	31.3 (861)	30.0 (832)	27.5 (745)	28.8 (772)	N/A	15.4 (425)	12.5 (344)	10.0 (274)	7.4 (200)	7.7 (208)
REPRO_PL	N/A	45.5 (46)	67.0 (65)	N/A	N/A	N/A	N/A	29.7 (30)	26.8 (26)	N/A	N/A	N/A

Rhea	N/A	21.2 (117)	N/A	N/A	53.5 (318)	N/A	N/A	22.8 (126)	N/A	N/A	75.1 (405)	N/A
STEPS	78.1 (557)	97.4 (686)	99.1 (566)	N/A	N/A	N/A	3.6 (26)	9.2 (65)	13.0 (74)	N/A	N/A	N/A
SWS	83.3 (1,010)	N/A	N/A	N/A	N/A	N/A	12.0 (238)	17.7 (349)	19.4 (388)	16.0 (314)	N/A	N/A
Whistler	9.7 (140)	35.0 (503)	66.4 (955)	80.9 (1,163)	88.8 (1,277)	94.6 (1,360)	N/A	N/A	N/A	N/A	N/A	N/A
Total	41.2 (36,564)	62.9 (58,949)	46.0 (27,119)	47.7 (35,641)	42.8 (11,159)	42.6 (19,424)	6.7 (3,587)	23.0 (13,297)	16.0 (9,045)	16.0 (11,117)	11.8 (2,354)	15.0 (5,783)

Values are valid percentages (absolute numbers). N/A: not available.

# Supplementary Table S3. Characteristics of covariates

	Participants
Maternal characteristics	
Age, mean (SD)	30.0 (4.69)
Ethnicity	
European (%)	68,534 (89.1)
Non-European (%)	8,354 (10.9)
Education	
Low (%)	33,432 (25.2)
Middle (%)	44,238 (33.3)
High (%)	55,145 (41.5)
Smoking during pregnancy	
Yes (%)	21,680 (15.4)
No (%)	119,272 (84.6)
Asthma	
Yes (%)	16,362 (11.5)
No (%)	126,038 (88.5)
Atopy	
Yes (%)	35,744 (28.7)
No (%)	88,871 (71.3)
Parity	
Nulliparous (%)	62,547 (25.3)
Multiparous (%)	65,848 (74.7)
Child characteristics	
Gender	
Female (%)	72,871 (49.9)

Male (%)	72,964 (50.1)
Gestational age at birth, median (5-95% range)	40.0 (36.7, 42.0)
Birth weight, mean (SD)	3,502 (571)
Season of birth	
Spring (%)	36,781 (26.0)
Summer (%)	38,220 (27.0)
Autumn (%)	33,376 (23.6)
Winter (%)	33,040 (23.4)
Breastfeeding	
Yes (%)	94,231 (88.2)
No (%)	12,554 (11.8)
Daycare attendance	
Yes (%)	24,603 (19.5)
No (%)	101,247 (81.5)
Pet keeping	
Yes (%)	53,722 (41.1)
No (%)	76,835 (58.9)

Numbers are means (SD), valid percentages (absolute numbers) or medians (9-95% range).

	FEV <sub>1</sub> Z-score (95% CI) n = 25,903	FVC Z-score (95% Cl) n = 25,903	FEV₁/FVC Z-score (95% Cl) n = 25,903	FEF <sub>75</sub> Z-score (95% CI) n = 14,426	Asthma Odds Ratio (95% Cl) n = 140,385
Upper respiratory tract infections					
Age 6 months	0.06 (0.01, 0.11)*	0.03 (-0.02, 0.08)	0.05 (0.00, 0.10)*	0.10 (0.03, 0.19)*	1.27 (1.20, 1.33)**
Age 1 year	0.00 (-0.03, 0.03)	0.02 (-0.02, 0.05)	-0.02 (-0.05, 0.01)	-0.02 (-0.07, 0.03)	1.28 (1.21, 1.37)**
Age 2 years	0.02 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.00 (-0.03, 0.04)	-0.01 (-0.06, 0.05)	1.65 (1.56, 1.74)**
Age 3 years	0.02 (-0.02, 0.05)	0.03 (-0.01, 0.06)	-0.02 (-0.06, 0.01)	-0.02 (-0.04, 0.07)	1.47 (1.39, 1.55)**
Age 4 years	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	0.02 (-0.03, 0.07)	1.57 (1.42, 1.74)**
Age 5 years	0.04 (0.00, 0.08)*	0.03 (-0.01, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.04, 0.09)	1.37 (1.25, 1.49)**
Lower respiratory tract infections					
Age 6 months	-0.15 (-0.21, -0.09)**	-0.05 (-0.11, 0.01)	-0.15 (-0.21, -0.09)**	-0.00 (-0.13, 0.12)	2.57 (2.37, 2.80)**
Age 1 year	-0.20 (-0.24, -0.15)**	-0.09 (-0.13, -0.05)**	-0.17 (-0.21, -0.13)**	-0.17 (-0.24, -0.11)**	2.27 (2.15, 2.41)**
Age 2 years	-0.10 (-0.15, -0.05)**	-0.04 (-0.09, 0.01)	-0.10 (-0.15, -0.05)**	-0.13 (-0.20, -0.06)**	3.49 (3.28, 3.71)**
Age 3 years	-0.18 (-0.23, -0.12)**	-0.02 (-0.07, 0.04)	-0.26 (-0.31, -0.20)**	-0.14 (-0.23, -0.05)**	3.73 (3.50, 3.97)**
Age 4 years	-0.09 (-0.14, -0.02)**	0.00 (-0.06, 0.06)	-0.13 (-0.19, -0.07)**	-0.11 (-0.20, -0.02)*	4.09 (3.56, 4.70)**
Age 5 years	-0.18 (-0.25, -0.11)**	0.01 (-0.05, 0.08)	-0.30 (-0.36, -0.23)**	-0.23 (-0.38, -0.08)**	6.66 (5.98, 7.42)**

Supplementary Table S4. Unadjusted associations of any upper and lower respiratory tract infections with lung function and asthma

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).

	FEV <sub>1</sub> Z-score (95% CI) n = 25,903	FVC Z-score (95% Cl) n = 25,903	FEV <sub>1</sub> /FVC Z-score (95% CI) n = 25,903	FEF <sub>75</sub> Z-score (95% CI) n = 14,426	Asthma Odds Ratio (95% CI) n = 140,385
Upper respiratory tract infections					
Age 6 months	0.04 (-0.01, 0.09)	0.02 (-0.03, 0.07)	0.05 (0.00, 0.10)*	0.10 (0.02, 0.18)*	1.25 (1.18, 1.32)**
Age 1 year	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.05)	-0.02 (-0.05, 0.01)	-0.03 (-0.08, 0.02)	1.25 (1.18, 1.34)**
Age 2 years	0.02 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0.01 (-0.03, 0.04)	-0.01 (-0.06, 0.04)	1.57 (1.48, 1.67)**
Age 3 years	0.02 (-0.02, 0.05)	0.03 (-0.01, 0.06)	-0.02 (-0.06, 0.01)	0.01 (-0.05, 0.06)	1.41 (1.34, 1.49)**
Age 4 years	0.04 (-0.00, 0.08)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	0.01 (-0.04, 0.06)	1.44 (1.29, 1.61)**
Age 5 years	0.05 (0.01, 0.08)*	0.04 (-0.00, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.04, 0.10)	1.34 (1.23, 1.46)**
Lower respiratory tract infections					
Age 6 months	-0.14 (-0.20, -0.08)**	-0.04 (-0.10, 0.01)	-0.15 (-0.21, -0.09)**	-0.01 (-0.13, 0.11)	2.38 (2.18, 2.60)**
Age 1 year	-0.19 (-0.23, -0.15)**	-0.08 (-0.12, -0.04)**	-0.17 (-0.21, -0.13)**	-0.18 (-0.24, -0.11)**	2.10 (1.98, 2.22)**
Age 2 years	-0.09 (-0.14, -0.04)**	-0.03 (-0.08, 0.02)	-0.10 (-0.15, -0.05)**	-0.14 (-0.21, -0.06)**	3.26 (3.06, 3.48)**
Age 3 years	-0.16 (-0.22, -0.11)**	-0.01 (-0.06, 0.04)	-0.25 (-0.30, -0.20)**	-0.15 (-0.23, -0.06)**	3.53 (3.30, 3.77)**
Age 4 years	-0.09 (-0.15, -0.02)**	-0.01 (-0.07, 0.06)	-0.13 (-0.19, -0.07)**	-0.12 (-0.21, -0.03)*	3.84 (3.33, 4.42)**
Age 5 years	-0.18 (-0.24, -0.11)**	0.02 (-0.05, 0.08)	-0.30 (-0.36, -0.23)**	-0.24 (-0.39, -0.09)**	6.30 (5.64, 7.04)**

Supplementary Table S5. Associations of any upper and lower respiratory tract infections with lung function and asthma

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. 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, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).

**Supplementary Table S6.** Associations of any upper and lower respiratory tract infections with lung function and asthma, additionally adjusted for preceding respiratory tract infections

	FEV <sub>1</sub> Z-score (95% Cl) n = 25,903	FVC Z-score (95% CI) n = 25,903	FEV₁/FVC Z-score (95% CI) n = 25,903	FEF <sub>75</sub> Z-score (95% CI) n = 14,426	Asthma Odds Ratio (95% CI) n = 140,385
Upper respiratory tract infections					
Age 6 months	0.04 (-0.01, 0.09)	0.02 (-0.03, 0.07)	0.05 (0.00, 0.10)*	0.10 (0.02, 0.18)*	1.25 (1.18, 1.32)**
Age 1 year	0.00 (-0.03, 0.04)	0.02 (-0.01, 0.05)	-0.03 (-0.06, 0.00)	-0.04 (-0.09, 0.01)	1.23 (1.16, 1.31)**
Age 2 years	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	-0.01 (-0.06, 0.05)	1.52 (1.44, 1.62)**
Age 3 years	0.01 (-0.02, 0.05)	0.02 (-0.01, 0.06)	-0.02 (-0.06, 0.01)	0.02 (-0.04, 0.08)	1.28 (1.21, 1.36)**
Age 4 years	0.03 (-0.01, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.01, 0.07)	0.02 (-0.04, 0.07)	1.28 (1.15, 1.43)**
Age 5 years	0.05 (0.01, 0.09)*	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.06)	0.03 (-0.04, 0.10)	1.30 (1.10, 1.31)**
Lower respiratory tract infections					
Age 6 months	-0.14 (-0.20, -0.08)**	-0.04 (-0.10, 0.01)	-0.15 (-0.21, -0.09)**	-0.01 (-0.13, 0.11)	2.38 (2.18, 2.60)**
Age 1 year	-0.17 (-0.22, -0.13)**	-0.08 (-0.12, -0.04)**	-0.16 (-0.20, -0.12)**	-0.18 (-0.25, -0.11)**	2.00 (1.88, 2.12)**
Age 2 years	-0.05 (-0.10, 0.01)	-0.01 (-0.06, 0.04)	-0.06 (-0.11, -0.01)*	-0.11 (-0.18, -0.03)**	2.88 (2.70, 3.08)**
Age 3 years	-0.12 (-0.17, -0.06)**	0.01 (-0.04, 0.07)	-0.21 (-0.26, -0.15)**	-0.10 (-0.19, -0.01)*	2.72 (2.54, 2.91)**
Age 4 years	-0.05 (-0.11, 0.01)	0.01 (-0.07, 0.08)	-0.09 (-0.15, -0.02)**	-0.08 (-0.17, 0.01)	2.55 (2.20, 2.95)**
Age 5 years	-0.11 (-0.18, -0.04)**	0.03 (-0.04, 0.10)	-0.21 (-0.28, -0.15)**	-0.21 (-0.36, -0.06)**	4.29 (3.82, 4.82)**

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. 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, birth weight, season of birth, breastfeeding and daycare attendance. Additionally, upper respiratory tract infections were adjusted for preceding upper respiratory tract infections, and lower respiratory tract infections for preceding lower respiratory tract infections. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF<sub>75</sub>).

	FEV <sub>1</sub> , wheeze - Z-score (95% CI)	FEV <sub>1</sub> , wheeze + Z-score (95% CI)	FVC, wheeze - Z-score (95% CI)	FVC, wheeze + Z-score (95% CI)	FEV <sub>1</sub> /FVC, wheeze - Z-score (95% CI)	FEV <sub>1</sub> /FVC, wheeze + Z-score (95% CI)	FEF <sub>75</sub> , wheeze - Z-score (95% CI)	FEF <sub>75</sub> , wheeze + Z-score (95% CI)
Upper respiratory tract infections								
Age 6 months	0.05 (-0.01, 0.11)	0.17 (0.08, 0.27)**	0.03 (-0.03, 0.09)	0.13 (0.02, 0.23)*	0.05 (-0.01, 0.11)	0.09 (-0.01, 0.19)	0.11 (0.02, 0.21)*	0.16 (-0.01, 0.32)
Age 1 year	0.01 (-0.03, 0.05)	0.04 (-0.03, 0.11)	0.02 (-0.02, 0.05)	0.03 (-0.04, 0.10)	-0.01 (-0.05, 0.03)	0.03 (-0.05, 0.10)	-0.02 (-0.08, 0.04)	0.00 (-0.10, 0.11)
Age 2 years	0.01 (-0.04, 0.05)	0.11 (0.02, 0.21)*	-0.01 (-0.05, 0.03)	0.08 (-0.01, 0.18)	0.02 (-0.02, 0.06)	0.03 (-0.07, 0.13)	0.01 (-0.05, 0.07)	0.08 (-0.04, 0.20)
Age 3 years	0.03 (-0.01, 0.07)	0.04 (-0.07, 0.15)	0.04 (-0.00, 0.08)	0.01 (-0.10, 0.11)	-0.02 (-0.06, 0.02)	0.07 (-0.04, 0.19)	0.07 (-0.04, 0.08)	0.07 (-0.10, 0.24)
Age 4 years	0.03 (-0.02, 0.08)	0.10 (0.00, 0.21)*	0.04 (-0.04, 0.05)	0.04 (-0.06, 0.14)	0.04 (-0.01, 0.09)	0.11 (0.01, 0.22)*	0.03 (-0.04, 0.09)	0.12 (-0.05, 0.29)
Lower respiratory								
Age 6 months	-0.06 (-0.21, 0.10)	-0.05 (-0.13, 0.03)	-0.03 (-0.18, 0.13)	-0.01 (-0.10, 0.07)	-0.03 (-0.18, 0.12)	-0.05 (-0.14, 0.04)	0.23 (0.04, 0.43)*	-0.13 (-0.33, 0.07)
Age 1 year	-0.14 (-0.20, -0.07)**	-0.17 (-0.24, -0.10)**	-0.07 (-0.14, -0.01)*	-0.09 (-0.16, -0.02)*	-0.11 (-0.17, -0.04)**	-0.10 (-0.18, -0.03)**	-0.19 (-0.31, -0.07)**	-0.03 (-0.17, 0.10)
Age 2 years	-0.03 (-0,04, 0.10)	-0.08 (-0.18, 0.01)	0.04 (-0.29, 0.11)	-0.11 (-0.21, -0.01)*	0.03 (-0.09, 0.04)	0.04 (-0.05, 0.14)	-0.01 (-0.11, 0.09)	-0.04 (-0.17, 0.10)
Age 3 years	-0.08 (-0.17, 0.01)	-0.04 (-0.14, 0.06)	-0.03 (-0.12, 0.06)	0.03 (-0.07, 0.13)	-0.08 (-0.17, 0.00)	-0.11 (-0.21, -0.00)*	-0.03 (-0.14, 0.08)	-0.14 (-0.30, 0.03)
Age 4 years	-0.04 (-0.12, 0.06)	-0.11 (-0.25, 0.04)	0.03 (-0.06, 0.12)	-0.11 (-0.25, 0.02)	-0.10 (-0.18, 0.01)*	0.00 (-0.14, 0.14)	-0.01 (-0.16, 0.14)	-0.07 (-0.34, 0.19)

Supplementary Table S7. Associations of any upper and lower respiratory tract infections with lung function, stratified for wheezing

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic regression models. \*p-value <0.05, \*\*p-value <0.01. 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, birth weight, season of birth, breastfeeding and daycare attendance. Wheeze – or + reflects whether the child did not or did wheeze in the first year of life (infections at age 6 months or 1 year), the second year of life (infections age 2 years), the third year of life (infections age 3 years) or the fourth year of life (infections age 4 years).

**Supplementary Figure S8.** Associations of any upper or lower respiratory tract infections with lung function and asthma assessed by a two-stage individual participant meta-analysis

## Upper respiratory tract infections age 6 months

## A. FEV<sub>1</sub>/FVC

## B. Asthma

	2013	0.225		Beta	Beta				Odds Ratio	Ode	Is Ratio
Study or Subgroup	Beta	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Shidy or Subgroup	log[Oths Ratio] SE	Weight	IV, Random, 95% CI	IV, Ran	tom, 95% CI
ABIS (Sweden)	0	0		Notestimable		ABIS (Sweden)	0 0		Notestimable		
ALSPAC (United Kingdom)	-0.009	0.049	17.4%	-0.01 [-0.11, 0.09]		ALSPAC (United Kingdom)	0.144 0.096	14.4%	1.15 [0.96, 1.39]		
BAMSE (Sweden)	0	0		Not estimable		BAMSE (Sweden)	0 0		Notestimable		
BIB (United Kingdom)	0	0		Notestimable		BIB (United Kingdom)	0.323 0.288	3.0%	1.38 [0.79, 2.43]		10
BILD (Switzerland)	0	0		Not estimable		BILD (Switzerland)	0 0		Notestimable		
Co.N.ER (Italy)	0.061	0.085	10.3%	0.06 [-0.11, 0.23]		Co.N.ER (Isly)	1.104 8.998	0.3%	3.02 (0.53, 17.19)	2	
COPSAC 2000 (Denmark)	0	0		Not estimable		COPSAC 2000 (Denmark)	0 0		Notestimable		
COPSAC 2010 (Denmark)	0	0		Not estimable		COPSAC 2010 (Denmark)	0.0		Notestimable		0.00
DNBC (Denmark)	0	0		Not estimable		DNBC (Denmark)	0.166 0.046	23.0%	118[108,129]		
EDEN (France)	0.248	0.078	11.4%	0.25 [0.09, 0.40]		EDEN (France)	0.681 0.193	5.8%	1.98 [1.35, 2.98]		
FLEHS (Belgium)	0	. 0		Notestimable		FLEHS (Belgium)	-0.03 1.179	0.2%	0.97 [0.10, 9.78]	•	-
GASPII (Italy)	-0.212	0.198	2.8%	-0.21 [-0.60, 0.17]		GASPII (Italy)	-0.676 0.754	0.5%	0.51 [0.12, 2.23]		<u> </u>
Generation R (The Netherlands)	0.01	0.058	15.7%	0.01 [-0.10, 0.12]	-	Generation R (The Netherlands)	0.358 0.186	6.2%	1.43 [0.99, 2.06]		-
Generation XXI (Portugal)	-0.456	0.351	0.9%	-0.46[-1.14, 0.23]		Generation XXX (Portugal)	0.12 0.362	2.0%	1.13[0.55, 2.29]		
GINI (Germany)	0	.0		Notestimable		GINI (Germany)	0 0		Notestimable		0.00
HUMIS (Norway)	0	0		Not estimable		HUMIS (Norway)	0.512 0.233	4.3%	1.67 [1.06, 2.63]		
INMA Olpuzkoa (Spain)	0	0		Not estimable		INMA Gipuzkoa (Spain)	0 0		Notestimable		
INMA Menorca (Spain)	0	0		Not estimable		INMA Menorica (Spain)	0 0		Notestimable		
INMA Sabadell (Spain)	0	0		Not estimable		INMA Sabadell (Spain)	0 0		Not estimable		
INMA Valencia (Spain)	0.174	0.176	3.4%	0.17[-0.17, 0.52]		INMA Valencia (Spain)	0 0		Not estimable		
Iste of Wight (United Kingdom)	0	0		Not estimable		Iste of Wight (United Kingdom)	0 0		Notestimable		
KOALA (The Netherlands)	-0.12	0.121	6.3%	-0.12 F0.36. 0.121		KOALA (The Netherlands)	0.296 0.286	3.0%	1.34 (0.77, 2.36)		
Lifeways (ireland)	0	0		Not estimable		Lifeways (ireland)	0 0		Not estimable		
LISA (Germany)	0.056	0.068	13.2%	0.06 (-0.08, 0.19)		LISA (Germany)	-0.188 0.272	3.3%	0.85 (0.50, 1.44)		
LRC (United Kingdom)	0	0		Not estimable		LRC (United Kingdom)	0 0		Notestimable		
Lucki (The Netherlands)	0	0		Not estimable		Lucki (The Netherlands)	-0.827 0.709	0.5%	0.44(0.11, 1.76)		
LUKAS (Finland)	0	0		Notestimable		LUKAS (Finland)	0 0		Notestimable		
MAS90 (Germany)	0.11	0.1	8.3%	0.111-0.09.0.311		MASB0 (Germany)	0.279 0.372	1.9%	1 32 [0 64, 2 74]		
Millennium Cohort Study (United Kingdom)	0	0	1.519.001	Notestimable		Millennium Cohort Study (United Kingdom)	0 0		Notestimable		
MoBa (Norway)	0	0		Not estimable		MoBa (Norway)	0.301 0.048	22.6%	1,3511,23,1,481		
MINFEA (traiv)	0	0		Notestimable		NINFEA (tab)	-0.059 0.48	1.1%	0.94 (0.37, 2.42)		
PELAGIE (France)	8	8		Not estimable		PELAGIE (France)	0 0		Notestimable		
PIAMA (The Netherlands)	0	0		Not estimable		PlaMA (The Netherlands)	0 0		Notestimable		
REPRO PL (Poland)	0	0		Not estimable		REPRO PL (Poland)	0 0		Notestimable		
Rhea (Greece)	0	0		Not estimable		Rhea (Oreece)	0.0		Notestimable		
STEPS (FINLAND)	0	0		Not estimable		STEPS (FINLAND)	-0.3 0.343	2.2%	0.74/0.38 1.451		
SWS (United Kingdom)	0.154	0.102	8.1%	0.11 F0.09. 0.311		SWS (United Kingdom)	0.015 0.225	4.6%	1.0210.65.1.591	_	-
WHISTLER (The Netherlands)	0.34	0.219	2.3%	0.34 [-0.09, 0.77]		WHISTLER (The Netherlands)	-0.62 0.492	1.1%	0.54 (0.21, 1.38)		-
Total (95% CI)			100.0%	0.06 [-0.01, 0.12]	•	Total (95% CI)		100.0%	1.24 [1.12, 1.37]		•
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 17.14, df = Test for overall effect: Z = 1.61 (P = 0.11)	: 11 (P = (	0.10);*	= 38%	-1	-0.5 0 0.5	Heterogenety Tau <sup>2</sup> = 0.01, Chi <sup>2</sup> = 26.13, df = Test for overall effect. Z = 4.08 (P < 0.0001)	= 18 (P = 0.10); P = 31%		<ul> <li></li></ul>	0.1 0.2 0.5	1 2 3

# Upper respiratory tract infections age 2 years

# A. FEV<sub>1</sub>/FVC

## B. Asthma

	(Labor			Beta	Beta		10.000	1.121		Odds Ratio	Odds Ratio
way or scoproup	Beta	SE	weight	IV, Ralidom, 95% CI	rv, Kandom, 95% Cl	study or Subgroup	log[Odds Ratio]	st	Weight	IV, Handom, 95% CI	TV, Random, 95% CI
IIS (Sweden)	0	0		Notestimable		ABIS (Sweden)	0	0		Not estimable	
SPAC (United Kingdom)	0		02/12/2	Not estimable	2	ALSPAC (United Kingdom)	0	0	10000	Not estimable	
AMSE (Sweden)	-0.005 0.	044	18.8%	-0.04 Foroa' 0.981		BAMSE (Sweden)	0.414	0.113	8.8%	1.51 [1.21, 1.89]	
B (United Kingdom)	0	0	~~~~	Notestimable		BIB (United Kingdom)	0.538	0.206	6.7%	1.71 [1.14, 2.56]	
LD (Switzerland)	0.107 0.	148	1.7%	0.11 [-0.18, 0.40]	2-12-2	BILD (Switzerland)	0.866	0.916	0.9%	2.38 [0.39, 14.32]	
N.ER (Italy)	0	0		Notestimable		Co.N.ER (Italy)	0	0		Not estimable	
JPSAC 2000 (Denmark)	0	0		Not estimable		COPSAC 2000 (Denman)	0	0		Not estimable	
PSAC 2010 (Denmark)	-0.052 0	888	4.7%	-0.05[-0.22, 0.12]		COPSAC 2010 (Denmark)	0.394	0.221	6.4%	1.48 [0.96, 2.29]	
IBC (Denmark)	0	0		Not estimable		DNBC (Denmark)	0	0		Not estimable	
(France)	0.024 0	078	80%	0.02[-0.13, 0.18]		EDEN (France)	0.113	0.181	7.3%	1.12 (0.79, 1.60)	
EHS (Belgium)	0	0		Not estimable		FLEHS (Belgium)	-0.553	1.548	0.3%	0.58 [0.03, 11.95] *	
SPII (Bally)	0	0		Not estimable		GASPII (Italy)	0	0		Not estimable	
ineration R (The Netherlands)	0.045 0.	035	29.7%	0.04 [-0.02, 0.11]		Generation R (The Netherlands)	0.547	0.126	8.5%	1.73 [1.35, 2.21]	
Ineration XXX (Portugal)	-0.002 0	0.13	2.2%	-0.00 [-0.26, 0.25]		Generation XXX (Portugal)	8.607	0.435	3.1%	1.83 [0.78, 4.30]	
Al (Germany)	-0.061 0.	065	8.6%	-0.06 [-0.19, 0.07]		GINI (Germany)	0.363	0.234	6.1%	1.44 [0.91, 2.27]	
JMIS (Norway)	0	.0		Not estimable		HUMIS (Norway)	0.956	0.208	6.7%	2.60 [1.73, 3.91]	
MA Gipuzkoa (Spain)	0	0		Not estimable		INMA Gipuzkoa (Spain)	0	0		Not estimable	
NA Menorca (Spain)	-0.077 0	119	2.6%	-0.081-0.31, 0.161		INMA Menorca (Spain)	-0.317	0.46	2.8%	0.73 [0.38, 1.79]	
AA Sabadell (Spain)	-0.102 0	102	3.5%	-0.101-0.30.0.101		INMA Sabadell (Spain)	0	0		Not estimable	
dA Valencia (Spain)	0.232 0	114	2.8%	0.23/0001 0.461		INMA Valencia (Spain)	0	0		Not estimable	
e af Wight (Linited Kinodom)	0	0	05/5366	Not estimable		Isle of Wight (United Kingdom)	0	- ô		Not estimable	
ALA (The Netherlands)	0.204 0	194	1.0%	0.2016018-0.58		KOALA (The Netherlands)	-0.017	0.367	3.9%	0 98 10 48 2 021	
awage //reland)	0	.0		Notestmable		Lifeways (instand)	6.647	117	0.6%	2 32 80 23 22 000	
A (Germany)	-0.061 01	000	3.0%	-0.061-0.25 0.131		LISA (Germani)	0.685	0.458	2 0%	1 79 10 73 4 401	
C (Linited Kingdom)	0		्यत्र स	Notestimable		1 BC (I Inited Kingdom)	0		*10-10	Not estimable	
ki (The Metherlands)	ő	- ñ		Matestratio		Lucid (The Netherlands)	n			Notestimable	
V&G (Einland)	0.757 0	205	0.4%	0.261.0.84.0.221 -		Lilkas (Finiand)	0	n n		Notectimable	
POD (Cormona)	0424 0	000	3.08	0121007 0 241		M6R07 (Germania)	0.027	0.363	109	1 03 10 60 3 001	<u> </u>
Sourcemany/	0.121 0.	000	2.071	bid octimable		Milloonium Cohort Study (Linited Vinations)	0.027	0.303	9.040	Not optimable	
Pa Alaguad				Alidiostimobile		MoRo (Nonvol)	0.483	0.039	10.0%	1 63 11 60 1 751	+
Da (NOWAY)	0			Not esamable		AINUERA (troba	0.403	0.000	10.0%	Not octionable	
ALE (Research	0	8		Notestimable		PELAGE (Erando)	0.363	0 220	5.09	1 44 10 00 3 201	
LAGE (France)	0000 0		1000	NUL ESTIMATE		Plante (riance)	0.002	0.200	0.400	1.64 [0.00, 2.20]	
ana (me Nemenands)	-0.015 0	262	7.0%	-0.01 [-0.16, 0.13]		DEDDO DI (Doland)	0.014	0.13	0.4%	1.07 [1.30, 2.10]	63-5-22
PRO_PL (Poland)	-0.229 0.	202	0.5%	-0.23[-0.74, 0.20]		REPRO_PL (Positio)	0			Not estimable	
ea (Oreece)	0	.0		NOTestmadle		Potea (oteace)	1 020	+ 220		NOLESTIMADIE	
EPS (FINLAND)	8	8		Notestmable		STEPS (FINLAND)	+1.039	1.229	0.5%	0.32 [0.03, 3.83] .	24
VS (United Kingdom)	8	9	101217	Not estimable		SWS (United Kingdom)	U	0	and and the second	Not estimable	
HISTLER (The Netherlands)	0.03 0	111	3.0%	0.03 [-0.19, 0.25]		wers filler (The Netherlands)	-1.195	8.233	0.1%	0.30 (0.19, 0.48)	
tal (95% CI)			100.0%	0.01 [-0.03, 0.05]	•	Total (95% Ct)			108.0%	1.36 [1.14, 1.63]	•
sterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 13.42; df = est for overall effect; Z = 0.56 (P = 0.58)	: 16 (P = 0.64	4); i <sup>p</sup> =	0%	-1	-0.5 0 0.5	<ul> <li>Heterogeneity: Tau<sup>2</sup> = 0.08, Chi<sup>2</sup> = 69.51, df = 1 Test for overall effect Z = 3.40 (P = 0.0007)</li> </ul>	= 19 (P × 0.00801), 1	*= 7.39		6	1 0 2 0 5 2

# Lower respiratory tract infections age 6 months

# A. FEV<sub>1</sub>/FVC

# B. Asthma

				Beta	Beta					Odds Ratio	Od	ds Ratio
tudy or Subgroup	Beta	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Ran	dom, 95% CI
BIS (Sweden)	0	0		Not estimable		ABIS (Sweden)	0	0	i and a second	Notestimable	1000700	11 (A. 16 (A) (A)
SPAC (United Kingdom)	-0.193	0.047	33.5%	-0.19 [-0.29, -0.10]		ALSPAC (United Kingdom)	0.7 (	1.087	19.6%	2.01 [1.70, 2.39]		-
MSE (Sweden)	0	0		Not estimable		BAMSE (Sweden)	0			Notestimable		
(United Kingdom)	0	0		Not estimable		BIB (United Kingdom)	-0.114 (	1.394	5.2%	0.89 (0.41, 1.93)		+
D (Switzerland)	0	0		Not estimable		BILD (Switzerland)	0	0		Not estimable		1
N.ER (Italy)	-0.238	0.11	10.4%	-0.24 [-0.45, -0.02]		Co.N.ER (taly)	-1.025 1	236	0.7%	0.36 (0.03, 4.05)	· · · · ·	
PSAC 2000 (Denmark)	0	0		Notestimable		COPSAC 2000 (Denmark)	0	0		Notestimable		
PSAC 2010 (Denmark)	.0	0		Not estimable		COPSAC 2010 (Denmark)	0.	0		Not estimable		
BC (Denmark)	0	0		Not estimable		DNBC (Denmark)	0	Û		Not estimable		
EN (France)	0.169	0.127	8.1%	0.171-0.08.0.421		EDEN (France)	0.968 (	251	9.8%	2.63(1.61, 4.31)		
HS (Belgium)	0	0		Notestimable		FLEHS (Belgium)	0	- Ø		Notestimable		
SPII (Italy)	-0.736	0.141	6.7%	-0.741-0.51, 0.041		GASPII (Italy)	0.778 0	1.376	5.5%	218/104.4551		
veration R (The Netherlands)	-0107	0.07	20.9%	-0.111-0.24, 0.031		Generation R (The Netherlands)	0.808 0	1001	12.1%	2 24 (1 51 3 33)		
neration XXI (Portugal)	0	0	ACR (10.75)	Notestmable		Generation 300 (Portugal)	0	0		Notestimable		
4/Germany)	0	.0		Notestimable		GINI (Germany)	0	0		Not estimable		
MIS (Norway)	0	0		Not estimable		HUMIS (Norway)	0.917 0	1406	4.9%	2501113 554		
A (lipuzina (Spain)	0	0		Not estimable		INMA Giouzista (Spain)	0	n		Notestimable		
A Menorita (Snain)	8	0		Not estimable		INMA Menorica (Spain)	0	n.		Notestimable		
A Sahadell (Snain)	0	0		Not estimable		INMA Sebadell (Spain)	0	n		Notestimable		
A Valencia (Snain)	-0.197	0137	71%	-0 201-0 47 0 071		INMA Valencia (Sosin)	0	n		Notestimable		
of Wight (United Kinodom)	0	0	1.1.1.1	Notestimable		Iste of Might & Isted Kinodom)	0	n		Notestimable		
U.A. (The Netherlands)	0	0		Notestimable		KOALA (The Netherlands)	0	ñ		Notestimable		
wave /ireland)	0	ñ		Notestmable		Lifeways dretand)	0	n		Notestimable		
A (Germany)	0	0		Not estimable		LISA (Germana)	0	n.		Notestimable		
C (J inited kingdom)	ñ			Notestimable		(BC (Inited Kinotom)	0	ñ		Notestimable		
ki (The Netherlands)	ő			Notestimable		Lució (The Netherlands)	0.794 (	1946	1.1%	210/024 13:000		
AS (Finland)		- 6		Notestimable		11 B/69 (Finland)	0.037			Not estimable		
Anconsol (Generation )	.0 197	0.212	3.0%	0191061 0 241		MAGER (Germany)	0.746	0.72	1.95	211061824		
appium Cohort Study / Inited //incdcon)	0.107	0.410	2.00	Not octimable		Millennium Cobort Study (United Kingdom)	0.740	0.12	1.0.0	Not estimable		
hinner contraction of contract rangeory				Ministernatio		MoRo (Norway)	1047 /	1062	71.1%	296/242 3 11		-
FF& /Bold	ň	0		Notestimable		MINEFA (tob)	0.584	1667	21%	1 70 ID 40 6 561	22 <u>—</u>	
AGIE /Franca)	ě			Notestimable		PELAGE (Franca)	0.004	6	-1W	Not actimable		- 55
MA (The Method and c)	õ			Not estimable		Platta (The Methodande)	n.			Notactimakia		
PDO PL (Poloni)		ñ		Notostimable		DEEDO PI (Poland)	n.	0		Notestimakia		
(Greene)		a.		Notestimable		Phas (Oppara)	0	0		Notestimakia		
PR ATINE ANDA	ě			Not estimable		RTEDC (CHECC)	1 405 1	1612	៍ខេត្តស្ទ	A 46.01 60, 10 411		
C d ložed klandomi	-0125	0.111	10.2%	0.01410.05 0.001		Clark (Internation)	0.512 (	1104	121%	1671116.3401		
(ISTLER (The Netherlands)	0	0	10.2.1	Not estimable		WHISTLER (The Netherlands)	0.513 0	0	12.1 %	Notestimable		
al (95% CI)			100.0%	-0.15 [-0.22, -0.07]	•	Total (95% CI)			100.0%	2.17 [1.78, 2.65]		•
sterogeneity: $Tau^{\mu} = 0.00$ ; $Chi^{\mu} = 8.65$ , of = est for overall effect: $Z = 3.81$ (P = 0.0001)	7 (P = 0.2	8); (*= 1	9%	-1	-0.5 0 0.5 Lower Z-score Higher Z-score	I         Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 26.22; df           I         Test for overall effect: Z = 7.81 (P < 0.00001)	= 12 (P = 0.01); F = 54 )	19			0.1 0.2 0.5 Lower Odds Rat	to Higher Odds Ratio

## Lower respiratory tract infections age 2 years

## A. FEV<sub>1</sub>/FVC

#### B. Asthma

				Beta	Beta					Odds Ratio	Odds Ratio
Study or Subgroup	Beta	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI	Study or Subgroup	log[Odds Ratio]	5E	Weight	IV, Random, 95% Cl	IV, Random, 95%-CI
ABIS (Sweden)	0	0		Not estimable		ABIS (Sweden)	0	Û	position	Not estimable	
ALSPAC (United Kingdom)	0	0		Not estimable		ALSPAC (United Kingdom)	0	0		Not estimable	
BAMSE (Sweden)	-0.041	0.061	16.3%	-0.04 (-0.16, 0.08)		BAMSE (Sweden)	1.207	0.13	9.3%	3.34 [2.69, 4.31]	-
BiB (United Kingdom)	0	0		Not estimable		BIB (United Kingdom)	0.923	0.206	6.8%	2.52 [1.68, 3.77]	
BILD (Switzerland)	0	0		Not estimable		BILD (Switzerland)	0	0		Not estimable	
Co N ER (tab)	0	0		Not estimable		Co.N.ER (Italy)	0	0		Not estimable	
COPSAC 2000 (Denmark)	0	0		Not estimable		COPSAC 2000 (Denmark)	0	0		Not estimable	
COPSAC 2010 (Denmark)	-0.162	0.102	5.8%	-0.16 [-0.36, 0.04]		COPSAC 2010 (Denmark)	0.949	0.235	6.0%	2.58 [1.63, 4.09]	
DNBC (Denmark)	0	0		Not estimable		DNBC (Denmark)	0	0		Not estimable	
EDEN (France)	-0.074	0.08	9.5%	-0.07 (-0.23, 0.08)		EDEN (France)	0.984	0.184	7.4%	2.68 [1.87, 3.84]	
FLEHS (Belgium)	0	0		Not estimable		FLEHS (Belgium)	1.052	1.679	0.2%	2.86 [0.11, 76.92]	
GASPII (Italy)	0	0		Not estimable		OASPII (Italy)	0	0		Not estimable	
Generation R (The Netherlands)	-0.172	0.051	23.3%	-0.17 5-0.27, -0.071		Generation R (The Netherlands)	1,535	0.143	8.8%	4,65 [3.51, 6.15]	
Generation XXI (Portugal)	-0.121	0.153	2.6%	-0.121-0.42.0.18		Generation XXX (Portugal)	1.662	0.381	3.2%	5.27 [2.50, 11.12]	
GiNI (Germann)	0	0		Not estimable		GINI (Germany)	0	0		Not estimable	
HUMIS (Norway)	0	0		Not estimable		HUMIS (Norway)	1.19	0.237	5.9%	3.29 [2.07, 5.23]	
(NMA Gipuzkoa (Spain)	0	0		Not estimable		INMA Gipuzkoa (Spain)	0	0		Not estimable	
(NMA Menorca (Spain)	0.057	0.122	4.1%	0.061-0.18.0.301		INMA Menorca (Spain)	1.582	0.574	1.7%	4.86 [1.58, 14.98]	
NMA Sabadell (Spain)	-0.092	0.094	6.9%	-0.091-0.28.0.091		INMA Sabadell (Spain)	0	0		Not estimable	
NMA Valencia (Spain)	-0.234	0.114	4.7%	-0.231-0.46 -0.011		INMA Valencia (Spain)	0	0		Not estimable	
isle of Wight (United Kingdom)	0	Ó	0.0000000	Not estimable		Isle of Wight (United Kingdom)	0	0		Not estimable	
KOALA (The Netherlands)	-0.155	0.128	3.7%	-0.151-0.41 0.100		KOALA (The Netherlands)	1.468	0.198	7.0%	4.34 [2.94, 6.40]	
Lifeways (Ireland)	0	0	12033	Not estimable		Lifeways (Ireland)	0.842	1.17	0.4%	2.32 [0.23, 22.99]	
LISA (Germany)	0	0		Not estimable		LISA (Germany)	0	0		Not estimable	
LRC (United Kingdom)	0	0		Not estimable		LRC (United Kingdom)	0	0		Not estimable	
ucki (The Netherlands)	0	0		Not estimable		Lució (The Netherlands)	0	0		Not estimable	
LUKAS (Finland)	0.091	0.183	1.8%	0.091-0.27.0.457		LUKAS (Finland)	1.568	0.52	2.0%	4.80 [1.73, 13.29]	
MAS90 (Germany)	-0.259	0.127	3.8%	-0.261-0.51 -0.011		MAS90 (Germany)	0.837	0.39	3.1%	2.31 [1.08, 4.96]	
Milennium Cohort Study (United Kingdom)	-0.273	0.127	3.8%	-0.271-0.52 -0.021		Millennium Cohort Study (United Kingdom)	0	0		Not estimable	
MoBa (Norway)	0	0		Not estimable		MoBa (Norwas)	1.145	0.043	11.9%	3.14 [2.89, 3.42]	•
NINFEA (ttab)	Ó	0		Not estimable		NINFEA (Italy)	0	0		Not estimable	
PELAGIE (France)	0	0		Not estimable		PELAGIE (France)	0.764	0.248	5.6%	2.16 [1.32, 3.49]	
PIAMA (The Netherlands)	-0.055	0.099	6.2%	-0.061-0.25.0.141		PIAMA (The Netherlands)	1.328	0.15	8.6%	3.77 [2.81, 5.05]	
REPRO PL (Poland)	0.163	0.306	0.6%	0 16 1-0 44 0 761		REPRO_PL (Poland)	0	0		Not estimable	
Rhea (Greece)	0	0	2001025	Not estimable		Rhea (Greece)	0	0		Not estimable	
STEPS (FINI AND)	ñ	ő		Not estimable		STEPS (FINLAND)	3.032	0.37	3.4%	20.74 [10.04, 42.83]	
SAS (Linited Kingdom)	8.027	0.092	7.2%	0.0340.15.0.21		SWS (United Kingdom)	1.025	0.146	8.7%	2.79 [2.09, 3.71]	
AHISTLER (The Netherlands)	0	0		Not estimable		WHISTLER (The Netherlands)	0	0		Not estimable	
Total (95% CI)			100.0%	-0.11 [-0.15, -0.06]	•	Total (95% CI)			100.0%	3.46 [2.96, 4.04]	•
Heterogeneity: Tau <sup>a</sup> = 0.00, Chi <sup>a</sup> = 13.96, df	= 14 (P = 0	1.45); P	= 0%	1	-0.5 0 0.5	<ul> <li>Heterogeneity: Tau<sup>x</sup> = 0.15; Chi<sup>z</sup> = 46.14, df = 1 Test for overall effect. Z = 15.52 (P &lt; 0.0000)</li> </ul>	= 17 (P = 0.0002); P 1)	= 63%			0.01 0.1 10 1/
rest for orderall effect. Z = 4.29 (P < 0.0001)					Lower Z-score Higher Z-score		0.00				Lower Gous reals regiter Gous Ratio

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from logistic or linear regression models, respectively. The cohorts for which no estimate was provided had no or not sufficient data available for that particular analysis. 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, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC).

Supplementary Table S9. Associations of any upper and lower respiratory tract infections with lung function and asthma in complete cases, in cohorts who used an ISAAC based questionnaire to assess asthma, in cohorts that assessed respiratory tract infections by questionnaire and in children aged < 9 years and  $\geq$  9 years, respectively

	Complete cases	Asthma assessed by ISAAC based questionnaire	Respiratory tract infections assessed by questionnaire	Age <9 years	Age ≥ 9 years
			FEV <sub>1</sub> /FVC		
Upper respiratory tract infections, age 6 months	n = 2,586	NA	n = 24,268	n = 9,368	n = 4,135
	0.15 (0.06, 0.25)**		0.05 (-0.00, 0.10)	0.07 (0.01, 0.13)*	0.00 (-0.08, 0.09)
Upper respiratory tract infections, age 2 years	n = 5,431	NA	n = 24,268	n = 5,911	n = 7,468
	0.01 (-0.04, 0.07)		0.00 (-0.04, 0.04)	0.01 (-0.04, 0.07)	-0.00 (-0.05, 0.05)
Lower respiratory tract infections, age 6 months	n = 2,183	NA	n = 24,268	n = 8,499	n = 3,214
	-0.10 (-0.23, 0.04)		-0.15 (-0.21, -0.09)**	-0.16 (-0.23, -0.09)**	-0.13 (-0.26, -0.01)*
Lower respiratory tract infections, age 2 years	n = 5,381	NA	n = 24,268	n = 6,335	n = 4,873
	-0.09 (-0.16, -0.03)**		-0.09 (-0.14, -0.04)**	-0.09 (-0.15, -0.02)**	-0.11 (-0.20, -0.03)**
			Asthma		
Upper respiratory tract infections, age 6 months	n = 8,201	n = 57,212	n = 142,576	n = 82,059	n = 6,689
	1.31 (1.05, 1.63)*	1.20 (1.11, 1.30)**	1.25 (1.19, 1.33)	1.21 (1.17, 1.31)**	1.24 (0.98, 1.57)
Upper respiratory tract infections, age 2 years	n = 12,807	n = 57,212	n = 142,576	n = 44,504	n = 12,363
	1.47 (1.27, 1.70)**	1.32 (1.16, 1.49)**	1.32 (1.52, 1.72)	1.54 (1.44, 1.64)**	1.70 (1.47, 1.96)**
Lower respiratory tract infections, age 6 months	n = 5,915	n = 57,212	n = 142,576	n = 48,075	n = 6,199
	2.22 (1,63, 3.03)**	2.02 (1.62, 2.52)**	2.38 (2.18, 2.60)	2.38 (2.17, 2.60)**	2.21 (1.64, 2.99)**
Lower respiratory tract infections, age 2 years	n = 12,700	n = 57,212	n = 142,576	n = 44,844	n = 10,020
	3.34 (2.88, 3.86)**	3.46 (3.50, 3.93)**	3.24 (3.03,3.46)	3.20 (2.98, 3.42)**	3.68 (3.08, 4.40)**

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. 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, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC).

	FEV <sub>1</sub> /FVC Z-score	Asthma Odds Ratio					
Omitted cohort	(95% CI)	(95% CI)					
	Upper	respiratory tract infections					
	age 6 months						
ABIS	NA	NA					
ALSPAC	n = 19,939	n = 138,978					
	0.08 (0.02, 0.13)**	1.26 (1.19, 1.33)**					
DNBC	NA	n = 111,932					
		1.27 (1.19, 1.37)**					
MoBa	NA	n = 111,827					
		1.20 (1.12, 1.28)**					
	Lowe	er respiratory tract infections					
		age 6 months					
ABIS	NA	NA					
	40.000						
ALSPAC	n = 19,939	n = 138,978					
	-0.11 (-0.20, -0.03)**	2.56 (2.31, 2.83)**					
DNBC	NA	n = 111,932					
		2.39 (2.19, 2.61)**					
МоВа	NA	n = 111,827					
		1.16 (1.01, 1.32)*					

**Supplementary Table S10.** Associations of any upper and lower respiratory tract infections with lung function and asthma, after excluding cohorts who determine >5% of the population

Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic or linear regression models, respectively. \*p-value <0.05, \*\*p-value <0.01. 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, birth weight, season of birth, breastfeeding and daycare attendance. Forced Expiratory Volume in 1 second (FEV<sub>1</sub>). Forced Vital Capacity (FVC), not applicable (NA).

## Supplementary Figure S1. Flowchart of included cohorts and participants

