ERJ Express. Published on September 12, 2018 as doi: 10.1183/13993003.00504-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Does early-onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts

Zuelma A. Contreras, Zhanghua Chen, Theano Roumeliotaki, Isabella Annesi-Maesano, Nour Baïz, Andrea von Berg, Anna Bergström, Sarah Crozier, Liesbeth Duijts, Sandra Ekström, Esben Eller, Maria P. Fantini, Henrik Fomsgaard Kjaer, Francesco Forastiere, Beatrix Gerhard, Davide Gori, Margreet W. Harskamp-van Ginkel, Joachim Heinrich, Carmen Iñiguez, Hazel Inskip, Thomas Keil, Manolis Kogevinas, Susanne Lau, Irina Lehmann, Dieter Maier, Evelien R. van Meel, Monique Mommers, Mario Murcia, Daniela Porta, Henriëtte A Smit, Marie Standl, Nikos Stratakis, Jordi Sunyer, Carel Thijs, Maties Torrent, Tanja GM Vrijkotte, Alet H Wijga, Kiros Berhane, Frank Gilliland, Leda Chatzi

Please cite this article as: Contreras ZA, Chen Z, Roumeliotaki T, *et al*. Does early-onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.00504-2018).

Title: Does early-onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts

Authors:

Zuelma A Contreras PhD[1], Zhanghua Chen PhD[1], Theano Roumeliotaki MPH[2], Isabella Annesi-Maesano PhD[3], Nour Baïz PhD[3], Andrea von Berg PhD[4], Anna Bergström PhD[5,6], Sarah Crozier PhD[7], Liesbeth Duijts PhD[8,9,10], Sandra Ekström PhD[5], Esben Eller PhD[11], Maria P Fantini MD[12], Henrik Fomsgaard Kjaer PhD[11], Francesco Forastiere PhD[13], Beatrix Gerhard PhD[14], Davide Gori MD[12], Margreet W Harskamp-van Ginkel MD[15], Joachim Heinrich PhD[16,17], Carmen Iñiguez PhD[18,19,20], Hazel Inskip PhD[7,21], Thomas Keil MD[22], Manolis Kogevinas PhD[20,23-25], Susanne Lau MD[26], Irina Lehmann PhD[27], Dieter Maier PhD[14], Evelien R van Meel MD[8,9,28], Monique Mommers PhD[29], Mario Murcia MSc[19,20], Daniela Porta MSc[13], Henriëtte A Smit PhD[30], Marie Standl PhD[16], Nikos Stratakis PhD[2,31], Jordi Sunyer PhD[23], Carel Thijs PhD[29], Maties Torrent PhD[32], Tanja GM Vrijkotte PhD[15], Alet H Wijga PhD[33], Kiros Berhane PhD[1], Frank Gilliland PhD[1], Leda Chatzi PhD[1,2,31]

[1]Department of Preventive Medicine, University of Southern California, Los Angeles, CA, United States

[2]Department of Social Medicine, University of Crete, Heraklion, Greece

[3]Department of Epidemiology of Allergic and Respiratory Diseases, IPLESP, INSERM, UPMC, Medical School Saint-Antoine, Paris, France

[4]Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany

[5]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

[6]Center for Occupational and Environmental Medicine, Stockholm County Council,

Stockholm, Sweden

[7]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, United Kingdom

[8]Department of Pediatrics, Division of Respiratory Medicine and Allergology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

[9]Department of Epidemiology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

[10]Department of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

[11]Department of Dermatology and Allergy Center, Odense Research Centre for Anaphylaxis (ORCA), Odense, Denmark

[12]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

[13]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy

[14]Biomax Informatics AG, Planegg, Germany

[15]Department of Public Health, Amsterdam Public Health Research Institute, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

[16]Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[17]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Inner City Clinic, University Hospital of Munich (LMU), Munich, Germany

[18]Department of Statistics and Operational Research, University of Valencia, Valencia, Spain

[19]Epidemiology and Environmental Health Joint Research Unit, FISABIO-Universitat Jaume I-Universitat de València, Valencia, Spain

[20]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

[21]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton, Southampton, UK

[22]Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany

[23]ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

[24]Universitat Pompeu Fabra (UPF), Barcelona, Spain

[25]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[26]Department of Paediatric Pneumology & Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany

[27]Department of Environmental Immunology/Core Facility Studies, Helmholtz Centre for Environmental Research-UFZ, Leipzig, Germany

[28]The Generation R Study Group, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

[29]Department of Epidemiology, CAPHRI Care and Public Health Research Institute, Maastricht University Medical Centre+, Maastricht, Netherlands

[30]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands

[31]NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, Netherlands

[32]Ib- salut, Area de Salut de Menorca, Menorca, Spain

[33]Centre for Nutrition, Prevention and Health Services, National Institute of Public Health and the Environment, Bilthoven, Netherlands

Corresponding author:

Leda Chatzi, MD PhD

Department of Preventive Medicine,

University of Southern California,

2001 North Soto St. 230-07

Los Angeles, California 90032

Phone: (323) 442-5521

Email: chatzi@usc.edu

Abstract

The parallel epidemics of childhood asthma and obesity over the past few decades have spurred research into obesity as a risk factor for asthma. However, little is known regarding the role of asthma in obesity incidence. We examined whether early-onset asthma and related phenotypes are associated with the risk of developing obesity in childhood.

This study includes 21130 children born from 1990 to 2008 in Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, and United Kingdom**.** We followed non-obese children at 3-4 years of age for incident obesity up to 8 years of age. Physician-diagnosed asthma, wheezing, and allergic rhinitis were assessed up to 3-4 years of age.

Children with physician-diagnosed asthma had a higher risk for incident obesity than those without asthma (adjusted hazard ratio (aHR): 1.66, 95% CI: 1.18, 2.33). Children with active asthma (wheeze in the last 12 months and physician-diagnosed asthma), exhibited a higher risk for obesity (aHR: 1.98, 95% CI: 1.31, 3.00) than those without wheeze and asthma. Persistent wheezing was associated with increased risk for incident obesity compared to never wheezers (aHR: 1.51, 95% CI: 1.08, 2.09).

Early-onset asthma and wheezing may contribute to an increased risk of developing obesity in later childhood.

Introduction

Asthma and obesity are among the most important chronic childhood disorders, both having had a parallel increase in prevalence worldwide in recent decades [1]. The concomitant rise in these conditions has stimulated research into their potential relation yet the temporality between asthma and obesity development across the life course has not been well-established. Both disorders are thought to have their origins in early life further complicating the assessment of a causal relation between these conditions [2]. Although there is convincing evidence that childhood obesity increases the risk of asthma or asthma-like symptoms [3-6], there is limited evidence on whether early life asthma could trigger obesity onset.

Two US longitudinal studies examined the potential impact of asthma on obesity development in school-aged children. The first studied 2171 non-obese kindergarten and first-grade children with 10 years follow up, and showed that children with a diagnosis of asthma were at 51% increased risk of developing obesity compared to those without asthma [7]. The other examined the bidirectional association between asthma and obesity in a sample of 6452 children from kindergarten to middle school and observed that asthma was associated with increased risk for subsequent obesity onset, but overweight or obesity was not associated with subsequent asthma onset [8]. A pooled study of eight European birth cohorts found that children with rapid BMI growth in the first 2 years had a higher risk of incident asthma up to age 6 years [6], but no European studies have examined the impact of early life asthma on incident obesity.

If most cases of childhood obesity have their origins in the preschool years, it is plausible to surmise that the asthma-obesity association may also be established in this critical time window, yet no studies to date have evaluated the impact of early-onset asthma on obesity risk in childhood. Importantly, results from previous studies need to be replicated across different,

population-based longitudinal studies, examining not only asthma but associated phenotypes. In this study, we sought to leverage the rich data on early life asthma and asthma-related comorbidities from sixteen European birth cohorts to conduct a pooled analysis on the potential association between early-onset asthma and related phenotypes, and subsequent obesity risk.

Methods

Study population

Sixteen European birth cohorts from the Mechanisms of the Development of Allergy (MeDALL) consortium and the Child Cohort Research Strategy for Europe (CHICOS) FP7 Collaborative research grants contributed data on asthma and related phenotypes at 3-4 years of age or younger and anthropometric information at 3-4 years of age and at any point up to 8 years of age. The participating cohorts included: ABCD [9], BAMSE [10], DARC [11], EDEN [12], Generation R [13], GINIplus [14], INMA Menorca and Valencia [15], KOALA [16], LISAplus [14], MAS [17], PIAMA [18], RHEA [19], ROBBIC Bologna and Roma [20], and SWS [21]. The recruitment period of these cohorts' span births from 1990 to 2008. Given the small sample sizes and the similarities in data collection of the ROBBIC Bologna and ROBBIC Roma cohorts, we pooled the data for these two cohorts together. All cohorts obtained informed consent from parents or legal guardians and ethical approval from the local authorized institutional review boards. A data transfer agreement document was signed by each study and anonymized data sets were transferred to the University of Crete for analysis. There were 27,117 children who had available information on our exposures or outcomes. We excluded 5,420 children because they did not have information for at least one asthma or asthma-related phenotype and BMI information for at least 2 follow-ups. An additional 567 children were excluded because they were obese at baseline, leaving us with 21,130 children for our analyses. Detailed information on

the participating cohorts is shown in Table 1. We also provide information comparing the maternal and child characteristics of the children excluded from our analyses due to missing data to those included in our study (Table E1).

Asthma and related phenotypes

Information on asthma, wheeze, and allergic rhinitis in the participating cohorts was obtained from questionnaires that were adapted from the International Study on Asthma and Allergy in childhood (ISAAC) and administered to parents [22]. Cohort-specific information on data collection for asthma and related phenotypes is shown in Table E2. Presence of asthma at baseline (yes/no) was determined by report of physician diagnosis of asthma at any point up to 3-4 years of age. Wheeze (yes/no) at baseline was based on report of wheezing or whistling in the chest in the past 12 months at 3-4 years of age. Early wheeze (yes/no) was based on report of wheezing or whistling in the chest in the past 12 months assessed at any time in infancy (0-2 years of age). Allergic rhinitis (yes/no) at baseline was based on report of rhinitis (sneezing, or a runny or blocked nose, when not a cold or flu) in the past 12 months at 3-4 years of age. Asthma history was based on responses to the baseline asthma and wheeze questions and categorized as: 1) active asthma (have baseline asthma and baseline wheeze), 2) have baseline asthma, but no baseline wheeze, 3) have no baseline asthma, but have baseline wheeze, and 4) have no baseline asthma and no baseline wheeze (reference category). Based on previous studies, we defined distinct wheezing phenotypes throughout childhood [23, 24]. Wheezing history was constructed using responses to the baseline wheeze and early wheeze questions: persistent wheezing (have early wheeze and baseline wheeze), late-onset wheezing (have no early wheeze, but have baseline wheeze), transient wheezing (have early wheeze, but no baseline wheeze), and never wheezing (have no early wheeze and no baseline wheeze) (reference category). Since we lacked

information on IgE sensitization, we created a measure of asthma and allergic rhinitis comorbidity based on responses to the baseline asthma and allergic rhinitis questions: have baseline asthma and allergic rhinitis, have baseline asthma and no allergic rhinitis, and have no baseline asthma and no allergic rhinitis. We also created a combined measure of the joint impact of asthma and medication use categorized as: yes asthma/yes medication use, yes asthma/no medication use, no asthma/yes medication use, no asthma/no medication use (reference category).

Obesity

Cohorts provided weight and height information based on clinical exams, health records, or parental-reported questionnaires at 3-4 years of age and at least one other time point between 5-8 years of age. BMI was calculated as weight (kg) divided by height (m) squared. Since our primary outcome was incident obesity we restricted the analysis to normal weight or overweight children at baseline. Obese status was defined according to the 2012 Cole-International Obesity Task Force age and sex-specific cutoffs [25]. We also used the 2007 World Health Organization cutoffs for obesity in sensitivity analyses [26, 27].

Covariate assessments

Potential covariates were defined as similarly as possible among the cohorts. Information on maternal smoking during pregnancy (yes/no), birthweight (grams), and child sex (male or female) was collected through interviews or self-administered questionnaires, ad hoc measurements, birth records, or medical registries. Information on maternal education (cohort-specific definitions of low, medium or high), any breastfeeding (months), parity (primiparous or multiparous), any dampness or mold in the home at 0-4 years (yes/no), passive smoke (childhood exposure to smoking by others in the household at 0-4 years, yes/no), medication for asthma or

breathing problems in the last 12 months at 3-4 years of age (yes/no), parental history of asthma, and pets in the home during infancy (0-2 years) (yes/no) was obtained via interviews or self-administered questionnaires. Birthweight was subsequently categorized as low (<2500 g), normal (2500-3999 g), high (4000+ g) and breastfeeding was categorized as <3 months and ≥3 months [28, 29]. Physical activity was available for only 3 out of 16 cohorts, thus we were not able to include it as a potential covariate. More detailed information on the type of medication use was available for four cohorts (BAMSE, DARC, PIAMA, ROBBIC) and defined as use of inhaled corticosteroids (ICS) ever (yes/no) at 3-4 years of age.

Statistical analyses

Our main analysis was a pooled analysis in which we combined the data from sixteen different cohorts. To account for potential differences between cohorts, we introduced a random effect for cohort or a fixed effect (ie. indicator variable) for cohort. Since we observed no differences between estimates derived from random effects and fixed effects models, we present results from fixed effects models as they are more likely to provide unbiased estimates in large samples [30]. We estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the associations of childhood asthma and related phenotypes at baseline with obesity incidence during follow-up using Cox proportional hazards models with a sex-specific baseline hazard. We used age at study visit as the time scale in our analysis and onset of obesity was defined as happening when the child first become obese during follow-up at the midpoint of the follow-up period between the visit when they were not obese and the subsequent visit when they were assessed as obese. Children who did not become obese during follow-up were censored at the end of study follow-up or when lost to follow-up. Selection of confounders for adjustment was based on directed acyclic graphs (DAGs), informed by previous knowledge and constructed

using DAGitty version 3.0 (Figure E1) [31]. The confounders included in final models were age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, and birthweight. All cohorts had information available for these confounders, with the exception of maternal education and smoking during pregnancy for the MAS cohort and parity information for the INMA Menorca cohort. Children with missing covariate information were included in the analysis using the missing indicator method, in which missing values were used as an additional group in categorical variables. Though dampness or mold in the home and pets in the home during infancy were potential confounders based on our DAG, further adjustment for these covariates did not substantially change effect estimates, and thus, these variables were not included in final models. Since medication use may be a potential mediator of the asthma and obesity relation we explored its role further by conducting several analyses: 1) we examined the impact of medication use on obesity incidence without adjusting for asthma status, 2) we assessed the impact of asthma and medication use on incident obesity when mutually adjusting for both in the same model 3) we modeled the joint impact of asthma and medication use on obesity incidence using a combined measure of asthma and medication use. We confirmed that the proportional hazards assumption was met using Schoenfeld residuals.

We performed several sensitivity analyses. First, we adjusted for overweight at baseline to determine whether our results were disproportionately impacted by children who were overweight at baseline. Second, we restricted our sample to those who were normal weight at baseline, and conducted separate analyses examining the incidence of overweight or obesity, and obesity only to further assess the impact of the overweight at baseline. Third, we adjusted for baseline BMI as a continuous variable to assess whether initial BMI status impacts our results. Fourth, we excluded children who developed asthma during follow-up to assess whether our

results were impacted by new asthma cases. Fifth, we assessed whether effects vary according to factors (sex, birthweight, parental asthma, maternal education, asthma medication, and breastfeeding (never, <6 months, 6+ months) that may make certain groups more vulnerable by conducting stratified analyses and introducing interaction terms [32]. Sixth, we repeated our analysis using the WHO cutoffs for obesity to compare our results using an alternative definition of obesity. Seventh, we assessed whether adjustment for height at the end of follow-up changed our results to tease apart whether changes in weight are mainly driving the association. Eighth, we restricted our definition of obesity to children who were obese for at least two visits. Lastly, we explored whether estimates differed in complete-case analyses.

Further, we performed an individual participant meta-analysis as a supplementary analysis to assess whether our results were consistent with those from our pooled analyses. We used Cox proportional hazards models with a sex-specific baseline hazard and the aforementioned set of confounders to estimate cohort-specific aHRs and 95% CIs for the associations of baseline asthma and other related phenotypes with obesity incidence during follow-up. We combined cohort-specific estimates using random effects meta-analysis in which the weight assigned to each study was based on both the within- and between-study variability. We examined heterogeneity between cohort-specific estimates with the I^2 statistic and the X^2 test from Cochran's Q. We also tested the robustness of the results by repeating the meta-analyses and excluding one cohort at a time. We also explored potential heterogeneity by region of participating cohorts, based on the United Nations' classification (Southern Europe, Western Europe, Northern Europe), by conducting meta-regression analyses.

All analyses were performed using Stata 14.2 software (StataCorp LLC, College Station, TX, USA).

Results

The analysis included 21130 children at cohort entry with a mean age at baseline of 4.1 ±0.6 years (Table 1). Table E1 displays the maternal and child characteristics of our total study population as compared to those that were excluded from our study due to missing data. Overall, we did not observe any substantial differences in characteristics between these groups except for a slightly higher prevalence of low maternal education (60.2% vs. 55.0) and shorter breastfeeding duration (63.1% vs 67.7%) in excluded children. Overall, the prevalence of physician-diagnosed asthma at baseline was 6.0%, while the prevalence of baseline wheeze and early wheeze was 12.5% and 18.1%, respectively (Table 2). About 13.7% of children had allergic rhinitis. The prevalence of asthma and related phenotypes for each cohort at baseline is shown in Table E3. The number of follow-ups and age at end of follow-up varied by cohort with an overall mean age at endpoint of 7.1 ±1.2 years and 3.2 visits on average (Table 1). During follow-up, 483 (2.3%) children developed obesity. Cohort-specific prevalences of baseline obesity and incident obesity are shown in Table E4. Baseline maternal and child characteristics by cohort are presented in Table E5.

Table 2 displays the pooled analysis results for the association between asthma and related phenotypes at baseline and incident obesity at follow-up. Children with physician-diagnosed asthma had a 66% higher risk of incident obesity than those without an asthma diagnosis (adjusted HR (aHR): 1.66, 95% CI: 1.18, 2.33, Table 2). Children with wheeze at baseline had an increased risk of obesity compared to those with no baseline wheeze (aHR: 1.29, 95% CI: 1.00, 1.67). Children with active asthma, exhibited an even greater risk for developing obesity (aHR: 1.98, 95% CI: 1.31, 3.00) than those without asthma and wheeze. Wheeze in infancy had a similar impact on incident obesity as baseline wheeze (aHR: 1.22, 95% CI: 0.99,

1.52). However, for wheezing history, compared to children who never wheezed, obesity risk was more pronounced for children with persistent wheezing (aHR: 1.51, 95% CI: 1.08, 2.09) than late-onset (aHR: 1.12, 95% CI: 0.77, 1.63) or transient wheezing (aHR: 1.06, 95% CI: 0.81, 1.39). Allergic rhinitis was positively associated with obesity onset (aHR: 1.29, 95% CI: 0.98, 1.68). Children with asthma and no allergic rhinitis had a higher risk of incident obesity than those without asthma (aHR: 2.04, 95% CI: 1.32, 3.13).

Table 3 shows the results for the joint associations of asthma and medication use with incident obesity. Medication use for asthma or breathing difficulties increased the risk of incident obesity (aHR=1.37, 95% CI: 1.04, 1.80). When adjusting for asthma status, the impact of medication use on obesity was attenuated slightly and no longer statistically significant (aHR=1.23, 95% CI: 0.91, 1.66). In contrast, adjustment for medication use did not change the significant positive association between asthma and incident obesity (aHR=1.57, 95% CI: 1.04, 2.37). When assessing the combined impact of asthma and medication use, we found that compared to children with no asthma and no medication use, asthmatic children taking medication had a higher risk of incident obesity (aHR=1.91, 95% CI: 1.25, 2.92) than asthmatic children not taking medication (aHR=1.65, 95% CI: 0.73, 3.73) and non-asthmatic children taking medication (aHR=1.24, 95% CI: 0.90, 1.69). ICS use was positively associated with incident obesity with (aHR=1.42, 95% CI: 0.82, 2.26) and without adjustment for asthma (aHR=1.45, 95% CI: 0.97, 2.18).

Figure 1 presents the cohort-specific estimates and combined estimates from the random effects meta-analysis for the association between asthma and related phenotypes and incident obesity. Cohort-specific estimates were not estimable for INMA Menorca and LISA for physician-diagnosed asthma, and for DARC for allergic rhinitis due to zero exposed incident

obesity cases within the respective cohorts. The combined effect estimates were consistent with those of our pooled analyses, albeit stronger in magnitude. There was no evidence of significant heterogeneity between cohorts (I^2=0, p-value >0.48) and by geographical region of cohorts. The results remained similar when omitting one cohort at a time (Table E6).

When adjusting for overweight at baseline in our pooled analysis, the associations we observed were attenuated slightly, but remained significant (Table E7). After restricting our sample to the normal weight at baseline, observed associations were attenuated and no longer statistically significant, but still indicative of a positive association for incident obesity (Table E8). After adjustment for baseline BMI, our observed associations were similarly attenuated and non-significant, albeit still positively associated with incident obesity (Table E9). When excluding new asthma cases during follow-up (n=448), the association between asthma and incident obesity did not change (aHR=1.65, 95% CI: 1.17, 2.32). There was no evidence of interaction or differences in stratified analyses between asthma, and sex, birthweight, parental asthma, maternal education, asthma medication, and breastfeeding. Adjustment for child's height at the end of follow-up did not change the relation between asthma and incident obesity (aHR: 1.64, 95% CI: 1.17, 2.31). We observed similar results when using the WHO definition of obesity and slightly attenuated results when we defined obesity as remaining obese for at least two visits (data not shown). No differences in our results were observed in complete-case analyses (data not shown).

Discussion

We found that early-onset asthma and wheezing were associated with a higher incidence of childhood obesity. The evidence for allergic rhinitis was less strong, but still indicative of a higher risk for obesity. This is the only longitudinal, multicenter study to date that has examined

the impact of early-onset asthma on obesity development in children. The inclusion of birth cohorts from numerous European countries and the absence of heterogeneity between our cohort-specific effect estimates supports the robustness and generalizability of our results.

Although many studies have assessed the effect of childhood obesity on asthma development, the temporal order between these conditions remains unclear, largely due to the scarcity of studies examining whether asthma can affect obesity onset. We were able to assess the impact of early life diagnosis of asthma on subsequent childhood obesity risk. Our study corroborates the findings of two previous US longitudinal studies that observed an increased risk of obesity in school-aged children with asthma [7, 8]. The diagnosis of asthma in young children is difficult, and physicians may be hesitant to make the diagnosis at an early age, thus wheezing in childhood is often used as an indicator of future asthma development. Although this measure lacks specificity, our finding that the risk of obesity is highest in children with persistent wheeze is important because children who have persistent wheeze are more likely to develop early-onset asthma than those with transient or late-onset wheeze[24, 33]. Additionally, our results for active asthma suggest that asthmatic children who are currently experiencing wheezing symptoms are at highest risk. The only previous study to have assessed the impact of active asthma on obesity development found similar results [7].

Recent studies suggest that there are at least two distinct asthma phenotypes associated with obesity, early-onset asthma complicated by obesity and late-onset asthma arising because of obesity. Early-onset asthma is characterized by a higher prevalence of allergic disease and Th2 inflammation, whereas late-onset asthma has a lower prevalence of allergic disease and is less related to Th2 inflammation [34]. It is possible that in children with the severe, allergic asthma phenotype, asthma itself may lead to obesity, though this hypothesis has not been well-explored

in studies to date [2, 35]. However, in our study we found a stronger effect estimate for asthmatics without allergic rhinitis than those with rhinitis. Although the presence of allergic rhinitis is strongly associated with allergic asthma, these results are inconclusive as they are not based on atopy measures (ie. specific IgE measures). Further studies are needed in this direction to differentiate childhood obesity risk between IgE sensitized and unsensitized individuals, and those with allergic asthma and non-allergic asthma.

The association between asthma and obesity may also be explained by common biological pathways that promote the development of these conditions in early life. A recent study in mice found that the chitinase 3-like protein 1 (Chi3l1) plays a key role in white adipose tissue accumulation and lung Th2 inflammation. A high fat diet and aeroallergen challenge increased the expression of white adipose tissue and pulmonary Chi3l1, suggesting that a high-fat diet contributes to visceral adiposity and asthma by stimulating the Chi3l1 pathway, and that asthma itself can increase obesity [36]. Other hypothesized pathways underlying asthma and obesity include systemic inflammation, adipokine dysregulation, shared genetics or epigenetic changes, and the gut microbiome, however the evidence for these pathways is limited [34, 37].

Common lifestyle factors related to both asthma and obesity may partially explain their association. For instance, studies have shown that asthmatic children have lower physical activity levels and poorer sleep which are also risk factors for obesity [38]. We lacked information on child's physical activity and sleep, thus, we could not test this hypothesis in our study. Additionally, given the early life origin of these disorders, shared *in utero* exposures may also account for the relation we observe, for instance, prenatal diet, maternal obesity and early infant growth have been associated with increased risk of both disorders [37, 39].

Weight gain due to medication use for asthma has also been posited as a potential mechanism linking asthma and obesity. Two prospective studies found greater increases in BMI in asthmatic children on higher doses of ICS compared to those on lower doses [40, 41]. Medication use itself may increase obesity risk or it may be that children with more severe asthma who are also on higher doses of steroids have reduced activity levels or other factors that predispose them to obesity. In our study, we lacked detailed information on medication dosage and asthma severity. However, we observed the strongest risk of obesity for asthma with medication use than asthma without medication use or medication use in the absence of asthma. When we mutually adjusted for asthma and medication, the positive association between medication use and incident obesity was attenuated, but the association between asthma and obesity did not change markedly. For the four cohorts with available data, inhaled steroid use was positively associated with obesity even after adjustment for asthma. Thus, our results suggest that the joint presence of asthma and medication use has the greatest impact on obesity risk and that the association between asthma and obesity cannot be fully explained by medication use. In addition, our results for the impact of medication use on obesity, though inconclusive, suggest that it can increase the risk of obesity independently of asthma status.

Strengths of our study include the population-based longitudinal design and the inclusion of individual participant data from several European birth cohorts with different background characteristic and behaviors. Other strengths include the large sample size of the study and the standardized exposure definitions and harmonized covariate information. Given the discrepancy in the literature on the definition of childhood obesity [42], we tested three definitions and found comparable results, suggesting that our results are not subject to different definition criteria and represent a true onset of obesity.

While novel and large in scale, our study has several limitations. Some cohorts did not have data available for all confounding variables and the use of an extra category for missing confounder information could have introduced residual confounding. However, when we performed complete case analyses, we observed comparable results. Although we controlled for breastfeeding, there is the possibility of residual confounding by the mother or child's early life dietary patterns and energy intake [37]. We may also have uncontrolled confounding due to maternal BMI, since studies suggest that pre-pregnancy obesity may increase the risk of childhood asthma, but our study lacks data for adjustment for maternal obesity status [43]. When we excluded overweight children from the baseline group, or when we adjusted for baseline BMI, the association between asthma and obesity was attenuated but results were in the same direction, possibly due to the few years of follow-up and low obesity incidence in our study. Therefore, based on our results we cannot exclude the possibility of reverse causality, however in analyses in which we adjusted for overweight at baseline, we still observed significantly elevated effect estimates. We acknowledge that there are substantial variations in the prevalence of asthma and wheezing by country because asthma may be more readily diagnosed in some countries and underdiagnosed in others [44]. In addition, the prevalence of obesity varies by country, which is partly explained by differences in diet, physical activity and sedentary behaviors [45, 46]. However, the absence of heterogeneity in the study-specific estimates suggests that any potential misclassification of exposure is not a major source of bias. The children excluded from our study due to missing data were more likely to have lower SES and shorter breastfeeding duration, which are both thought to be risk factors for asthma and obesity. Since both factors are positively associated with our exposure and outcome, selection bias resulting from their exclusion would likely negatively bias our results. Given the magnitude of

the association between asthma and incident obesity we observed, it is unlikely that this potential source of bias is a major threat to the validity of our study. Asthma and related comorbidities were assessed by parental-report which could introduce misclassification, but questionnaires were well-validated based on the ISAAC study [22]. We also had less power in our analyses in which we combined the presence of multiple asthma and asthma-related conditions since not all children had complete data on these conditions. Since anthropometric measures were based on a mix of parental-report and clinical assessments information, there is the potential for misclassification of obesity in our study. However, we do not expect any misclassification reported weight information to be informed by asthma status, and thus the resulting bias would be towards the null.

This large, multi-center longitudinal study suggests that early-onset asthma and wheezing may contribute to an increased incidence of developing obesity in later childhood. Our findings lend support for further investigation of the factors driving the increased risk of obesity in asthmatic children to better tailor future obesity prevention efforts.

Author contributions:

Contreras, Roumeliotaki, and Chatzi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chatzi

Acquisition of data: All authors

Statistical analysis: Contreras, Roumeliotaki

Interpretation of data: All authors

Drafting of the manuscript: Contreras, Chatzi

Critical revision of the manuscript for important intellectual content: All authors

Study supervision: Chatzi

Conflicts of interest: None

Sources of support:

This work was partially supported by the Southern California Environmental Health Sciences Center (grant # P30ES007048) funded by the National Institute of Environmental Health Sciences [PI Gilliland]. Dr.Contreras was supported by a grant from the NIH T32 ES013678.

MEDALL and CHICOS Projects: The research leading to these results has received funding from the European Community's Seventh Framework Program (Health –F2-grant agreements No. 261357 and 241604).

Per cohort

ABCD: Data of the Amsterdam Born Children and their Development cohort study used in this research was in part supported by funds from the Netherlands Organisation for Health Research and Development (ZonMw 40–00812-98–11010). The study sponsors had no role in study design, data analysis, interpretation of data, or writing of this report.

BAMSE: We acknowledge all funding sources: The Swedish Research Council, The Swedish Heart and Lung Foundation, The Swedish Research Council for Working Life and Social Welfare, the Swedish Asthma and Allergy Association Research Foundation, The Swedish Research Council Formas, Stockholm County Council, and the European Commission's Seventh Framework 29 Program MeDALL under grant agreement No. 261357. We thank all the children and their parents for participating in the BAMSE cohort and the nurses and other staff members working in the BAMSE project.

EDEN: We acknowledge all the funding sources for the EDEN study: 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 programmes (FP7/2007-2013, HELIX, ESCAPE, ENRIECO, Medall projects), Diabetes National Research Program (through a collaboration with the French Association of Diabetic Patients (AFD)), French Agency for Environmental Health Safety (now ANSES), Mutuelle Générale de l'Education Nationale a complementary health insurance (MGEN), French national agency for food security, French speaking association for the study of diabetes and metabolism (ALFEDIAM).

We acknowledge the commitment of the EDEN mother-child cohort study group: I. Annesi-Maesano, JY. 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.

The Generation R Study: The Generation R study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), the Ministry of Health, Welfare and Sport and the Ministry of Youth and Families. The project received funding from the

European Union's Horizon 2020 research and innovation programme (LIFECYCLE project, grant agreement no 733206; 2016), the European Research Council (ERC-2014-CoG-648916) and 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 researchers are independent from the funders. The study sponsors had no role in study design, data analysis, interpretation of data, or writing of this report.

INMA: Data used for this research was provided by the INMA- Environment and Childhood Project (www.proyectoinma.org). This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176 and CB06/02/0041), Spanish Ministry of Health (FIS-PIO41436, PI06/0867, PI081151, and FIS-FEDER 03/1615, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314 and 09/02647), Generalitat de Catalunya-CIRIT 1999SGR00241, the Conselleria de Sanitat Generalitat Valenciana, Department of Health of the Basque Government (2005111093 and 2009111069), the Provincial Government of Gipuzkoa (DFG06/004 and DFG08/001).

KOALA: The collection of the data from the KOALA Birth Cohort Study used in this analysis was financially supported by Friesland Foods (now FrieslandCampina), Netherlands Asthma Foundation (grant numbers 3.2.07.022 and 3.2.03.48), Netherlands Heart Foundation (grant number 2014 T037, the Netherlands Organization for Health Research and Development (ZonMw Prevention Program number 1.210-00-090), Triodos Foundation, Phoenix Foundation, Raphaël Foundation, Iona Foundation, Foundation for the Advancement of Heilpedagogie, all in the Netherlands.

MAS: The MAS birth cohort was funded by grants from the German Federal Ministry of Education and Research (BMBF; reference numbers 07015633, 07 ALE 27, 01EE9405/5, 01EE9406) and the German Research Foundation (DFG; reference number KE 1462/2-1).

PIAMA: The PIAMA study has been funded by The Netherlands Organisation for Health Research and Development; The Netherlands Organisation 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.

RHEA: The Rhea project was financially supported by European projects (EU FP6-003-Food-3-NewGeneris - Contract No16320, EU FP6 STREP Hiwate - Contract No36224, EU FP7 ENV.2007.1.2.2.2. Project No 211250 Escape, EU FP7-2008-ENV-1.2.1.4 Envirogenomarkers Contract No226756, EU FP7-HEALTH-2009-single stage CHICOS Contract No241604, EU FP7 ENV.2008.1.2.1.6. Proposal No 226285 ENRIECO, EU-FP7, Proposal No 264357 MeDALL, EU- FP7- HEALTH-2012 Proposal No 308333 HELIX), and the Greek Ministry of Health (Program of Prevention of obesity and neurodevelopmental disorders in preschool children, in Heraklion district, Crete, Greece: 2011-2014; "Rhea Plus": Prevention Program of Environmental Risk Factors for Reproductive Health, and Child Health: 2012-2015).

ROBBIC: Data of the Rome cohort was in part supported by funds from the Italian Ministry of Health (Programma speciale ex art. 12, comma 2, lettera b) del D. Lgs. 502/92**,** 2001, 2003). We thank all the fields workers and the families for their contribution to the study.

SWS: We thank the members of the Southampton Women's Survey Study group and the many participants in the SWS for their contribution to the study. The Southampton

Women’s Survey is supported by grants from the Medical Research Council, British Heart Foundation, Food Standards Agency, British Lung Foundation, Arthritis Research UK, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, and the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement n°289346.

References

1. Eder W, Ege MJ, von Mutius E. The Asthma Epidemic. *N Engl J Med* 2006: 355(21): 2226-2235.

2. Martinez FD, Guerra S. Early Origins of Asthma: Role of Microbial Dysbiosis and Metabolic Dysfunction. *Am J Respir Crit Care Med* 2017: rccm.201706-201091PP.

3. Chen Y-C, Liou T-H, Chen P-C, Chiang B-L, Yang Y-H, Fan H-Y, Lee YL. Growth trajectories and asthma/rhinitis in children: a longitudinal study in Taiwan. *Eur Respir J* 2017: 49(1): 1600741-1600741.

4. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, Avol E, Peters JM. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol* 2003: 158(5): 406-415.

5. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-Mass Index as a Predictor of Incident Asthma in a Prospective Cohort of Children. *Pediatr Pulmonol* 2003: 36(6): 514-521.

6. Rzehak P, Wijga AH, Keil T, Eller E, Bindslev-Jensen C, Smit HA, Weyler J, Dom S, Sunyer J, Mendez M, Torrent M, Vall O, Bauer CP, Berdel D, Schaaf B, Chen CM, Bergström A, Fantini MP, Mommers M, Wahn U, Lau S, Heinrich J. Body mass index trajectory classes and incident asthma in childhood: Results from 8 European Birth Cohorts - A Global Allergy and Asthma European Network initiative. *J Allergy Clin Immunol* 2013: 131(6).

7. Chen Z, Salam MT, Alderete TL, Habre R, Bastain TM, Berhane K, Gilliland FD. Effects of childhood asthma on the development of obesity among school-aged children. *Am J Respir Crit Care Med* 2017: 195(9): 1181-1188.

8. Green TL. Examining the temporal relationships between childhood obesity and asthma. *Econ Hum Biol* 2014: 14(1): 92-102.

9. van Eijsden M, Vrijkotte TG, Gemke RJ, van der Wal MF. Cohort profile: the Amsterdam Born Children and their Development (ABCD) study. *Int J Epidemiol* 2011: 40(5): 1176-1186.

10. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE Project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002: 13(s15): 11-13.

11. Johnke H, Vach W, Norberg LA, Bindslev-Jensen C, Host A, Andersen KE. A comparison between criteria for diagnosing atopic eczema in infants. *Br J Dermatol* 2005: 153(2): 352-358.

12. Heude B, Forhan A, Slama R, Douhaud L, Bedel S, Saurel-Cubizolles MJ, Hankard R, Thiebaugeorges O, De Agostini M, Annesi-Maesano I, Kaminski M, Charles MA, group Em-ccs. Cohort Profile: The EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. *Int J Epidemiol* 2016: 45(2): 353-363.

13. Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC, Hofman A. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010: 25(11): 823-841.

14. Heinrich J, Bruske I, Schnappinger M, Standl M, Flexeder C, Thiering E, Tischer C, Tiesler CM, Kohlbock G, Wenig CM, Bauer CP, Schaaf B, von Berg A, Berdel D, Kramer U, Cramer C, Lehmann I, Herbarth O, Behrendt H, Ring J, Kuhnisch J, Koletzko S. [Two German Birth Cohorts: GINIplus and LISAplus]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2012: 55(6-7): 864-874.

15. Guxens M, Ballester F, Espada M, Fernandez MF, Grimalt JO, Ibarluzea J, Olea N, Rebagliato M, Tardon A, Torrent M, Vioque J, Vrijheid M, Sunyer J, Project I. Cohort Profile:

the INMA--INfancia y Medio Ambiente--(Environment and Childhood) Project. *Int J Epidemiol* 2012: 41(4): 930-940.

16. Kummeling I, Thijs C, Penders J, Snijders BE, Stelma F, Reimerink J, Koopmans M, Dagnelie PC, Huber M, Jansen MC, de Bie R, van den Brandt PA. Etiology of atopy in infancy: the KOALA Birth Cohort Study. *Pediatr Allergy Immunol* 2005: 16(8): 679-684.

17. Nickel R, Niggemann B, Grüber C, Kulig M, Wahn U, Lau S. How should a birth cohort study be organised? Experience from the German MAS cohort study. *Paediatr Respir Rev* 2002: 3(3): 169-176.

18. Wijga AH, Kerkhof M, Gehring U, de Jongste JC, Postma DS, Aalberse RC, Wolse AP, Koppelman GH, van Rossem L, Oldenwening M, Brunekreef B, Smit HA. Cohort profile: the prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol* 2014: 43(2): 527-535.

19. Chatzi L, Leventakou V, Vafeiadi M, Koutra K, Roumeliotaki T, Chalkiadaki G, Karachaliou M, Daraki V, Kyriklaki A, Kampouri M, Fthenou E, Sarri K, Vassilaki M, Fasoulaki M, Bitsios P, Koutis A, Stephanou EG, Kogevinas M. Cohort Profile: The Mother-Child Cohort in Crete, Greece (Rhea Study). *Int J Epidemiol* 2017: 46(5): 1392-1393k.

20. Porta D, Fantini M. Prospective cohort studies of newborns in Italy to evaluate the role of environmental and genetic characteristics on common childhood disorders. *Ital J Pediatr* 2006: 32(6): 350.

21. Inskip HM, Godfrey KM, Robinson SM, Law CM, Barker DJ, Cooper C, Group SWSS. Cohort profile: The Southampton Women's Survey. *Int J Epidemiol* 2006: 35(1): 42-48.

22. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, Strachan D, Weiland SK, Williams HC. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. *Eur Respir J* 1995: 8(3): 483-491.

23. Deliu M, Belgrave D, Sperrin M, Buchan I, Custovic A. Asthma phenotypes in childhood. *Expert Rev Clin Immunol* 2017: 13(7): 705-713.

24. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and Wheezing in the First Six Years of Life. *N Engl J Med* 1995: 332(3): 133-138.

25. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes* 2012: 7(4): 284-294.

26. De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bulletin of the World Health Organisation* 2007: 85(10): 812-819.

27. group WMgrs. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr* 2006: Suppl 450: 76-85.

28. Berner A, Bornehag C. Breastfeeding less than three months increases the risk for airway and rhinitis symptoms in children. *J Allergy Clin Immunol* 2004: 113(2): S274-S275.

29. United Nations Children's F, World Health O. Low Birthweight: Country, regional and global estimates, 2004.

30. Clark TS, Linzer DA. Should I Use Fixed or Random Effects? *Political Science Research and Methods* 2015: 3(02): 399-408.

31. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology (Cambridge, Mass)* 2011: 22(5): 745-745.

32. Subbarao P, Mandhane PJ, Sears MR. Asthma: Epidemiology, etiology and risk factors. *CMAJ* 2009: 181(9).

33. Ly NP, Gold DR, Weiss ST, Celedón JC. Recurrent wheeze in early childhood and asthma among children at risk for atopy. *Pediatrics* 2006: 117(6): e1132-e1138.

34. Dixon AE, Poynter ME. Mechanisms of asthma in obesity pleiotropic aspects of obesity produce distinct asthma phenotypes. *Am J Respir Cell Mol Biol* 2016: 54(5): 601-608.

35. Holguin F. Obesity as a risk factor for increased asthma severity and allergic inflammation; cause or effect? *Clin Exp Allergy* 2012: 42(5): 612-613.

36. Ahangari F, Sood A, Ma B, Takyar S, Schuyler M, Qualls C, Dela Cruz CS, Chupp GL, Lee CG, Elias JA. Chitinase 3-like-1 regulates both visceral fat accumulation and asthma-like Th2 inflammation. *Am J Respir Crit Care Med* 2015: 191(7): 746-757.

37. Litonjua AA, Gold DR. Asthma and obesity: Common early-life influences in the inception of disease. *J Allergy Clin Immunol* 2008: 121(5): 1075-1084.

38. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005: 115(5): 897-909; quiz 910.

39. Duijts L. Growing large and fast: is infant growth relevant for the early origins of childhood asthma? *Thorax* 2016: 71(12): 1071-1072.

40. Jani M, Ogston S, Mukhopadhyay S. Annual increase in body mass index in children with asthma on higher doses of inhaled steroids. *J Pediatr* 2005: 147(4): 549-551.

41. Han J, Nguyen J, Kim Y, Geng B, Romanowski G, Alejandro L, Proudfoot J, Xu R, Leibel S. Effect of inhaled corticosteroid use on weight (BMI) in pediatric patients with moderate-severe asthma. *J Asthma* 2018: 1-7.

42. Monasta L, Lobstein T, Cole TJ, Vignerová J, Cattaneo A. Defining overweight and obesity in pre-school children: IOTF reference or WHO standard? *Obes Rev* 2011: 12(4): 295-300.

43. Zugna D, Galassi C, Annesi-Maesano I, Baiz N, Barros H, Basterrechea M, Correia S, Duijts L, Esplugues A, Fantini MP, Forastiere F, Gascon M, Gori D, Inskip H, Larsen PS, Mommers M, Nybo Andersen AM, Penders J, Petersen MS, Pike K, Porta D, Sonnenschein-van der Voort A, Steuerwald U, Sunyer J, Torrent M, Vrijheid M, Richiardi L, Rusconi F. Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. *Int J Epidemiol* 2015: 44(1): 199-208.

44. Uphoff EP, Bird PK, Antó JM, Basterrechea M, von Berg A, Bergström A, Bousquet J, Chatzi L, Fantini M, Ferrero A, Gehring U, Gori D, Heinrich J, Keil T, Kull I, Lau S, Maier D, Momas I, Narduzzi S, Porta D, Ranciere F, Roumeliotaki T, Schikowski T, Smit HA, Standl M, Sunyer J, Wright J. Variations in the prevalence of childhood asthma and wheeze in MeDALL cohorts in Europe. *ERJ Open Research* 2017: 3(3): 00150-02016.

45. Janssen I, Katzmarzyk PT, Boyce WF, Vereecken C, Mulvihill C, Roberts C, Currie C, Pickett W, Health Behaviour in School-Aged Children Obesity Working G. Comparison of overweight and obesity prevalence in school-aged youth from 34 countries and their relationships with physical activity and dietary patterns. *Obes Rev* 2005: 6(2): 123-132.

46. World Health Organization Regional Office for Europe. Childhood Obesity Surveillance Initiative Factsheet. Highlights 2015-2017. 2018 [cited; Available from: http://www.euro.who.int/__data/assets/pdf_file/0006/372426/wh14-cosi-factsheets-eng.pdf?ua=1

Table 1. Description of participating cohorts*

Cohort	Enrollment period	Total n	Age anthropometric measurements collected (y)	Mean age at baseline (y) (SD)	Mean age at end of follow-up (y) (SD)
Amsterdam Born Children and their Development study (ABCD), the Netherlands	2003-2004	2783	4, 5, 7	4.1 (0.6)	6.8 (0.9)
Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE), Sweden	1994-1996	2268	4, 8	4.0 (0.2)	8.1 (0.4)
Danish Allergy Research Centre study (DARC), Denmark	1998-1999	348	3, 6	3.0 (0.2)	6.1 (0.1)
Study of determinants of pre- and postnatal development (EDEN), France	2003-2006	592	4, 5, 6, 7, 8	4.8 (0.8)	7.8 (0.6)
Generation R study, the Netherlands	2002-2006	1169	4, 6	3.8 (0.1)	6.1 (0.3)
German Infant Nutritional Intervention study PLUS environmental and genetic influences on allergy development (GINIplus), Germany	1995-1998	3309	4, 5, 6	4.2 (0.4)	5.8 (0.5)
Environment and Childhood project (INMA_M), Menorca, Spain	1997-1998	249	4, 6	4.2 (0.1)	6.7 (0.2)
Environment and Childhood project (INMA_V), Valencia, Spain	2003-2005	426	4, 7, 9	4.3 (0.1)	8.0 (0.6)
Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study (KOALA), the Netherlands	2002-2003	1471	4, 6, 8	5.0 (0.5)	7.8 (0.6)
Influences of Lifestyle-related factors on the Immune System and the Development of Allergies in Childhood PLUS environmental and genetic influences on allergy development (LISAplus), Germany	1997-1998	1881	4, 5, 6	4.3 (0.4)	5.8 (0.4)
Multi-centre Allergy Study (MAS), Germany	1990	969	4, 5, 6, 7	4.1 (0.1)	7.0 (0.5)
Prevention and Incidence of Asthma and Mite Allergy (PIAMA), the Netherlands	1996-1997	2989	4, 5, 6, 7, 8	4.4 (0.6)	8.0 (0.6)
Mother Child Cohort in Crete (RHEA), Greece	2007-2008	526	4, 7	3.6 (0.6)	6.6 (0.3)
Bologna Birth Cohort (ROBBIC), Italy	2004-2005	189	3, 8	3.6 (0.4)	7.8 (0.5)
Roma Birth Cohort (ROBBIC), Italy	2003-2004	452	3-4, 7, 8	4.1 (0.2)	8.6 (0.3)
Southampton's Women Survey (SWS), United Kingdom	1998-2007	1509	3, 6, 8	3.1 (0.1)	8.3 (1.2)
All participants	NA	21130	NA	4.1 (0.6)	7.1 (1.2)

Abbreviations: NA, not applicable.

*Only included children with BMI data for at least two follow-ups, who were non-obese at baseline, and had information on at least 1 asthma or asthma-related phenotype.

Table 2. Association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years in a pooled sample of 21130 children from 16 European birth cohorts

Asthma/asthma-related phenotypes	n (%)	Crude HR* (95% CI)	aHR† (95% CI)
Baseline asthma			
Yes	945 (6.0)	1.43 (1.03, 1.99)	1.66 (1.18, 2.33)
No	14731 (94.0)	ref	ref
Baseline wheeze in the last 12 months			
Yes	2254 (12.5)	1.24 (0.96, 1.59)	1.29 (1.00, 1.67)
No	15724 (87.5)	ref	ref
Asthma history			
Active asthma (have baseline asthma and baseline wheeze)	543 (3.5)	1.61 (1.07, 2.40)	1.98 (1.31, 3.00)
Have baseline asthma, but no baseline wheeze	387 (2.5)	1.28 (0.74, 2.23)	1.37 (0.78, 2.41)
Have no baseline asthma, but have baseline wheeze	1438 (9.3)	1.14 (0.83, 1.57)	1.16 (0.84, 1.60)
Have no baseline asthma and no baseline wheeze	13084 (84.7)	ref	ref
Early wheeze at 0-2 years of age			
Yes	3814 (18.1)	1.48 (1.20, 1.81)	1.22 (0.99, 1.52)
No	17216 (81.9)	ref	ref
Wheezing history			
Persistent wheezing (have early wheeze and baseline wheeze)	1133 (6.3)	1.49 (1.08, 2.06)	1.51 (1.08, 2.09)
Late-onset wheezing (have no early wheeze but have baseline wheeze)	1135 (6.3)	1.11 (0.77, 1.61)	1.12 (0.77, 1.63)
Transient wheezing (have early wheeze but no baseline wheeze)	2355 (13.1)	1.30 (1.00, 1.70)	1.06 (0.81, 1.39)
Never wheezing (have no early wheeze and no baseline wheeze)	13417 (74.4)	ref	ref
Baseline allergic rhinitis in the last 12 months			
Yes	1886 (13.7)	1.15 (0.88, 1.49)	1.29 (0.98, 1.68)
No	11843 (86.3)	ref	ref
Asthma and allergic rhinitis			
Have baseline asthma and allergic rhinitis	241 (2.2)	1.25 (0.66, 2.36)	1.66 (0.87, 3.16)
Have baseline asthma and no allergic rhinitis	491 (4.5)	1.61 (1.06, 2.45)	2.04 (1.32, 3.13)
Have no baseline asthma and no allergic rhinitis	10092 (93.2)	ref	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.

*Cox proportional hazards model used sex-specific baseline hazard.

†Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard.

Table 3. Association of early-onset asthma and asthma medication use with incident obesity up to age 8 years in a pooled sample of 11,788 children from 8 European birth cohorts

Asthma/asthma-related phenotypes	n (%)	aHR* (95% CI)
Baseline medication use for asthma or breathing difficulties in the last 12 months		
Yes	2062 (17.5)	1.37 (1.04, 1.80)
No	9726 (82.5)	ref
Baseline medication use for asthma or breathing difficulties in the last 12 months adjusted for baseline asthma		
Yes	1918 (16.9)	1.23 (0.91, 1.66)
No	9416 (83.1)	ref
Baseline asthma adjusted for baseline medication use for asthma or breathing difficulties in the last 12 months		
Yes	721 (6.4)	1.57 (1.04, 2.37)
No	10614 (93.6)	ref
Baseline asthma and medication use		
Yes asthma/yes medication use	505 (4.5)	1.91 (1.25, 2.92)
Yes asthma/no medication use	216 (1.9)	1.65 (0.73, 3.73)
No asthma/yes medication use	1413 (12.5)	1.24 (0.90, 1.69)
No asthma/no medication use	9201 (81.2)	ref

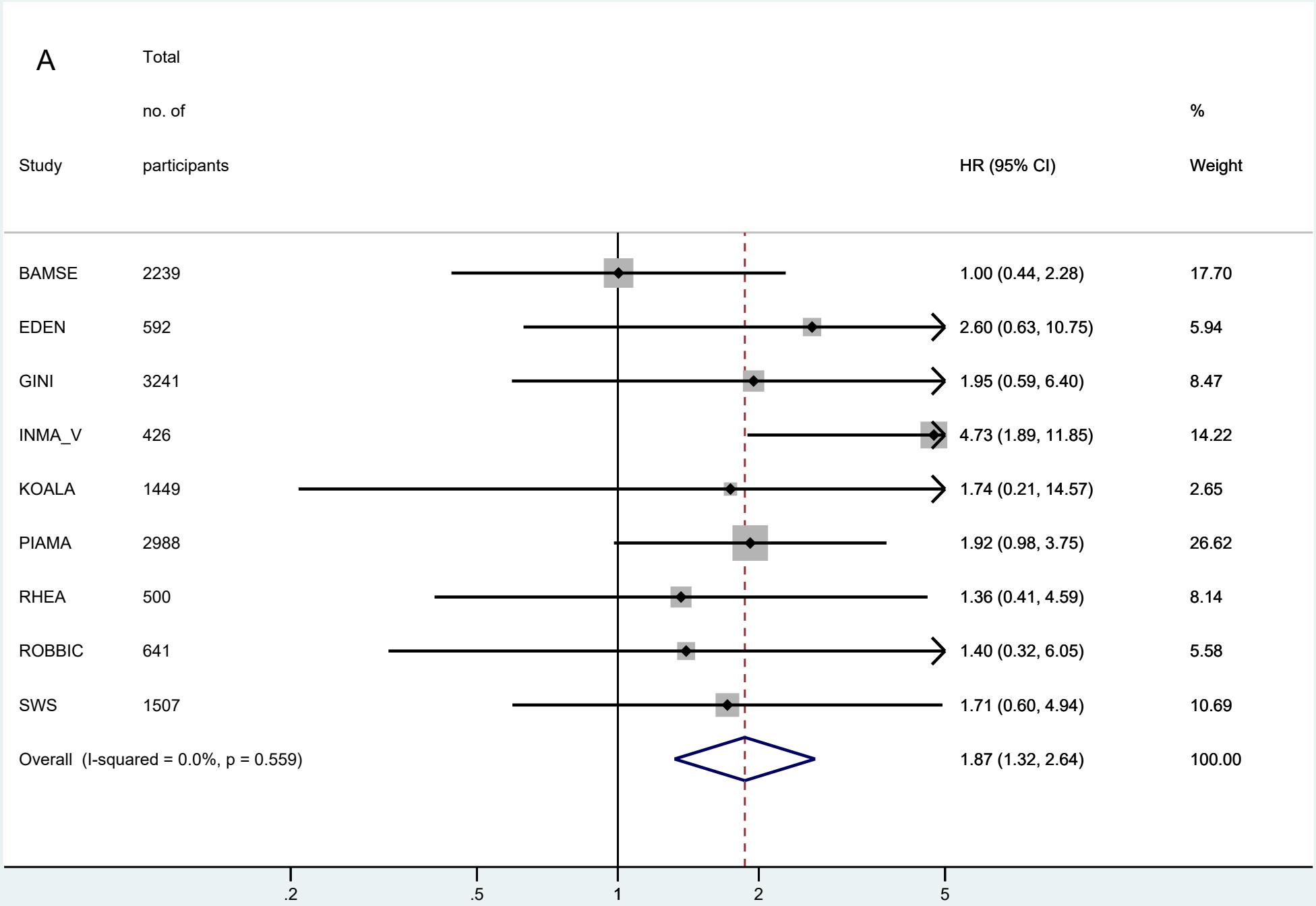
Abbreviations: aHR, adjusted hazard ratio; ref, reference category.

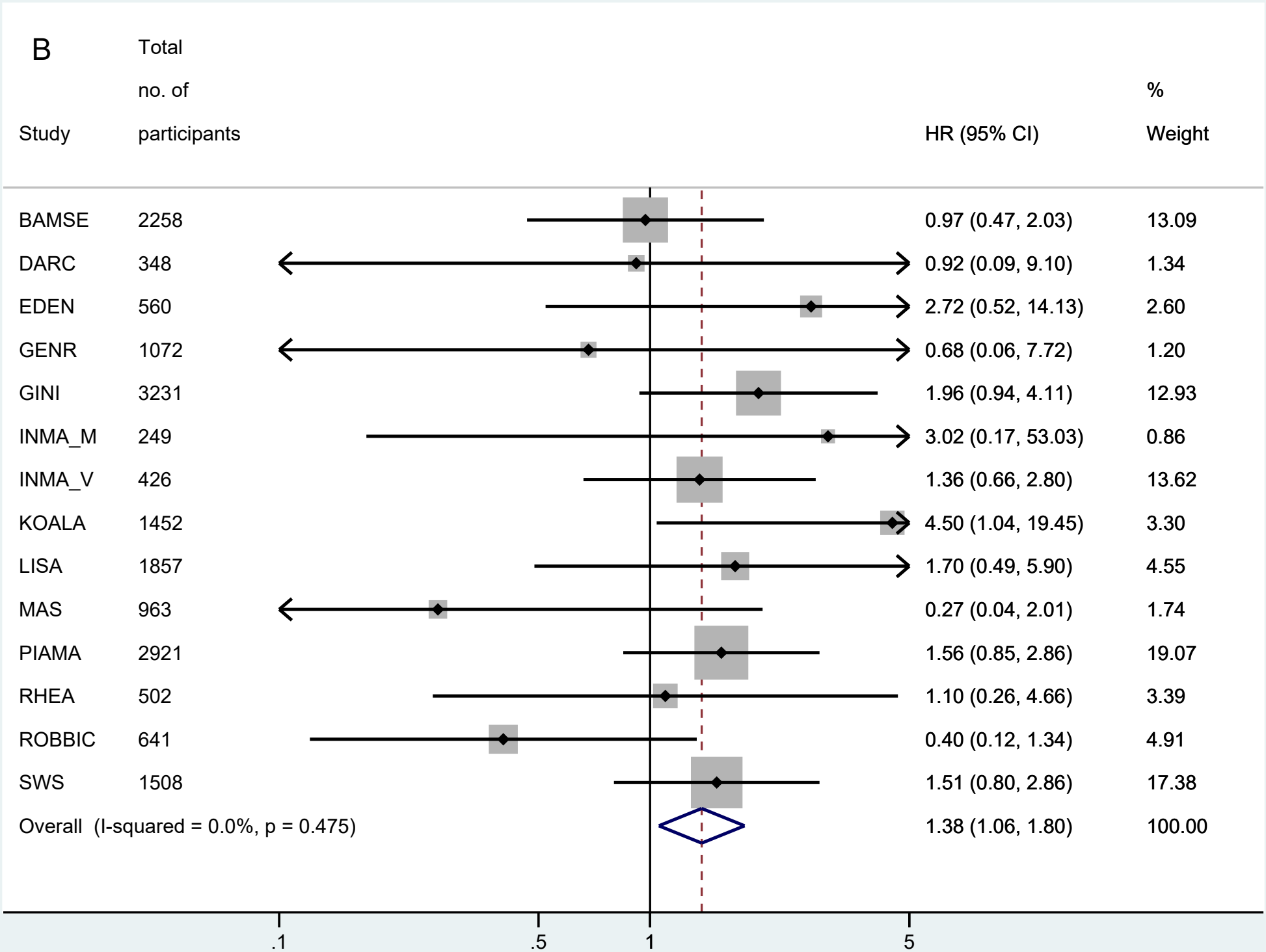
*Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard.

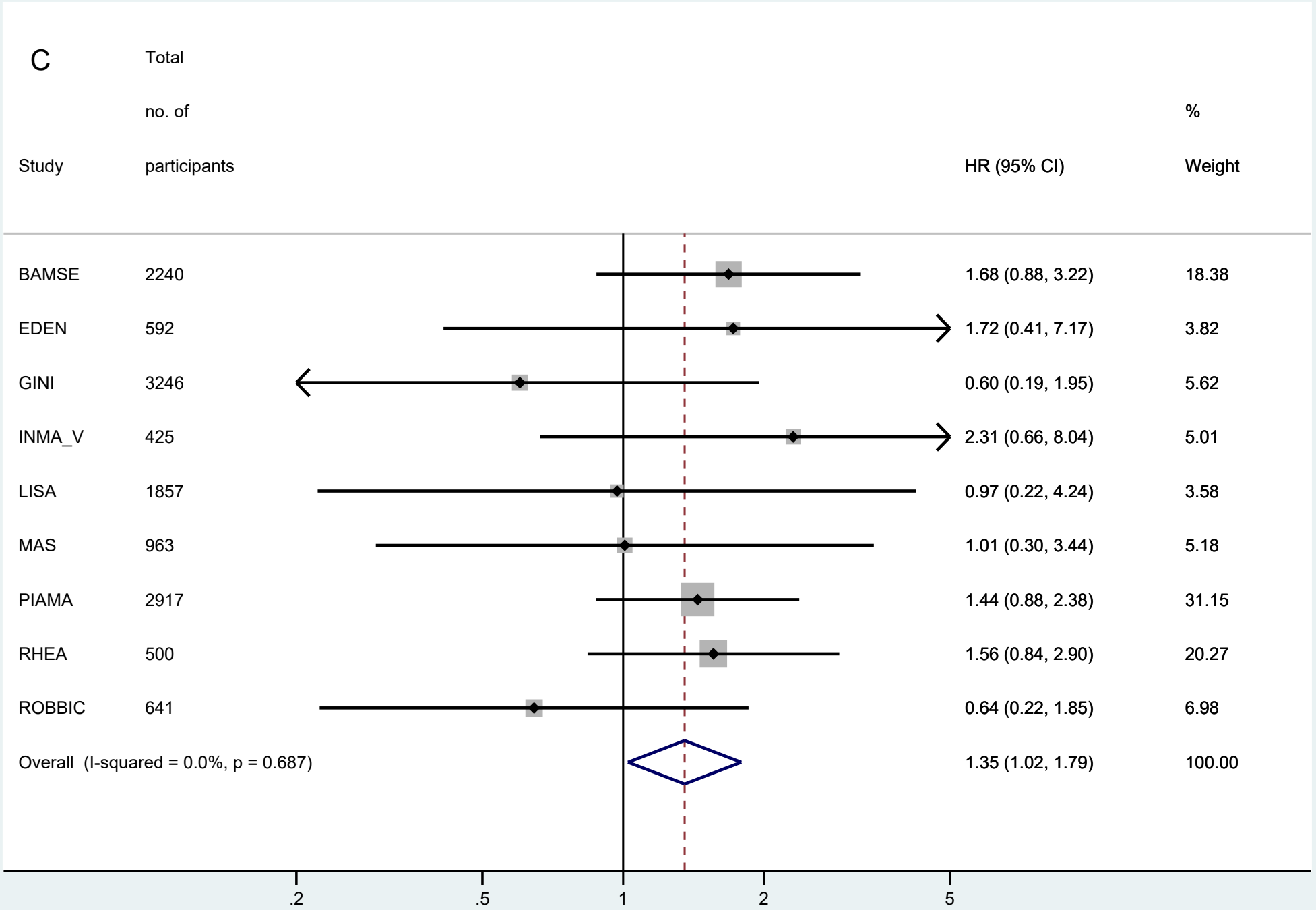
Figure legend

Figure 1. Individual participant meta-analyses results for the association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years.

A) Association between baseline asthma and incident obesity, B) Association between baseline wheeze in the last 12 months at 3-4 years of age and incident obesity C) Association between baseline allergic rhinitis in the last 12 months and incident obesity. Hazard ratios (95% CIs) by cohort were obtained by using Cox proportional hazards models adjusted for age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard. Combined estimates were obtained by using a random-effects meta-analysis. The squares represent the point estimate of each study and the size of the square is proportional to the weight assigned to each cohort based on both the within- and between-study variability; horizontal lines denote 95% CIs; and diamonds represent overall estimates. The arrows on some of the confidence intervals denote that the upper or lower bound of the confidence interval is past the range of the values shown on the x-axis.


A
Total no. of participants
Study
HR (95% CI)
% Weight
BAMSE 2239 1.00 (0.44, 2.28) 17.70
EDEN 592 2.60 (0.63, 10.75) 5.94
GINI 3241 1.95 (0.59, 6.40) 8.47
INMA_V 426 4.73 (1.89, 11.85) 14.22
KOALA 1449 1.74 (0.21, 14.57) 2.65
PIAMA 2988 1.92 (0.98, 3.75) 26.62
RHEA 500 1.36 (0.41, 4.59) 8.14
ROBBIC 641 1.40 (0.32, 6.05) 5.58
SWS 1507 1.71 (0.60, 4.94) 10.69
Overall (I-squared = 0.0%, p = 0.559) 1.87 (1.32, 2.64) 100.00
.2
.5
1
2
5


B
Total no. of participants
%
Study
HR (95% CI)
Weight
BAMSE 2258 0.97 (0.47, 2.03) 13.09
DARC 348 0.92 (0.09, 9.10) 1.34
EDEN 560 2.72 (0.52, 14.13) 2.60
GENR 1072 0.68 (0.06, 7.72) 1.20
GINI 3231 1.96 (0.94, 4.11) 12.93
INMA_M 249 3.02 (0.17, 53.03) 0.86
INMA_V 426 1.36 (0.66, 2.80) 13.62
KOALA 1452 4.50 (1.04, 19.45) 3.30
LISA 1857 1.70 (0.49, 5.90) 4.55
MAS 963 0.27 (0.04, 2.01) 1.74
PIAMA 2921 1.56 (0.85, 2.86) 19.07
RHEA 502 1.10 (0.26, 4.66) 3.39
ROBBIC 641 0.40 (0.12, 1.34) 4.91
SWS 1508 1.51 (0.80, 2.86) 17.38
Overall (I-squared = 0.0%, p = 0.475) 1.38 (1.06, 1.80) 100.00
.1
.5
1
5


C
Total no. of participants
Study
HR (95% CI)
% Weight
BAMSE 2240 1.68 (0.88, 3.22) 18.38
EDEN 592 1.72 (0.41, 7.17) 3.82
GINI 3246 0.60 (0.19, 1.95) 5.62
INMA_V 425 2.31 (0.66, 8.04) 5.01
LISA 1857 0.97 (0.22, 4.24) 3.58
MAS 963 1.01 (0.30, 3.44) 5.18
PIAMA 2917 1.44 (0.88, 2.38) 31.15
RHEA 500 1.56 (0.84, 2.90) 20.27
ROBBIC 641 0.64 (0.22, 1.85) 6.98
Overall (I-squared = 0.0%, p = 0.687) 1.35 (1.02, 1.79) 100.00
.2
.5
1
2
5

Online data supplement

Table E1. Distribution of maternal and child characteristics comparing those excluded due to missing data to those included in our study

	Excluded at baseline due to missing exposure/outcome information*, n=5,420		Total study population at baseline†, n=21,130	
	Total n with data	**No. (%)**	**Total n with data**	**No. (%)**
Child sex				
male	5420	2806 (51.8)	21130	10791 (51.1)
Maternal education				
low/medium	5186	3120 (60.2)	19943	10975 (55.0)
Parity				
multiparous	5281	2508 (47.5)	20754	9819 (47.3)
Birthweight (g)				
median (IQR)	5229	3460 (640)	20689	3460 (645)
Breastfeeding				
≥3 months	5063	3195 (63.1)	20507	13874 (67.7)
Parental asthma				
yes	4507	876 (19.4)	20519	3407 (16.6)
Smoking during pregnancy				
yes	5304	797 (15.0)	20012	2737 (13.7)
Passive smoke				
yes	5178	1464 (28.3)	21096	5916 (28.0)

*Excluded at baseline due to not having information for at least 1 exposure of interest & BMI information for at least 2 follow-ups

†Total study population after excluding the 5,420 participants with missing exposure/outcome information and 567 prevalent obesity cases

Table E2.Information on data collection for early-onset asthma and asthma-related phenotypes by cohort

	Asthma diagnosis ever prior to baseline visit	Wheeze	Wheeze in the last 12 months of baseline visit	Allergic rhinitis in the last 12 months of baseline visit	Medication in the last 12 months of baseline visit
ABCD	Not collected	Ever wheeze collected at 1y	Not collected	Not collected	Not collected
BAMSE	Ever physician diagnosed asthma collected at 1 y, 2 y, 4 y	Wheeze in last 12 months collected at 1 y, 2y, 4 y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4y	Treatment for asthma or breathing problems in the last 24 months collected at 4y
DARC	Not collected	Wheeze in last 12 months collected at 3m, 6m, 9m, 18m, 3y	Wheezing in the last 12 months collected at 3 y	Allergic rhinitis in the last 12 months collected at 3 y	Treatment for asthma or breathing problems in the last 12 months collected at 3y
EDEN	Ever physician diagnosed asthma collected at 4y	Wheeze in last 12 months collected at 1 y, 2y, 3y, 4 y	Wheezing in the last 12 months collected at 4y	Allergic rhinitis in the last 12 months collected at 4 y	Not collected
GENR	Not collected	Wheeze in last 12 months collected at 2y, 4y	Wheeze in the past 12 months at 4 y	Not collected	Not collected
GINIplus	Ever physician diagnosed asthma collected at 1 y, 2 y, 3 y, 4 y	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Treatment for asthma in the last 12 months collected at 3 y
INMA_M	Ever physician diagnosed asthma collected at 2 y, 3 y, 4 y	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Not collected	Not collected
INMA_V	Ever physician diagnosed asthma in the last 12 months collected at 4 y	Wheeze in last 12 months collected at 2y, 4y	Wheezing in the last 12 months collected at 4 y	Self-report of allergic rhinitis in the last 12 months collected at 4 y	Medication for wheezing in the last 12 months collected at 4 y
KOALA	Doctor diagnosed asthma collected at 4 y	Wheeze in last 12 months collected at 2y, 4y	Wheeze in the past 12 months collected at 4 y	Not collected	Medication in the last 12 months at 4 y
LISAplus	Ever physician diagnosed asthma collected at 1 y, 2 y, 3 y, 4 y	Wheeze in last 12 months collected at 1y, 2y, 4y;	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months at 4 y	Not collected
MAS	Not collected	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Not collected
PIAMA	Ever physician diagnosed asthma collected at 1 y, 2y, 3 y, 4y	Wheeze in last 12 months collected at 1y, 2y, 3y, 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Treatment for respiratory or lung problems in the last 12 months collected at 4 y
RHEA	Ever physician diagnosed asthma collected at 4 y	Ever wheeze collected at 9m; wheeze in last 12 months collected at 4y	Wheezing in the last 12 months collected at 4 y	Allergic rhinitis in the last 12 months collected at 4 y	Treatment for asthma or breathing problems in the last 12 months collected at 4 y
ROBBIC	Ever physician diagnosed asthma collected at 6m, 15m, 3-4 y	Wheeze in last 12 months collected at 6m, 15m, 3y	Wheezing in the last 12 months collected at 3-4 y	Allergic rhinitis in the last 12 months collected at 3-4 y	Treatment for asthma or breathing problems in the last 12 months at 3-4 y
SWS	Ever physician diagnosed asthma collected at 3 y	Wheeze in last 12 months collected at 2y, 4y	Wheeze in the past 12 months collected at 3 y	Not collected	Not collected

Table E3.Prevalence of baseline early-onset asthma and asthma-related phenotypes by cohort

	Baseline asthma		Baseline wheeze in the last 12 months		Early wheeze at 0-2 years		Baseline allergic rhinitis in the last 12 months		Baseline medication use for asthma/breathing difficulties in the last 12 months	
	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)	Total n with data	Yes No. (%)
ABCD	NA	NA	NA	NA	2783	272 (9.8)	NA	NA	NA	NA
BAMSE	2239	246 (11.0)	2258	343 (15.2)	2265	441 (19.5)	2240	275 (12.3)	2249	588 (26.1)
DARC	NA	NA	348	51 (14.7)	348	60 (17.2)	348	35 (10.1)	348	130 (37.4)
EDEN	592	81 (13.7)	560	60 (10.7)	587	83 (14.1)	592	128 (21.6)	NA	NA
GENR	NA	NA	1072	109 (10.2)	1149	195 (17.0)	NA	NA	NA	NA
GINI	3241	106 (3.3)	3231	321 (9.9)	3302	362 (11.0)	3246	318 (9.8)	3309	54 (1.6)
INMA_M	249	5 (2.0)	249	25 (10.0)	249	67 (26.9)	NA	NA	NA	NA
INMA_V	426	17 (4.0)	426	83 (19.5)	426	149 (35.0)	425	14 (3.3)	417	69 (16.6)
KOALA	1449	98 (6.8)	1452	149 (10.3)	1467	213 (14.5)	NA	NA	1439	143 (9.9)
LISA	1844	28 (1.5)	1847	209 (11.3)	1873	647 (34.5)	1857	193 (10.4)	NA	NA
MAS	NA	NA	963	96 (10.0)	966	116 (12.0)	963	125 (13.0)	NA	NA
PIAMA	2988	217 (7.3)	2921	333 (11.4)	2981	512 (17.2)	2917	599 (20.5)	2533	355 (12.3)
RHEA	500	28 (5.6)	502	19 (3.8)	486	119 (24.5)	500	112 (22.4)	497	298 (60.0)
ROBBIC	641	25 (3.9)	641	98 (15.3)	639	178 (27.9)	641	87 (13.6)	641	425 (66.3)
SWS	1507	94 (6.2)	1508	358 (23.7)	1509	400 (26.5)	NA	NA	NA	NA

Abbreviations: NA, not available.

Table E4. Distribution of obese at baseline and incident obesity up to age 8 years in a pooled sample of children from 16 European birth cohorts

	Total at baseline including prevalent obese cases	Obese at baseline	Total at baseline after excluding prevalent obese cases	Obesity incidence by end of follow-up
	N	Yes No. (%)		Yes No. (%)
ABCD	2872	89 (3.1)	2783	24 (0.9)
BAMSE	2357	89 (3.8)	2268	60 (2.7)
DARC	356	8 (2.3)	348	7 (2.0)
EDEN	598	6 (1.0)	592	10 (1.7)
GENR	1189	20 (1.7)	1169	10 (0.8)
GINIplus	3358	49 (1.5)	3309	47 (1.4)
INMA_M	263	14 (5.3)	249	6 (2.4)
INMA_V	453	27 (6.0)	426	44 (10.3)
KOALA	1484	13 (0.9)	1471	9 (0.6)
LISAplus	1903	22 (1.2)	1881	21 (1.1)
MAS	987	18 (1.8)	969	26 (2.7)
PIAMA	3061	72 (2.4)	2989	81 (2.7)
RHEA	557	31 (5.6)	526	53 (10.1)
ROBBIC		53 (7.6)	641	39 (6.1)
SWS	1565	56 (3.6)	1509	46 (3.1)
All participants	21697	567 (2.6)	21130	483 (2.3)

Table E5.Distribution of maternal and child characteristics by cohort

	Child sex (male)		Maternal education (low/medium)		Parity (multiparous)		Birthweight (g)		Breastfeeding (≥3 months)		Parental asthma (yes)		Smoking during pregnancy (yes)		Passive smoke (yes)	
	Total n with data	**Yes No. (%)**	**Total n with data**	**Yes No. (%)**	**Total n with data**	**Yes No. (%)**	**Total n with data**	**Median (IQR)**	**Total n with data**	**Yes No. (%)**	**Total n with data**	**Yes No. (%)**	**Total n with data**	**Yes No. (%)**	**Total n with data**	**Yes No. (%)**
ABCD	2783	1404 (50.5)	2773	1293 (46.6)	2783	1161 (41.7)	2783	3492 (655)	2783	1821 (65.4)	2667	409 (15.3)	2783	232 (8.3)	2783	340 (12.2)
BAMSE	2268	1153 (50.8)	2257	1309 (58.0)	2268	1073 (47.3)	2251	3540 (675)	2219	2107 (95.0)	2255	456 (20.2)	2268	272 (12.0)	2268	319 (14.1)
DARC	348	174 (50.0)	348	267 (76.7)	348	188 (54.0)	348	3594 (700)	326	260 (79.8)	336	65 (19.3)	348	103 (29.6)	348	58 (16.7)
EDEN	592	322 (54.4)	587	349 (59.5)	592	300 (50.7)	591	3320 (600)	592	290 (49.0)	592	101 (17.1)	592	102 (17.2)	592	251 (42.4)
GENR	1169	590 (50.5)	1162	399 (34.3)	1169	481 (41.2)	1169	3540 (655)	882	565 (64.1)	962	121 (12.6)	1169	263 (22.5)	1163	270 (23.2)
GINIplus	3309	1670 (50.5)	3212	1737 (54.1)	3191	1587 (49.7)	3263	3455 (615)	3262	2448 (75.1)	3208	443 (13.8)	3267	430 (13.1)	3307	825 (25.0)
INMA_M	249	118 (47.4)	237	200 (84.4)	NA	NA	249	3220 (530)	249	150 (60.2)	248	25 (10.1)	249	86 (34.5)	249	158 (63.5)
INMA_V	426	215 (50.5)	426	297 (69.7)	426	190 (44.6)	426	3250 (600)	423	227 (53.7)	426	57 (13.4)	426	95 (22.3)	426	224 (52.6)
KOALA	1471	752 (51.1)	1454	677 (46.6)	1471	825 (56.1)	1471	3530 (595)	1471	1017 (69.1)	1452	237 (16.3)	1471	79 (5.4)	1471	287 (19.5)
LISAplus	1881	905 (51.9)	1863	808 (43.4)	1879	853 (45.4)	1881	3450 (590)	1772	1557 (87.9)	1811	229 (12.6)	1822	256 (14.1)	1858	476 (25.6)
MAS	969	508 (52.4)	NA	NA	969	392 (40.4)	963	3400 (590)	968	585 (60.4)	940	143 (15.2)	NA	NA	969	544 (56.2)
PIAMA	2989	1518 (50.8)	2975	1877 (63.1)	2989	1479 (49.5)	2981	3520 (650)	2966	1378 (46.5)	2968	398 (13.4)	2972	476 (15.7)	2989	938 (31.4)
RHEA	526	286 (54.4)	503	323 (64.2)	522	284 (54.4)	411	3200 (620)	499	257 (51.5)	522	41 (7.9)	500	103 (20.6)	523	216 (41.3)
ROBBIC	641	330 (51.5)	641	393 (61.3)	638	283 (44.4)	641	3351 (570)	639	463 (72.5)	639	126 (19.7)	636	62 (9.8)	641	354 (55.2)
SWS	1509	786 (52.1)	1505	1046 (69.5)	1509	723 (47.9)	1509	3470 (646)	1456	749 (51.4)	1493	556 (37.2)	1509	187 (12.4)	1509	656 (43.5)

Abbreviations: NA, not available.

Table E6.Individual participant meta-analyses results for the association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years after omitting one cohort at a time[*]

	Baseline asthma	Baseline wheeze in the last 12 months	Baseline allergic rhinitis in the last 12 months
Overall	1.87 (1.32, 2.64)	1.38 (1.06, 1.80)	1.35 (1.02, 1.79)
Cohort omitted			
ABCD	NA	NA	NA
BAMSE	2.13 (1.46, 3.13)	1.45 (1.09, 1.93)	1.29 (0.95, 1.76)
DARC	NA	1.38 (1.05, 1.82)	NE
EDEN	1.82 (1.28, 2.61)	1.35 (1.03, 1.77)	1.34 (1.01, 1.78)
GENR	NA	1.39 (1.05, 1.82)	NA
GINIplus	1.86 (1.30, 2.67)	1.31 (0.98, 1.74)	1.42 (1.07, 1.89)
INMA_M	NE	1.37 (1.04, 1.80)	NA
INMA_V	1.60 (1.10, 2.33)	1.37 (1.01, 1.86)	1.32 (0.99, 1.75)
KOALA	1.87 (1.32, 2.66)	1.32 (1.01, 1.73)	NA
LISAplus	NE	1.36 (1.02, 1.80)	1.37 (1.03, 1.82)
MAS	NA	1.41 (1.08, 1.86)	1.38 (1.03, 1.83)
PIAMA	1.85 (1.24, 2.77)	1.34 (0.98, 1.81)	1.31 (0.94, 1.84)
RHEA	1.92 (1.34, 2.75)	1.38 (1.04, 1.84)	1.31 (0.96, 1.78)
ROBBIC	1.89 (1.33, 2.71)	1.47 (1.12, 1.93)	1.43 (1.07, 1.91)
SWS	1.89 (1.31, 2.72)	1.34 (0.99, 1.83)	NA

Abbreviations: NA, not applicable; NE, cohort-specific estimate not estimable due to no exposed incident obesity cases within the cohort.

[*]Hazard ratios (95% CIs) by cohort were obtained by using Cox proportional hazards models adjusted for age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard. Combined estimates were obtained by using a random-effects meta-analysis.

Table E7.Association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years in a pooled sample of 21130 children from 16 European birth cohorts with additional adjustment for overweight children at baseline

Asthma/asthma-related phenotypes	n (%)	aHR* (95% CI)
Baseline asthma		
Yes	945 (6.0)	1.47 (1.05, 2.08)
No	14731 (94.0)	ref
Baseline wheeze in the last 12 months		
Yes	2254 (12.5)	1.15 (0.89, 1.50)
No	15724 (87.5)	ref
Asthma history		
Active asthma (have baseline asthma and baseline wheeze)	543 (3.5)	1.75 (1.15, 2.66)
Have baseline asthma, but no baseline wheeze	387 (2.5)	1.22 (0.69, 2.16)
Have no baseline asthma, but have baseline wheeze	1438 (9.3)	1.06 (0.76, 1.46)
Have no baseline asthma and no baseline wheeze	13084 (84.7)	ref
Early wheeze at 0-2 years of age		
Yes	3814 (18.1)	1.11 (0.90, 1.38)
No	17216 (81.9)	ref
Wheezing history		
Persistent wheezing (have early wheeze and baseline wheeze)	1133 (6.3)	1.28 (0.92, 1.80)
Late onset wheezing (have no early wheeze but have baseline wheeze)	1135 (6.3)	1.08 (0.74, 1.57)
Transient wheezing (have early wheeze but no baseline wheeze)	2355 (13.1)	1.00 (0.76, 1.31)
Never wheezing (have no early wheeze and no baseline wheeze)	13417 (74.4)	ref
Baseline allergic rhinitis in the last 12 months		
Yes	1886 (13.7)	1.30 (0.99, 1.70)
No	11843 (86.3)	ref
Asthma and allergic rhinitis		
Have baseline asthma and allergic rhinitis	241 (2.2)	1.41 (0.74, 2.69)
Have baseline asthma and no allergic rhinitis	491 (4.5)	2.12 (1.36, 3.30)
Have no baseline asthma and no allergic rhinitis	10092 (93.2)	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.

*Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, birthweight, & overweight status at baseline with sex-specific baseline hazard.

Table E8. Association of early-onset asthma and asthma-related phenotypes with incident overweight or obesity up to age 8 years in a pooled sample of 19230 children from 16 European birth cohorts among children who were normal weight at baseline

Asthma/asthma-related phenotypes	n (%)	Incident obesity (n=210) aHR* (95% CI)	Incident overweight or obesity (n=1816) aHR* (95% CI)
Baseline asthma			
Yes	830 (5.9)	1.25 (0.70, 2.23)	1.10 (0.89, 1.35)
No	13334 (94.1)	ref	ref
Baseline wheeze in the last 12 months			
Yes	1997 (12.3)	1.18 (0.78, 1.78)	1.10 (0.95, 1.27)
No	14310 (87.8)	ref	ref
Asthma history			
Active asthma (have baseline asthma and baseline wheeze)	468 (3.4)	1.40 (0.67, 2.89)	1.04 (0.78, 1.37)
Have baseline asthma, but no baseline wheeze	349 (2.5)	1.18 (0.48, 2.92)	1.24 (0.92, 168)
Have no baseline asthma, but have baseline wheeze	1277 (9.2)	1.22 (0.75, 1.98)	1.16 (0.97, 1.38)
Have no baseline asthma and no baseline wheeze	11862 (85.0)	ref	ref
Early wheeze at 0-2 years of age			
Yes	3374 (17.6)	1.22 (0.88, 1.69)	1.07 (0.95, 1.20)
No	15768 (82.4)	ref	ref
Wheezing history			
Persistent wheezing (have early wheeze and baseline wheeze)	980 (6.0)	1.30 (0.75, 2.24)	1.05 (0.85, 1.28)
Late onset wheezing (have no early wheeze but have baseline wheeze)	1030 (6.3)	1.22 (0.70, 2.13)	1.18 (0.97, 1.42)
Transient wheezing (have early wheeze but no baseline wheeze)	2105 (12.9)	1.22 (0.82, 1.81)	1.11 (0.96, 1.28)
Never wheezing (have no early wheeze and no baseline wheeze)	12254 (74.9)	ref	ref
Baseline allergic rhinitis in the last 12 months			
Yes	1700 (13.7)	1.45 (0.98, 2.14)	0.98 (0.84, 1.14)
No	10727 (86.3)	ref	ref
Asthma and allergic rhinitis			
Have baseline asthma and allergic rhinitis	209 (2.1)	1.45 (0.65, 3.11)	0.98 (0.65, 1.48)
Have baseline asthma and no allergic rhinitis	434 (4.5)	1.43 (0.65, 3.11)	1.24 (0.96, 1.62)
Have no baseline asthma and no allergic rhinitis	9114 (93.4)	ref	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.

*Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, & birthweight with sex-specific baseline hazard.

Table E9. Association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years in a pooled sample of 21130 children from 16 European birth cohorts with additional adjustment for baseline BMI

Asthma/asthma-related phenotypes	n (%)	aHR* (95% CI)
Baseline asthma		
Yes	945 (6.0)	1.32 (0.93, 1.86)
No	14731 (94.0)	ref
Baseline wheeze in the last 12 months		
Yes	2254 (12.5)	1.09 (0.84, 1.41)
No	15724 (87.5)	ref
Asthma history		
Active asthma (have baseline asthma and baseline wheeze)	543 (3.5)	1.60 (1.05, 2.43)
Have baseline asthma, but no baseline wheeze	387 (2.5)	1.05 (0.59, 1.86)
Have no baseline asthma, but have baseline wheeze	1438 (9.3)	1.00 (0.72, 1.38)
Have no baseline asthma and no baseline wheeze	13084 (84.7)	ref
Early wheeze at 0-2 years of age		
Yes	3814 (18.1)	1.03 (0.84, 1.29)
No	17216 (81.9)	ref
Wheezing history		
Persistent wheezing (have early wheeze and baseline wheeze)	1133 (6.3)	1.15 (0.82, 1.60)
Late onset wheezing (have no early wheeze but have baseline wheeze)	1135 (6.3)	1.06 (0.73, 1.54)
Transient wheezing (have early wheeze but no baseline wheeze)	2355 (13.1)	0.95 (0.73, 1.25)
Never wheezing (have no early wheeze and no baseline wheeze)	13417 (74.4)	ref
Baseline allergic rhinitis in the last 12 months		
Yes	1886 (13.7)	1.19 (0.90, 1.56)
No	11843 (86.3)	ref
Asthma and allergic rhinitis		
Have baseline asthma and allergic rhinitis	241 (2.2)	1.42 (0.74, 2.73)
Have baseline asthma and no allergic rhinitis	491 (4.5)	1.71 (1.10, 2.66)
Have no baseline asthma and no allergic rhinitis	10092 (93.2)	ref

Abbreviations: aHR, adjusted hazard ratio; ref, reference category.

*Cox proportional hazards model adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding, birthweight & baseline BMI with sex-specific baseline hazard.

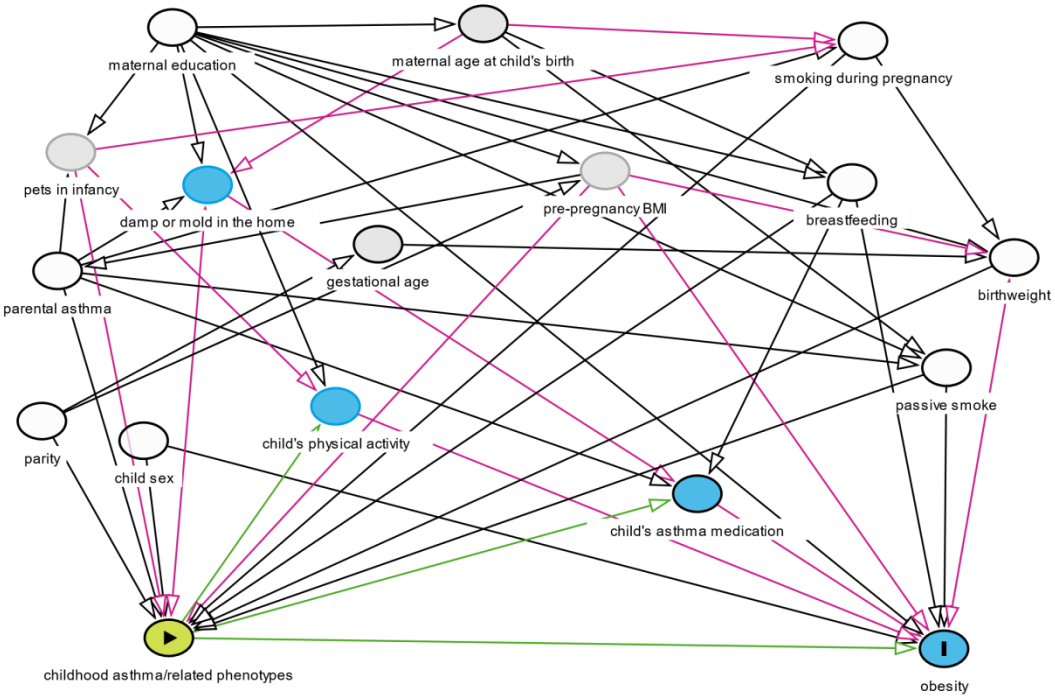


Figure E1. Directed acyclic graph for assessing the impact of early-onset asthma and asthma-related phenotypes on obesity risk. Yellow node represents our exposures of interest. Blue nodes represent our outcome of interest or risk factors for the outcome. All white nodes are variables we controlled for in adjusted models. Gray nodes denote other variables which we did not adjust for in our final analysis. Pink paths denote potentially biasing paths. Green paths denote potentially causal paths.