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Early View

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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_1), forced vital capacity (FVC), FEV_1/FVC, forced expiratory flow at 75% of FVC (FEF_{75}), 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_1, FEV_1/FVC and FEF_{75} (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[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 system[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 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)[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 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 mother-child 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_1), forced vital

capacity (FVC), FEV_1/FVC and forced expiratory flow after 75% of the FVC is exhaled (FEF_{75}). 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[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 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[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 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 asthma as the outcome. Our first model was unadjusted, our second model was adjusted 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_1/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^2 values[22].

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_1/FVC trajectories[23]. 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_1/FVC and FEF_{75} (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_1 (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_1 and FEV_1/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_{75} (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 I^2: 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_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.

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[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 percentage predicted FEV_1 at the age of 7.5 to 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 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_1/FVC and FEF_{75} 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[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 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_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 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[16]. 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[34-36]. Additionally, lung function trajectories, either obstructive of 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 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_{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 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[17]

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.

Al other authors contributed equally to study design, data analysis plan, data collection, reviewing the manuscript critically and gave consent for submission.

CONFLICT OF INTEREST

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DATA SHARING

Individual participant data will not be available for sharing

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REFERENCES

1. Chonmaitree T, Revai K, Grady JJ, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clin Infect Dis* 2008; **46**(6): 815-23.

2. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ* 2008; **86**(5): 408-16.

3. Openshaw PJ, Tregoning JS. Immune responses and disease enhancement during respiratory syncytial virus infection. *Clin Microbiol Rev* 2005; **18**(3): 541-55.

4. Holt PG. Programming for responsiveness to environmental antigens that trigger allergic respiratory disease in adulthood is initiated during the perinatal period. *Environ Health Perspect* 1998; **106 Suppl 3**: 795-800.

5. Daley D. The evolution of the hygiene hypothesis: the role of early-life exposures to viruses and microbes and their relationship to asthma and allergic diseases. *Curr Opin Allergy Clin Immunol* 2014; **14**(5): 390-6.

6. Wark PAB, Ramsahai JM, Pathinayake P, Malik B, Bartlett NW. Respiratory Viruses and Asthma. *Semin Respir Crit Care Med* 2018; **39**(1): 45-55.

7. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; **178**(7): 667-72.

8. Bonnelykke K, Vissing NH, Sevelsted A, Johnston SL, Bisgaard H. Association between respiratory infections in early life and later asthma is independent of virus type. *J Allergy Clin Immunol* 2015.

9. Kusel MM, de Klerk NH, Kebadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007; **119**(5): 1105-10.

10. Montgomery S, Bahmanyar S, Brus O, Hussein O, Kosma P, Palme-Kilander C. Respiratory infections in preterm infants and subsequent asthma: a cohort study. *BMJ Open* 2013; **3**(10): e004034.

11. James KM, Gebretsadik T, Escobar GJ, et al. Risk of childhood asthma following infant bronchiolitis during the respiratory syncytial virus season. *J Allergy Clin Immunol* 2013; **132**(1): 227-9.

12. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010; **65**(12): 1045-52.

13. Balekian DS, Linnemann RW, Hasegawa K, Thadhani R, Camargo CA, Jr. Cohort Study of Severe Bronchiolitis during Infancy and Risk of Asthma by Age 5 Years. *J Allergy Clin Immunol Pract* 2017; **5**(1): 92-6.

14. Chan JY, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. *Pediatrics* 2015; **135**(4): 607-16.

15. Guilbert TW, Singh AM, Danov Z, et al. Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma. *J Allergy Clin Immunol* 2011; **128**(3): 532-8.e1-10.

16. Gray DM, Turkovic L, Willemse L, et al. Lung Function in African Infants in the Drakenstein Child Health Study. Impact of Lower Respiratory Tract Illness. *Am J Respir Crit Care Med* 2017; **195**(2): 212-20.

17. van Meel ER, den Dekker HT, Elbert NJ, et al. A population-based prospective cohort study examining the influence of early-life respiratory tract infections on school-age lung function and asthma. *Thorax* 2018; **73**(2): 167-73.

18. Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; **6**(7): 535-44.

19. Jaddoe VWV, Felix JF, Andersen AN, et al. The LifeCycle Project-EU Child Cohort Network: a federated analysis infrastructure and harmonized data of more than 250,000 children and parents. *Eur J Epidemiol* 2020; **35**(7): 709-24.

20. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**(6): 1324-43.

21. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**(3): 483-91.

22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**(11): 1539-58.

23. Quanjer PH, Stanojevic S, Stocks J, et al. Changes in the FEV_1/FVC ratio during childhood and adolescence: an intercontinental study. *Eur Respir J* 2010; **36**(6): 1391-9.

24. Liu L, Pan Y, Zhu Y, et al. Association between rhinovirus wheezing illness and the development of childhood asthma: a meta-analysis. *BMJ Open* 2017; **7**(4): e013034.

25. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *Bmj* 2001; **322**(7283): 390-5.

26. Perret JL, Lodge CJ, Lowe AJ, et al. Childhood pneumonia, pleurisy and lung function: a cohort study from the first to sixth decade of life. *Thorax* 2020; **75**(1): 28-37.

27. Kouzouna A, Gilchrist FJ, Ball V, et al. A systematic review of early life factors which adversely affect subsequent lung function. *Paediatr Respir Rev* 2016; **20**: 67-75.

28. de Vries E, de Groot R, de Bruin-Versteeg S, Comans-Bitter WM, van Dongen JJ. Analysing the developing lymphocyte system of neonates and infants. *Eur J Pediatr* 1999; **158**(8): 611-7.

29. Dunnill MS. Postnatal growth of the lung. *Thorax* 1962; **17**(4): 329-33.

30. Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Ther* 2007; **114**(2): 129-45.

31. Larsen JM, Brix S, Thysen AH, Birch S, Rasmussen MA, Bisgaard H. Children with asthma by school age display aberrant immune responses to pathogenic airway bacteria as infants. *J Allergy Clin Immunol* 2014; **133**(4): 1008-13.

32. Heinonen S, Rodriguez-Fernandez R, Diaz A, Oliva Rodriguez-Pastor S, Ramilo O, Mejias A. Infant Immune Response to Respiratory Viral Infections. *Immunol Allergy Clin North Am* 2019; **39**(3): 361-76.

33. Ramette A, Spycher BD, Wang J, Goutaki M, Beardsmore CS, Kuehni CE. Longitudinal Associations Between Respiratory Infections and Asthma in Young Children. *Am J Epidemiol* 2018; **187**(8): 1714-20.

34. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986; **1**(8489): 1077-81.

35. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *Bmj* 1991; **303**(6804): 671-5.

36. Backman K, Ollikainen H, Piippo-Savolainen E, Nuolivirta K, Korppi M. Asthma and lung function in adulthood after a viral wheezing episode in early childhood. *Clin Exp Allergy* 2018; **48**(2): 138-46.

37. Wang G, Hallberg J, Charalampopoulos D, et al. Spirometric phenotypes from early childhood to young adulthood: a Chronic Airway Disease Early Stratification study. *ERJ Open Res* 2021; **7**(4).

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

	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)

Values are valid percentages (absolute numbers).

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

Cohort name (Country)	Age outcome	N	Asthma, % (N)	FEV_1 z-score (SD)	FVC z-score (SD)	FEV_1/FVC z-score (SD)	FEF_{75} 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

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).

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 Odds Ratio (95% CI)	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)**

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_1, FEV_1/FVC and $FEF_{75,}$ 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_1). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF_{75}).

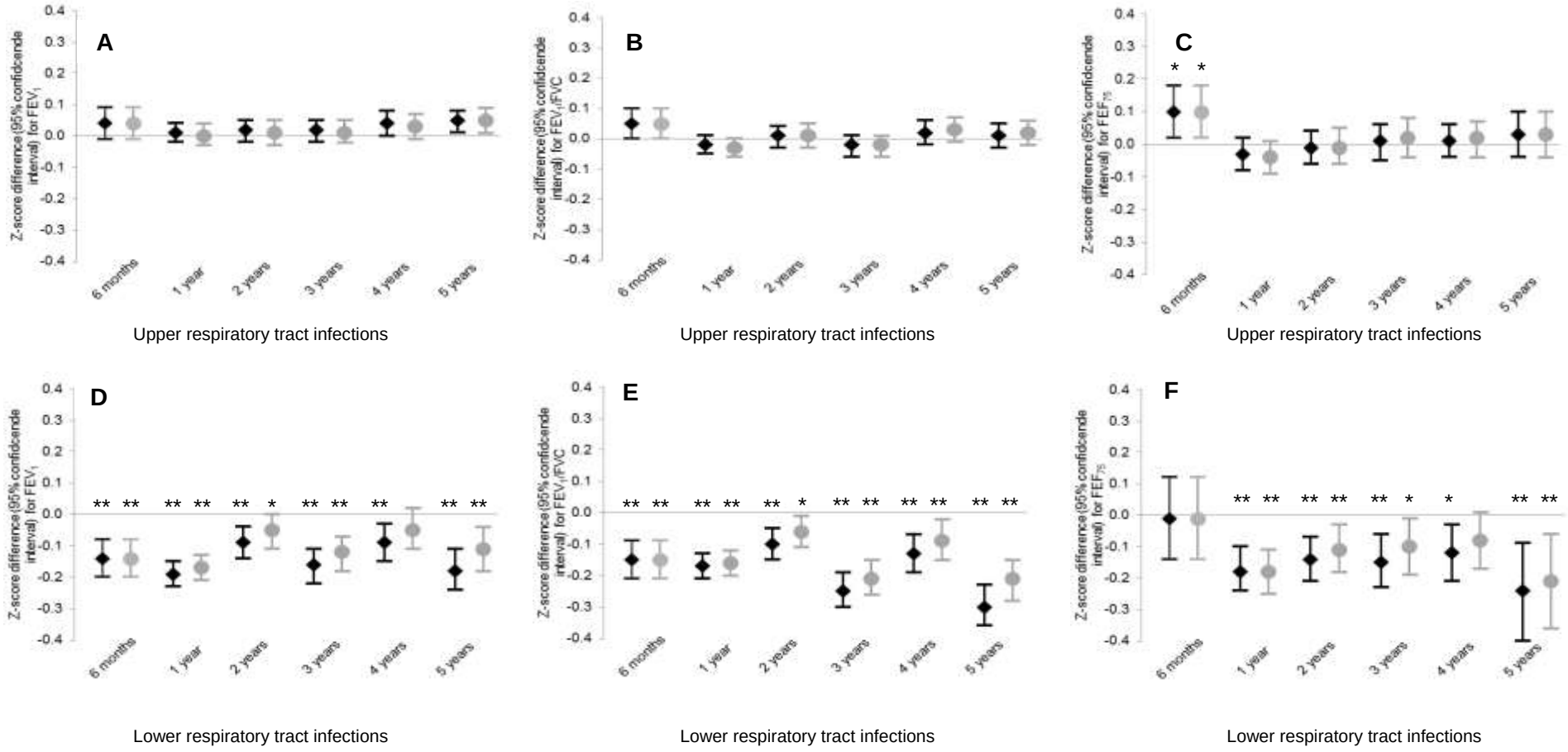
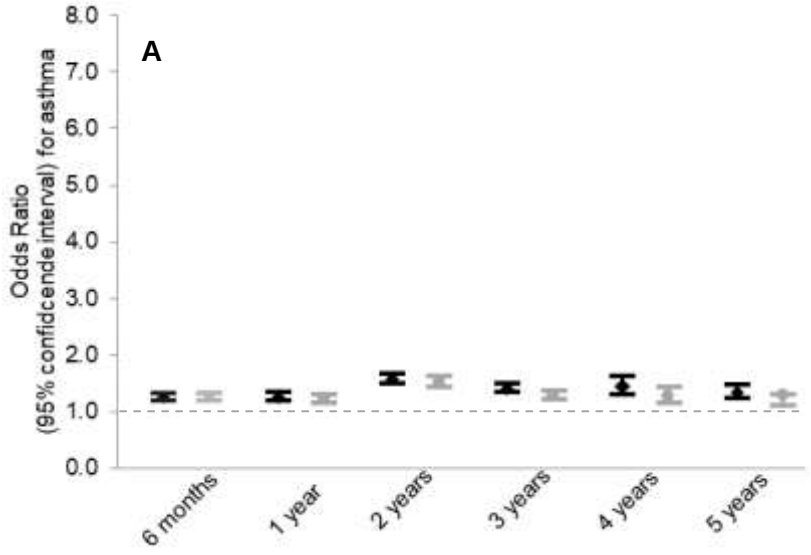
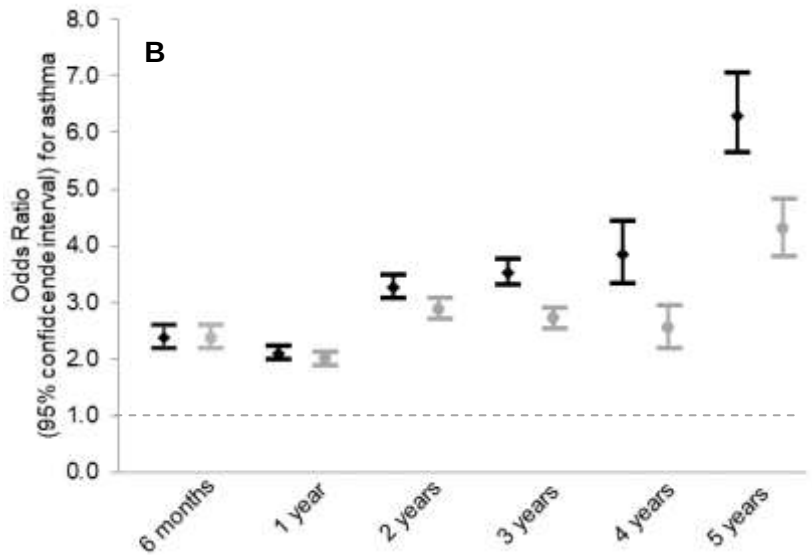


Figure 2. Associations of early-life upper **(A)** and lower **(B)** respiratory tract infections with school-age asthma. Values are Odds

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.



Upper respiratory tract infections



Lower 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.

REFERENCES

1. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The ‘Children of the 90s’; the index offspring of The Avon Longitudinal Study of Parents and Children (ALSPAC). International Journal of Epidemiology 2013; 42: 111-127.

2. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International Journal of Epidemiology 2013; 42:97-110.

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

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

(Swiss)	team member, parental report			age 6 years (ISAAC based)	
CoNER (Italy)	Questionnaire, parental report	6 months, 1, 3 years	Other	Questionnaire, parental report of doctor diagnosis at age 8 years	Questionnaire and parental report
COPSAC 2000 (Denmark)	Parental report of symptoms	3 years	ATS/ERS	Diagnosed by physicians in the research clinic according to symptom algorithm, at age 7 years	Interview questionnaire
COPSAC 2010 (Denmark)	Parental report of symptoms	1, 2, 3 years	ATS/ERS	Diagnosed by physicians in the research clinic according to symptom algorithm, at age 5 years	Interview questionnaire
DNBC (Denmark)	Questionnaire, parental report	6 months, 1 year	N/A	Questionnaire, ISAAC based, at age 7 years	Questionnaire and register data
EDEN (France)	Questionnaire, parental report	6 months, 1, 2, 3 years	ATS/ERS	Questionnaire, ISAAC based, at age 6 years	Questionnaire
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 (Italy)	Questionnaire, parental report	6 months, 1, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis at age 9 years	Questionnaire
Generation R (Netherlands)	Questionnaire, parental report of doctor diagnosis	6 months, 1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 10 years	Questionnaire
Generation XXI (Portugal)	Questionnaire, parental report of doctor diagnosis	6 months, 2, 4 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 7 years	Questionnaire
GINI (Germany)	Questionnaire, parental report of doctor diagnosis	1, 2, 3, 4, 5 years	ATS/ERS	Questionnaire, parental report of doctor diagnosis (ISAAC based), at age 15 years	Questionnaire
HUMIS (Norway)	Questionnaire, parental report of doctor diagnosis	6 months, 1, 2, 3 years	N/A	Registry data, hospital or specialist visit for asthma at age 9 years	Questionnaire and register data
IMNA Gipuzkoa	Questionnaire, parental report	1, 4 years	ATS/ERS	N/A	Questionnaire

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

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

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

	Upper respiratory tract infections						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

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).

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

	FEV_1 Z-score (95% CI) n = 25,903	FVC Z-score (95% CI) n = 25,903	FEV_1/FVC Z-score (95% CI) n = 25,903	FEF_{75} Z-score (95% CI) n = 14,426	Asthma Odds Ratio (95% CI) 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)**

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_1). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF_{75}).

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

	FEV_1 Z-score (95% CI) n = 25,903	FVC Z-score (95% CI) n = 25,903	FEV_1/FVC Z-score (95% CI) n = 25,903	FEF_{75} 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)**

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_1). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF_{75}).

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_1 Z-score (95% CI) n = 25,903	**FVC Z-score (95% CI) n = 25,903**	**FEV_1/FVC Z-score (95% CI) n = 25,903**	**FEF_{75} 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_1). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF_{75}).

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

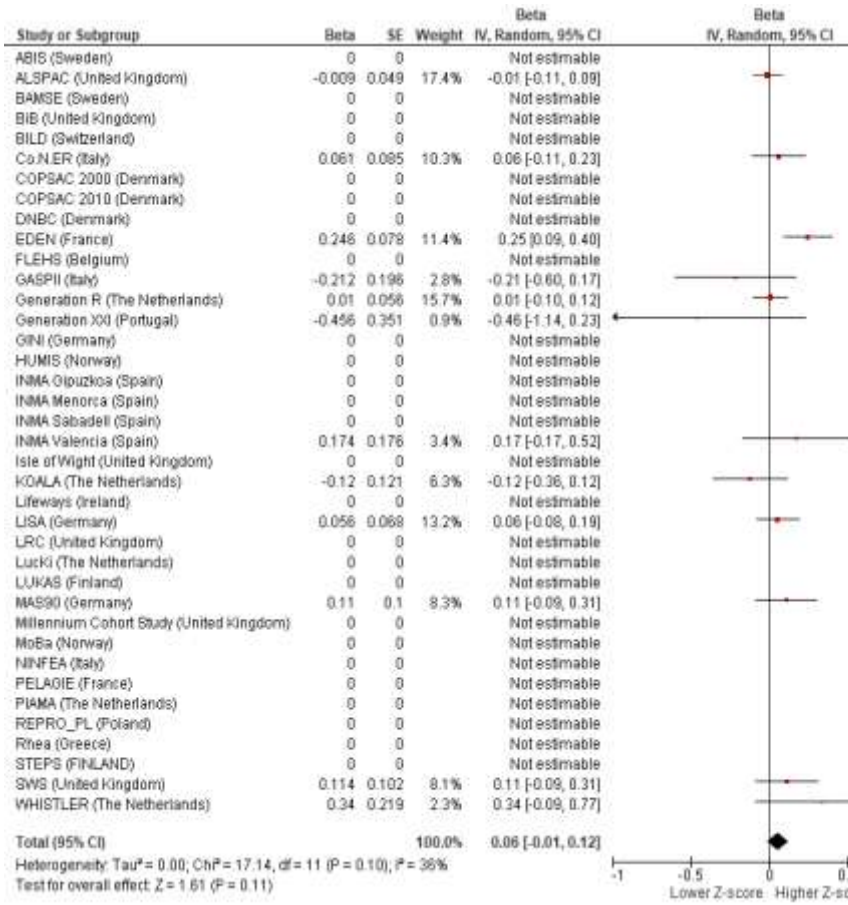
	FEV_1, wheeze - Z-score (95% CI)	FEV_1, wheeze + Z-score (95% CI)	FVC, wheeze - Z-score (95% CI)	FVC, wheeze + Z-score (95% CI)	FEV_1/FVC, wheeze - Z-score (95% CI)	FEV_1/FVC, wheeze + Z-score (95% CI)	FEF_{75}, wheeze - Z-score (95% CI)	FEF_{75}, wheeze + Z-score (95% CI)
Upper respiratory tract infections								
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 tract infections								
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)

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).

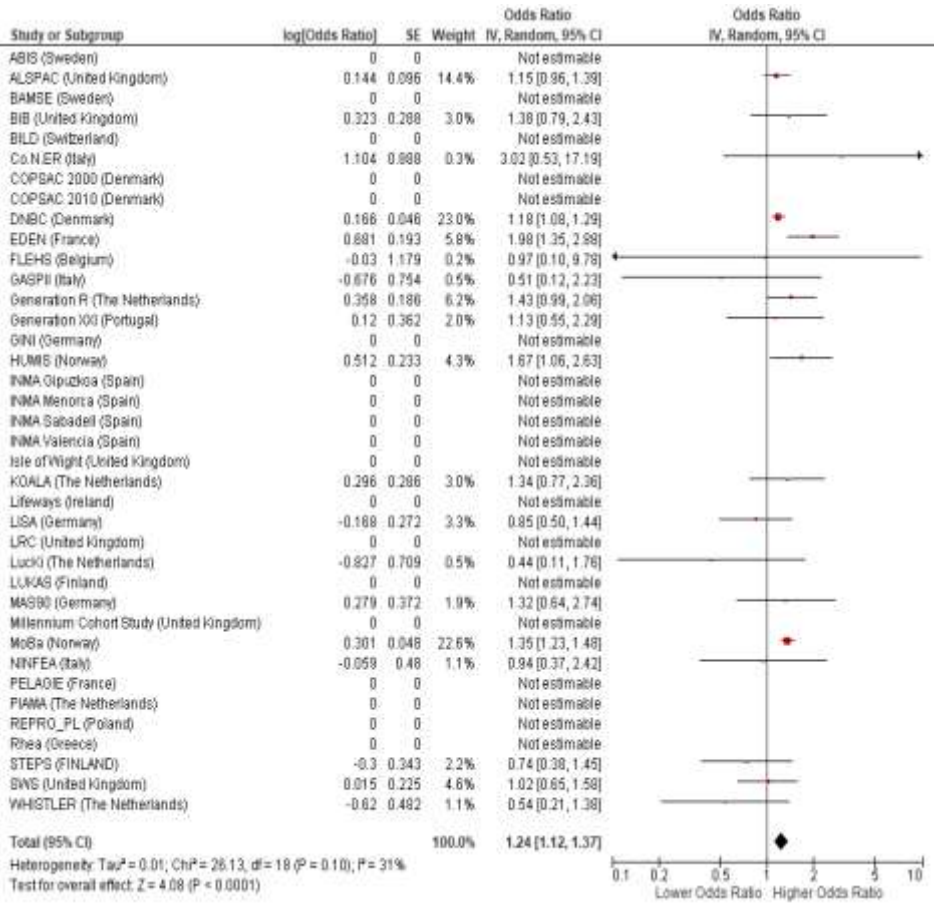
Supplementary Figure S8. Associations of any upper or lower respiratory tract infections with lung function and asthma assessed by a two-stage individual participant meta-analysis

Upper respiratory tract infections age 6 months

A. FEV_1/FVC

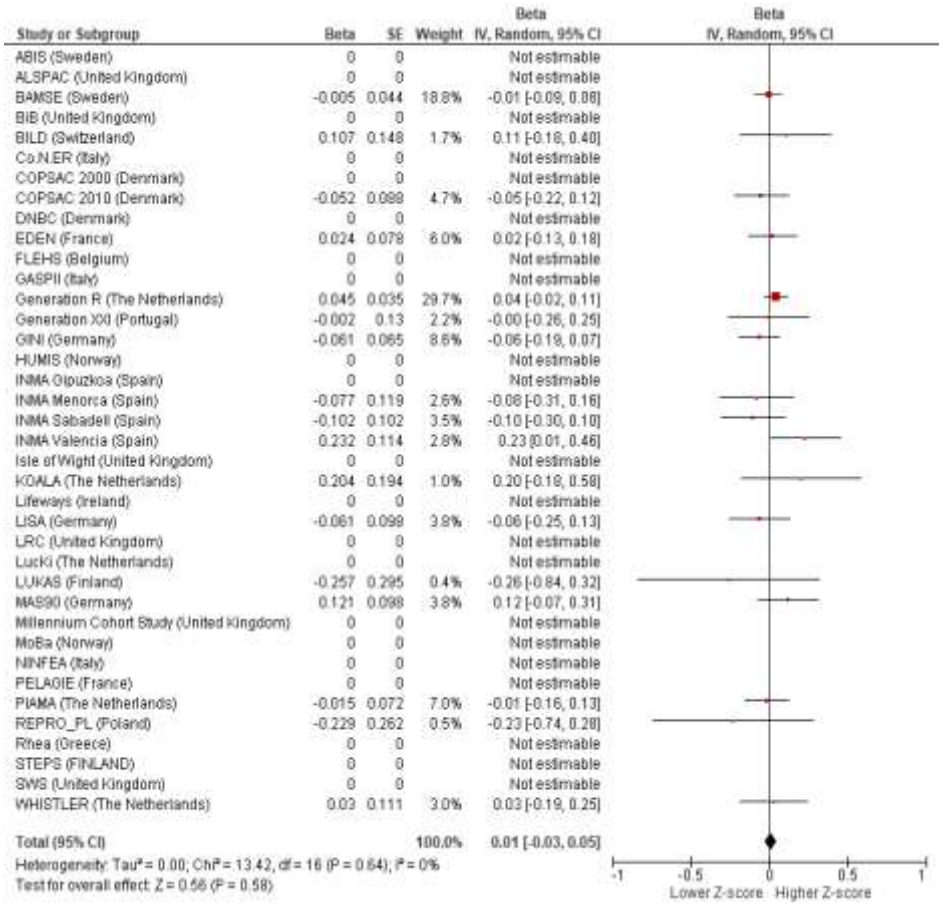


B. Asthma



Upper respiratory tract infections age 2 years

A. FEV_1/FVC

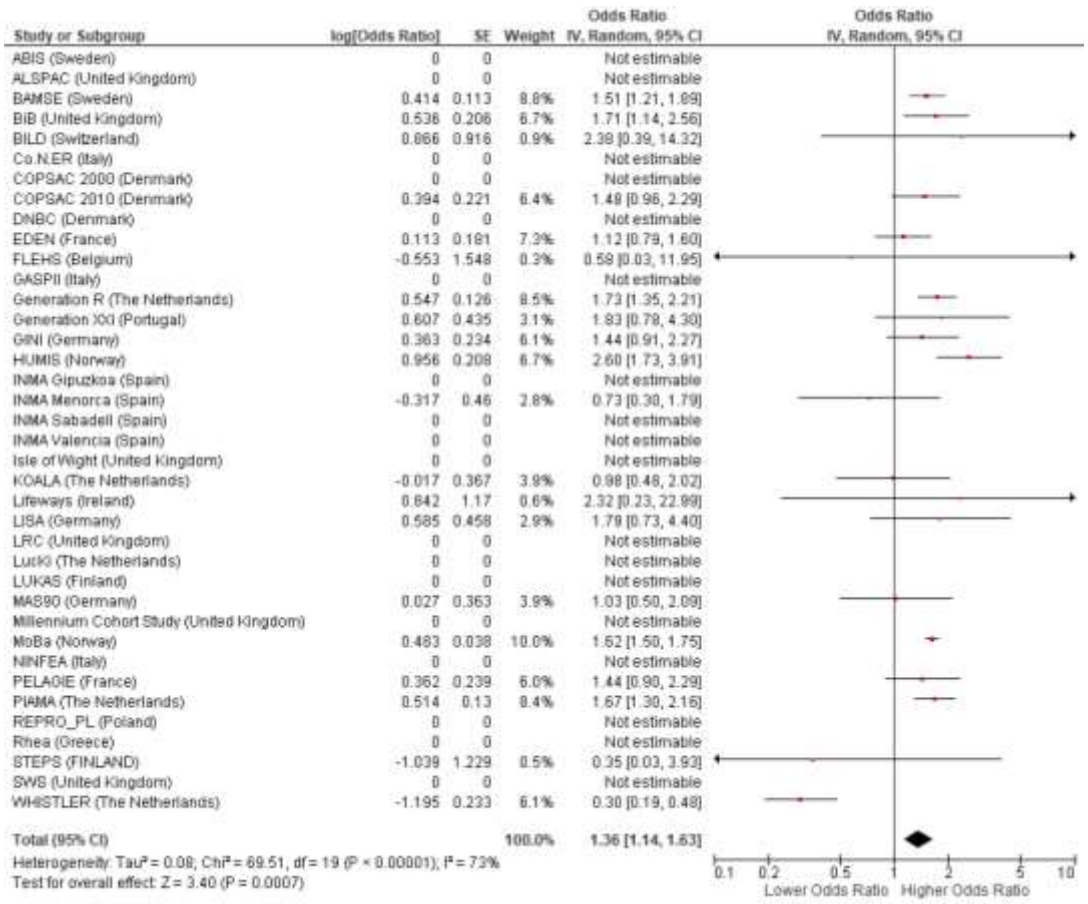


Study or Subgroup	Beta	SE	Weight	Beta IV, Random, 95% CI
ABIS (Sweden)	0	0		Not estimable
ALSPAC (United Kingdom)	0	0		Not estimable
BAMSE (Sweden)	-0.005	0.044	18.8%	-0.01 [-0.09, 0.08]
BiB (United Kingdom)	0	0		Not estimable
BILD (Switzerland)	0.107	0.148	1.7%	0.11 [-0.18, 0.40]
Co.N.ER (Italy)	0	0		Not estimable
COPSAC 2000 (Denmark)	0	0		Not estimable
COPSAC 2010 (Denmark)	-0.052	0.088	4.7%	-0.05 [-0.22, 0.12]
DNBC (Denmark)	0	0		Not estimable
EDEN (France)	0.024	0.078	6.0%	0.02 [-0.13, 0.18]
FLEHS (Belgium)	0	0		Not estimable
GASPII (Italy)	0	0		Not estimable
Generation R (The Netherlands)	0.045	0.035	29.7%	0.04 [-0.02, 0.11]
Generation XXI (Portugal)	-0.002	0.13	2.2%	-0.00 [-0.26, 0.25]
GINI (Germany)	-0.061	0.065	8.6%	-0.06 [-0.19, 0.07]
HUMIS (Norway)	0	0		Not estimable
INMA Gipuzkoa (Spain)	0	0		Not estimable
INMA Menorca (Spain)	-0.077	0.119	2.6%	-0.08 [-0.31, 0.16]
INMA Sabadell (Spain)	-0.102	0.102	3.5%	-0.10 [-0.30, 0.10]
INMA Valencia (Spain)	0.232	0.114	2.8%	0.23 [0.01, 0.46]
Isle of Wight (United Kingdom)	0	0		Not estimable
KOALA (The Netherlands)	0.204	0.194	1.0%	0.20 [-0.18, 0.58]
Lifeways (Ireland)	0	0		Not estimable
LISA (Germany)	-0.061	0.099	3.8%	-0.06 [-0.25, 0.13]
LRC (United Kingdom)	0	0		Not estimable
LucKi (The Netherlands)	0	0		Not estimable
LUKAS (Finland)	-0.257	0.295	0.4%	-0.26 [-0.84, 0.32]
MAS90 (Germany)	0.121	0.098	3.8%	0.12 [-0.07, 0.31]
Millennium Cohort Study (United Kingdom)	0	0		Not estimable
MoBa (Norway)	0	0		Not estimable
NINFEA (Italy)	0	0		Not estimable
PELAGIE (France)	0	0		Not estimable
PIAMA (The Netherlands)	-0.015	0.072	7.0%	-0.01 [-0.16, 0.13]
REPRO_PL (Poland)	-0.229	0.262	0.5%	-0.23 [-0.74, 0.28]
Rhea (Greece)	0	0		Not estimable
STEPS (FINLAND)	0	0		Not estimable
SWS (United Kingdom)	0	0		Not estimable
WHISTLER (The Netherlands)	0.03	0.111	3.0%	0.03 [-0.19, 0.25]
Total (95% CI)			100.0%	0.01 [-0.03, 0.05]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.42$, df = 16 (P = 0.64); $I^2 = 0\%$
Test for overall effect: Z = 0.56 (P = 0.58)

Beta IV, Random, 95% CI
-1 -0.5 0 0.5 1
Lower Z-score Higher Z-score

B. Asthma



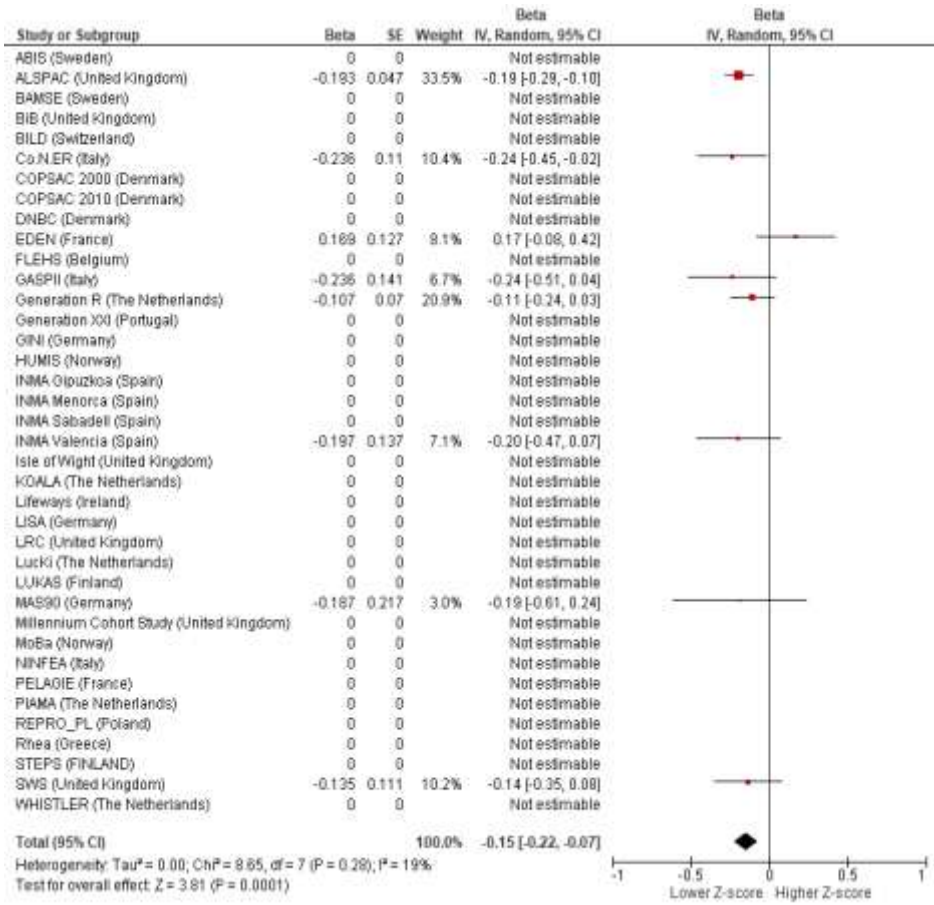
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
ABIS (Sweden)	0	0		Not estimable
ALSPAC (United Kingdom)	0	0		Not estimable
BAMSE (Sweden)	0.414	0.113	8.8%	1.51 [1.21, 1.89]
BiB (United Kingdom)	0.536	0.206	6.7%	1.71 [1.14, 2.56]
BILD (Switzerland)	0.866	0.916	0.9%	2.38 [0.39, 14.32]
Co.N.ER (Italy)	0	0		Not estimable
COPSAC 2000 (Denmark)	0	0		Not estimable
COPSAC 2010 (Denmark)	0.394	0.221	6.4%	1.48 [0.96, 2.29]
DNBC (Denmark)	0	0		Not estimable
EDEN (France)	0.113	0.181	7.3%	1.12 [0.79, 1.60]
FLEHS (Belgium)	-0.553	1.548	0.3%	0.58 [0.03, 11.95]
GASPII (Italy)	0	0		Not estimable
Generation R (The Netherlands)	0.547	0.126	8.5%	1.73 [1.35, 2.21]
Generation XXI (Portugal)	0.607	0.435	3.1%	1.83 [0.78, 4.30]
GINI (Germany)	0.363	0.234	6.1%	1.44 [0.91, 2.27]
HUMIS (Norway)	0.956	0.208	6.7%	2.60 [1.73, 3.91]
INMA Gipuzkoa (Spain)	0	0		Not estimable
INMA Menorca (Spain)	-0.317	0.46	2.8%	0.73 [0.30, 1.79]
INMA Sabadell (Spain)	0	0		Not estimable
INMA Valencia (Spain)	0	0		Not estimable
Isle of Wight (United Kingdom)	0	0		Not estimable
KOALA (The Netherlands)	-0.017	0.367	3.9%	0.98 [0.48, 2.02]
Lifeways (Ireland)	0.842	1.17	0.6%	2.32 [0.23, 22.99]
LISA (Germany)	0.585	0.458	2.9%	1.79 [0.73, 4.40]
LRC (United Kingdom)	0	0		Not estimable
LucKi (The Netherlands)	0	0		Not estimable
LUKAS (Finland)	0	0		Not estimable
MAS90 (Germany)	0.027	0.363	3.9%	1.03 [0.50, 2.09]
Millennium Cohort Study (United Kingdom)	0	0		Not estimable
MoBa (Norway)	0.483	0.038	10.0%	1.62 [1.50, 1.75]
NINFEA (Italy)	0	0		Not estimable
PELAGIE (France)	0.362	0.239	6.0%	1.44 [0.90, 2.29]
PIAMA (The Netherlands)	0.514	0.13	8.4%	1.67 [1.30, 2.16]
REPRO_PL (Poland)	0	0		Not estimable
Rhea (Greece)	0	0		Not estimable
STEPS (FINLAND)	-1.039	1.229	0.5%	0.35 [0.03, 3.93]
SWS (United Kingdom)	0	0		Not estimable
WHISTLER (The Netherlands)	-1.195	0.233	6.1%	0.30 [0.19, 0.48]
Total (95% CI)			100.0%	1.36 [1.14, 1.63]

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 69.51$, df = 19 (P < 0.00001); $I^2 = 73\%$
Test for overall effect: Z = 3.40 (P = 0.0007)

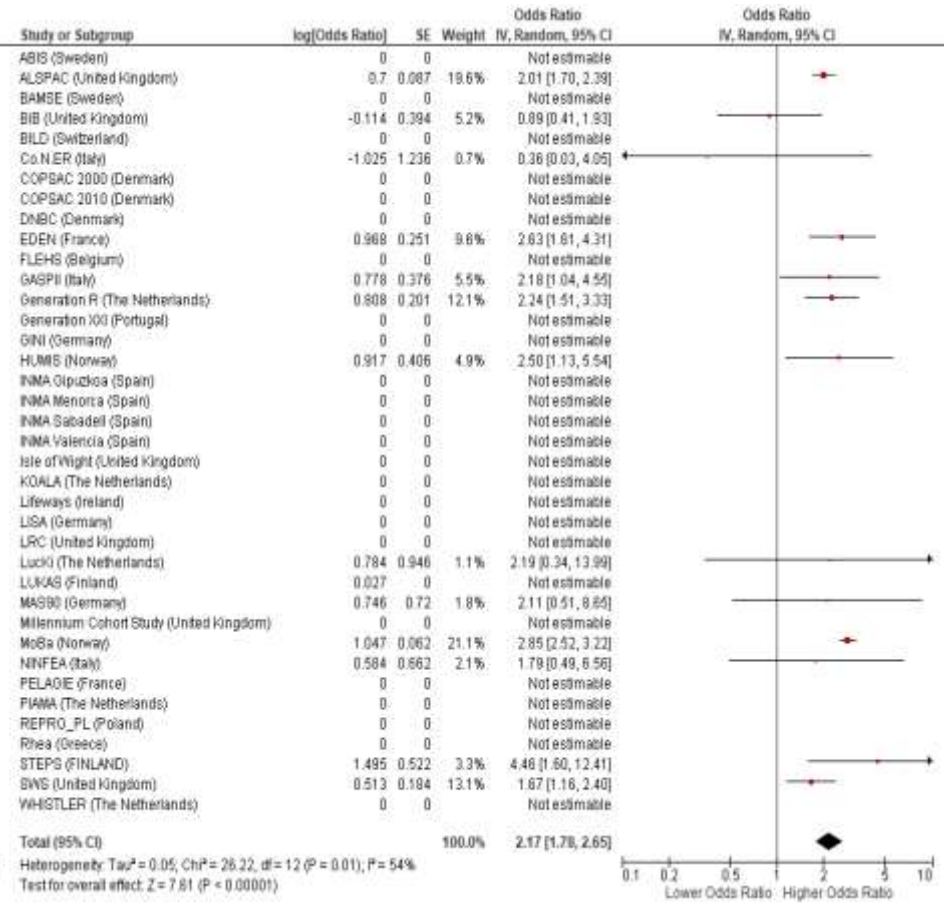
Odds Ratio IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Lower Odds Ratio Higher Odds Ratio

Lower respiratory tract infections age 6 months

A. FEV_1/FVC

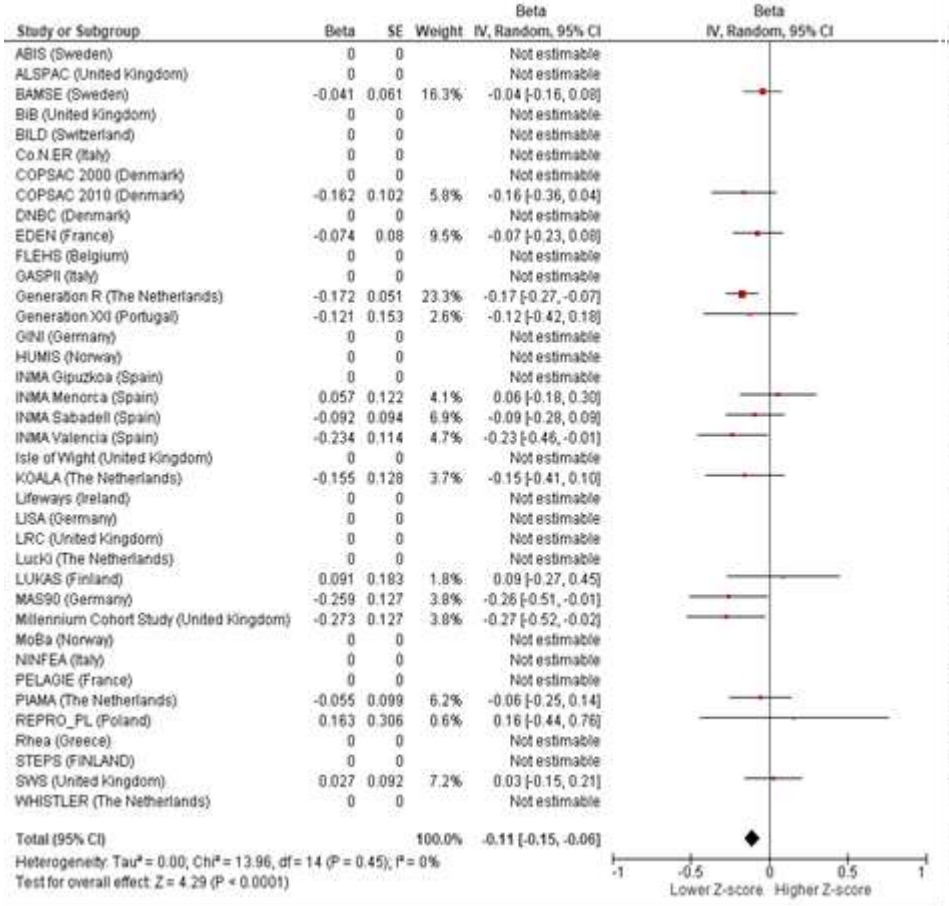


B. Asthma

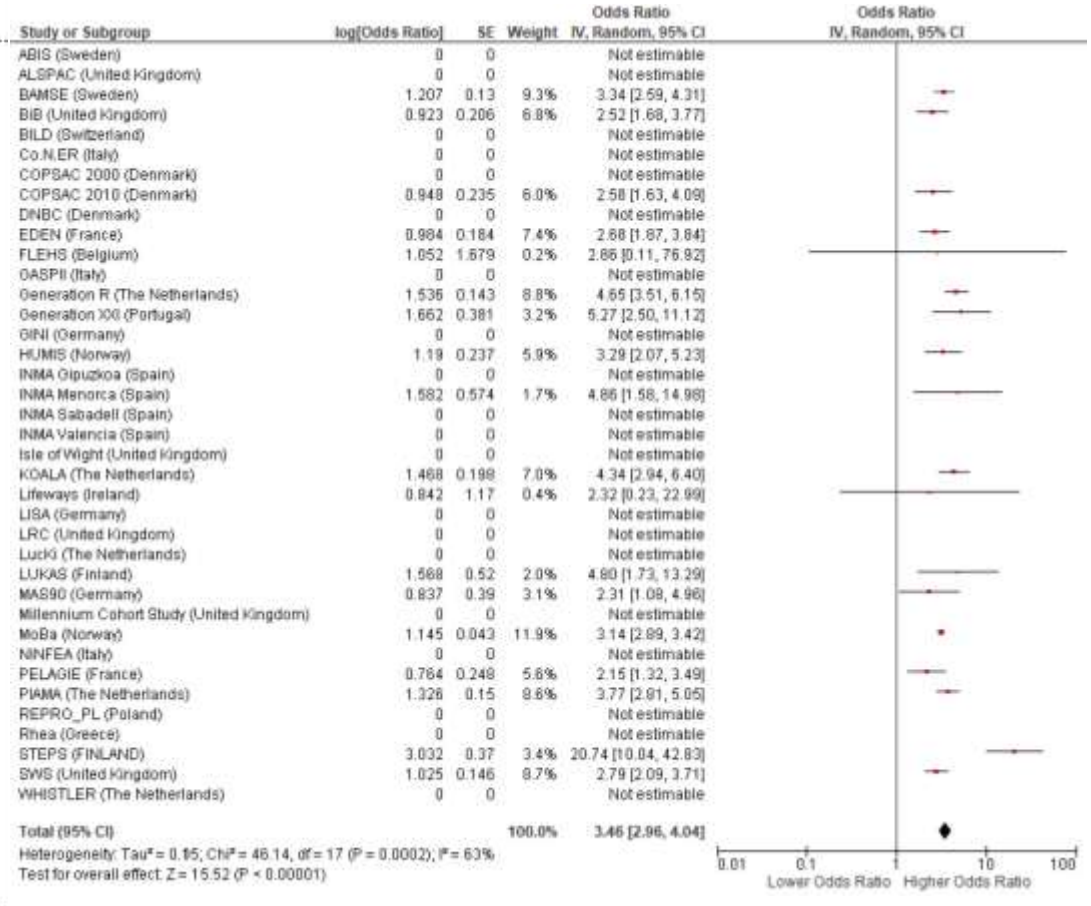


Lower respiratory tract infections age 2 years

A. FEV_1/FVC



B. Asthma



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_1). 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 ≥ 9 years, respectively

	Complete cases	Asthma assessed by ISAAC based questionnaire	Respiratory tract infections assessed by questionnaire	Age <9 years	Age ≥ 9 years
			FEV_1/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_1). Forced Vital Capacity (FVC).

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

Omitted cohort	FEV_1/FVC Z-score (95% CI)	Asthma Odds Ratio (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)**
	Lower respiratory tract infections	
	age 6 months	
ABIS	NA	NA
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)**
MoBa	NA	n = 111,827
		1.16 (1.01, 1.32)*

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_1). Forced Vital Capacity (FVC), not applicable (NA).

Supplementary Figure S1. Flowchart of included cohorts and participants