

Asthma-associated comorbidities in children with and without secondhand smoke exposure

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ABSTRACT

Background: Secondhand smoke (SHS) exposure is known to trigger asthma, but asthma disease severity and comorbidities in children exposed to SHS are not very well quantified.

Objective: To identify comorbidities and understand health care usage in children with asthma exposed to SHS (cases) compared with children with asthma but without SHS exposure (controls).

Methods: A retrospective nested matched case-and-control study was conducted with children 5 to 18 years old who were enrolled in the Pediatric Asthma Management Program. Pulmonary function testing (spirometry, methacholine challenges, and exhaled nitric oxide) and body mass index were reviewed. Influenza vaccination rates, oral steroid usage, emergency department visits, and hospitalizations were assessed. Network analysis of the 2 groups also was conducted to evaluate for any associations between the variables.

Results: Cases had significantly higher body mass index percentiles (>75%, odds ratio [OR] 1.64, 95% confidence interval [CI] 1.22–2.2, $P = .001$). Cases were less likely to have had a methacholine challenge (OR 0.49, 95% CI 0.36–0.68, $P < .001$) and an exhaled nitric oxide (OR 0.6, 95% CI 0.37–0.97, $P = .04$) performed than controls. The ratio of forced expiration volume in 1 second to forced vital capacity and forced expiration volume in 1 second were lower in cases than in controls ($P < .05$). Cases were less likely to have received an influenza vaccination (OR 0.61, 95% CI 0.45–0.82, $P = .001$) than controls. Unsupervised multivariable network analysis suggested a lack of discrete and unique subgroups between cases and controls.

Conclusion: Children with asthma exposed to SHS are more likely to have comorbid conditions such as obesity, more severe asthma, and less health care usage than those not exposed to SHS. Smoking cessation interventions and addressing health disparities could be crucial in this vulnerable population.

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Introduction

Secondhand smoke (SHS) exposure kills nearly 38,000 nonsmoking Americans each year and is a leading cause of preventable death in the United States.^{1,2} In 2011, more than half of high school students (53%) who were nonsmokers reported SHS exposure at some time in the past 7 days.² SHS triggers childhood asthma³ and increases the risk of more severe asthma compared with children not exposed to SHS exposure.^{3–6} SHS exposure can affect allergic sensitization, asthma severity, and asthma associated

comorbidities.^{7–9} In addition, there is a higher rate of hospital readmission for asthma in children exposed to SHS.¹⁰

In this nested matched case-and-control study, the authors sought to identify demographic (sex, weight, height, and body mass index [BMI]) and clinical (spirometry, methacholine challenge, exhaled nitric oxide [eNO], influenza vaccination, flulike illness, steroid use, emergency department [ED] visits, urgent care visits, and hospitalizations) factors that differentiated cases from controls to identify comorbidities and health care usage.

Methods

Study Design, Setting, and Participant Identification

A nested matched case-controlled retrospective sample of children 5 to 18 years old who were enrolled in the Pediatric Asthma

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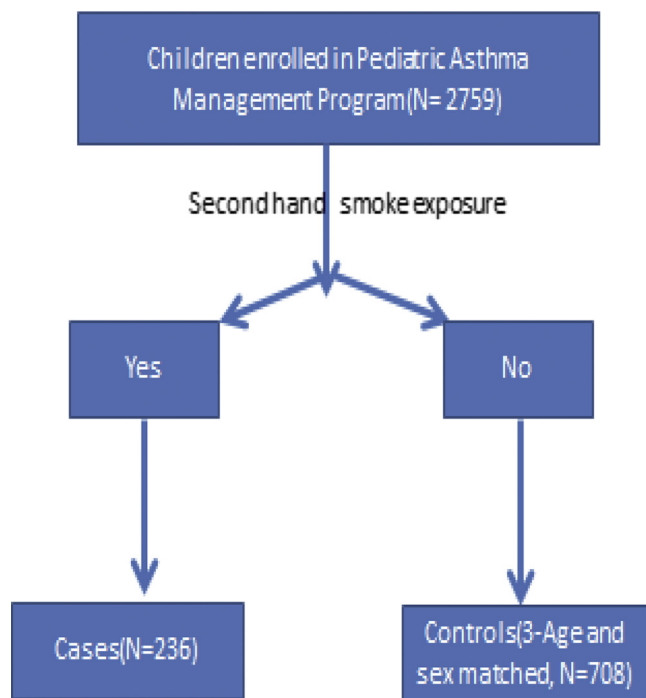


Figure 1. Algorithm of matched case-and-control study of children with asthma in the Pediatric Asthma Management Program.

Management Program (PAMP) with (cases) and without (controls) parental report of documented SHS comprised the study population ($n = 944$, 236 cases, 708 controls). The matching was 1:3, with the matching criteria being age and sex of the child to address and minimize the issue of confounding by indication. Children eligible for enrollment in care management had persistent asthma (requiring daily inhaled corticosteroid), a history of an ED visit or hospitalization for asthma during the past 12 months, or uncontrolled asthma symptoms according to National Education and Prevention Program Expert Panel Report 3 (NAEPP-3) guidelines.¹¹ The PAMP was set in an employee and community health practice, an integrated primary care medical practice with 6 clinic sites in Rochester, Minnesota, serving a population of 40,000 children. Prevalence of pediatric asthma in this population was estimated to be 12%.¹² The study was performed with approval from the Mayo Clinic institutional review board.

Network analysis¹³ also was performed to evaluate for associations between variables with the addition of 5 variables (no patient portal [defined below], poor compliance <75%, >1 day of school missed, Asthma Control Test score <19, and green-level control on the Asthma Control Assessment). Twelve clinical variables assessing respiratory health and asthma burden were chosen for cluster analysis. Data were organized in a nominal format and subjects with missing values were excluded from the analysis. Network graphs were generated using Gephi 0.8.2,¹⁴ with subjects (cases or controls) and clinical variable as nodes and the edge (line) connecting the nodes denoting the presence of the relation. A force-directed algorithm was applied to allow for “similar” nodes to be pulled together and “dissimilar” nodes to be pushed apart. A weighted degree centrality algorithm was applied across the network to calculate the degree and strength of connections made. Agglomerative hierarchical cluster analysis was performed, with significant breaks on the dendrogram calculated based on the joining distance parameter for cluster disjointedness ($P < .05$).

Study Subjects

Children were identified for the study using a database of participants in the PAMP. Only children and their families who did not

deny research authorization for medical record review were included in the sample. Of the 2,759 subjects in the PAMP, 300 families had documented SHS exposure. SHS exposure history was obtained by asking the question, “What is your child’s smoke exposure?” obtained from the Pediatric Asthma Control Test Assessment. Of those families, 236 children were available for chart review and were designated the cases. The 708 age- and-sex-matched subjects who answered “no” to SHS exposure question were designated the controls (Fig 1).

Description of PAMP

The PAMP was developed with an interdisciplinary team of primary care providers, with enrollment of the first child in March 2009.¹¹ The PAMP, modeled on the NAEPP-3 guidelines,¹⁵ was set in an employee and community health practice, an integrated primary care medical practice with 6 clinic sites in Rochester, Minnesota, serving a patient panel of approximately 140,000 including approximately 40,000 children receiving primary care from 18 pediatricians, 57 family medicine physicians, 8 pediatric nurse practitioners, 20 family medicine nurse practitioner or physician assistants, and 65 pediatric and family medicine residents. The PAMP has a medical director, with 4 other primary care providers (physician or nurse practitioner), a nursing supervisor providing oversight, and a team of 8 nurses acting as “care managers” for asthma. The main assessment tool used in the PAMP was the Asthma Control Assessment, a questionnaire adapted from the NAEPP-3 to target the risk and impairment domains of asthma. In addition, the Asthma Control Assessment had questions about adherence, confidence, and smoke exposure. The goals of the PAMP are to (1) follow NAEPP-3 guidelines to provide consistent care within and across sites; (2) provide proactive, longitudinal non-visit care as opposed to reactive, episodic care; (3) generate and use an electronic medical record-based registry for population management; and (4) provide support for busy primary care providers by the completion of forms.

Data Abstraction

Data were abstracted by the authors from the medical record during 2010, which included asthma care management flow sheets, notes from providers and nurse care managers, and pulmonary function test results. Data were entered into a database and analyzed using JMP 7.0.1 software (SAS Institute, Cary North Carolina).

Definitions

Cases were defined as children with asthma and SHS exposure enrolled in the PAMP.

Controls were defined as children with asthma and without SHS exposure enrolled in the PAMP.

The SHS history was obtained by parent questionnaire and parental report.

A positive methacholine challenge¹⁶ reaction was defined as a 20% decrease in forced expiratory volume in 1 second (FEV₁) from baseline FEV₁ after administration of 25 mg/mL of methacholine using the 5-breath dosimeter protocol (1 breath at 25 mg/mL of methacholine = 0.225 mg).

Exhaled nitric oxide (oral) was obtained using the Aerocrine Mino device (Aerocrine, Solna, Sweden) and reported in parts per billion.

Body mass index percentiles were calculated using the Centers for Disease Control and Prevention BMI Percentile Calculator for Child and Teen Metric Version.¹⁷

Corticosteroid administrations, ED visits, and hospitalizations were documented if they were due to asthma exacerbations only.

Table 1
Patient characteristics—demographic variables

Variable	Cases (n = 236)	Controls (n = 708)	t Test or OR	95% CI	P value
Age (y), mean (SEM)	10.24 (0.236)	10.18 (0.130)	Matched dataset		NS
Boys, n (%)	124 (52.5)	372 (52.5)	Matched dataset		NS
Girls, n (%)	112 (47)	336 (47)	Matched dataset		NS
Weight (kg), mean (SEM)	44.3 (1.45)	41.4 (0.90)	1.80	0.3–6.7	.07
Height (cm), mean (SEM)	140.7 (1.45)	141.1 (0.78)	0.25	3.5–2.7	.8
BMI (kg/m ²), mean (SEM)	24.1 (3.31)	20.03 (0.56)	1.9	0.1–8.2	.057
BMI percentile, mean (SEM)	69.7 (1.8)	63.1 (1.1)	3.04	2.3–10.9	.002 ^a
>75th percentile, n (%)	131 (55.5)	308 (43.5)	1.64	1.22–2.2	.001 ^a
<75th percentile, n (%)	105 (44.5)	400 (56)	0.61	0.5–0.84	.001 ^a
Girls with BMI >75th percentile, n (%)	68/112 (61)	159/336 (47)	Z = 8.67		.001 ^a

Abbreviations: BMI, body mass index; CI, confidence interval; NS, not significant; OR, odds ratio.

^aStatistically significant ($P < .05$).

Flu illness was documented only if the patient had influenza A or B positivity by polymerase chain reaction analysis of a nasal swab.

Secondhand smoke exposure was reported by parents. An objective measurement of nicotine exposure was not used because this was a retrospective study.

The patient portal is a secure online way for patients to access their health information and communicate with their care team.

Statistical Analysis

Standard descriptive statistics were used for categorical variables. The *t* test was used for continuous variables. Contingency tables were used to assess the association between SHS exposure and various demographic and clinical variables and attributes. An age- and sex-matched analysis was performed to estimate the odds ratio (OR) and each matched set was treated as a unique stratum. Statistical analysis was performed using a conditional logistic regression model (JMP 7.0.1) and all reported *P* values were 2-sided with a type 1 error rate of .05.

Results

Demographic Data

Of the 944 subjects enrolled in this study, 236 cases and 708 age- and sex-matched controls (1:3) were identified. The cases and

controls were matched by age and sex, with anthropometric data presented in Table 1. There was a statistically significant difference in the BMI between cases and controls, with cases having a higher overall BMI percentile (70 vs 63, $P = .002$) and a BMI above the 75th percentile ($P = .001$). The case group had a larger proportion of girls with a BMI above the 75th percentile compared with controls (Z score 8.67, $P = .001$). The demographic data of the 2 groups are presented in Tables 1 and 2.

Clinical Data

Asthma severity

The breakdown of severity class is presented in Table 2.

Controls were more likely to have mild to persistent asthma than cases (30% vs 23%, $P = .03$); however, there was no statistically significant difference between cases and controls for the other asthma severity groups. When evaluating the pulmonary function testing results between cases and controls, cases were less likely than controls to have undergone methacholine challenge (30% vs 47%, OR 0.49, 95% confidence interval [CI] 0.36–0.68, $P < .001$) or eNO (10% vs 15%, OR 0.6, 95% CI 0.37–0.97, $P = 0.04$; Table 2). The ratio of FEV₁ to forced vital capacity (FVC) and FEV₁ were lower in cases than in controls ($P < .05$).

Table 2
Patient characteristics—clinical variables

Variable	Cases (n = 236), n (%)	Controls (n = 708), n (%)	t Test or OR	95% CI	P value
Asthma severity					
Intermittent	126 (53.3)	358 (50.5)	1.19	0.83–1.5	.45
Mild persistent	55 (23.3)	215 (30.3)	0.69	0.49–0.98	.03 ^a
Moderate persistent	44 (18.6)	115 (16.2)	1.18	0.81–1.73	.39
Severe persistent	11 (4.6)	20 (2.8)	1.68	0.79–3.56	.17
Methacholine challenge performed	71 (30)	330 (46.6)	0.4929	0.36–0.68	<.0001 ^a
Positive result	64 (90)	292 (88.4)	1.19	0.5–2.78	.6887
Negative result	7 (10)	330 (11.5)			
1 breath	40 (62.5)	153 (52.4)	1.51	0.86–2.6	.14
2 breaths	1 (1.5)	6 (2.05)	0.76	0.09–6.39	.79
3 breaths	5 (7.8)	31 (10.6)	0.71	0.26–1.91	.5
4 breaths	0 (0)	0 (0)	—	—	—
5 breaths	18 (28.1)	99 (33.9)	0.76	0.42–1.38	.37
eNO performed	23 (9.7)	107 (15.1)	0.6	0.37–0.97	.04 ^a
eNO	25.8 (6.83)	21.1 (1.71)	0.97	–4.8 to 14.2	.3
Received influenza vaccine	125 (47)	459 (64.9)	0.6109	0.45–0.82	.0012 ^a
ED visit for asthma	20 (8.4)	54 (7.63)	1.1214	0.66–1.92	.6750
Steroid use for asthma	33 (13.9)	107 (15.2)	0.9131	0.59–1.39	.6724
Hospitalizations for asthma	3 (1.3)	5 (0.7)	1.8103	0.43–7.63	.4189
FEV ₁	96.28 (1.5)	99.9 (0.59)	–3.7	–0.49 to 6.8	.01 ^a
FEV ₁ /FVC ratio	81.8 (0.73)	84.3 (0.33)	–2.5	–0.92 to 4.1	.002 ^a

Abbreviations: BMI, body mass index; CI, confidence interval; ED, emergency department; eNO, exhaled nitric oxide; FEV₁, forced expiration volume in 1 second; FVC, forced vital capacity; OR, odds ratio.^aStatistically significant ($P < .05$).

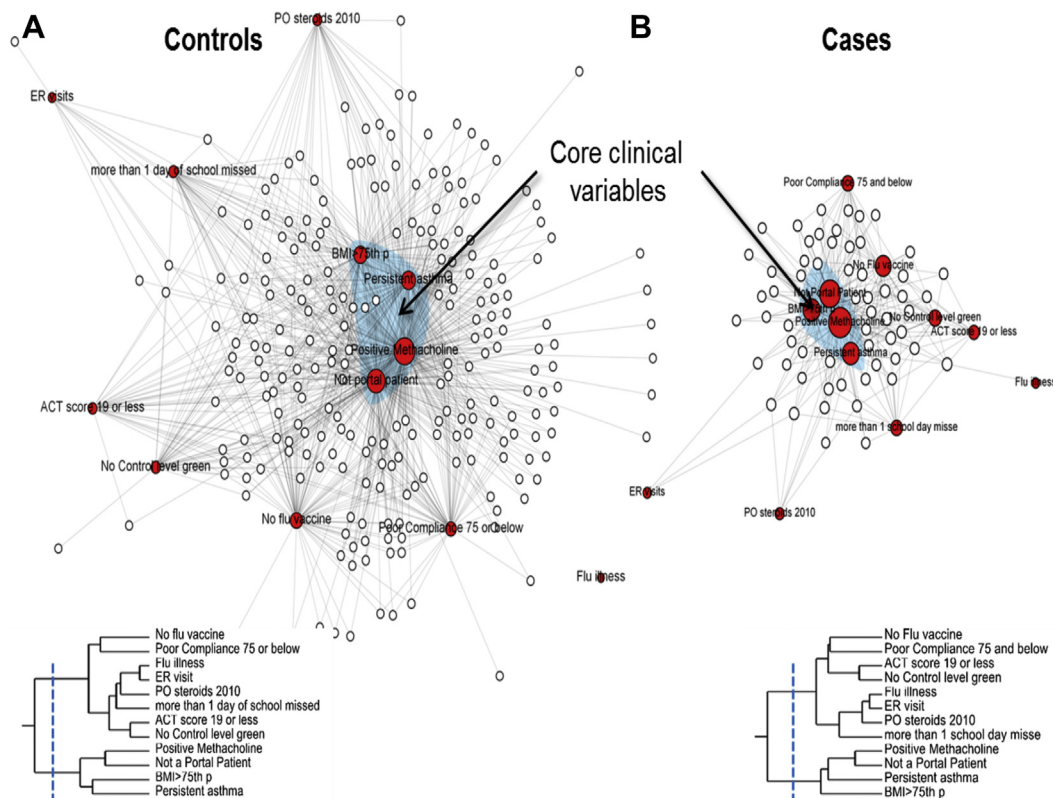


Figure 2. Network analysis of (A) controls and (B) cases. Subjects are represented as white nodes and clinical variables as red nodes. An edge connecting the nodes represents the relation between the set of nodes. ACT, Asthma Control Test; BMI > 75th p, body mass index above 75th percentile; ER, emergency room; PO, per oral.

Influenza vaccination for 2010

Cases were less likely to receive the influenza vaccine compared with controls (47% vs 65%, OR 0.61, 95% CI 0.45–0.82, $P = .001$; however, flu illness rates were not reported because there were insufficient data.

There was no statistical difference between cases and controls with regard to ED visits, steroid use, or hospitalizations for asthma. Clinical data for the 2 groups are presented in Table 2.

Network Analysis

To assess the co-occurrence of clinical variables related to asthma burden and respiratory disease, a bipartite network of variables and subjects (SHS-exposed children) and controls (those not exposed to SHS) was performed. Analysis of the graphs comparing the topology of networks showed a core vs periphery layout in the 2 instances. For the control group (Fig 2), the variables formed 2 distinct clusters, with core variables being methacholine positivity, not using an electronic patient portal, history of persistent asthma, and BMI higher than the 75th percentile. This result suggests that these 4 clinical variables were the predominant clinical features of the control group. Clustering of variables seen in the control network also was observed in the agglomerative hierarchical cluster analysis (Fig 2, inset) and boundaries of the clusters defined (Fig 2, blue area). There were no discrete subject clusters and overall modularity (measurement of discrete clustering) of the network was low (0.175, values >0.3 considered significant),¹⁸ suggesting there were no distinct subgroups of subject and variable nodes in the network. Similar results were obtained for the cases-only network (Fig 2). Network analysis suggested a lack of discrete and unique subgroups between children exposed to SHS and those not exposed to SHS.

Discussion

In this case-controlled retrospective study, children with asthma exposed to SHS were more likely to have comorbid conditions such as obesity, more severe asthma, and less health care usage than children with asthma not exposed to SHS.

Children with asthma and SHS exposure had significantly higher BMI percentiles (>75%) and overall higher BMIs than controls (Table 1). The present result is supported by the literature that suggests an association between childhood obesity and the propensity to develop asthma and could be a unique phenotype of asthma.¹⁹ In addition, recent studies have reported that there might be a clear dose–response relation between BMI and asthma or wheeze that might be related to genetic polymorphisms.²⁰ Obesity in children also could be an indicator of socioeconomic status,^{20–22} where poverty can perpetuate a cycle of stress and inflammation,²³ but was not explored in this study and could be considered a limitation.

Furthermore, this was a retrospective chart review study in which parental self-report was used as a subjective measurement of SHS; objective measurement of SHS was not performed. Murray and Morrison²⁴ showed a correlation between asthma severity and the number of years the child had been exposed to the mother's smoke, so evaluating which parent(s) smoked would have been helpful to examine this finding further. There is a possibility of under-reporting of SHS, because nearly 80% of children with asthma in a recent study had elevated salivary cotinine levels, although only 35% of parents reported SHS.¹⁰ This discrepancy could have contributed the observed lack of differences in asthma severity and impairment. Poverty is an additional variable; children with asthma were more likely to be exposed to SHS if their family income was below 350% of the federal poverty guidelines²² and if they were Mexican American; however, the authors did not have

complete information on race, medical insurance, and family income, which could have helped understand the barriers to access to care. The authors tried to assess for online patient portal access as a surrogate for medical literacy and possible socioeconomic status and found that only 18% of the cohort had online patient portal access.

Despite the effect of SHS exposure, cases had a higher BMI compared with controls. Most children in this cohort were peripubertal (mean age 10 years), which might indicate endocrine and neuro-biochemical influences that affect airway hyperreactivity.²¹ Only subject reports were used for ascertainment of tobacco exposure, so if there were any dose–response relation between the amount of nicotine exposure (objective measurement of nicotine exposure) and BMI,²² then that effect would have been underestimated.²³

The authors also found that children with asthma and SHS exposure were less likely to have had a methacholine challenge and an eNO performed than controls (Table 2). It is unclear why there was a discrepancy in usage between these tests. One possibility could be access to care owing to differences in health literacy.^{25,26} Another possibility could be due to specialist (ie, allergist or pulmonologist) vs non-specialist (ie, pediatric or family medicine physicians) care and scope of practice,²⁷ but this was not explored in the present study and is a limitation.

The authors found no difference in the rates of methacholine positivity with airway hyperreactivity between cases and controls. This result is similar to previous studies with primary tobacco exposure, where there might be a component of nonspecific airway hyperreactivity with some differences based on sex.²⁸ Methacholine challenges were based on adult dosing, with the lowest dose being 0.225 mg (1 breath; 1.125 mg for 5 breaths). The 5-breath cutoff might be slightly higher than the total methacholine dose reported in the literature (6.6 mmol) and, hence, could contribute to an overall higher prevalence of positive methacholine challenge results in cases and controls.²⁹

The FEV₁/FVC ratio and FEV₁ were lower in cases than in controls, which is similar to published studies on SHS exposure and its effect on pulmonary function testing.⁶ In addition, the observed decrease in pulmonary function in the case population could have been a result of a high BMI rather than SHS, but this could be an area for further research.

Children with asthma and SHS exposure were less likely to have received an influenza vaccination than controls (Table 2). Many factors could play a role in this difference, including compliance, financial stresses, parental refusal, and access to care. Beliefs and attitudes rather than asthma control parameters have been shown to influence parental decisions for immunization,³⁰ which were not explored in the present study. Influenza can be more severe and trigger asthma exacerbation in children with asthma³¹ and children exposed to SHS,³² so routine yearly vaccination is strongly recommended in this population, irrespective of SHS exposure. Healthy People 2020 has set a target of an 80% vaccination rate for children 6 months to 17 years old, thus highlighting the need to educate health care providers and persons with asthma about the importance of annual influenza vaccination.²⁶ The cases (47%) and controls (65%) did not achieve the target for influenza vaccine uptake of 80% for 2010.

Network graphs (Fig 2) in the case and control networks shared a core-vs-periphery topology signifying the presence of influential clinical variables, which in this study were a positive methacholine test reaction, BMI higher than the 75th percentile, carrying a diagnosis of persistent asthma, and not using the electronic communication portal. Other variables had limited presence and were pushed to the periphery of the network. The subjects did not form discrete clusters within themselves of co-clusters with the variables, suggesting an absence of distinct subgroups in the population.

Physicians caring for children with asthma should not only focus on asthma severity and control but also be aware of other health issues, including body weight,³³ environmental exposures, and emotional well-being,³⁴ which can affect the asthma status of the child. Smoking cessation intervention with motivational counseling alone might be insufficient in the pediatric setting,³⁵ and a comprehensive family-based program consisting of motivational counseling and referral to a smoking cessation specialist and pharmacotherapy³⁶ should be integral to care for children with SHS exposure (Joshi et al, manuscript under review, submitted in May 2015). Furthermore, studies have shown that if parents are aware that SHS will aggravate their child's asthma, then the child will be exposed to fewer cigarettes, which leads to less severe asthma.³⁷

This study concluded that children with asthma exposed to SHS are more likely to have comorbid conditions such as obesity, more severe asthma, and less health care usage than children with asthma not exposed to SHS. In addition to smoking cessation interventions (which have the potential to decrease airway hyperreactivity and progression of airway obstruction), understanding and addressing the barriers to health care usage could be crucial in this vulnerable population.

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