# Title: Effects of Childhood Asthma on the Development of Obesity among School-aged Children

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Word Counts: (Text: 3498, limit 3500/Abstract: 246, limit 250) Tables: 3 Figure: 1
Supplementary Tables: 10

**Short Running Title:** Asthma Increases the Development of Obesity
**Contributions of All Authors:**

Z.C. and F.D.G. conducted the analyses and wrote the article. F.D.G. and K.B. contributed to study design and data collection. M.T.S., T.L.A., K.B., R.K., and T.M.B edited the article and contributed to discussion. All authors reviewed the article. Z.C. and F.D.G. are the guarantors of this work, and as such, 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. All authors declare that they have no conflict of interest.

**Key words:** Asthma, Wheeze, Obesity, Overweight, Children, Longitudinal

## ABSTRACT

***Rationale:*** Asthma and obesity often occur together in children. It is unknown whether asthma contributes to the childhood obesity epidemic.

***Objectives:*** We aimed to investigate the effects of asthma and asthma medication use on the development of childhood obesity.

***Methods:*** The primary analysis was conducted among 2,171 non-obese children who were 5-8 years of age at study enrollment in the Southern California Children's Health Study (CHS) and were followed for up to 10 years. A replication analysis was performed in an independent sample of 2,684 CHS children followed from mean age of 9.7 to 17.8 years.

***Measurements and Main Results:*** Height and weight were measured annually to classify children into normal, overweight and obese categories. Asthma status was ascertained by parent- or self-reported physician-diagnosed asthma. Cox proportional hazards models were fitted to assess associations of asthma history with obesity incidence during follow-up.





***Results:*** We found that children with a diagnosis of asthma at cohort entry were at 51% increased risk of developing obesity during childhood and adolescence compared to children without asthma at baseline [HR (95% CI)=1.51 (1.08, 2.10)] after adjusting for confounders. Use of asthma rescue medications at cohort entry reduced the risk of developing obesity [HR (95% CI)=0.57 (0.33, 0.96)]. Additionally, the significant association between asthma history and increased risk of developing obesity was replicated in an independent CHS sample.

***Conclusions:*** Children with asthma may be at higher risk of obesity. Asthma rescue medication use appeared to reduce obesity risk independent of physical activity.

## INTRODUCTION

The prevalence of obesity and asthma among both children and adults have increased dramatically over the past several decades (1). A large body of evidence has documented the co-occurrence of asthma and obesity suggesting that the pathobiology of these common conditions may be related (2). Several mechanisms have been proposed that link obesity and asthma, including obesity-influenced lung physiology such as reductions in pulmonary compliance and limitations in airflow, systemic inflammation, dysfunctions of the sympathetic nervous system and common genetic factors (3).

Numerous studies have shown increased risk of asthma and more severe respiratory symptoms among overweight or obese children (4, 5) and adults (6, 7). Although longitudinal studies have documented obesity as a risk factor for asthma incidence (8-11), it is unclear whether children with asthma are at higher risk for the development of obesity. Several risk factors for obesity are more prevalent among children with asthma including reduced physical activity (12) and potential adverse effects from corticosteroid medications (13). If asthma 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 the effects of a common etiologic factor. It follows that early interventions for children with asthma could play a role in preventing obesity and related metabolic diseases since obese children are at higher risk for adult obesity and other metabolic diseases (14-16).



In this study, we investigated the effects of asthma and related phenotypes on the development of obesity in a cohort of non-obese kindergarten and 1st grade children (ages 5.2-7.9 years) participating in the southern California Children's Health Study (CHS). We selected children who were not obese at cohort entry and examined obesity incidence over a 10-year follow-up to assess the hypothesis that children presenting with asthma in early life are at increased risk of developing obesity during childhood and adolescence. In order to confirm the robustness of our findings, we performed a replication analysis in an independent cohort of CHS children who were non-obese at cohort entry and were followed from mean age of 9.7 to 17.8 years. Additionally, we assessed whether asthma medication use influenced the risk of developing obesity in primary study cohort.

## METHODS



### Study Design

The CHS study design has been described in detail previously (17-19). Briefly, children from eight Southern California communities were followed from kindergarten or 1st grade to high school graduations with an original enrollment of 3,474 subjects in Cohort E. In the primary analysis, we included 2,706 who were non-obese at study entry. We then excluded 348 subjects with only one assessment (no follow-up data), 19 subjects with baseline age greater than 8 years old, and 168 subjects who did not have complete asthma history information at study entry. The current analysis focused on 2,171 children who were recruited from schools in eight communities starting in year 2002 and 2003, and were followed up till 10 years after up to year 2012. Additionally, a replication study was performed in an independent CHS study sample (Cohorts C and D combined), in which children were recruited from 4th grade in year 1992 and 1994, and followed untill high school graduation. From the original 3,887 children, we excluded children who were obese (n=448), missing BMI data (n=186) at cohort entry, had only one visit with BMI data (n=471), or were missing asthma history data (n=98) at the cohort entry. As such, 2,684 children contributed to the replication sample. The University of Southern California Institutional Review Board approved the study protocol.

**Exposure and Outcomes Assessment**

At study entry, written parental informed consent and student assent were obtained for all CHS participants. Children were examined annually or bi-annually during the follow-up period. Parents completed a self-administered questionnaire on socio-demographic factors, history of respiratory illness, physical activity patterns, smoking exposures at home, and other household characteristics. Questionnaires were completed by parents from baseline to year 5, and by children from follow-up year 6 (ages 10-13 years) onwards. At each study visit, asthma history was classified based on a yes/no response to the question “Has a doctor ever diagnosed this child as having asthma?” Agreement of parental report of asthma has been previously assessed by reviewing a sample of medical records and 96% agreement was observed (20). Active asthma was defined as children with lifetime asthma and wheeze during the previous year of the study visit. History of asthma medication use was assessed based on questions about any rescue, controller and other medication use for asthma or wheezing in the last 12 months. Photographic charts of medications and inhalers were used to collect information on use of specific medications. The age of asthma onset was classified into “early” (up to and including four years of age) and “late” (after four years of age). Physical activity status was collected based on responses to questions about the number of exercise classes attended and weekly days of outdoor sports in the last 12 months. Smoking exposures at home were defined based on yes/no responses to questions “Does anyone living in this child’s home currently smoke cigarettes, cigars or pipes on a daily basis?” and “Did this child’s biologic mother smoke while she was pregnant with this child?”. Similar parents- or self-reported questionnaires were also collected annually in the replication study sample, except the category of asthma medication use was not collected, and the physical activity status was collected based on responses to the question about the number of sports teams participated in the last 12 months.

Children enrolled in the CHS had height and weight measured by a trained technician at every study visit following a standardized protocol. These objective measures of height and weight were used to calculate body mass index (BMI: kg of weight/height in $m^2$). BMI-defined overweight and obese categories were determined using the $85^{th}$ and $95^{th}$ BMI percentile thresholds based on the age and sex-specific Center for Disease Control (CDC) 2000 BMI growth curves (21). An incidence case of obesity was defined as the first occurrence of obesity in a child who was not obese at the cohort entry.



**Statistical Analysis**

Socio-demographic, physical activity and smoking exposures were classified into categories for descriptive analyses. Baseline history of asthma medication use was classified into no medication use, using rescue medications, using non-steroid controller medications, and using steroid asthma medications. Participants who developed obesity during the study follow-up were censored at the midpoint of the follow-up period between the prior visit when they were not obese and the next visit when they were first determined to be obese. Participants who were not obese during the entire study follow-up were either censored at the end of study follow-up or when they were lost to follow-up. Cox proportional hazards models were fitted to explore univariate associations between baseline characteristics and obesity incidence during follow-up from the baseline visit to the time when participants were censored. Cox proportional hazards models with sex-specific baseline hazards were used to analyze the association of asthma and other asthma-related respiratory health at cohort entry (wheezing and asthma medication usage) with obesity incidence during follow-up. Baseline child and home characteristics such as age, sex, race/ethnicity, overweight status, parent's education, household annual income, child's health insurance coverage, physical activity status, and second-hand and *in utero* smoking exposure, and a fixed effect of the community of residence were included as confounders. Follow-up physical activity status and asthma medication use during follow-up were additionally considered in the analysis using time-dependent variables. Missing data was not imputed in the analysis. Participants with missing covariate information were included in the analysis using the missing indicator method. Interactions between baseline asthma status and baseline characteristics were tested for by including a multiplicative interaction term in the model. Stratified analysis was conducted to explore heterogeneity in effects by sex, Hispanic ethnicity, and baseline overweight status.



For sensitivity analysis, we first investigated whether asthma and asthma-related respiratory phenotypes were associated with the risk of becoming either overweight or obese using Cox proportional hazards models, adjusted for the aforementioned confounders. In this analysis, we studied a subsample of children who had normal BMI at baseline and used the outcome as occurrence of being overweight or obese during the follow-up. Second, we investigated whether our results were significantly influenced by children who had no asthma history at baseline but developed asthma during the follow-up period. Third, we restricted obesity incidence as children who developed obesity and were obese at two or more study visits during the entire follow-up. This analysis was conducted to determine if our results were influenced by the recurrence of obesity. Lastly, we assessed potential biases from loss to follow-up by excluding subjects who did not complete the entire 10-year study follow-up. In addition, a replication analysis was performed in the CHS replication sample for associations between asthma and other asthma-related respiratory health at cohort entry with the risk of developing obesity during follow-up using similar cox proportional hazards model adjusting for potential confounders including the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage, number of teams sports attended in the previous year, overweight status, past and current second-hand smoke, and follow-up number of teams sports attended as a time-dependent variable with a sex-specific baseline hazard. All statistical tests were two-sided at a 0.05 significance level. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used for data analysis.

## RESULTS

Participant characteristics at study entry are presented in Tables 1 and 2. At entry, the mean age was 6.6±0.6 years, 1,084 (49.9%) were girls, 398 (18.3%) children were overweight, and 292 (13.5%) children had diagnosed asthma. The median length of follow-up was 6.9 (inter-quartile range: 2.3 - 8.6) years with 4.3 follow-up visits on average. During the follow-up, 342 (15.8%) children developed obesity.

Table 1 presents univariate associations of child and family characteristics at study entry with obesity incidence during the follow-up period. Baseline overweight status was the strongest predictor of the follow-up obesity incidence rate [HR=12.2, 95% confidence interval (CI) = (9.8, 15.3)]. Additionally males, Hispanic White children, and children from families with lower annual income and education levels were at higher risk for obesity (all $p \leq 0.035$). We also observed that children taking at least two exercise classes in the previous year had almost 60% lower risk of developing obesity than children taking no exercise classes [HR=0.41, 95% CI = (0.21, 0.79)]. However, this association was attenuated and not statistically significant after adjusting for sex, ethnicity, family income and education levels [HR=0.69, 95% CI = (0.34, 1.38)]. Univariate analysis also showed a borderline significant association between baseline asthma history and the increased risk of developing obesity [HR=1.30, 95% CI = (0.98, 1.72)]. No significant association was found between exposures *in utero to* maternal smoking or to secondhand tobacco smoke and the risk for obesity (all $p > 0.41$).



After adjusting for potential confounders, we found that early childhood asthma contributed to the development of obesity during later childhood and adolescence (Table 2). For example, the predicted annual obesity incidence rate at age 14 was 4.2 *versus*

2.7 per 100 person-years among girls and 6.6 *versus* 4.3 per 100 person-years among boys when comparing non-obese children who had asthma history at the study entry with children who had no asthma history (Figure 1). The association result from the entire cohort suggests that non-obese children with asthma at baseline were 51% more likely to develop obesity [HR=1.51, 95% CI = (1.08, 2.09)] during follow-up compared to children without asthma at baseline, after adjusting for the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), exposures to second-hand smoke and maternal smoking exposure *in utero*, and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports, and any asthma medication use with a sex-specific baseline hazard. Children with history of wheeze before study entry were also at 42% higher risk of developing obesity [HR=1.42, 95% CI = (1.08, 1.85)] during follow-up compared to children who never experienced wheeze after adjusting for confounders. Age of asthma onset did not substantially affect the associated obesity risk [HR (95% CI) for early onset asthma =1.46 (0.95, 2.23), and for late onset asthma = 1.39 (0.62, 3.08)]. Among children who had no asthma history at baseline, no significant association was found between new-onset asthma during follow-up and the incidence of obesity after adjusting for confounders [HR=0.90, 95% CI = (0.52, 1.55)].



The associations of asthma phenotypes and obesity were replicated in an independent replication cohort of 2,684 children who were followed from mean age of 9.7 to 17.8 years (baseline characteristics are shown in Table E8). Baseline asthma history was significantly associated with higher obesity risk after adjusting for potential confounders [HR=1.56, 95% CI = (1.11, 2.19), Table E9].

Conditional on baseline asthma history status, children who used asthma rescue medications at study entry had significantly reduced risk of developing obesity during the follow-up after adjusting for other controller and/or steroid asthma medication usage and potential confounders, compared to children who did not use asthma medications [Table 3, HR=0.57, 95% CI=(0.33, 0.96)]. The use of controller and steroid medications were not associated with the risk of developing obesity (all $p>0.67$). We were unable to replicate these results because the independent replication cohort lacked detailed information on asthma medication use.

We found little evidence to support heterogeneity in the effects of asthma status on obesity based on the baseline characteristics described in Table 1 (all interaction $p>0.28$, data not shown). Stratified analysis suggests that the association between baseline asthma history and follow-up obesity risk may be stronger among boys (Table E1), Hispanic Whites (Table E2), and baseline overweight children (Table E3) comparing to girls, non-Hispanic Whites, and baseline normal weight children, respectively.



Several sensitivity analyses were conducted after adjusting for potential confounders. First, among 1,773 children who had normal weight at baseline, we investigated whether asthma and asthma-related respiratory health were associated with the risk of becoming overweight or obese (Table E4). Although the associations were not statistically significant, normal weight children with asthma at baseline tended to have higher risk of being overweight or obese during the follow-up [HR=1.22, 95% CI = (0.89, 1.67)]. Second, after excluding children who had new-onset asthma during the follow-up (n=235) and who did not have follow-up asthma information (n=12), significant associations between asthma history at baseline and the follow-up risk of obesity remained [HR=1.50, 95% CI = (1.07, 2.10), Table E5]. Third, after excluding 120 children who were obese only at one of all follow-up visits, we found consistent association between asthma history at baseline and higher risk of obesity development during the follow-up [HR=1.71, 95% CI = (1.13, 2.57), Table E6]. Lastly, there were 845 subjects who were lost to follow-up. The analysis excluding these subjects showed that the positive association between baseline asthma history and obesity risk remained significant [HR=1.43, 95% CI = (1.05, 1.96), Table E7].

**DISCUSSION**



In this prospective study, we followed children from mean age of 6.6 to 15.2 years and observed that children with an early-life history of asthma or wheeze by study entry were at higher risk of developing obesity. The longitudinal finding of the association between early-life asthma history and increased risk of developing obesity during the follow-up is novel, although the association effect size of asthma on the risk of obesity is smaller than some other well-known obesity risk factors such as baseline overweight status, low parental education levels and Hispanic ethnicity. Children who used rescue asthma medications at study entry had a reduced risk of developing obesity. This association was independent of physical activity and other asthma medications use. Results from the independent replication cohort further supported our hypothesis that early-life asthma history was associated with higher risk of childhood obesity among children who were followed from mean age of 9.7 to 17.8 years. These findings were not explained by difference in age, sex, ethnicity, social-economic status, smoking exposures, physical activity, and overweight status at baseline.

Although most previous studies documented that obesity precedes and predicts the development of asthma (4, 8, 22), no unanimity exists. A recent prospective study following subjects from age 20 to 40 showed that active asthma was associated with later weight gain and later obesity among women, whereas weight gain and obesity were not associated with later asthma (12). However, no association was found among men. Because children with asthma tended to be more physically inactive (23) and many asthma medications have side effects of weight gain (24), it is plausible that children with asthma are at a higher risk of developing obesity. However, there is a lack of epidemiological studies that investigate this hypothesis, especially in pediatric populations. Results from our prospective study support the hypothesis that children with early-life asthma and wheeze are at increased risk of developing obesity during later childhood. This association was independent of physical activity, although we have limited information about daily physical activity. Interestingly, our results also suggested that using asthma rescue medication in early childhood may have the potential to prevent development of obesity in the later life. Thus, early diagnosis and treatment of asthma may avoid the vicious cycle of asthma increasing the development of obesity with obesity subsequently causing increased asthma symptoms and morbidity leading to further weight gain. Since asthma treatments are largely efficacious, they may have the potential to help prevent obesity through early diagnosis and treatment of childhood asthma.

The biological mechanisms underlying the increased risk of obesity due to asthma are uncertain. Some studies showed that long-term treatment with glucocorticosteroids in asthmatic children can influence lipid metabolism by increasing the uptake of lipids from digestive system and enhancing lipids storage in tissues, especially in the trunk (25). However, results of the association between asthma medication treatment and increased risk of obesity have not been consistent (26). Interestingly, our results suggested that asthma rescue medication treatment prevented obesity risk. This association was independent of physical acitivity and other asthma medication use. We speculate that the use of β-agonists for asthma symptoms could have direct effects on adipocytes and lipolysis and protect against obesity (27, 28). β2-adrenergic receptors are present in adipose tissue and skeletal muscle, which mediates responses to sympathetic stimulation and regulate fat and protein metabolism (29). Animal studies showed that β2-adrenergic stimulation increased energy expenditure and enhances lipolysis (30, 31). Contrastly, chronic use of β-blockers to inhibit the β2-adrenergic system was shown to reduce energy expenditure, fat utilization and resulted in weight gain (32). A small trial further supported the beneficial effect of β2-adrenergic agonists on ameliorating obesity, where the treatment of Formoterol, a new generation of highly β2-selective agonist was shown to increase energy expenditure and fat oxidation among 12 study participants of around 30 years old (33).



The strengths of this study include long-term, prospective follow-up of a large cohort of children, with exposure and outcome data obtained consistently. The prospective design with non-obese children at baseline allows us to confirm that asthma onset precedes the occurrence of obesity. Additionally, our significant findings from the primary CHS study cohort was successfully replicated in an independent CHS sample from an earlier time period with a similar longitudinal study design. There are several limitations that need to be considered in interpreting these results. First, information about asthma was self-reported in questionnaires, so misclassification could exist in our data. However, this misclassification is limited based on our previous review of medical records (20) and likely non-differential in relation to measured height and weight data, leading to bias towards the null. Second, we have limited physical activity information and no dietary information on the children in this analysis. Diet and/or physical activity have the possibility to mediate or bias our observed results between asthma and obesity incidence. Third, we used BMI and CDC BMI growth curve to define overweight and obesity. Future studies using direct measures of body fat mass and distribution are needed to extend and confirm our findings. Lastly, selection bias might exist by excluding non-obese children with incomplete data or extremely elder at baseline as described in the study design. However, we compared characteristics among 535 excluded children with our analysis cohort, and found no significant difference between the two samples (Table E10). Additionally, our sensitivity analysis excluding children who did not complete the study showed that the bias caused by loss to follow-up was limited in our results.



In conclusion, children with asthma were at higher risk of developing obesity in later childhood and adolescence. Rescue medication use may reduce obesity risk independent of asthma diagnosis. In addition to excess caloric intake and lack of physical activity, (34), our findings suggest that childhood asthma also contributes to the development of childhood obesity. Early interventions for children with asthma and/or wheezing may be warranted to prevent a vicious cycle of worsening obesity and asthma that could contribute to the development of other metabolic diseases including prediabetes and type 2 diabetes in later life.

**Figure Legend**

**Figure 1.** Baseline asthma history was associated with a higher risk of developing obesity during an average of 6.8 follow-up years among A) 1087 Boys and B) 1084 Girls in the Children's Health Study Cohort E (as described in METHODS). The model predicted annual obesity incidence rates and 95% confidence intervals during the entire study follow-up from a mean age of 6.6 to 15.2 years old are presented comparing children with early-life asthma history and children having no asthma history at baseline among boys and girls. Cox proportional hazards model was used to predict annual obesity incidence rates during the study follow-up, adjusting for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), second-hand smoke and maternal smoking exposure *in utero*, and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports, and any asthma medication use with a sex-specific baseline hazard.



**ACKNOWLEDGEMENTS**

This work was supported by the Southern California Environmental Health Sciences Center grant (5P30ES007048) funded by the National Institute of Environmental Health Sciences; National Institute of Environmental Health Sciences (5P01ES011627); and the Hastings Foundation.

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**Table 1. Univariate associations of child and home characteristics with the risk of developing obesity during a mean follow-up of seven years among 2171 children in the Children's Health Study Cohort E* who were not obese at study entry.**

| Baseline variables | N (%)§ | Hazard Ratio | 95% CI |
|---|---|---|---|
| Age (Years) | | | |
| [5-6) | 502 (23.1) | *Ref* | |
| [6-7) | 1070 (49.3) | 1.00 | (0.77 - 1.29) |
| [7-8) | 599 (27.6) | 1.05 | (0.77 - 1.44) |
| Sex | | | |
| Girls | 1084 (49.9) | *Ref* | |
| Boys | 1087 (50.1) | 1.69 | (1.36 - 2.10) |
| Overweight† | | | |
| No | 1773 (81.7) | *Ref* | |
| Yes | 398 (18.3) | 12.24 | (9.83 - 15.26) |
| Ethnicity | | | |
| Non-Hispanic Whites | 687 (31.6) | *Ref* | |
| Hispanic Whites | 1235 (56.9) | 1.93 | (1.49 - 2.51) |
| Others | 249 (11.5) | 1.39 | (0.93 - 2.06) |
| Annual Family income | | | |
| Less than $50,000 | 868 (40.0) | *Ref* | |
| $50,000 to $99,999 | 590 (27.2) | 0.71 | (0.54 - 0.92) |
| $100,000 or more | 395 (18.2) | 0.47 | (0.33 - 0.67) |
| Parental education | | | |
| Less than 12th grade | 390 (18.0) | *Ref* | |
| Completed grade 12 | 386 (17.8) | 0.69 | (0.49 - 0.97) |
| Some college or technical school | 756 (34.8) | 0.61 | (0.46 - 0.82) |
| More than Completed 4 years of college | 547 (25.2) | 0.52 | (0.37 - 0.71) |
| Baseline asthma history | | | |
| No | 1879 (86.5) | *Ref* | |
| Yes | 292 (13.5) | 1.30 | (0.98 - 1.72) |
| Child had health insurance | | | |
| No | 214 (9.9) | *Ref* | |
| Yes | 1897 (87.4) | 0.72 | (0.52 – 0.99) |
| Physical Activity | | | |
| Weekly days of outdoor sports | | | |
| 0 | 353 (16.3) | *Ref* | |
| 1-2 | 469 (21.6) | 1.06 | (0.75 - 1.50) |
| 3-4 | 636 (29.3) | 1.06 | (0.76 - 1.46) |
| 5-7 | 661 (30.5) | 0.96 | (0.69 - 1.34) |
| Prior 1-year no. of exercise classes‡ | | | |
| 0 | 1380 (63.6) | *Ref* | |
| 1 | 550 (25.3) | 0.69 | (0.53 - 0.90) |
| ≥2 | 119 (5.5) | 0.41 | (0.21 - 0.79) |
| Smoking | | | |
| Exposure to Second-hand Smoke | | | |
| No | 1988 (91.6) | *Ref* | |
| Yes | 93 (4.3) | 1.08 | (0.63 - 1.85) |
| Yes only when children are not present | 39 (1.8) | 0.84 | (0.35 - 2.00) |
| Exposure to Maternal Smoking *In Utero* | | | |
| No | 1977 (91.1) | *Ref* | |
| Yes | 131 (6.0) | 1.05 | (0.67 - 1.64) |



*Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for univariate association analysis using cox proportional hazards models.

† Overweight children were defined as children having BMI ≥85 percentile compared to sex-specific CDC growth curve (21).

‡ Exercise classes include dance, aerobics, gymnastics or tumbling, martial arts, and other self-reported exercise classes.

§ Total number of subjects may differ due to missing values of different baseline variables.

**Table 2. Associations between baseline histories of asthma and asthma-related health outcomes with the risk of developing obesity during a mean follow-up of seven years among children in the Children's Health Study Cohort E who were not obese at study entry* (Total N=2171).**

| Baseline Histories | N (%)\|\| | Univariate† | | Covariate Adjusted‡ | |
|---|---|---|---|---|---|
| | | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| **Asthma** | | | | | |
| No | 1879 (86.5) | *Ref* | | *Ref* | |
| Yes | 292 (13.5) | 1.30 | (0.98 - 1.72) | 1.51 | (1.08 – 2.09) |
| **Ever wheeze** | | | | | |
| No | 1540 (70.9) | *Ref* | | *Ref* | |
| Yes | 582 (26.8) | 1.06 | (0.83 - 1.34) | 1.42 | (1.08 – 1.85) |
| **Wheeze in prior 1 year** | | | | | |
| No | 1876 (86.4) | *Ref* | | *Ref* | |
| Yes | 272 (12.5) | 0.97 | (0.70 - 1.33) | 1.22 | (0.84 - 1.78) |
| **Age of asthma onset** | | | | | |
| No asthma | 1879 (86.6) | *Ref* | | *Ref* | |
| Early onset asthma (≤4 years) | 178 (8.2) | 1.22 | (0.85 – 1.75) | 1.46 | (0.95 – 2.23) |
| Late onset asthma (>4 years) | 46 (2.1) | 1.29 | (0.65 – 2.55) | 1.39 | (0.62 – 3.08) |
| **Active asthma** | | | | | |
| Have no baseline asthma history and no current wheeze | 1750 (80.6) | *Ref* | | *Ref* | |
| Have no baseline asthma history, but have current wheeze | 108 (5.0) | 0.56 | (0.30 - 1.04) | 0.91 | (0.46 - 1.77) |
| Have baseline asthma history, but no current wheeze | 126 (5.8) | 1.22 | (0.80 - 1.86) | 1.42 | (0.93 - 2.19) |
| Have baseline asthma history and current wheeze | 164 (7.6) | 1.26 | (0.88 - 1.81) | 1.50 | (0.96 - 2.33) |



*Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.
†Univariate: model used sex-specific baseline hazard.
‡Covariates adjusted: model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports, and any asthma medication use with a sex-specific baseline hazard.
§Total number of subjects may differ due to missing values of different variables of baseline asthma history and related phenotypes.

**Table 3. Joint associations of asthma and asthma medication use with the risk of developing obesity during a mean follow-up of seven years among children in the Children's Health Study Cohort E who were not obese at study entry[*] (Total N=2171).**

| Baseline Histories of Asthma and Medication use | N (%)[‡] | Multivariate Model[†] | |
|---|---|---|---|
| | | Hazard Ratio | 95% CI |
| **Baseline asthma history** | | | |
| No | 1879 (86.5) | Ref | |
| Yes | 292 (13.5) | 2.21 | (1.47 – 3.34) |
| **Use rescue medications** | | | |
| No | 1866 (86.0) | Ref | |
| Yes | 256 (11.8) | 0.57 | (0.33 – 0.96) |
| **Use controller medications** | | | |
| No | 2008 (92.5) | Ref | |
| Non-steroid controller medication | 14 (0.6) | 1.34 | (0.35 – 4.97) |
| Inhaled corticosteroid | 100 (4.6) | 0.97 | (0.49 – 1.93) |
| **Use additional steroid pills or liquids** | | | |
| No | 2081 (95.9) | Ref | |
| Yes | 41 (1.9) | 0.87 | (0.35 – 2.19) |



* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.

† Multivariate Model: multivariate cox proportional hazards model was used to jointly model obesity incidence rate as a function of baseline histories of asthma, use of rescue medications, controller medications and additional steroid pills or liquids, adjusting for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), second-hand smoke and maternal smoking exposure *in utero*., and time-dependent variables including number of exercise classes attended, and any asthma medication use during the follow-up with a sex-specific baseline hazard.

‡ Total number of subjects may differ due to missing values of different baseline variables of asthma history and asthma medication use.

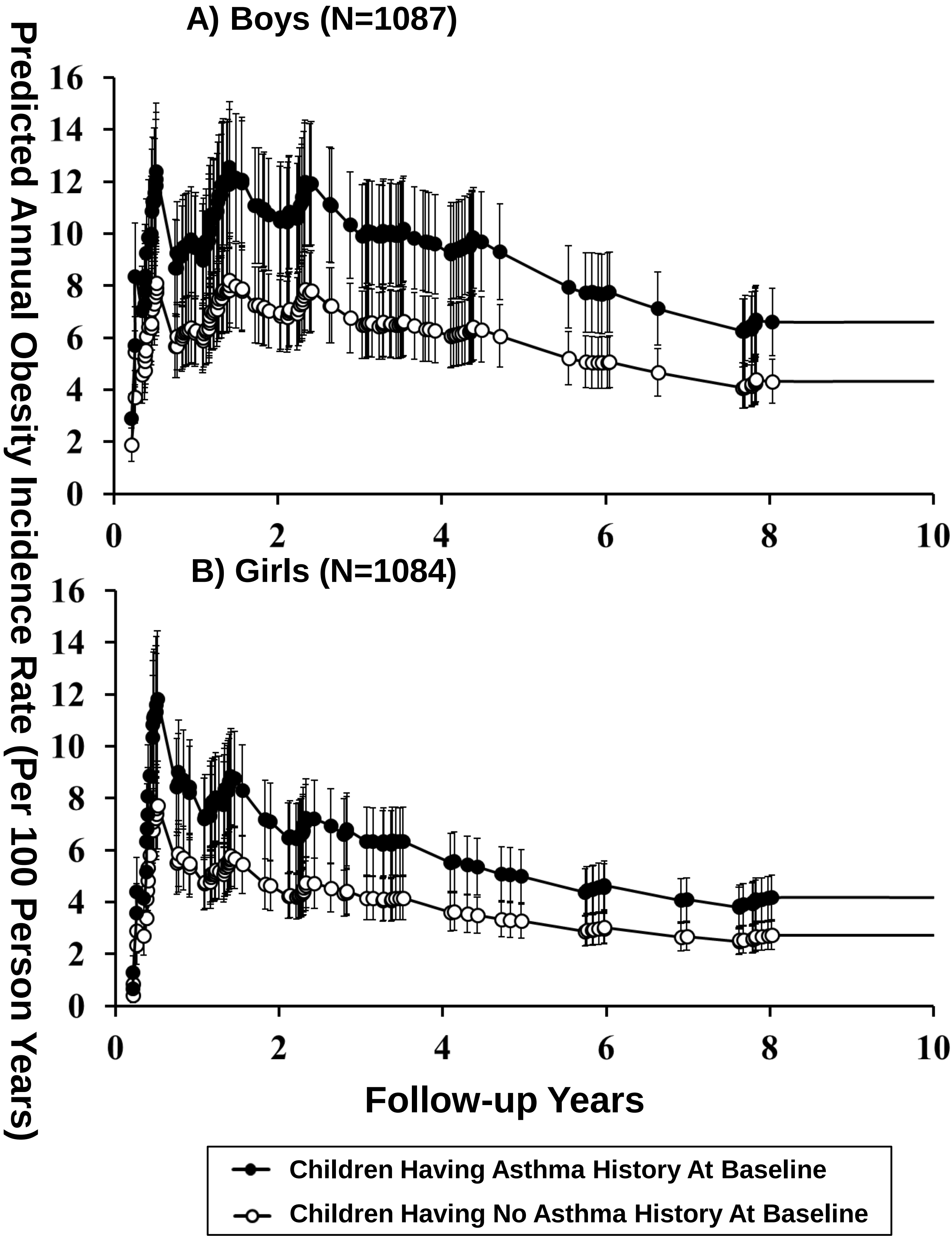
A) Boys (N=1087)
B) Girls (N=1084)
Predicted Annual Obesity Incidence Rate (Per 100 Person Years)
Follow-up Years
0 2 4 6 8 10 12 14 16
0 2 4 6 8 10
Children Having Asthma History At Baseline
Children Having No Asthma History At Baseline

**Table E1. Stratified associations between baseline histories of asthma and asthma-related health with the risk of developing obesity during a mean follow-up of seven years among boys and girls in the Children's Health Study Cohort E*.**

| Baseline Histories | Boys (n=1087) | | | Girls (n=1084) | | |
|---|---|---|---|---|---|---|
| | N (%)‡ | HR† | 95% CI | N (%)‡ | HR† | 95% CI |
| **Asthma** | | | | | | |
| No | 906 (83.4) | *Ref* | | 973 (89.8) | *Ref* | |
| Yes | 181 (16.7) | 1.53 | (1.04 - 2.26) | 111 (10.2) | 1.05 | (0.54 – 2.05) |
| **Ever wheeze** | | | | | | |
| No | 724 (66.6) | *Ref* | | 816 (75.3) | *Ref* | |
| Yes | 336 (30.9) | 1.57 | (1.12 - 2.20) | 246 (22.7) | 0.97 | (0.62 - 1.52) |
| **Wheeze in prior 1 year** | | | | | | |
| No | 909 (83.6) | *Ref* | | 967 (89.2) | *Ref* | |
| Yes | 167 (15.4) | 1.40 | (0.91 - 2.14) | 105 (9.7) | 0.85 | (0.46 - 1.57) |
| **Age of asthma onset** | | | | | | |
| No asthma | 906 (83.4) | *Ref* | | 973 (89.8) | *Ref* | |
| Early onset asthma (≤4 years) | 111 (10.2) | 1.53 | (0.93 - 2.52) | 67 (6.2) | 1.12 | (0.48 - 2.65) |
| Late onset asthma (>4 years) | 32 (2.9) | 0.94 | (0.33 - 2.67) | 14 (1.3) | 1.60 | (0.40 - 6.42) |
| **Active asthma** | | | | | | |
| Have no baseline asthma history and no current wheeze | 837 (77.0) | *Ref* | | 913 (84.2) | *Ref* | |
| Have no baseline asthma history, but have current wheeze | 60 (5.5) | 1.23 | (0.57 - 2.65) | 48 (4.4) | 0.37 | (0.10 - 1.29) |
| Have baseline asthma history, but no current wheeze | 72 (6.6) | 1.57 | (0.96 - 2.57) | 54 (5.0) | 0.65 | (0.19 - 2.22) |
| Have baseline asthma history and current wheeze | 107(9.8) | 1.43 | (0.84 - 2.42) | 57 (5.3) | 1.25 | (0.59 - 2.67) |



* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old.
† Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports and any asthma medication use. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.
‡ Total number of subjects may differ due to missing values of different baseline variables.

**Table E2. Stratified associations between baseline histories of asthma and asthma-related health with the risk of developing obesity during a mean follow-up of seven years among non-Hispanic and Hispanic White children in the Children's Health Study Cohort E*.**

| Baseline Histories | Non-Hispanic White (n=687) | | | Hispanic White (n=1235) | | |
|---|---|---|---|---|---|---|
| | N (%)‡ | HR† | 95% CI | N (%)‡ | HR† | 95% CI |
| **Asthma** | | | | | | |
| No | 582 (84.7) | *Ref* | | 1084 (87.8) | *Ref* | |
| Yes | 105 (15.3) | 0.88 | (0.41 - 1.85) | 151 (12.2) | 1.42 | (0.92 – 2.21) |
| **Ever wheeze** | | | | | | |
| No | 461 (67.1) | *Ref* | | 896 (72.6) | *Ref* | |
| Yes | 216 (31.4) | 1.25 | (0.71 - 2.22) | 304 (24.6) | 1.18 | (0.83 - 1.68) |
| **Wheeze in prior 1 year** | | | | | | |
| No | 569 (82.8) | *Ref* | | 1095 (88.7) | *Ref* | |
| Yes | 116 (16.9) | 0.97 | (0.49 - 1.90) | 119 (9.6) | 1.02 | (0.60 - 1.73) |
| **Age of asthma onset** | | | | | | |
| No asthma | 582 (84.7) | *Ref* | | 1084 (87.8) | *Ref* | |
| Early onset asthma (≤4 years) | 67 (9.8) | 0.94 | (0.36 - 2.47) | 91 (7.4) | 1.27 | (0.69 - 2.32) |
| Late onset asthma (>4 years) | 21 (3.1) | 0.91 | (0.23 - 3.60) | 18 (1.5) | 0.81 | (0.16 - 4.14) |
| **Active asthma** | | | | | | |
| Have no baseline asthma history and no current wheeze | 532 (77.4) | *Ref* | | 1019 (82.5) | *Ref* | |
| Have no baseline asthma history, but have current wheeze | 48 (7.0) | 0.91 | (0.34 - 2.42) | 46 (3.7) | 0.86 | (0.32 - 2.29) |
| Have baseline asthma history, but no current wheeze | 37 (5.4) | 0.70 | (0.17 - 2.90) | 76 (6.2) | 1.61 | (0.98 - 2.64) |
| Have baseline asthma history and current wheeze | 68 (9.9) | 0.94 | (0.40 - 2.20) | 73 (5.9) | 1.07 | (0.52 - 2.18) |



* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old.
† Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports and any asthma medication use with a sex-specific baseline hazard. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.
‡ Total number of subjects may differ due to missing values of different baseline variables.

**Table E3. Stratified associations between baseline histories of asthma and asthma-related health with the risk of developing obesity during a mean follow-up of seven years among baseline normal weight and overweight children in the Children's Health Study Cohort E[*].**

| Baseline Histories | Baseline normal weight (n=1773) | | | Baseline overweight (n=398) | | |
|---|---|---|---|---|---|---|
| | N (%)[‡] | HR[†] | 95% CI | N (%)[‡] | HR[†] | 95% CI |
| **Asthma** | | | | | | |
| No | 1541 (86.9) | *Ref* | | 338 (84.9) | *Ref* | |
| Yes | 232 (13.1) | 1.45 | (0.86 - 2.43) | 60 (15.1) | 1.63 | (1.09 – 2.44) |
| **Ever Wheeze** | | | | | | |
| No | 1256 (70.8) | *Ref* | | 284 (71.4) | *Ref* | |
| Yes | 479 (27.0) | 1.36 | (0.90 - 2.04) | 103 (25.9) | 1.48 | (1.05 - 2.08) |
| **Wheeze in prior 1 year** | | | | | | |
| No | 1530 (86.3) | *Ref* | | 346 (86.9) | *Ref* | |
| Yes | 227 (12.8) | 1.13 | (0.67 - 1.91) | 45 (11.3) | 1.44 | (0.90 - 2.31) |
| **Age of asthma onset** | | | | | | |
| No asthma | 1541 (86.9) | *Ref* | | 338 (84.9) | *Ref* | |
| Early onset asthma (≤4 years) | 142 (8.0) | 1.43 | (0.75 – 2.75) | 36 (9.1) | 1.69 | (0.99 – 2.87) |
| Late onset asthma (>4 years) | 35 (2.0) | 1.61 | (0.57 – 4.49) | 11 (2.8) | 1.15 | (0.39 – 3.41) |
| **Active Asthma** | | | | | | |
| Have no baseline asthma history and no current wheeze | 1430 (80.7) | *Ref* | | 320 (80.4) | *Ref* | |
| Have no baseline asthma history, but have current wheeze | 96 (5.4) | 0.62 | (0.22 - 1.73) | 12 (3.0) | 1.37 | (0.59 - 3.19) |
| Have baseline asthma history, but no current wheeze | 100 (5.6) | 1.14 | (0.51 - 2.57) | 26 (6.5) | 1.59 | (0.94 - 2.71) |
| Have baseline asthma history and current wheeze | 131(7.4) | 1.58 | (0.84 - 2.96) | 33 (8.3) | 1.60 | (0.92 - 2.77) |



* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old.
† Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports and any asthma medication use with a sex-specific baseline hazard. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.
‡ Total number of subjects may differ due to missing values of different baseline variables.

**Table E4. Associations between baseline history of asthma and asthma-related health with the risk of becoming overweight and obese during a mean follow-up of seven years among 1773 children in the Children's Health Study Cohort E* who were normal-weighted at the study entry.**

| Baseline Histories | N (%)§ | Univariate† Hazard Ratio | Univariate† 95% CI | Fully Adjusted‡ Hazard Ratio | Fully Adjusted‡ 95% CI |
|---|---|---|---|---|---|
| **Asthma** | | | | | |
| No | 1541 (86.9) | *Ref* | | *Ref* | |
| Yes | 232 (13.1) | 1.10 | (0.82 - 1.46) | 1.22 | (0.89 - 1.67) |
| **Ever Wheeze** | | | | | |
| No | 1256 (70.8) | *Ref* | | *Ref* | |
| Yes | 479 (27.0) | 1.19 | (0.95 - 1.47) | 1.30 | (1.03 - 1.63) |
| **Wheeze in prior 1 year** | | | | | |
| No | 1530 (86.3) | *Ref* | | *Ref* | |
| Yes | 227 (12.8) | 1.17 | (0.88 - 1.56) | 1.23 | (0.90 - 1.68) |
| **Age of asthma onset** | | | | | |
| No asthma | 1541 (86.9) | *Ref* | | *Ref* | |
| Early onset asthma (≤4 years) | 142 (8.0) | 1.27 | (0.90 - 1.79) | 1.40 | (0.96 - 2.04) |
| Late onset asthma (>4 years) | 35 (2.0) | 1.34 | (0.68 - 2.65) | 1.41 | (0.70 - 2.84) |
| **Active Asthma** | | | | | |
| Have no baseline asthma history and no current wheeze | 1430 (80.7) | *Ref* | | *Ref* | |
| Have no baseline asthma history, but have current wheeze | 96 (5.4) | 1.18 | (0.77 - 1.80) | 1.20 | (0.77 - 1.87) |
| Have baseline asthma history, but no current wheeze | 100 (5.6) | 1.02 | (0.66 - 1.57) | 1.18 | (0.76 - 1.84) |
| Have baseline asthma history and current wheeze | 131 (7.4) | 1.17 | (0.81 - 1.69) | 1.30 | (0.87 - 1.93) |

* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.

† Univariate: Cox proportional hazards model used sex-specific baseline hazard.

‡ Fully adjusted: Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports and any asthma medication use with a sex-specific baseline hazard.

§ Total number of subjects may differ due to missing values of different baseline variables.

**Table E5. Associations between baseline histories of asthma and asthma-related health with the risk of developing obesity during a mean follow-up of seven years among 1924 children in the Children's Health Study Cohort E* who were not obese at study entry and who did not have new-onset asthma during the study follow-up.**

| Baseline Histories | N (%)§ | Univariate† | | Fully Adjusted‡ | |
|---|---|---|---|---|---|
| | | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| **Asthma** | | | | | |
| No | 1632 (84.8) | Ref | | Ref | |
| Yes | 292 (15.2) | 1.21 | (0.91 - 1.61) | 1.50 | (1.07 - 2.10) |
| **Ever Wheeze** | | | | | |
| No | 1395 (72.5) | Ref | | Ref | |
| Yes | 489 (25.4) | 1.12 | (0.87 - 1.43) | 1.53 | (1.16 - 2.03) |
| **Wheeze in prior 1 year** | | | | | |
| No | 1674 (87.0) | Ref | | Ref | |
| Yes | 231 (12.0) | 0.93 | (0.66 - 1.31) | 1.21 | (0.82 - 1.79) |
| **Age of asthma onset** | | | | | |
| No asthma | 1632 (84.8) | Ref | | | |
| Early onset asthma (≤4 years) | 178 (9.3) | 1.14 | (0.79 - 1.64) | 1.44 | (0.93 - 2.22) |
| Late onset asthma (>4 years) | 46 (2.4) | 1.20 | (0.61 - 2.38) | 1.40 | (0.63 - 3.12) |
| **Active Asthma** | | | | | |
| Have no baseline asthma history and no current wheeze | 1548 (80.5) | Ref | | Ref | |
| Have no baseline asthma history, but have current wheeze | 67 (3.5) | 0.35 | (0.13 - 0.93) | 0.67 | (0.27 - 1.61) |
| Have baseline asthma history, but no current wheeze | 126 (6.6) | 1.14 | (0.79 - 1.64) | 1.38 | (0.89 - 2.13) |
| Have baseline asthma history and current wheeze | 164 (8.5) | 1.18 | (0.82 - 1.69) | 1.51 | (0.96 - 2.37) |



* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.

† Univariate: Cox proportional hazards model used sex-specific baseline hazard.

‡ Fully adjusted: Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports, and any asthma medication use with a sex-specific baseline hazard.

§ Total number of subjects may differ due to missing values of different baseline variables.

**Table E6. Sensitivity Analysis of associations between baseline histories of asthma and asthma-related health with the risk of developing obesity and maintaining obesity for more than two follow-up visits during a mean follow-up of seven years among 2051 children in the Children's Health Study Cohort E* who were not obese at study entry.**

| Baseline Histories | N (%)§ | Univariate† Hazard Ratio | Univariate† 95% CI | Fully Adjusted‡ Hazard Ratio | Fully Adjusted‡ 95% CI |
|---|---|---|---|---|---|
| **Asthma** | | | | | |
| No | 1778 (86.7) | Ref | | Ref | |
| Yes | 273 (13.3) | 1.35 | (0.95 - 1.90) | 1.71 | (1.13 - 2.57) |
| **Ever Wheeze** | | | | | |
| No | 1456 (71.0) | Ref | | Ref | |
| Yes | 546 (26.6) | 1.02 | (0.76 - 1.38) | 1.40 | (1.00 - 1.95) |
| **Wheeze in prior 1 year** | | | | | |
| No | 1771 (86.4) | Ref | | Ref | |
| Yes | 257 (12.5) | 0.99 | (0.67 - 1.47) | 1.35 | (0.86 - 2.11) |
| **Age of asthma onset** | | | | | |
| No asthma | 1778 (86.7) | Ref | | | |
| Early onset asthma (≤4 years) | 169 (8.2) | 1.36 | (0.89 - 2.07) | 1.72 | (1.04 - 2.83) |
| Late onset asthma (>4 years) | 44 (2.2) | 1.52 | (0.70 - 3.27) | 1.74 | (0.70 - 4.30) |
| **Active Asthma** | | | | | |
| Have no baseline asthma history and no current wheeze | 1654 (80.6) | Ref | | Ref | |
| Have no baseline asthma history, but have current wheeze | 103 (5.0) | 0.44 | (0.18 - 1.06) | 0.84 | (0.32 - 2.19) |
| Have baseline asthma history, but no current wheeze | 117 (5.7) | 1.14 | (0.67 - 1.96) | 1.51 | (0.86 - 2.67) |
| Have baseline asthma history and current wheeze | 154 (7.5) | 1.37 | (0.89 - 2.11) | 1.73 | (1.05 - 2.85) |





* Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old. Obesity incidence was defined as children who were observed to be obese in at least 2 follow-up visits. 120 children who developed obesity at only one follow-up visit were excluded from this analysis. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.

† Univariate: Cox proportional hazards model used sex-specific baseline hazard.

‡ Fully adjusted: Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports and any asthma medication use with a sex-specific baseline hazard.

§ Total number of subjects may differ due to missing values of different baseline variables.

**Table E7. Associations between baseline histories of asthma and asthma-related health with the risk of developing obesity during the study follow-up among 1326 children who completed the full ten-year study follow-up in the Children's Health Study Cohort E[*].**

| Baseline Histories | N (%)[§] | Univariate[†] Hazard Ratio | Univariate[†] 95% CI | Fully Adjusted[‡] Hazard Ratio | Fully Adjusted[‡] 95% CI |
|---|---|---|---|---|---|
| **Asthma** | | | | | |
| No | 1142 (86.1) | Ref | | Ref | |
| Yes | 184 (13.9) | 1.23 | (0.92 - 1.64) | 1.43 | (1.05 - 1.96) |
| **Ever Wheeze** | | | | | |
| No | 954 (72.0) | Ref | | Ref | |
| Yes | 340 (25.6) | 1.10 | (0.87 - 1.39) | 1.51 | (1.16 - 1.97) |
| **Wheeze in prior 1 year** | | | | | |
| No | 1141 (86.1) | Ref | | Ref | |
| Yes | 171 (12.9) | 0.89 | (0.65 - 1.23) | 1.11 | (0.77 - 1.60) |
| **Age of asthma onset** | | | | | |
| No asthma | 1142 (86.1) | Ref | | | |
| Early onset asthma (≤4 years) | 110 (8.3) | 1.17 | (0.81 - 1.69) | 1.47 | (0.97 - 2.20) |
| Late onset asthma (>4 years) | 29 (2.2) | 1.17 | (0.59 - 2.35) | 1.21 | (0.54 - 2.67) |
| **Active Asthma** | | | | | |
| Have no baseline asthma history and no current wheeze | 1065 (80.3) | Ref | | Ref | |
| Have no baseline asthma history, but have current wheeze | 64 (4.8) | 0.53 | (0.28 - 0.98) | 0.78 | (0.39 - 1.54) |
| Have baseline asthma history, but no current wheeze | 76 (5.7) | 1.21 | (0.79 - 1.85) | 1.35 | (0.88 - 2.08) |
| Have baseline asthma history and current wheeze | 107 (8.1) | 1.15 | (0.80 - 1.65) | 1.39 | (0.92 - 2.10) |

* The study design of Children in the Children's Health Study Cohort E is described in METHODS. Results in this table are from a subsample of the cohort who had complete 10-year follow-ups. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.

† Univariate: Cox proportional hazards model used sex-specific baseline hazard.

‡ Covariates adjusted: Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of exercise classes attended in the previous year, weekly days of outdoor sports, overweight status (yes/no), second-hand smoke and maternal smoking exposure *in utero*., and follow-up time-dependent variables including number of exercise classes attended, weekly days of outdoor sports and any asthma medication use with a sex-specific baseline hazard.

§ Total number of subjects may differ due to missing values of different baseline variables.

**Table E8. Univariate associations of child and home characteristics with the risk of developing obesity during a mean follow-up of six years among 2684 children in the replication sample of Children's Health Study Cohorts C and D* who were not obese at study entry.**

| Baseline variables | N (%)§ | Hazard Ratio | 95% CI |
|---|---|---|---|
| Age (Years) | | | |
| [8-10) | 1433 (53.4) | *Ref* | |
| [10-11) | 1184 (44.1) | 1.29 | (1.00 - 1.67) |
| [11-13) | 67 (2.5) | 1.39 | (0.56 - 3.42) |
| Sex | | | |
| Girls | 1360 (50.7) | *Ref* | |
| Boys | 1324 (49.3) | 1.50 | (1.18 - 1.90) |
| Overweight† | | | |
| No | 2231 (83.1) | *Ref* | |
| Yes | 453 (16.9) | 24.37 | (18.33 - 32.39) |
| Ethnicity | | | |
| Non-Hispanic Whites | 1536 (57.2) | *Ref* | |
| Hispanic Whites | 219 (8.2) | 1.04 | (0.66 - 1.65) |
| Others | 899 (33.5) | 1.26 | (0.98 - 1.63) |
| Annual Family income | | | |
| Up to $14,999 | 367 (13.7) | *Ref* | |
| $15,000 to $49,999 | 942 (35.1) | 0.96 | (0.67 - 1.36) |
| $50,000 or more | 1012 (37.7) | 0.55 | (0.37 - 0.80) |
| Parental education | | | |
| Less than or completed 12th grade | 833 (31.0) | *Ref* | |
| Some college or technical school | 1161 (43.3) | 0.86 | (0.65 - 1.15) |
| More than Completed 4 years of college | 613 (22.8) | 0.94 | (0.68 - 1.30) |
| Baseline asthma history | | | |
| No | 2319 (86.4) | *Ref* | |
| Yes | 365 (13.6) | 1.19 | (0.86 - 1.65) |
| Child had health insurance | | | |
| No | 375 (14.0) | Ref | |
| Yes | 2265 (84.4) | 0.88 | (0.63 – 1.23) |
| Physical Activity | | | |
| Prior 1-year no. of sports teams‡ | | | |
| 0 | 1185 (44.2) | *Ref* | |
| 1 | 832 (31.0) | 0.57 | (0.43 - 0.78) |
| ≥2 | 614 (22.9) | 0.72 | (0.53 - 0.98) |
| Smoking | | | |
| Exposure to Second-hand Smoke in the Past | | | |
| No | 1851 (69.0) | *Ref* | |
| Yes | 740 (27.6) | 1.13 | (0.87 - 1.47) |
| Current Exposure to Second-hand Smoke | | | |
| No | 2139 (79.7) | *Ref* | |
| Yes | 499 (18.6) | 1.14 | (1.02 - 1.83) |



* Children in the Children's Health Study Cohorts C and D (as described in METHODS) were enrolled in year 1992 and1994, and were followed-up from a mean age of 9.7 to 16.8 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for univariate association analysis using cox proportional hazards models.

† Overweight children were defined as children having BMI ≥85 percentile compared to sex-specific CDC growth curve (21).

‡ Sports teams include baseball, basketball, football, soccer, swimming, tennis, volleyball and other self-reported specified sports.

§ Total number of subjects may differ due to missing values of different baseline variables.

**Table E9. Associations between baseline histories of asthma and asthma-related health outcomes with the risk of developing obesity during a mean follow-up of six years among 2684 children in the replication sample of Children's Health Study cohorts C and D* who were not obese at study entry.**

| Baseline Histories | N (%)§ | Univariate† | | Covariate Adjusted‡ | |
|---|---|---|---|---|---|
| | | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| **Asthma** | | | | | |
| No | 2319 (86.4) | *Ref* | | *Ref* | |
| Yes | 365 (13.6) | 1.19 | (0.86 - 1.65) | 1.56 | (1.11 – 2.19) |
| **Ever wheeze** | | | | | |
| No | 1731 (64.5) | *Ref* | | *Ref* | |
| Yes | 839 (31.3) | 1.22 | (0.95 - 1.57) | 1.28 | (0.98 – 1.67) |
| **Wheeze in prior 1 year** | | | | | |
| No | 1904 (70.9) | *Ref* | | *Ref* | |
| Yes | 440 (16.4) | 1.36 | (1.01 - 1.84) | 1.21 | (0.89 - 1.65) |
| **Age of asthma onset** | | | | | |
| No asthma | 2319 (86.4) | *Ref* | | *Ref* | |
| Early onset asthma (≤4 years) | 316 (11.8) | 1.19 | (0.85 – 1.68) | 1.65 | (1.16 – 2.35) |
| Late onset asthma (>4 years) | 48 (1.8) | 1.21 | (0.50 – 2.92) | 1.06 | (0.40 – 2.75) |
| **Active asthma** | | | | | |
| Have no baseline asthma history and no current wheeze | 1809 (67.4) | *Ref* | | *Ref* | |
| Have no baseline asthma history, but have current wheeze | 224 (8.4) | 1.11 | (0.72 - 1.72) | 0.80 | (0.51 - 1.25) |
| Have baseline asthma history, but no current wheeze | 95 (3.5) | 0.84 | (0.41 - 1.71) | 1.01 | (0.48 - 2.11) |
| Have baseline asthma history and current wheeze | 216 (8.1) | 1.58 | (1.09 - 1.30) | 1.86 | (1.26 - 2.75) |

*Children in the Children's Health Study Cohorts C and D (as described in METHODS) were enrolled in year 1992 and1994, and were followed-up from a mean age of 6.6 to 15.2 years old. Hazard ratios and 95% confidence intervals (CIs) are presented for association analysis using various models.
†Univariate: Cox proportional hazards model used sex-specific baseline hazard.
‡Covariates adjusted: Cox proportional hazards model was adjusted for baseline characteristics including a fixed effect of the community, age, ethnicity, annual family income, parental education levels, children's health insurance coverage (yes/no), number of teams sports attended in the previous year, overweight status (yes/no), past and current second-hand smoke, and follow-up number of teams sports attended as a time-dependent variable with a sex-specific baseline hazard.
§Total number of subjects may differ due to missing values of different baseline variables.

**Table E10. Characteristics of 535 children in the Children's Health Study Cohort E* who were non-obese at study entry and were excluded from the main analysis in this paper.**

| Baseline variables | N (%)§ |
|---|---|
| Age (Years) | |
| (4-5) | 2 (0.4) |
| (5-6) | 118 (22.1) |
| (6-7) | 249 (46.5) |
| (7-8) | 141 (26.4) |
| (8-9) | 25 (4.7) |
| Sex | |
| Girls | 240 (44.9) |
| Boys | 295 (55.1) |
| Overweight† | |
| No | 455 (85.1) |
| Yes | 80 (15.0) |
| Ethnicity | |
| Non-Hispanic Whites | 119 (22.2) |
| Hispanic Whites | 335 (62.6) |
| Others | 81 (15.1) |
| Income | |
| Less than $50,000 | 274 (51.2) |
| $50,000 to $99,999 | 95 (17.8) |
| $100,000 or more | 47 (8.8) |
| Education | |
| Less than 12th grade | 131 (24.5) |
| Completed grade 12 | 116 (21.7) |
| Some college or technical school | 154 (28.8) |
| More than Completed 4 years of college | 81 (15.1) |
| Child had health insurance | |
| No | 78 (14.6) |
| Yes | 382 (71.4) |
| Physical Activity | |
| Weekly days of outdoor sports | |
| 0 | 91 (17.0) |
| 1-2 | 128 (23.9) |
| 3-4 | 133 (24.9) |
| 5-7 | 142 (26.5) |
| Prior 1-year no. of exercise classes‡ | |
| 0 | 366 (68.4) |
| 1 | 98 (18.3) |
| ≥2 | 16 (3.0) |
| Smoking | |
| Second-hand Smoke | |
| No | 447 (83.6) |
| Yes | 36 (6.7) |
| Yes only when children are not present | 9 (1.7) |
| Maternal Smoking Exposure *In Utero* | |
| No | 441 (82.4) |
| Yes | 45 (8.4) |



*Children in the Children's Health Study Cohort E (as described in METHODS) were enrolled in year 2002, and were followed-up from a mean age of 6.6 to 15.2 years old.
† Overweight among children was defined as ≥85 percentile compared to sex-specific CDC growth curve.
‡ Exercise classes include dance, aerobics, gymnastics or tumbling, martial arts, and other self-reported exercise classes.
§Total number of subjects may differ due to missing values of different baseline variables.