



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 150 000 European children

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Please cite this article as: van Meel ER, Mensink-Bout SM, den Dekker HT, *et al.* Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150 000 European children. *Eur Respir J* 2022; in press (<https://doi.org/10.1183/13993003.02395-2021>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

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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Word count manuscript: 3,406 Word count abstract: 238

Number of tables: 3; Number of figures: 2

Supplementary material: yes

Key words: Epidemiology, meta-analysis, pediatrics, respiratory tract infections, respiratory function tests, asthma

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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 (FEV₁), forced vital capacity (FVC), FEV₁/FVC, forced expiratory flow at 75% of FVC (FEF₇₅), 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 FEV₁, FEV₁/FVC and FEF₇₅ (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 system³⁻⁶. 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 risk⁷⁻¹³. 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 adulthood¹⁴⁻¹⁸. 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 (FEV₁), forced vital

capacity (FVC), FEV₁/FVC and forced expiratory flow after 75% of the FVC is exhaled (FEF₇₅). 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 analyst²⁰. 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 years²¹. 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 FEV₁/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 I² values²².

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 FEV₁/FVC trajectories²³. 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 FEV₁/FVC and FEF₇₅ (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 FEV₁ (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 FEV₁ and FEV₁/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 FEF₇₅ (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 I²: 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 FEV₁, FEV₁/FVC and FEF₇₅ 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 ages²⁴. 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 risk²⁵. One study demonstrated that pneumonia in childhood was associated with a lower FEV₁/FVC at age 7 years, but only in those with current asthma²⁶. Another study demonstrated that severe bronchiolitis during infancy was associated with a 2.5-fold increased risk of asthma at age 5 years¹³. 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 FEV₁ at the age of 7.5 to 20 years²⁷. 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 FEV₁ but also lower FEV₁/FVC and FEF₇₅, 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 associated with lower lung function. Although the effect sizes for the associations of upper respiratory tract infections with asthma remained when additionally adjusted for concomitant lower respiratory tract infections (data not shown), we cannot fully rule out that this observed association is due to misclassifications of infections or concomitant infections. We consider the observed associations of upper respiratory tract infections at age 6 months with a higher FEV₁/FVC and FEF₇₅ 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 life²⁸⁻³¹. 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 asthma³². 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 FEV₁, FEV₁/FVC and FEF₇₅, 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 weeks¹⁶. 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 adulthood³⁴⁻³⁶. Additionally, lung function trajectories, either obstructive or restrictive phenotypes, are shown to persist into adolescence and adulthood³⁷. Whether early-life risk factors, altered lung function, and diagnosis of asthma in childhood either separately or combined lead to adverse respiratory health such as asthma or 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 asthma¹⁷

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.

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

CONFLICT OF INTEREST

TA received funding for the current manuscript from the Novo Nordisk Foundation grant NNF180C0052457. IA-M is member of the ATS Environment Health Policy Committee, the ERS Ethics and Integrity Committee, and the French IRD Ethics Committee. SA received funding for the manuscript from Asthma UK (grant no 364) and National Institutes of Health USA (grant no R01 HL082925). HB received funding for the current manuscript from the Lundbeck Foundation (grant no R16-A1694), the Ministry of Health (grant no 903516), Danish Council for Strategic Research (grant no 0603-00280B) and the Capital Region Research Foundation. ME received paid honorarium for making small video's relating to allergy and asthma, by the Norwegian LHL organization. UF received funding for the manuscript from the Swiss National Science Foundation (grant nr 320030_204717/1), and is chair of the National Steering Board, Swiss Personalized Health Network SPHN). HI received funding for the manuscript from the UK Medical Research Council and the European Union, and was President for the Society for Social Medicine and Population Health. JJ received funding for the current manuscript from the National Science Centre, Poland (DEC-2014/15/B/N27/00998). AK received funding for the present manuscript from the Academy of Finland (grants 139021; 287675; 296814; 296817; 308254), the Juho Vainio Foundation, EVO/VTR funding, Pavivikki and Sakari Sohlberg Foundation, Farmers' Social Insurance Institution (Mela), the Finnish Cultural Foundation, the Foundation for Pediatric Research and the European Union (QLK4-CT-2001-0250). MM received grants from the Research Council of Norway (262700) and European Research Council (947684). AP-M received a Lundbeck

Foundation fellowship (R264-2017-3099). VP received funding for the present manuscript from the Academy of Finland and the Foundation for Pediatric Research Finland. Katy Pike received consulting fees from Novartis and Spiriva, payment or honoraria for lectures from Novartis and is participating on a Data Safety Monitoring Board or Advisory Board Adherium. Kinga Polanska received funding for the current manuscript from the National Science Centre, Poland (DEC-2014/15/B/N27/00998), grant PRNF-218-AI-1/07 from Norway through the Norwegian Financial Mechanisms within the Polish-Norwegian Research Fund, and the Ministry of Science and Higher Education, Poland (PBZ-MEiN-/8/2//2006). GR is president of the BSACI. AS received funding for the current manuscript from FCT Investigators contracts (IF/01060/2015). JS received a grant from the ERC (Prenatal exposure to urban AIR pollution and pre- and postNatal Brain development (AIR-NB, contract number 785994). JU received grants from the Palatin Foundation, University of Basel Switzerland, Swiss Cancer League and Swiss Lung Foundation, and payments or honoraria for lectures from Vertex and Zurich Lung Foundation. All other authors declare no conflict of interest. VJ received a grant from the European Research Council (ERC-2014-CoG-648916). LD received funding from cofunded ERA-Net on Biomarkers for Nutrition and Health (ERA HDHL), Horizon 2020 (grant agreement no. 696295; 2017), ZonMW The Netherlands (no. 529051014; 2017), Science Foundation Ireland (no. SFI/16/ERA-HDHL/3360) and the European Union (ALPHABET project).

DATA SHARING

Individual participant data will not be available for sharing

ACKNOWLEDGEMENTS AND FUNDING

ABIS

ABIS has been supported by Swedish Research Council (K2005-72X-11242-11A and K2008-69X-20826-01-4) and the Swedish Child Diabetes Foundation (Barndiabetesfonden), JDRF Wallenberg Foundation (K 98-99D-12813-01A), Medical Research Council of

Southeast Sweden (FORSS) and the Swedish Council for Working Life and Social Research (FAS2004–1775) and Östgöta Brandstodsbolag.

ALSPAC

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council *and* Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and EM and LD will serve as guarantors for the contents of this paper. A comprehensive list of grants funding is available on the ALSPAC website (<http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf>);

BAMSE

BAMSE was funded by the Swedish Research Council, the Swedish Heart Lung Foundation, ALF Region Stockholm, SFO Epidemiology Karolinska Institutet. EM is supported by a European Research Council grant (TRIBAL, No 757919).

BiB

Born in Bradford is only possible because of the enthusiasm and commitment of the children and parents in BiB. We are grateful to all the participants, practitioners and researchers who have made Born in Bradford happen. The BiB study presents independent research commissioned by the National Institute for Health Research Collaboration for Applied Health Research and Care (NIHR CLAHRC) and the Programme Grants for Applied Research funding scheme [grant number RP-PG-0407-10044]. Core support for BiB is also provided by the Wellcome Trust [grant number WT101597MA].

BILD

This study was funded by Swiss national science foundation grant 320030_163311.

CoNER

Funds were obtained from the special program (Programmi speciali - Art.12 bis, comma 6 D.lgs.229/99 Sanitaria e della Vigilanza sugli Enti) funded by the Italian Ministry of Health. Approval for the study was obtained from the ethics committee of the S. Orsola-Malpighi Teaching Hospital in April 2004 (52/2004/U/Tess).

COPSAC 2000 and COPSAC 2010

All funding received by COPSAC is listed on www.copsac.com. The Lundbeck Foundation (Grant no R16-A1694); The Ministry of Health (Grant no 903516); Danish Council for Strategic Research (Grant no 0603-00280B) and The Capital Region Research Foundation have provided core support to the COPSAC research center. We express our deepest gratitude to the children and families of the COPSAC 2000 and COPSAC 2010 cohort studies for all their support and commitment. We acknowledge and appreciate the unique efforts of the COPSAC research team.

DNBC

The authors would like to thank the participants, the first Principal Investigator of DNBC Prof. Jørn Olsen, the scientific managerial team, and DNBC secretariat for being, establishing, developing and consolidating the Danish National Birth Cohort. The Danish National Birth Cohort was established with a significant grant from the Danish National Research Foundation. Additional support was obtained from the Danish Regional Committees, the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Health Foundation and other minor grants. The DNBC Biobank has been supported by the Novo Nordisk Foundation and the Lundbeck Foundation. Follow-up of mothers and children have been supported by the Danish Medical Research Council (SSVF 0646, 271-08-0839/06-066023, O602-01042B, 0602-02738B), the Lundbeck Foundation (195/04, R100-A9193), The Innovation Fund Denmark 0603-00294B (09-067124), the

Nordea Foundation (02-2013-2014), Aarhus Ideas (AU R9-A959-13-S804), University of Copenhagen Strategic Grant (IFSV 2012), and the Danish Council for Independent Research (DFF – 4183-00594 and DFF - 4183-00152). AP is funded by a Lundbeck Foundation grant (R264-2017-3099)

EDEN

We thank the EDEN mother-child cohort study group (I. Annesi-Maesano, J.Y Bernard, J. Botton, M.A. Charles, P. Dargent-Molina, B. de Lauzon-Guillain, P. Ducimetière, M. de Agostini, B. Foliguet, A. Forhan, X. Fritel, A. Germa, V. Goua, R. Hankard, B. Heude, M. Kaminski, B. Larroque†, N. Lelong, J. Lepeule, G. Magnin, L. Marchand, C. Nabet, F. Pierre, R. Slama, M.J. Saurel-Cubizolles, M. Schweitzer, O. Thiebaugeorges). We thank all funding sources for the EDEN study (not allocated for the present study but for the cohort): Foundation for medical research (FRM), National Agency for Research (ANR), National Institute for Research in Public health (IRESP: TGIR cohorte santé 2008 program), French Ministry of Health (DGS), French Ministry of Research, INSERM Bone and Joint Diseases National Research (PRO-A) and Human Nutrition National Research Programs, Paris–Sud University, Nestlé, French National Institute for Population Health Surveillance (InVS), French National Institute for Health Education (INPES), the European Union FP7 programs (FP7/2007-2013, HELIX, ESCAPE, ENRIECO, Medall projects), Diabetes National Research Program (in collaboration with the French Association of Diabetic Patients (AFD), French Agency for Environmental Health Safety (now ANSES), Mutuelle Générale de l'Éducation Nationale complementary health insurance (MGEN), French national agency for food security, French speaking association for the study of diabetes and metabolism (ALFEDIAM). The funding source had no involvement in the conception of the present study.

FLEHS

This study was conducted within the framework of the Flemish Centre of Expertise on Environment and Health, funded by the Department Environment of the Flemish

Government, the Flemish Agency of Care and Health, and the Flemish Department of Economy, Science and Innovation.

GASP II

The Gasp II cohort was funded by Italian Ministry of Health (2001), the research leading to these results has received funding from the European Community's Seventh Framework Program under grant agreement numbers 261357 (MeDALL)

Generation R

This study was funded by The Erasmus Medical Centre, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development. Dr. Vincent Jaddoe received a grant from the European Research Council (ERC-2014-CoG-648916). Dr. Liesbeth Duijts received funding from cofunded ERA-Net on Biomarkers for Nutrition and Health (ERA HDHL), Horizon 2020 (grant agreement no. 696295; 2017), ZonMW The Netherlands (no. 529051014; 2017), Science Foundation Ireland (no. SFI/16/ERA-HDHL/3360) and the European Union (ALPHABET project). The project received funding from the European Union's Horizon 2020 research and innovation programme (LIFECYCLE, grant agreement No 733206, 2016; EUCAN-Connect grant agreement No 824989; ATHLETE, grant agreement No 874583). The researchers are independent from the funders. The study sponsors had no role in the study design, data analysis, interpretation of data, or writing of this report.

Generation XXI

Generation XXI was supported by the European Regional Development Fund (ERDF) through the Operational Programme Competitiveness and Internationalization and national funding from the Foundation for Science and Technology (FCT), Portuguese Ministry of Science, Technology and Higher Education and by the Unidade de Investigação em Epidemiologia - Instituto de Saúde Pública da Universidade do Porto (EPIUnit) (UIDB/04750/2020), Administração Regional de Saúde Norte (Regional Department of

Ministry of Health) and Fundação Calouste Gulbenkian. Ana Cristina Santos is funded by FCT Investigator contracts IF/01060/2015.

GINI

GINIplus study was mainly supported for the first three years of the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The four and six year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centers (Helmholtz Zentrum Munich (former GSF), Research Institute at Marien-Hospital, Wesel, LMU Munich, TU Munich and from six years onwards also from IUF - Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf).

HUMIS

We thank all mothers for participating in the HUMIS study. HUMIS was funded by a grant from the Norwegian Research Council grant agreement no.226402. The HUMIS study was approved by the Norwegian Data Inspectorate (refs.2002/1398) and by the Regional Ethics Committee for Medical Research in Norway (ref.S-02122) and the specific use in the current study was approved by the Ethics committee as well (2010/1259/REK sør-øst).

INMA

Gipuzkoa

This study was funded by grants from Instituto de Salud Carlos III (FIS-PI09/00090 and FIS-PI18/01142 incl. FEDER funds), CIBERESP, Department of Health of the Basque Government (2013111089), and annual agreements with the municipalities of the study area (Zumarraga, Urretxu, Legazpi, Azkoitia y Azpeitia y Beasain).

Menorca

This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; 97/0588; 00/0021-2, PI061756; PS0901958, PI14/00677 incl. FEDER funds),

CIBERESP, Beca de la IV convocatoria de Ayudas a la Investigación en Enfermedades Neurodegenerativas de La Caixa, and EC Contract No. QLK4-CT-200-00263.

Sabadell

This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds), Generalitat de Catalunya-CIRIT 1999SGR 00241, Fundació La marató de TV3 (090430). ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya. Maribel Casas holds a Miguel Servet fellowship (CP16/00128) funded by Instituto de Salud Carlos III and co-funded by European Social Fund "Investing in your future".

Valencia

This study was funded by Grants from UE (FP7-ENV-2011 cod 282957 and HEALTH.2010.2.4.5-1), Spain: ISCIII (Red INMA G03/176, CB06/02/0041; FIS-FEDER: PI03/1615, PI04/1509, PI04/1112, PI04/1931, PI05/1079, PI05/1052, PI06/1213, PI07/0314, PI09/02647, PI11/01007, PI11/02591, PI11/02038, PI13/1944, PI13/2032, PI14/00891, PI14/01687, PI16/1288, and PI17/00663; Miguel Servet-FEDER CP11/00178, CP15/00025, and CPII16/00051), Generalitat Valenciana: FISABIO (UGP 15-230, UGP-15-244, and UGP-15-249), and Alicia Koplowitz Foundation 2017.

Isle of Wight

This study was funded by grants from the National Institutes of Health USA (R01 HL082925), Asthma UK (No: 364), Isle of Wight NHS Trust and the British Medical Association.

KOALA

The collection of data relevant for this study was funded by grants from the Netherlands Organisation for Health Research and Development (ZonMw grant no. 2100.0090) and the Netherlands Asthma Foundation (grants nos. 3.2.03.48 and 3.2.07.022). The researchers are independent from the funders. The funders had no role in the study design, data analysis,

interpretation of data, or writing of this report. We thank the children and parents for their participation in the KOALA study.

Leicestershire Respiratory Cohorts

This study was funded by grants from the Swiss National Science Foundation (SNF, 320030-182628, 320030-162820), 3233-069348, ad 3200-069349) and .Asthma UK 07/048.

Lifeways Cross-Generation Cohort Study

This study was funded by the Health Research Board, Ireland, and the Irish Department of Health and Children's Health Promotion Policy Unit.

LISA

LucKi

LucKi is supported by Child and Youth Health Care Zuyderland, Public Health Service South Limburg and the Maastricht University. We thank all parents and children for their participation in LucKi.

LUKAS

This study was funded by research grants from the Academy of Finland (grants 139021; 287675;296814;296817;308254); the Juho Vainio Foundation; EVO/VTR funding; Päivikki and Sakari Sohlberg Foundation; Farmers' Social Insurance Institution (Mela); The Finnish Cultural Foundation; the Foundation for Pediatric Research; European Union QLK4-CT-2001-00250; and by the Finnish Institute for Health and Welfare, Finland.

MAS-90

This study was funded by grants from the German Federal Ministry of Education and Research (MBMF; reference numbers 07015633m 07ALE27, 01EE9405/5, 01EE9406) and the German Research Foundation (DFG; reference numbers KE1462/2-1).

Millennium Cohort Study

This study is supported by Health Data Research UK, an initiative funded by UK Research and Innovation, Department of Health and Social Care (England) and the devolved administrations, and leading medical research charities. This study was funded by the Economic and Social Research Council and a consortium of UK government funders. We are grateful to the participating families and the Centre for Longitudinal Studies (CLS), UCL Institute of Education, for the use of these data and to the UK Data Service for making them available. However, neither CLS nor the UK Data Service bear any responsibility for the analysis or interpretation of these data. This work was supported by the Wellcome Trust Grant Number 187389/B/08/Z.

MoBa

The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. This research was supported by the Research Council of Norway through its Centres of Excellence funding scheme, project number 262700.

NINFEA

The authors are grateful to all the participants of the NINFEA cohort. The NINFEA study was partially funded by the Compagnia San Paolo Foundation. This research was partially funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no. 733206, LIFE-CYCLE project.

PELAGIE

We are grateful to the families who participated and continue to participate in the study. The cohort is supported by INSERM and received funding from the French National Research Agency, the Fondation de France, the French Agency for Food, Environmental and Occupational Health & Safety, the National Institute for Public Health Surveillance (InVS), the French Ministry of Labor and French Ministry of Ecology.

PIAMA

This study was funded by the Netherlands Organization of Health Research and Development, the Netherlands Organization for Scientific Research, the Netherlands Asthma Fund, the Netherlands Ministry of Spatial Planning, Housing and the Environment, and the Netherlands Ministry of Health, Welfare and Sport.

REPRO-PL

This study was funded by the National Science Center Poland under grant DEC-2014/15/B/N27/00998.

Rhea

This study was funded by the European Union Social Fund and the Hellenic Ministry of Health ("Program of prevention and early diagnosis of obesity and neurodevelopment disorders in preschool age children in the prefecture of Heraklion, Crete, Greece " MIS number 349580, NSRF 2007-2013). Additional funding from the National Institute of Environmental Health Sciences (NIEHS) supported Dr Chatzi (R01ES030691, R01ES029944, R01ES030364, R21ES029681, R21ES028903, and P30ES007048)

STEPS

This study was funded by the University of Turku, The Abo Akademi University, the Turku University Hospital, the Academy of Finland (Grants no123571, 140251, 277535) and the Foundation for Pediatric Research Finland.

SWS

This study was funded by the Medical Research Council, British Heart Foundation, Arthritis Research UK, Food Standards Agency, NIHR Southampton Biomedical Research Centre, and the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition, under grant agreement 289346 and from the European Union's Horizon 2020 research and innovation programme (LIFECYCLE, grant agreement No 733206)

Whistler

The WHISTLER birth cohort was supported with a grant from the Netherlands Organization for Health Research and Development (grant nr 2001-1-1322) and by an unrestricted grant from Glaxo Smith Kline Netherlands. GlaxoSmithKline had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the report for publication. WHISTLER-Cardio was supported with an unrestricted strategic grant from the University Medical Center Utrecht (UMCU), The Netherlands.

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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)	FEV₁ z-score (SD)	FVC z-score (SD)	FEV₁/FVC z-score (SD)	FEF₇₅ 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 FEV₁, FEV₁/FVC and FEF₇₅, 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 (FEV₁). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF₇₅).

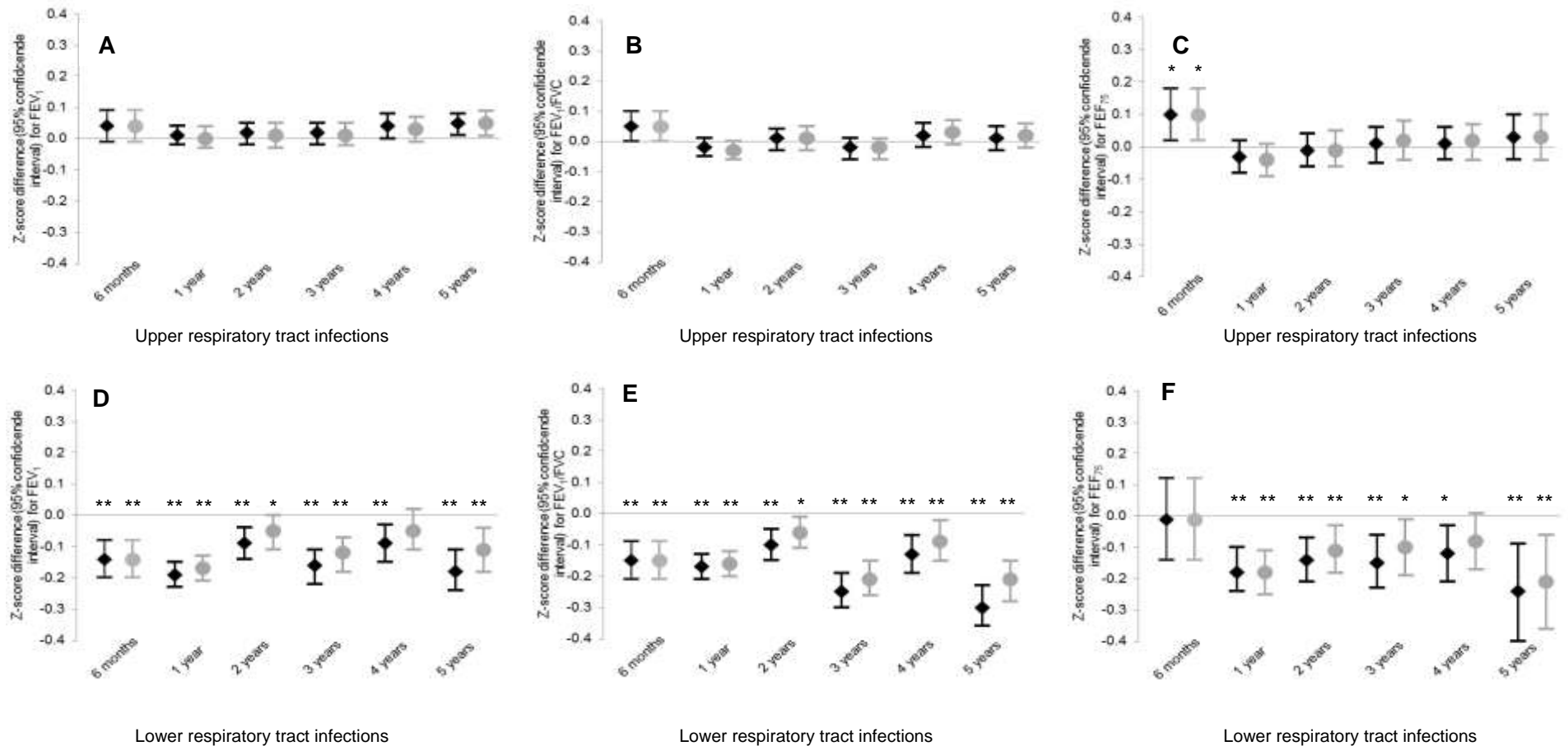
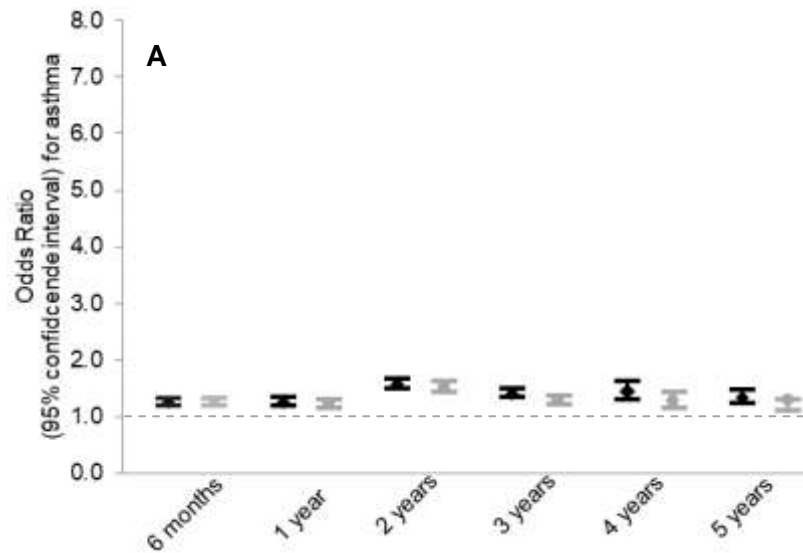
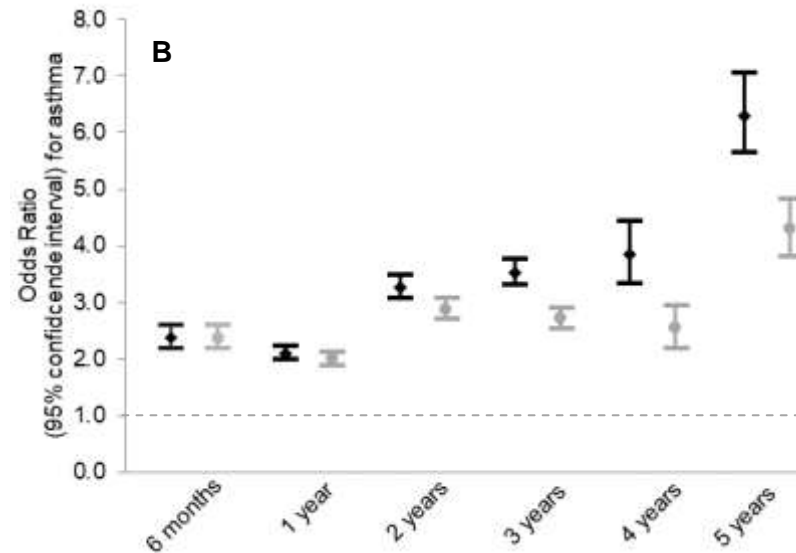


Figure 2. Associations of early-life upper **(A)** and lower **(B)** respiratory tract infections with school-age asthma. Values are Odds

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.

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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.

Cohort name (country)	Respiratory tract infections		Respiratory outcomes		Covariates
	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

NINFEA (Italy)	Questionnaire, parental report of doctor diagnosis	6 months, 1 year	N/A	age 7 years 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

Cohort name	Upper respiratory tract infections						Lower respiratory tract infections					
	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

	FEV₁ Z-score (95% CI) n = 25,903	FVC Z-score (95% CI) n = 25,903	FEV₁/FVC Z-score (95% CI) n = 25,903	FEF₇₅ 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 (FEV₁). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF₇₅).

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 (FEV₁). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF₇₅).

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

	FEV₁ Z-score (95% CI) n = 25,903	FVC Z-score (95% CI) n = 25,903	FEV₁/FVC Z-score (95% CI) n = 25,903	FEF₇₅ 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 (FEV₁). Forced Vital Capacity (FVC), Forced Expiratory Flow after exhaling 75% of FVC (FEF₇₅).

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)

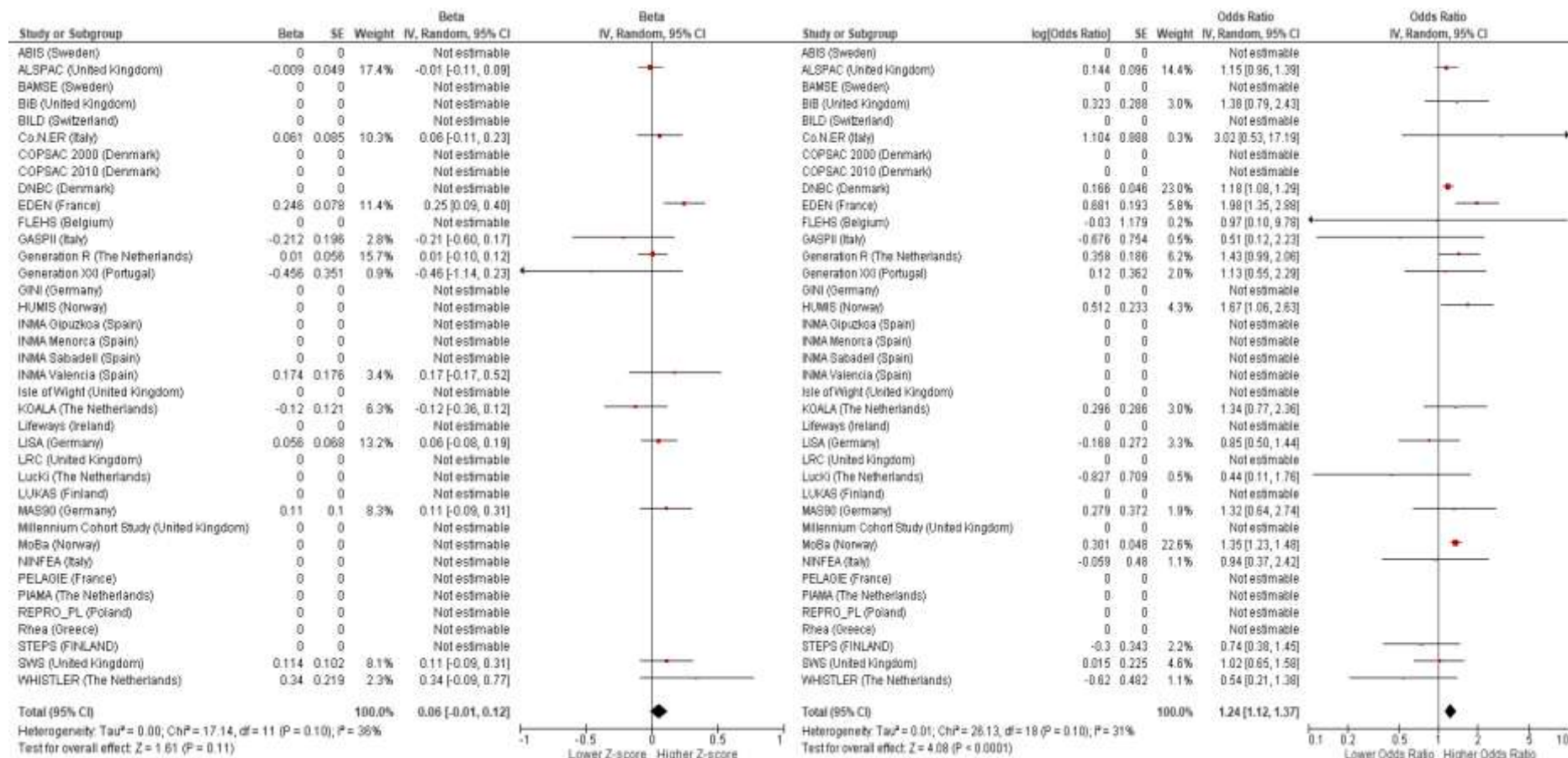
Values are odds ratios (OR) or changes in Z-score with 95% confidence interval, derived from multilevel logistic regression models. *p-value <0.05, **p-value <0.01. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, 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. FEV₁/FVC

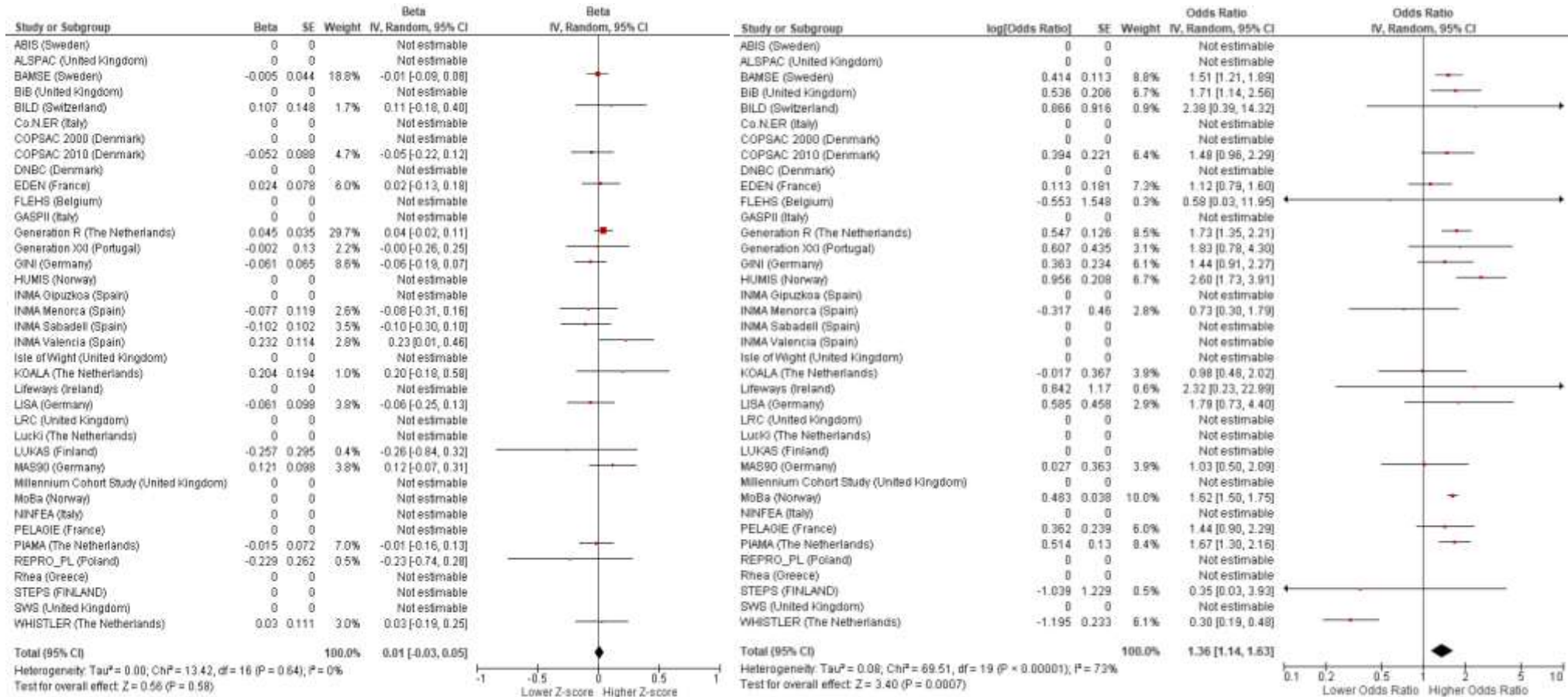
B. Asthma



Upper respiratory tract infections age 2 years

A. FEV₁/FVC

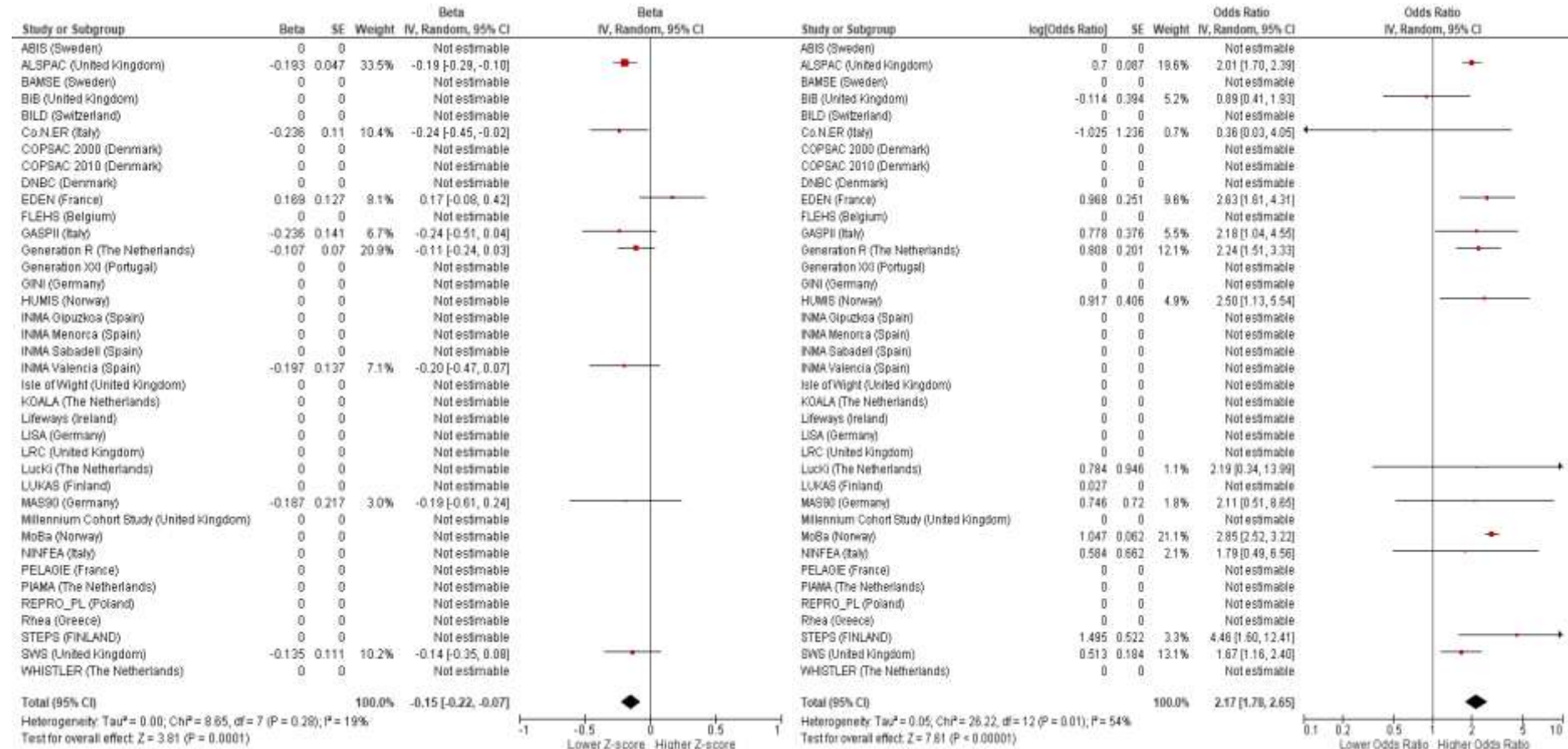
B. Asthma



Lower respiratory tract infections age 6 months

A. FEV₁/FVC

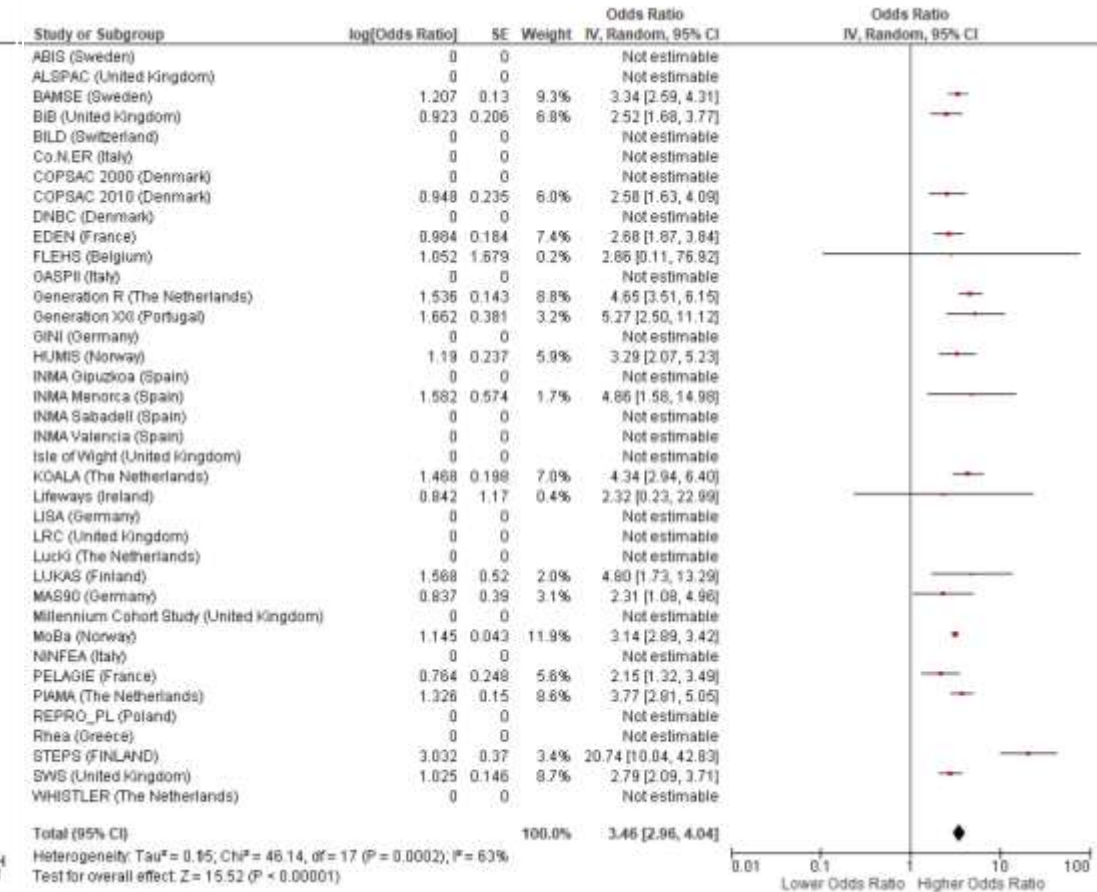
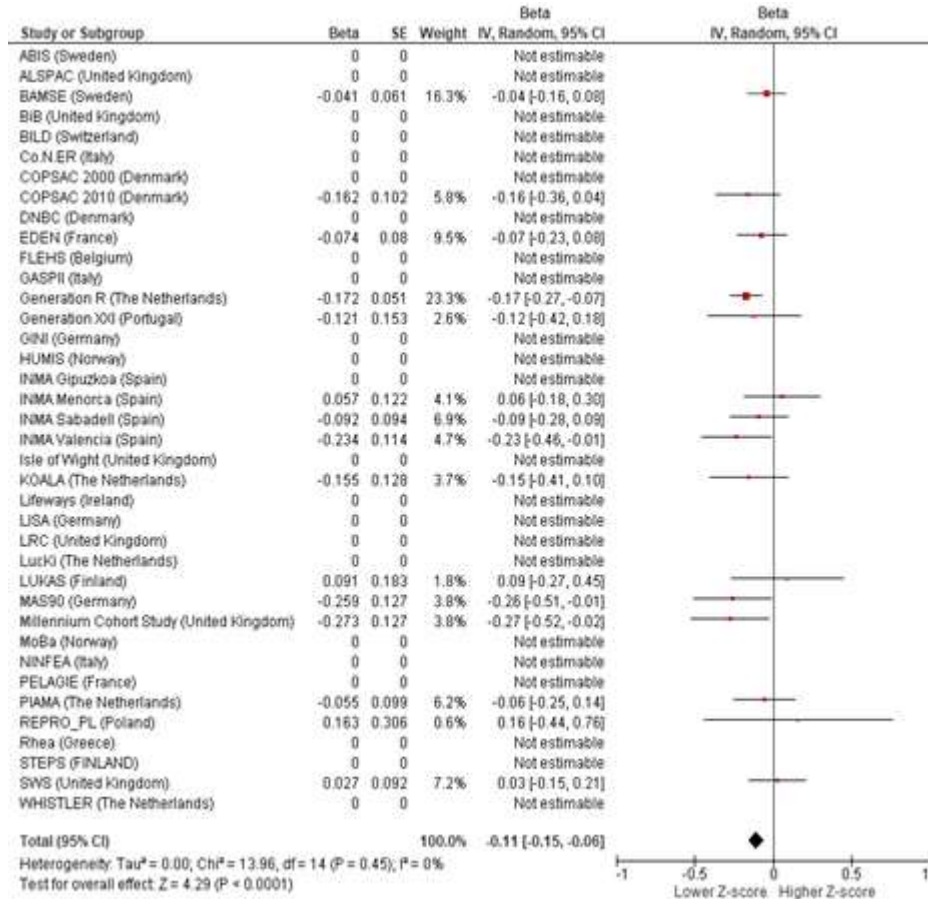
B. Asthma



Lower respiratory tract infections age 2 years

A. FEV₁/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 (FEV₁). 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
FEV₁/FVC					
Upper respiratory tract infections, age 6 months	n = 2,586 0.15 (0.06, 0.25)**	NA	n = 24,268 0.05 (-0.00, 0.10)	n = 9,368 0.07 (0.01, 0.13)*	n = 4,135 0.00 (-0.08, 0.09)
Upper respiratory tract infections, age 2 years	n = 5,431 0.01 (-0.04, 0.07)	NA	n = 24,268 0.00 (-0.04, 0.04)	n = 5,911 0.01 (-0.04, 0.07)	n = 7,468 -0.00 (-0.05, 0.05)
Lower respiratory tract infections, age 6 months	n = 2,183 -0.10 (-0.23, 0.04)	NA	n = 24,268 -0.15 (-0.21, -0.09)**	n = 8,499 -0.16 (-0.23, -0.09)**	n = 3,214 -0.13 (-0.26, -0.01)*
Lower respiratory tract infections, age 2 years	n = 5,381 -0.09 (-0.16, -0.03)**	NA	n = 24,268 -0.09 (-0.14, -0.04)**	n = 6,335 -0.09 (-0.15, -0.02)**	n = 4,873 -0.11 (-0.20, -0.03)**
Asthma					
Upper respiratory tract infections, age 6 months	n = 8,201 1.31 (1.05, 1.63)*	n = 57,212 1.20 (1.11, 1.30)**	n = 142,576 1.25 (1.19, 1.33)	n = 82,059 1.21 (1.17, 1.31)**	n = 6,689 1.24 (0.98, 1.57)
Upper respiratory tract infections, age 2 years	n = 12,807 1.47 (1.27, 1.70)**	n = 57,212 1.32 (1.16, 1.49)**	n = 142,576 1.32 (1.52, 1.72)	n = 44,504 1.54 (1.44, 1.64)**	n = 12,363 1.70 (1.47, 1.96)**
Lower respiratory tract infections, age 6 months	n = 5,915 2.22 (1.63, 3.03)**	n = 57,212 2.02 (1.62, 2.52)**	n = 142,576 2.38 (2.18, 2.60)	n = 48,075 2.38 (2.17, 2.60)**	n = 6,199 2.21 (1.64, 2.99)**
Lower respiratory tract infections, age 2 years	n = 12,700 3.34 (2.88, 3.86)**	n = 57,212 3.46 (3.50, 3.93)**	n = 142,576 3.24 (3.03, 3.46)	n = 44,844 3.20 (2.98, 3.42)**	n = 10,020 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 (FEV₁). 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 0.08 (0.02, 0.13)**	n = 138,978 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 -0.11 (-0.20, -0.03)**	n = 138,978 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 (FEV₁). Forced Vital Capacity (FVC), not applicable (NA).

Supplementary Figure S1. Flowchart of included cohorts and participants

