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The Role of Childhood Asthma in Obesity Development: A Nationwide U.S. Multi-cohort Study

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Data access statement:

Unfortunately the data used in this study are not able to be shared with external parties. This study was carried out prior to the central compilation of individual-level data in the ECHO program. Data for this study were centrally collected following the execution of analysis-specific Data Use Agreements between each cohort and the Data Analysis Center at Johns Hopkins University. Making this data available to an external party would be in violation of the Data Use Agreements. The investigators are willing to share the code for this analysis upon request.

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Abstract

Rationale: Asthma and obesity often co-occur. It has been hypothesized that asthma may contribute to childhood obesity onset.

Objectives: To determine if childhood asthma is associated with incident obesity and examine the role of asthma medication in this association.

Methods: We studied 8716 children between ages 6–18.5 years who were non-obese at study entry participating in 18 U.S. cohorts of the Environmental influences on Child Health Outcomes program (among 7299 children with complete covariate data mean [SD] study entry age=7.2 [1.6] years and follow-up=5.3 [3.1] years).

Measurements and Main results: We defined asthma based on caregiver report of provider diagnosis. Incident obesity was defined as the first documented body mass index ≥95th percentile for age and sex following asthma status ascertainment. Over the study period, 26% of children had an asthma diagnosis and 11% developed obesity. Cox proportional hazards models with sex-specific baseline hazards were fitted to assess the association of asthma diagnosis with obesity incidence. Children with asthma had a 23% (95%CI: 4%, 44%) higher risk for subsequently developing obesity compared to those without asthma. A novel mediation analysis was also conducted to decompose the total asthma effect on obesity into pathways mediated and not mediated by asthma medication use. Use of asthma medication attenuated the total estimated effect of asthma on obesity by 64% (excess HR:−0.64 [95%CI:−1.05,−0.23]).

Conclusions: This nationwide study supports the hypothesis that childhood asthma is associated with later risk of obesity. Asthma medication may reduce this association and merits further investigation as a potential strategy for obesity prevention among children with asthma.

Keywords

asthma; obesity; childhood; asthma medication; ECHO

INTRODUCTION

In the last several decades, prevalence of obesity and asthma in children have increased worldwide,[1,2] with long-term consequences on health and well-being.[3] This parallel rise has led to research into possible relationships between these two conditions; however, the temporal ordering of obesity and asthma development remains unclear.

While there is convincing evidence that obesity in childhood increases subsequent risk of asthma,[4,5] a handful of recent studies suggest asthma may contribute to onset of childhood obesity and that asthma medication use may play a role in this association.[6,7] For example, a study based on a prospective cohort of schoolchildren in Southern California reported that children with a diagnosis of asthma at 5–8 years of age had an increased risk of

developing obesity during a 10-year follow-up.[6] Use of asthma medication, especially rescue medication, was associated with reduced risk of developing obesity.[6] A study among 16 European pediatric cohorts also observed that young children with asthma at 3–4 years of age were at higher risk for incident obesity up to age 8 years compared to children without asthma.[7] In that study, asthma medication use was associated with increased, rather than decreased, risk of incident obesity.[7] However, asthma diagnosis at such young ages (3–4 years) is prone to misclassification as symptoms (e.g., cough, wheeze, breathlessness) in this age group are varied and might not be specific to asthma but due to a respiratory infection.[8,9] It has been shown that for most children with reported wheezing in early life, symptoms will disappear as they grow.[10] Further, the European study consisted mostly of white children, thus not allowing the possibility to examine whether the impact of asthma on obesity varies by race–ethnicity, which is considered an important demographic determinant of child health.[11] Recently, different asthma incidence rates were observed among non-Hispanic White and Black children in a multi-center analysis across the US.[12] Analysis across diverse populations are needed to examine potential differential associations of asthma with obesity. If asthma indeed increases the risk for developing obesity, then a portion of the obesity epidemic in children may be related to the increased occurrence of asthma or effects of a common etiologic factor. In clinical practice, early interventions for children with asthma may be warranted to prevent future obesity, especially among susceptible populations. However, epidemiologic evidence is limited, and the impact of asthma medication use is uncertain.

The Environmental Influences on Child Health Outcomes (ECHO) program, a National Institutes of Health–funded consortium of child cohorts initiated in 2016, offered the opportunity to examine if asthma was associated with risk of subsequent obesity during childhood and adolescence in a diverse set of US cohorts. We investigated this association for asthma at age 6 years and older due to uncertainty of asthma diagnosis in younger ages. We explored effect modification by race–ethnicity as well as sex. Additionally, we conducted a novel mediation analysis to determine the role of asthma medication use in the asthma–obesity association by quantifying both the mediated effect of asthma on obesity through asthma medication and the interaction between medication use and asthma. This mediation analysis could help uncover potential intervention strategies for obesity prevention for children with asthma.

METHODS

Data Source

We invited cohorts in the ECHO consortium to participate in this analysis based on meeting certain inclusion criteria. Individual data use agreements were signed between the central ECHO Data Analysis Center at the Johns Hopkins Bloomberg School of Public Health and each institution of the cohort that uploaded harmonized individual-level participant data to the Data Analysis Center. Details regarding central data compilation at the Data Analysis Center are provided in the eMethods, Supplemental Digital Content. All participating cohorts had Institutional Review Board approvals from their local institutions, and the work of the Data Analysis Center was approved by the Johns Hopkins Bloomberg School

of Public Health Institutional Review Board. A parent or legal guardian provided written informed consent for each participant.

Study Participants

There were 13,003 total participants from 19 cohorts with at least one valid visit and at least one visit with non-missing height and weight beyond age 6 years. We excluded participants if they met the Center for Disease Control and Prevention (CDC) Body Mass Index (BMI) criteria for obesity (BMI ≥95th percentile for age and sex)[13] at or prior to baseline (defined either at age 6 or at time of cohort entry if it occurred after age 6 years; n=2,202) or with missing BMI between age 3 and 6.5 years or within 6 months of cohort entry if it occurred after age 6 years (n=1,555). We also excluded participants with no data on asthma status (n=530). Applying exclusion criteria removed one cohort completely, leaving 18 cohorts. The final full study sample comprised 8,716 children, among whom 7,299 (from 15 cohorts) had complete data for covariates of interest. A flow diagram showing numbers of children excluded by different exclusion criteria is shown in Figure 1. Data collection among participating cohorts occurred between 1987 through 2018.

Asthma and obesity in childhood

The exposure of interest was asthma diagnosis, which was defined as parent or caregiver report of a healthcare provider diagnosis of asthma. For children who were diagnosed with asthma before 5 years of age, inclusion in this study as a case of asthma required indication of ongoing asthma hospitalizations, symptoms, or medication use at age 5 or later. Children with an early diagnosis of asthma who did not meet any of these criteria were considered to have “transient wheezing” and classified as not having asthma (n=211). For children with asthma, we collected age at asthma diagnosis from cohorts, if available, or set it as age at first visit at which asthma was reported. Participants could have been identified as having an asthma diagnosis any time during the study (i.e., at study entry or during follow-up) with asthma being treated as a time-dependent absorbing state: we categorized a child was categorized as not having asthma until meeting the definition of having asthma, and then we categorized the child as having asthma for the remainder of follow-up time.

Cohorts provided weight and height information for a total of 66,696 visits over the follow-up period (mean [SD] 1.6 [0.9] number of visits/year). Childhood obesity was defined as BMI ≥95th percentile for age and sex according to the U.S. CDC growth charts.[13] We defined an incident case of obesity as the first occurrence of obesity in a child who did not have obesity at baseline, and age of obesity onset as age at that follow-up visit.

Covariate Information

We included the following covariates in this analysis:[6,7] Sex was reported as “male” or “female” based from caregiver reports. Self-identified race and ethnicity were as recorded by the caregiver and harmonized as race–ethnicity being non-Hispanic Black, non-Hispanic White, non-Hispanic Asian, non-Hispanic Other, or Hispanic or Latino. We categorized maternal education as high school or less, some college, or Bachelor’s degree or above. We dichotomized maternal asthmatic history, primiparity, and prenatal smoking as yes or no. We classified calendar year of child’s birth in 5-year age groupings. We used birth weight

in kilograms as a continuous variable. We categorized child health insurance as private plan, public plan, other insurance, or none. We classified asthma medication as rescue medication (e.g., short-acting bronchodilators or B-agonist) and non-rescue medications (e.g., non-steroid controller medications, inhaled corticosteroids, long-acting beta-agonists, oral steroids). Because data were harmonized at the cohort level we decided against imputing missing data.

Data Analysis

Participants with both exposure and outcome information, even if covariate information were incomplete, constituted the "full" study sample, and the subset of the full sample who had complete information on all of the above-mentioned covariates constituted the data sample we refer to hereafter as "complete". Primary analysis was based on the subset with complete data. First, unadjusted Kaplan–Meier curves showing time to obesity by asthma status were fitted. Next, Cox proportional hazards models were applied using age as the time metric with sex-specific baseline hazards to estimate the hazards ratio (HR) for incident obesity associated with prior asthma diagnosis, adjusting for birth year, race–ethnicity, maternal education, maternal asthma history, parity, prenatal maternal smoking, and birth weight with a fixed effect for cohort. Follow-up time began at 6 years of age or at age of cohort entry if it occurred after age 6 years. Follow-up time ended at either age of obesity onset, at last visit with a valid BMI, or at age 18.5 years, whichever came first. We detected no apparent violations of the underlying assumption of proportional hazards per Schoenfeld residuals tests.

Several sensitivity analyses were performed. First, we applied a stricter definition of asthma where children with asthma additionally had to have ever reported wheeze or reported asthma medication use after diagnosis (children with asthma who did not meet this additional criterion were excluded from the analysis). Second, main models were separately re-estimated excluding (i) children who were also overweight (BMI $\geq 85^{th}$ to less than the 95^{th} percentile for age and sex) at baseline, (ii) children considered to have transient wheezing but not asthma, and (iii) children in the largest cohort contributing to this analysis to evaluate whether this single cohort was driving observed effect estimates. Third, we further adjusted for health insurance status as a proxy for healthcare access and socioeconomic status. Fourth, we evaluated effect modification by child's sex and race–ethnicity in separate models by including an interaction term for asthma diagnosis and the potential modifier. Fifth, analyses were repeated using the full study sample without covariate adjustment due to missing data for comparison to main results in complete data sample. Last, cohort-specific estimates were calculated and then combined with fixed effect meta-analysis. We assessed heterogeneity between cohort-specific estimates with the X^2 test from the Cochran Q and I^2 statistic.

To further explore the role of asthma medication use as an intermediate on the pathway between asthma diagnosis and incident obesity, we used a causal four-way decomposition mediation model to partition the total asthma effect into pathways mediated and not mediated by asthma medication use.[14] The four-way decomposition estimates the proportions of total effect attributable to the direct effect of asthma diagnosis (controlled

direct effect; evaluated for medication use=no), to mediation through asthma medication (pure indirect effect), to interaction between asthma diagnosis and medication (reference interaction; evaluated for medication use=no), and to both mediation and interaction (the mediated interaction).[14] This four-way decomposition, compared with the usual two-way decomposition, can provide a more nuanced understanding into the relations between asthma and asthma medication use with obesity risk, including elucidating the roles of mediation and interaction in these relations.[14] Interaction between asthma and medication use, even if effect estimates do not reach statistical significance, may be important in capturing the dynamics of mediation.[15] Asthma medication was treated as a time-dependent absorbing state: a child was categorized as not receiving asthma medication until medication use was reported, and then the child was categorized as receiving asthma medication for the remainder of follow-up time. Asthma medication use was defined as follows: use of asthma medication ever reported before end of follow-up for children without asthma; use of asthma medication reported at visits starting 12 months prior to or after asthma diagnosis through end of follow-up for children with asthma. Supporting the examination of interaction, it has been shown that while most children with asthma have some asthma medication use, about 10–20% do not use medication, and among children without an asthma diagnosis, about 10% have used asthma medication.[16,17] Outcome and mediator models adjusted for the same set of covariates as specified above. We modeled the mediator using logistic regression and additionally adjusted for sex as covariate. We modeled the outcome using a Cox proportional hazards regression with sex-specific baseline hazards; the model additionally included an interaction term between asthma diagnosis and medication use. A directed acyclic graph depicting potential confounding for the medication analysis is shown in eFigure 1, Supplemental Digital Content. Data analysis was performed from December 1, 2018 to April 30, 2020. All analyses were conducted in SAS software, Version 9.4 (SAS Institute Inc., Cary, NC) and Stata Version 16 (StataCorp LLC, College Station, TX).

RESULTS

eFigure 2, Supplemental Digital Content, shows locations of enrollment sites of all contributing cohorts as well as number of participants from each site. Table 1 demonstrates the distribution of sociodemographic and other characteristics among all study participants (n=8716) and the subset of participants with complete covariate data (n= 7299) included in the primary analysis. Overall characteristics of the full and restricted samples were similar. Distribution of characteristics among those excluded versus included in the complete covariate data subset are additionally presented in eTable 1, Supplemental Digital Content. Descriptive data presented here relate to the population with complete data. At study entry, mean (standard deviation [SD]) age was 7.2 (1.6) years, 3634 (50%) were females, and most children were either Non-Hispanic White (n=3607, 49%) or Hispanic (n=2331, 32%). Children with asthma had higher BMI z-scores at study entry compared with children without asthma. Distribution of BMI by sex and age at study entry are reported in eTable 2, Supplemental Digital Content. Mean (SD) length of the study follow-up was 5.3 (3.1) years. During the study period, 1,934 (26%) children were diagnosed with asthma (cumulative incidence) and 777 (11%) children developed obesity. Mean (SD) age at obesity onset was 10.3 (2.9) years. Among the 2,148 children with asthma medication use as defined for the

mediation analysis, 23% (n=490) did not have data for specific medication type, while 27% (n=586) reported using only rescue medication, 9% (n=192) reported using only non-rescue medication, and 41% (n=880) reported using both rescue and non-rescue medications. Mean (SD) age at first reported medication use among medication users (mediation analysis definition) was 6.3 (3.8) years. Children with asthma using medication were more likely to be Non-Hispanic Black and to have a mother with asthma, and less likely to be on a private health insurance plan (eTable 3, Supplemental Digital Content).

Kaplan–Meier curves showed that children with asthma were more likely to develop obesity than those without asthma (eFigure 3, Supplemental Digital Content). Results from main Cox regression models and sensitivity analyses using the population with complete data are presented in Table 2. Based on the adjusted model, children with an asthma diagnosis had a 23% (95% Confidence Interval [CI]: 4%, 44%) higher hazard of developing obesity compared to children without an asthma diagnosis. Crude and adjusted estimates did not differ substantially. Results were similar when a stricter definition of asthma status was used (n=7238; adjusted Hazards Ratio (aHR)=1.2 [95%CI: 1.0, 1.4]). Restricting the analysis to children who were not overweight at baseline produced similar results, albeit with slightly wider confidence intervals (n=5551; aHR=1.3 [95%CI: 0.97, 1.6]). Results from models excluding children with transient wheezing were not markedly different from main models (n=7114; aHR=1.2 [95%CI: 1.0, 1.5]). HRs were of similar magnitude and direction in analyses excluding participants from the largest cohort, but with wider confidence intervals possibly due to smaller sample size (n=2759; aHR=1.2 [95%CI: 0.91, 1.6]). Further adjusting for child health insurance did not markedly change the effect estimate (n=6000; aHR=1.2 [95%CI:1.0, 1.4]). Effect estimates were larger in males (aHR=1.31 [95%CI: 1.07, 1.61]) compared with females (aHR=1.09 [95%CI: 0.84, 1.42]), but confidence intervals were imprecise and there was no evidence of effect heterogeneity (p for interaction=0.27). Non-Hispanic White (aHR=1.5 [95%CI: 1.1, 1.9]) and non-Hispanic Black children (1.5 [95%CI: 1.0, 2.2]) had larger effect estimates compared with Non-Hispanic Other (aHR=1.2 [95%CI: 0.64, 2.2]) and Hispanic (0.96 [95%CI: 0.73, 1.3]), but there was no evidence of effect heterogeneity by race–ethnicity combined (p for interaction=0.10). We observed similar results when using the full study population (eTable 4, Supplemental Digital Content). Results from the main, pooled analysis (adjusted for cohort) were similar to those from the fixed effect meta-analysis (aHR=1.3 [95%CI: 1.1–1.5]) and there was no evidence of heterogeneity between cohort-specific estimates (I^2 = 0%, P for heterogeneity= 0.32; eFigure 4, Supplemental Digital Content).

A graph depicting a direct effect of asthma on obesity risk and an indirect effect mediated through asthma medication is shown in Figure 1. The decomposition of the total effect among the 7,016 children with medication use data are presented in Table 3 and interpreted in Figure 3 and eTable 5, Supplemental Digital Content, using the counterfactual framework. The controlled direct effect of asthma on obesity risk—the effect through pathways independent of medication use—was an excess HR of 0.82 (0.27, 1.4), indicating a positive relationship between asthma and subsequent obesity. We observed a negative pure indirect effect through asthma medication use (mediated main effect not due to interactions—i.e., effect of asthma medication use in the absence of asthma diagnosis multiplied by effect of asthma diagnosis on asthma medication use itself), with an excess HR of −0.34 (−0.47,

−0.20). The mediated interaction was suggestive of a negative relationship (excess HR= −0.30 [−0.73, 0.12]). This suggests that the estimated effect of being asthmatic and using medication on obesity risk is 30% less than the sum of those of asthma alone and medication use alone that occurs when asthma diagnosis affects likelihood of medication use. The four mediation-interaction components can be combined into two components representing the effect not mediated through medication use (pure direct effect) and the effect mediated through medication use (total indirect effect). As shown in Table 3 and Figure 3, we estimated that the pure direct effect was a positive excess HR of 0.78 (78% higher risk; [95%CI: 0.28, 1.3]) and the total indirect effect was a negative excess HR of −0.64 (64% lower risk; [95%CI: −1.1, −0.23]).

DISCUSSION

In this large, nationwide U.S. multi-cohort study, we found that asthma diagnosis was associated with a 23% higher incidence of subsequent obesity in childhood and adolescence. We also studied the role of asthma medication in this association using a novel mediation analysis and estimated a 64% lower obesity risk among children with asthma who were using asthma medication at a higher proportion compared with children with asthma who were using asthma medication at a lower

proportion. Inclusion of cohorts from several states around the U.S. and absence of heterogeneity between cohort-specific effect estimates support the robustness of our results. There was some suggestive evidence of differential effects of asthma on subsequent obesity by race–ethnicity. This may warrant further research, with careful discussion regarding potential hypotheses for differential effects.

Our findings of a positive association between asthma diagnosis and risk for incident obesity during childhood and adolescence extend previous epidemiologic evidence in both children[6,7] and adults[18,19] supporting a role of asthma in obesity development. In line with our findings of a potential protective role of asthma medication in the asthma–obesity association, a previous analysis from the Southern California Children's Health Study reported asthmatic children receiving medication had a reduced risk of developing obesity later in childhood and adolescence.[6] It may be that use of medication for treating asthma leads to better managed asthma, which helps to disrupt the cycle of asthma increasing obesity risk, with obesity in turn worsening asthma symptoms and related morbidity[20] leading to additional weight gain. Alternatively, medication use could represent more severe asthma, which we could not explore here due to insufficient data; however, we would expect more severe asthma would be associated with higher obesity risk, whereas we observed the opposite for medication use (i.e., lower obesity risk). Our study design controlled for the temporal relationship between asthma diagnosis, asthma medication use, and subsequent obesity in our analysis; however, additional assumptions are required for causal interpretation of the mediation analysis,[14] including no unmeasured confounding between asthma diagnosis, asthma medication use, and obesity, and that none of the mediator-outcome confounders are affected by exposure. We used a directed acyclic graph to evaluate potential confounding, but it is possible it may not include all potential confounding pathways. For example, socioeconomic status (SES), a complex determinant of health,

may confound medication use and obesity risk. Children from families with higher SES might experience better health care and access to medication.[21] High SES in turn has been associated with lower obesity, especially in high-income countries,[22,23] and thus, could negatively confound our results. In our analysis we did not observe strong confounding by race–ethnicity, maternal education, nor child health insurance which can capture SES variability; however, these variables may not fully account for SES variability and thus residual confounding is possible. Medication use could also be associated with higher physical activity, as physically active children with asthma may be more likely to be prescribed asthma medication. Because data on physical activity were limited, we could not examine the extent to which these factors could explain the effect of asthma medication on obesity risk. In the context of an observational study, such as this one, it is not possible to examine if assumptions for causality are fully met; hence, caution must be taken not to over-interpret our mediation results.

There are also some hypothesized biologic pathways supporting a direct effect of asthma medication on obesity development. B-agonists, a commonly prescribed asthma medication, might affect fat metabolism and protect against obesity.[24] B-adrenergic receptors, which are present in various tissues including adipose tissue and skeletal muscle, play a key role in sympathetic regulation of fat metabolism and thermogenesis.[25,26] Human trials support an anti-obesogenic role of B2-agonists by showing B2-agonist administration can augment fat utilization and energy expenditure in adults.[27–29] In contrast, inhaled corticosteroids, another type of asthma medication, have been suggested to affect the hypothalamic-pituitary-adrenal axis,[30] and higher doses have been associated with weight gain and obesity risk in some studies,[31,32] but not all.[33,34] In the present study, there was insufficient information on type and frequency of use of asthma medication (B-agonists *vs* inhaled corticosteroids), and, thus, we could not examine potential differential effects on obesity incidence among asthmatics. Further research incorporating information on medication type is needed to disentangle the potential influence of asthma medication on obesity.

This study has several strengths. First, use of individual participant data from several cohorts participating in the ECHO program throughout the U.S (from West to East) with varied background characteristics and behaviors and the absence of heterogeneity between individual cohort effect estimates suggests findings are not restricted to one cohort and improves generalizability of our findings. Second, pooling the study population across multiple cohorts allowed for a large sample size for analyses. Third, the centralized data analysis followed a consensus analytic protocol with standardized exposure and outcome definitions and harmonized covariate information across all cohorts. Last, the longitudinal design with children without obesity at baseline allowed us to confirm asthma onset preceded occurrence of obesity. Our study addresses several limitations of the few previous studies, such as small sample size, short duration of follow up, and potential asthma misclassification due to use of only baseline asthma at a young age rather than repeated assessment during childhood.

Our study has also some limitations. First, asthma diagnosis was assessed by parental report of healthcare provider diagnosis, rather than a clinical evaluation of asthma, thus misclassification in asthma status ascertainment is possible. Nevertheless, studies examining

the validity of questionnaire-based asthma diagnosis in children, using questions similar to those used in the current study, have reported a specificity higher than 95% compared with health claims as the reference standard[35,36] and a specificity higher than 87% compared with a clinical assessment as the standard.[37,38] Furthermore, use of a stricter definition of asthma to reduce potential misclassification yielded similar results. Second, there was limited information on SES and childhood lifestyle factors (e.g., physical activity, diet) to examine whether and to what extent these factors could confound the asthma–obesity association or the mediation analysis. However, our results were robust to adjustment for confounding by mother's education, child race–ethnicity, and health insurance status, which are proxies for SES variability previously linked to child health.[11,39–41] With an observed aHR=1.2 for the association of asthma with obesity risk, an unmeasured confounder that was associated with both asthma and obesity by a risk ratio of 1.75-fold each (75% increase), above and beyond the measured confounders, could explain away the estimate, but weaker confounding could not.[42] For comparison, HRs for obesity in relation to maternal education and race–ethnicity, two established SES-related risk factors for both asthma and obesity, ranged from 0.70 (30% decrease) to 1.50 (50% increase) in our study. Given our study design, we could not adjust for BMI at time of asthma diagnosis, and thus rule out any possibility of reverse causality. However, in an additional analysis in which we excluded children with overweight at baseline, results remained in the same direction but slightly attenuated (HR=1.26 [95% CI 0.97,1.64] for sensitivity analysis excluding overweight children at baseline vs 1.23 [95% CI 1.04, 1.44] for main analysis), possibly due to low obesity incidence. Finally, the obesity definition used in our analysis was derived from BMI, a measure that incorporates both lean and fat mass; however, a high BMI has been suggested as a sensitive marker for excess adiposity.[43] Further analyses using direct measurements of fat mass and body fat distribution to assess the relationship between asthma and obesity during childhood could shed light on the roles of fat mass and its distribution.

In summary, this large, nationwide U.S. study supports the hypothesis that children with asthma are at higher risk for developing obesity later in childhood and adolescence, and that this association may be differential by asthma medication use. Our findings highlight the need to further understand factors and mechanisms affecting obesity risk in asthmatic children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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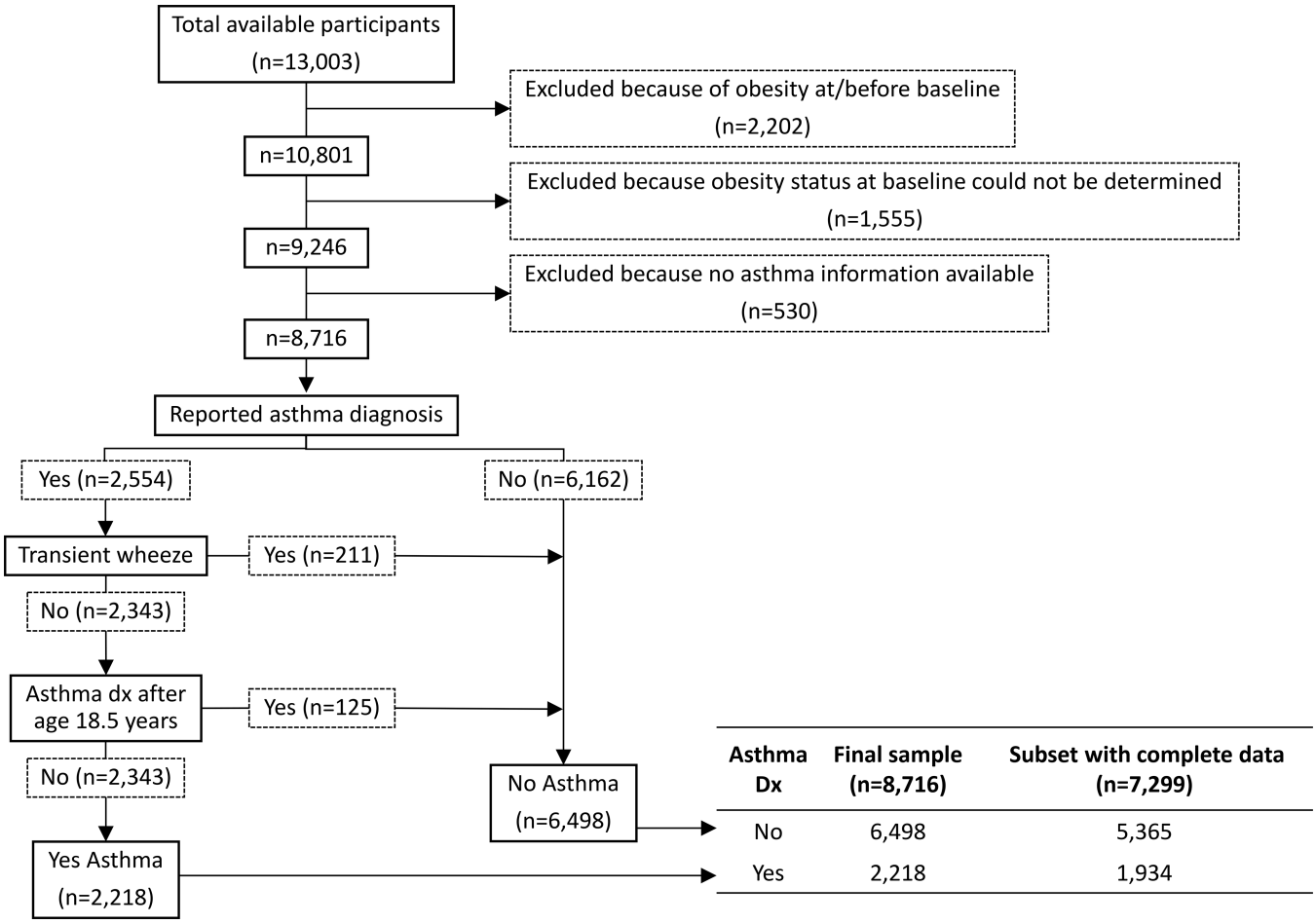
REFERENCES

1. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758–766. [PubMed: 17504817]
2. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–2642. [PubMed: 29029897]
3. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169–1179. [PubMed: 29627041]
4. Lang JE, Bunnell HT, Hossain MJ, et al. Being Overweight or Obese and the Development of Asthma. Pediatrics. 2018;142(6).
5. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. BMC Pediatr. 2013;13:121. [PubMed: 23941287]

6. Chen Z, Salam MT, Alderete TL, et al. Effects of Childhood Asthma on the Development of Obesity among School-aged Children. Am J Respir Crit Care Med. 2017;195(9):1181–1188. [PubMed: 28103443]
7. 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;52(3).
8. Trivedi M, Denton E. Asthma in Children and Adults-What Are the Differences and What Can They Tell us About Asthma? Front Pediatr. 2019;7:256. [PubMed: 31294006]
9. National Asthma Education and Prevention Program. Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007.
10. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332(3):133–138. [PubMed: 7800004]
11. Cheng TL, Goodman E, Committee on Pediatric R. Race, ethnicity, and socioeconomic status in research on child health. Pediatrics. 2015;135(1):e225–237. [PubMed: 25548336]
12. Johnson CC, Chandran A, Havstad S, et al. US Childhood Asthma Incidence Rate Patterns From the ECHO Consortium to Identify High-Risk Groups for Primary Prevention. JAMA Pediatr. 2021:e210667.
13. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002(246):1–190.
14. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. Epidemiology. 2014;25(5):749–761. [PubMed: 25000145]
15. VanderWeele T. Explanation in causal inference: methods for mediation and interaction. New York: Oxford University Press; 2015.
16. Korelitz JJ, Zito JM, Gavin NI, et al. Asthma-related medication use among children in the United States. Ann Allergy Asthma Immunol. 2008;100(3):222–229. [PubMed: 18426141]
17. Lozano P, Finkelstein JA, Hecht J, Shulruff R, Weiss KB. Asthma medication use and disease burden in children in a primary care population. Arch Pediatr Adolesc Med. 2003;157(1):81–88. [PubMed: 12517200]
18. Hasler G, Gergen PJ, Ajdacic V, et al. Asthma and body weight change: a 20-year prospective community study of young adults. Int J Obes (Lond). 2006;30(7):1111–1118. [PubMed: 16491113]
19. Moitra S, Carsin AE, Abramson M, et al. Effect of asthma on the development of obesity among adults: Results of the European Community Respiratory Health Survey (ECRHS). Eur Respir J. 2018;52: OA297.
20. Moreira A, Bonini M, Garcia-Larsen V, et al. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). Allergy. 2013;68(4):425–439. [PubMed: 23452010]
21. Stockholm Convention on Persistent Organic Pollutants. 2009; http://chm.pops.int/TheConvention/POPsReviewCommittee/ReportsandDecisions/tabid/3309/Default.aspx. Accessed May 18, 2020.
22. Frederick CB, Snellman K, Putnam RD. Increasing socioeconomic disparities in adolescent obesity. Proc Natl Acad Sci U S A. 2014;111(4):1338–1342. [PubMed: 24474757]
23. Datar A, Chung PJ. Changes in Socioeconomic, Racial/Ethnic, and Sex Disparities in Childhood Obesity at School Entry in the United States. JAMA Pediatr. 2015;169(7):696–697. [PubMed: 25984706]
24. Enoksson S, Talbot M, Rife F, Tamborlane WV, Sherwin RS, Caprio S. Impaired in vivo stimulation of lipolysis in adipose tissue by selective beta2-adrenergic agonist in obese adolescent girls. Diabetes. 2000;49(12):2149–2153. [PubMed: 11118019]
25. Bachman ES, Dhillon H, Zhang CY, et al. betaAR signaling required for diet-induced thermogenesis and obesity resistance. Science. 2002;297(5582):843–845. [PubMed: 12161655]
26. Arner P, Wahrenberg H, Lonnqvist F, Angelin B. Adipocyte beta-adrenoceptor sensitivity influences plasma lipid levels. Arterioscler Thromb. 1993;13(7):967–972. [PubMed: 8391311]
27. Lee P, Day RO, Greenfield JR, Ho KK. Formoterol, a highly beta2-selective agonist, increases energy expenditure and fat utilisation in men. Int J Obes (Lond). 2013;37(4):593–597. [PubMed: 22641064]

28. Onslev J, Jacobson G, Narkowicz C, et al. Beta2-adrenergic stimulation increases energy expenditure at rest, but not during submaximal exercise in active overweight men. Eur J Appl Physiol. 2017;117(9):1907–1915. [PubMed: 28702809]
29. Amoroso P, Wilson SR, Moxham J, Ponte J. Acute effects of inhaled salbutamol on the metabolic rate of normal subjects. Thorax. 1993;48(9):882–885. [PubMed: 8236068]
30. Zollner EW, Lombard CJ, Galal U, Hough FS, Irusen EM, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic school children. Pediatrics. 2012;130(6):e1512–1519. [PubMed: 23147980]
31. Han J, Nguyen J, Kim Y, et al. Effect of inhaled corticosteroid use on weight (BMI) in pediatric patients with moderate-severe asthma. J Asthma. 2019;56(3):263–269. [PubMed: 29672188]
32. 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. [PubMed: 16227047]
33. Salvatoni A, Nosetti L, Broggini M, Nespoli L. Body composition and growth in asthmatic children treated with inhaled steroids. Ann Allergy Asthma Immunol. 2000;85(3):221–226. [PubMed: 11030277]
34. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Evid Based Child Health. 2014;9(4):931–1046. [PubMed: 25504973]
35. Nwaru BI, Lumia M, Kaila M, et al. Validation of the Finnish ISAAC questionnaire on asthma against anti-asthmatic medication reimbursement database in 5-year-old children. Clin Respir J. 2011;5(4):211–218. [PubMed: 21801323]
36. Yang CL, To T, Foty RG, Stieb DM, Dell SD. Verifying a questionnaire diagnosis of asthma in children using health claims data. BMC Pulm Med. 2011;11:52. [PubMed: 22108202]
37. Hansen TE, Evjenth B, Holt J. Validation of a questionnaire against clinical assessment in the diagnosis of asthma in school children. J Asthma. 2015;52(3):262–267. [PubMed: 25233047]
38. Fuso L, de Rosa M, Corbo GM, et al. Repeatability of the ISAAC video questionnaire and its accuracy against a clinical diagnosis of asthma. Respir Med. 2000;94(4):397–403. [PubMed: 10845441]
39. Lewis KM, Ruiz M, Goldblatt P, et al. Mother's education and offspring asthma risk in 10 European cohort studies. Eur J Epidemiol. 2017;32(9):797–805. [PubMed: 28929268]
40. Le-Scherban F, Moore J, Headen I, Utidjian L, Zhao Y, Forrest CB. Are there birth cohort effects in disparities in child obesity by maternal education? Int J Obes (Lond). 2021;45(3):599–608. [PubMed: 33335294]
41. Mehta NK, Lee H, Ylitalo KR. Child health in the United States: recent trends in racial/ethnic disparities. Soc Sci Med. 2013;95:6–15. [PubMed: 23034508]
42. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268–274. [PubMed: 28693043]
43. Boeke CE, Oken E, Kleinman KP, Rifas-Shiman SL, Taveras EM, Gillman MW. Correlations among adiposity measures in school-aged children. BMC Pediatr. 2013;13:99. [PubMed: 23799991]



Asthma Dx	Final sample (n=8,716)	Subset with complete data (n=7,299)
No	6,498	5,365
Yes	2,218	1,934

Figure 1:

Flow diagram depicting exclusion of participants and exposure definition for asthma in the study. Obesity status at baseline could not be determined when body mass index (BMI) information was missing at baseline. Subset with complete data is a subset of the full study sample with no missing values for the covariates birth year, ethnicity/race, maternal education, maternal asthmatic history, parity, prenatal maternal smoking, and birth weight.

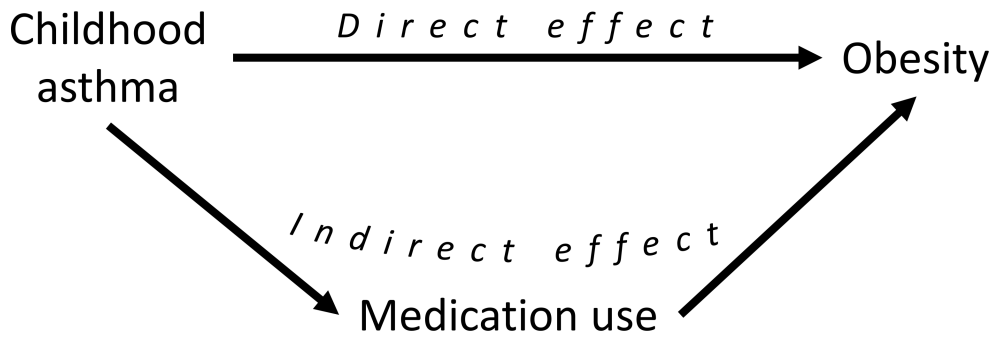


Figure 2.
Graph depicting a direct effect of childhood asthma on obesity risk and an indirect effect mediated through asthma medication use.

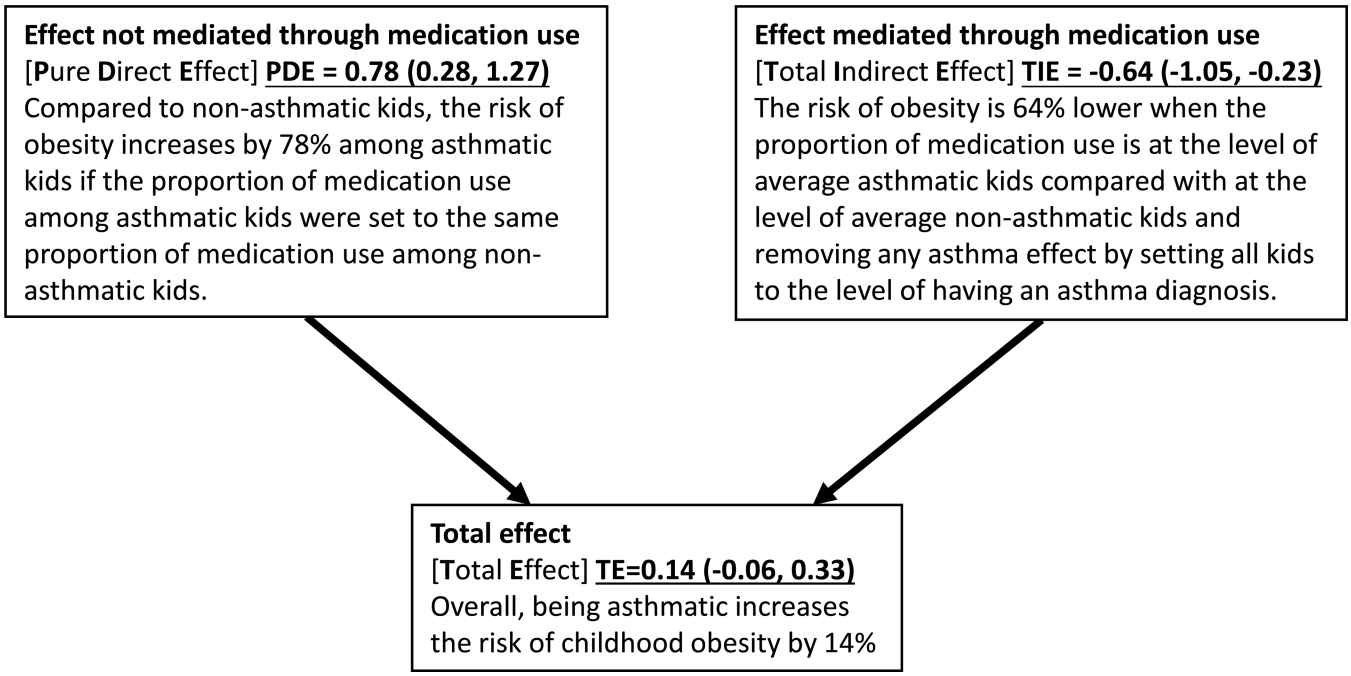


Figure 3.
Interpretations for effect estimates of being asthmatic on risk of childhood obesity from the mediation-interaction decomposition analysis using the counterfactual framework.

Table 1.

Distribution of sociodemographic and other characteristics among all study participants and subset of participants with complete data.

	Full Study Population (n=8716)			Complete Data (n=7299)
	Overall	Asthma (n=2218)	No Asthma (n=6498)	Overall
Age at entry (yrs), mean (SD)	7.27 (1.64)	7.29 (1.66)	7.26 (1.63)	7.21 (1.61)
Sex, N (%)				
Male	4376 (50.2)	1229 (55.4)	3147 (48.4)	3665 (50.2)
Female	4340 (49.8)	989 (44.6)	3351 (51.6)	3634 (49.8)
Birth weight (kg), mean (SD)	3.38 (0.55)	3.34 (0.58)	3.39 (0.54)	3.39 (0.56)
Birth year, median (IQR)	1996 (1986, 2001)	1996 (1986, 2001)	1996 (1986, 2001)	1996 (1986, 2000)
Prenatal maternal smoking, N (%)				
Yes	908 (10.4)	239 (10.8)	669 (10.3)	689 (9.4)
No	7630 (87.5)	1947 (87.8)	5683 (87.5)	6610 (90.6)
Missing	178 (2.0)	32 (1.4)	146 (2.2)	0 (0)
Race–ethnicity, N (%)				
Non-Hispanic White	4135 (47.4)	977 (44)	3158 (48.6)	3607 (49.4)
Non-Hispanic Black	955 (11)	357 (16.1)	598 (9.2)	821 (11.2)
Non-Hispanic Asian	211 (2.4)	52 (2.3)	159 (2.4)	155 (2.1)
Non-Hispanic Other	466 (5.3)	142 (6.4)	324 (5)	385 (5.3)
Hispanic	2790 (32)	667 (30.1)	2123 (32.7)	2331 (31.9)
Missing	159 (1.8)	23 (1)	136 (2.1)	0 (0)
Maternal asthmatic history, N (%)				
Yes	1361 (15.6)	553 (24.9)	808 (12.4)	1219 (16.7)
No	7034 (80.7)	1597 (72)	5437 (83.7)	6080 (83.3)
Missing	321 (3.7)	68 (3.1)	253 (3.9)	0 (0)
Parity: primiparous, N (%)				
Yes	4913 (56.3)	1210 (54.6)	3703 (57)	4217 (57.8)
No	3539 (40.6)	976 (44)	2563 (39.4)	3082 (42.2)
Missing	264 (3)	32 (1.4)	232 (3.6)	0 (0)
Maternal education, N (%)				
High school or less	2522 (28.9)	654 (29.5)	1868 (28.7)	2328 (31.9)
Some college	2796 (32.1)	748 (33.7)	2048 (31.5)	2590 (35.5)
College or above	2526 (29)	606 (27.3)	1920 (29.5)	2381 (32.6)
Missing	872 (10)	210 (9.5)	662 (10.2)	0 (0)
BMI z-score at study entry, mean (SD)				
Children with asthma	-	0.16 (0.93)	-	0.16 (0.91)
Children without asthma	-	-	0.09 (0.95)	0.09 (0.94)
Asthma medication use around or after asthma diagnosis[a], N (%)				
Yes	2441 (28)	1687 (76.1)	754 (11.6)	2148 (29.4)

	Full Study Population (n=8716)			Complete Data (n=7299)
	Overall	Asthma (n=2218)	No Asthma (n=6498)	Overall
No	5798 (66.5)	405 (18.3)	5393 (83)	4868 (66.7)
Missing	477 (5.5)	126 (5.7)	351 (5.4)	283 (3.9)

[a] As defined in the mediation analysis: Any asthma medication use before the end of follow-up for children without asthma; Any asthma medication use reported at visits starting 12 months prior to or after asthma diagnosis through the end of follow-up of children with asthma.

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 2.

Hazard Ratios (HR) and 95% confidence intervals (95% CI) for incident obesity associated with asthma diagnosis among study participants with complete data

	N	Unadjusted HR (95%CI)	Adjusted[a] HR (95%CI)
All	7299	1.2 (1.1, 1.5)	1.2 (1.0, 1.4)
Asthma definition further requiring a report wheeze or medication use after diagnosis	7238	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)
Excluding children overweight at baseline	5551	1.4 (1.1, 1.8)	1.3 (0.97, 1.6)
Excluding children with transient wheezing at baseline	7114	1.2 (1.1, 1.5)	1.2 (1.0, 1.5)
Excluding the largest cohort	2759	1.2 (0.9, 1.6)	1.2 (0.91, 1.6)
Further adjusting for child health insurance	6000	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)
Effect measure modification by sex			
Male	3665	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)
Female	3634	1.1 (0.85, 1.4)	1.1 (0.84, 1.4)
P-interaction		*0.26*	*0.27*
Effect measure modification by race–ethnicity			
Non-Hispanic White	3607	1.5 (1.2, 1.9)	1.5 (1.1, 1.9)
Hispanic	2331	0.94 (0.7, 1.2)	0.96 (0.73, 1.3)
Non-Hispanic Black	821	1.5 (1.0, 2.2)	1.5 (1.0, 2.2)
Other/Mixed	540	1.2 (0.7, 2.2)	1.2 (0.64, 2.2)
P-interaction		*0.08*	*0.10*

All models included fixed effect for cohort and sex-specific baseline hazards.

[a]Adjusted for cohort, birth year, race–ethnicity, maternal education, maternal asthma history, parity, prenatal maternal smoking, birth weight.

Table 3.

Excess Hazards Ratios (HR) estimated from four-way mediation-interaction decomposition adjusted models, n=7016.

Component	Excess HR (95%CI)
Pure Direct Effect	0.78 (0.28, 1.3)
Controlled Direct Effect	*0.82 (0.27, 1.4)*
Interaction$_{reference}$	*−0.04 (−0.10, 0.02)*
Total Indirect Effect	−0.64 (−1.1, −0.23)
Pure Indirect Effect	*−0.34 (−0.47, −0.20)*
Interaction$_{mediation}$	*−0.30 (−0.73, 0.12)*
Total effect	0.14 (−0.06, 0.33)

The four mediation-interaction components can be combined into two components representing the effect not mediated through medication use (pure direct effect) and the effect mediated through medication use (total indirect effect). Outcome and mediator models were adjusted for cohort as a fixed effect, birth year, race–ethnicity, maternal education, maternal asthma history, parity, prenatal maternal smoking, and birth weight. We modeled the outcome using a Cox proportional hazards regression with sex-specific baseline hazards. We modeled the mediator using logistic regression and additionally adjusted for sex.