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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 21 130 children born from 1990 to 2008 in Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, Sweden and the UK. 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.

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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 relationship 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 relationship 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; however, obesity or being overweight were not associated with subsequent asthma onset [8]. A pooled study of eight European birth cohorts found that children with rapid body mass index (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; however, 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 16 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 authorised 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 5420 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.

TABLE 1 Description of participating cohorts.

Study and enrolment period	Total subjects n	Measurement age[#] years	Age years	
			At baseline	At end of follow-up
ABCD, The Netherlands				
2003–2004	2783	4, 5, 7	4.1±0.6	6.8±0.9
BAMSE, Sweden				
1994–1996	2268	4, 8	4.0±0.2	8.1±0.4
DARC, Denmark				
1998–1999	348	3, 6	3.0±0.2	6.1±0.1
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
GINIplus, Germany				
1995–1998	3309	4, 5, 6	4.2±0.4	5.8±0.5
INMA_M, Menorca, Spain				
1997–1998	249	4, 6	4.2±0.1	6.7±0.2
INMA_V, Valencia, Spain				
2003–2005	426	4, 7, 9	4.3±0.1	8.0±0.6
KOALA, The Netherlands				
2002–2003	1471	4, 6, 8	5.0±0.5	7.8±0.6
LISAplus, Germany				
1997–1998	1881	4, 5, 6	4.3±0.4	5.8±0.4
MAS, Germany				
1990	969	4, 5, 6, 7	4.1±0.1	7.0±0.5
PIAMA, The Netherlands				
1996–1997	2989	4, 5, 6, 7, 8	4.4±0.6	8.0±0.6
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
SWS, UK				
1998–2007	1509	3, 6, 8	3.1±0.1	8.3±1.2
All participants				
NA	21 130	NA	4.1±0.6	7.1±1.2

Data are presented as mean±SD, unless otherwise stated. Only children with body mass index data for at least two follow-ups, who were non-obese at baseline and had information on at least one asthma or asthma-related phenotype were included. NA: not applicable. [#]: age when anthropometric measurements collected.

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 (supplementary 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 supplementary table E2. The presence of asthma at baseline (yes/no) was determined by reporting of a physician diagnosis of asthma at any point up to 3–4 years of age. Wheeze (yes/no) at baseline was based on reporting 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 reporting 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 reporting 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 categorised as: 1) have baseline asthma and baseline wheeze (active asthma); 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, and categorised as: 1) have early wheeze and baseline wheeze (persistent wheezing); 2) have no early wheeze, but have baseline wheeze (late-onset wheezing); 3) have early wheeze, but no baseline wheeze (transient wheezing); and 4) have no early wheeze and no baseline wheeze (never wheezing; the reference category). Since we lacked information on IgE sensitisation, we created a measure of asthma and allergic rhinitis comorbidity based on responses to the baseline asthma and allergic rhinitis questions, and categorised as: 1) have baseline asthma and allergic rhinitis; 2) have baseline asthma and no allergic rhinitis; and 3) have no baseline asthma and no allergic rhinitis. We also created a combined measure of the joint impact of asthma and medication use, categorised as: 1) yes asthma/yes medication use; 2) yes asthma/no medication use; 3) no asthma/yes medication use; and 4) no asthma/no medication use (reference category).

Obesity

Cohorts provided weight and height information based on clinical examinations, 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 cut-offs [25]. We also used the 2007 World Health Organization cut-offs 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 (g) 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 categorised as low (<2500 g), normal (2500–3999 g), or high (4000+ g) and breastfeeding was categorised as <3 months and ⩾3 months [28, 29]. Physical activity was available for only three out of 16 cohorts and 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 and ROBBIC) and defined as use of inhaled corticosteroids (ICS) ever at 3–4 years of age (yes/no).

Statistical analyses

Our main analysis was a pooled analysis in which we combined the data from 16 different cohorts. To account for potential differences between cohorts we introduced a "random effect for cohort" or a "fixed effect for cohort" (*i.e.* an indicator variable). 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% 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 (supplementary 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 these variables were thus not included in final models. Since medication use may be a potential mediator of the asthma and obesity relationship we explored its role further by conducting several analyses, as follows: 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; and 3) we modelled 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 in this category. Secondly, we restricted our sample to those who were normal weight at baseline and conducted separate analyses examining the incidence of overweight or obesity, as well as obesity only, to further assess the impact of the overweight at baseline. Thirdly, we adjusted for baseline BMI as a continuous variable to assess whether initial BMI status impacts our results. Fourthly, we excluded children who developed asthma during follow-up to assess whether our results were impacted by new asthma cases. Fifthly, 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]. Sixthly, we repeated our analysis using the World Health Organization (WHO) cut-offs for obesity to compare our results using an alternative definition of obesity. Seventhly, 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. Eighthly, 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.

Furthermore, 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-study 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. Finally, we explored potential heterogeneity by region of participating cohorts, based on the United Nations' classification (Southern Europe, Western Europe and 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 21 130 children at cohort entry with a mean age at baseline of 4.1±0.6 years (table 1). The maternal and child characteristics of our total study population, as compared to those that were excluded from our study due to missing data, are displayed in supplementary table E1. 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% *versus* 55.0%) and shorter breastfeeding duration (63.1% *versus* 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 supplementary table E3. The number of follow-ups and age at end of

TABLE 2 Association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years in a pooled sample of 21 130 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	14 731 (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	15 724 (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	13 084 (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	17 216 (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)	13 417 (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	11 843 (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	10 092 (93.2)	ref	ref

aHR: adjusted hazard ratio; ref: reference category. [#]: the Cox proportional hazards model used a sex-specific baseline hazard; [¶]: the Cox proportional hazards model was adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding and birthweight with a sex-specific baseline hazard.

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 children (2.3%) developed obesity. Cohort-specific prevalences of baseline obesity and incident obesity are shown in supplementary table E4, while baseline maternal and child characteristics by cohort are presented in supplementary table E5.

The pooled analysis results for the association between asthma and related phenotypes at baseline and incident obesity at follow-up are displayed in table 2. Children with physician-diagnosed asthma had a 66% higher risk of incident obesity than those without an asthma diagnosis (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 wheezing (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).

The results for the joint associations of asthma and medication use with incident obesity are shown in table 3. 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 was 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

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 eight 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	10 614 (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

aHR: adjusted hazard ratio; ref: reference category. #: the Cox proportional hazards model was adjusted for cohort, age at baseline, smoking during pregnancy, passive smoke, parity, maternal education, parental asthma, breastfeeding and birthweight with a sex-specific baseline hazard.

asthmatic children not taking medication (aHR 1.65, 95% CI 0.73–3.73) and nonasthmatic children taking medication (aHR 1.24, 95% CI 0.90–1.69). ICS use was positively associated with incident obesity both with adjustment for asthma (aHR 1.42, 95% CI 0.82–2.26) and without (aHR 1.45, 95% CI 0.97–2.18).

The cohort-specific estimates and combined estimates from the random effects meta-analysis for the association between asthma and related phenotypes and incident obesity are presented in figure 1. 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) or by geographical region of cohorts. The results remained similar when omitting one cohort at a time (supplementary table E6).

When adjusting for overweight at baseline in our pooled analysis, the associations we observed were attenuated slightly but remained significant (supplementary table E7). After restricting our sample to normal weight at baseline, observed associations were attenuated and no longer statistically significant, but were still indicative of a positive association for incident obesity (supplementary table E8). After adjustment for baseline BMI, our observed associations were similarly attenuated and nonsignificant, albeit still positively associated with incident obesity (supplementary 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 relationship 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 generalisability of our results.

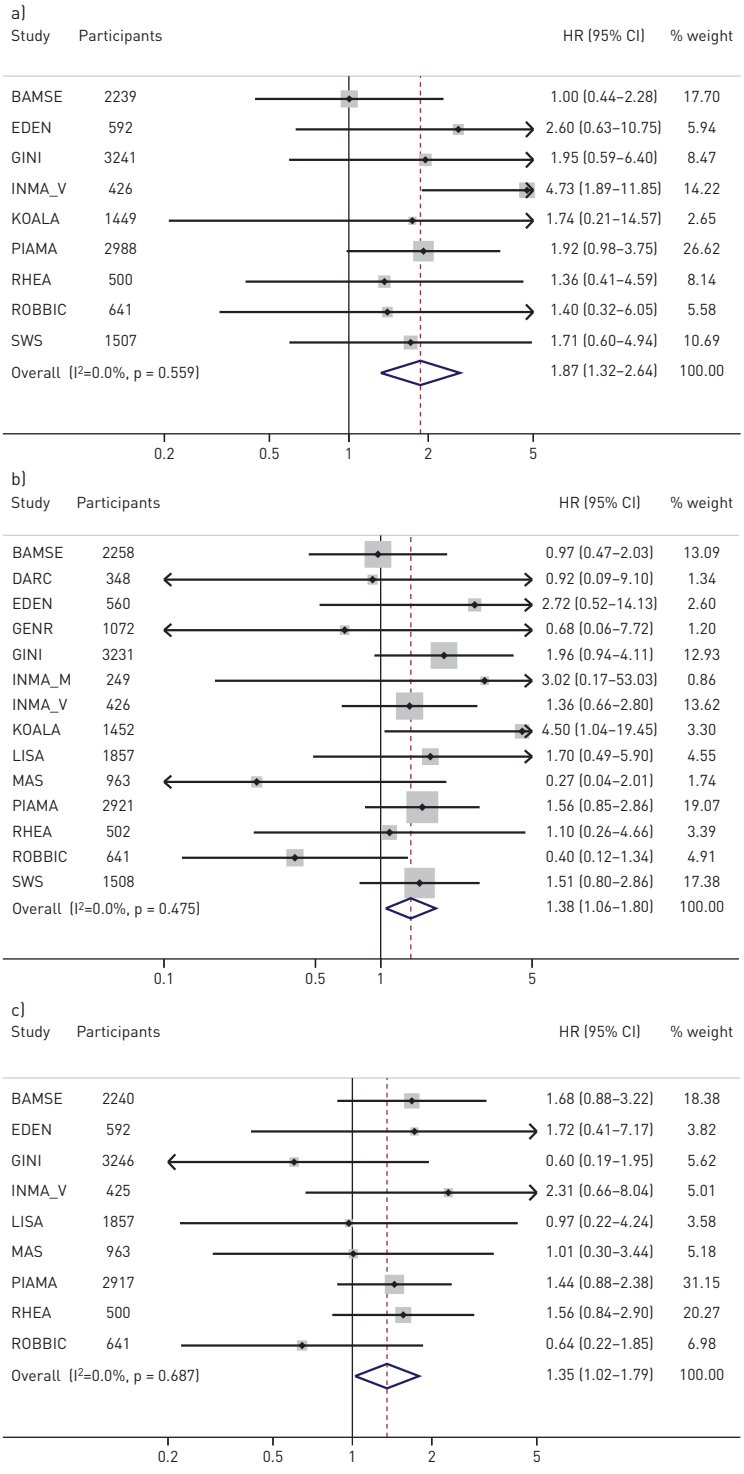

FIGURE 1 Results of individual participant meta-analyses for the association of early-onset asthma and asthma-related phenotypes with incident obesity up to age 8 years. a) Association between baseline asthma and incident obesity. b) Association between baseline wheeze in the last 12 months at 3–4 years of age and incident obesity. c) Association between baseline allergic rhinitis in the last 12 months and incident obesity. Hazard ratios (HR; 95% CI) 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 and birthweight with a 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-study and between-study variability. Horizontal lines denote 95% CIs and diamonds represent overall estimates. The arrows on some of the CIs denote that the upper or lower bound of the confidence interval is past the range of the values shown on the x-axis.

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. As such, 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 characterised by a higher prevalence of allergic disease and T-helper cell Type-2 (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 although 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 (*i.e.* specific IgE measures). Further studies are needed in this direction to differentiate childhood obesity risk between IgE-sensitised and IgE-unsensitised individuals, and those with allergic asthma and nonallergic 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 hypothesised pathways underlying asthma and obesity include systemic inflammation, adipokine dysregulation and shared genetics or epigenetic changes, as well as 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 a child's physical activity and sleep and 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 relationship 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 characteristics and behaviours. Other strengths include the large sample size of the study and the standardised exposure definitions and harmonised covariate information. Given the discrepancy in the literature on the definition

of childhood obesity [42], we tested three definitions and found comparable results that suggested our findings 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; however, 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 behaviours [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 socioeconomic status (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 assessment information, there is the potential for misclassification of obesity in our study. However, we do not expect any misclassification of 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 to the need for further investigation of the factors driving the increased risk of obesity in asthmatic children to better tailor future obesity prevention efforts.

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