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ORIGINAL ARTICLE

Household Smoking and Bronchial Hyperresponsiveness in Children with Asthma

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ABSTRACT

This study investigated whether household environmental tobacco smoke (ETS) exposure is associated with increased bronchial hyperresponsiveness (BHR) in children with asthma. Two hundred forty-nine children, ages 7–11 years, sampled from a larger group with reported asthma or multiple asthma symptoms identified in a community survey in Cape Town, underwent histamine challenge testing and had urinary cotinine

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measured. Parents were interviewed for information on smoking habits and a variety of covariates. Children with asthma whose mothers smoked had a lower frequency of BHR than asthmatic children of nonsmoking mothers, particularly if the mother smoked ≥15 cigarettes daily. BHR was also less common among children sharing a house with four or more smokers vs. fewer or none. BHR was unrelated to paternal smoking. In contrast, FEV_1 was lower among children whose mothers currently smoked. The findings do not support a mechanism whereby ETS exposure aggravates existing childhood asthma by increasing BHR. This association may be masked, however, by the degree to which mothers of asthmatic children adjust their smoking. The results are consistent with an adverse effect of maternal smoking on lung function in asthmatic children.

KEY WORDS: Asthma; Environmental tobacco smoke; Bronchial hyperresponsiveness.

INTRODUCTION

There is now considerable evidence from population studies that maternal smoking is associated with an increased frequency of asthma and wheezing illness in young children (1–3). In addition, some, but not all, general population studies of children have shown a positive association between environmental tobacco smoke (ETS) exposure, mainly from household sources, and bronchial hyperresponsiveness (BHR) (4–9).

In contrast to studies of general populations of children, investigations or analyses of samples of asthmatic children address the question of exacerbation of the condition by ETS rather than its initiation or induction. Studies of asthmatic children have shown positive associations between ETS and symptoms (10–12), daily peak flow variability (13), and frequency of emergency room visits (14) and a negative association between ETS and lung function (10–12,15,16). Some of these studies have also found an association between ETS exposure and BHR, a possible mechanism underlying the aggravation of asthma by ETS in susceptible children (4,5,10–12).

The objective of this study was to test the aggravation hypothesis, namely, that exposure to household ETS is associated with increased BHR in children identified as having asthma or (in the absence of the diagnosis) multiple asthma symptoms. Urinary cotinine was measured as an objective marker of current or recent exposure to ETS. The selection of children with asthma was population based, thus avoiding selection factors associated with clinic populations.

The study was part of a larger project examining the prevalence and reliability of asthma symptoms, household risk factors for asthma, and the extent of underdiagnosis and undertreatment in a young school-going population (17–19).

METHODS

Selection of Cases for Study

The study site was a lower-income residential area in Cape Town of approximately 210,000 people. A random sample of 16 schools was selected from the 35 primary schools in the area. Self-administered questionnaires, in English or Afrikaans, were distributed in winter months via the children to the parents of all 2172 grade 2 pupils (typically aged 7–9 years) on the class lists of the sample schools. The questionnaire was based on one in use in an international study of allergic disease in childhood, with the addition of a question on chest tightness, a term in common use in this population (20). The questions are reproduced in Appendix 1.

The prevalence findings have been reported elsewhere (17). Figure 1 illustrates how the study group was selected. Questionnaires were returned by 1955 parents (a response rate of 90%). Of these, 83 subsequently participated in a pilot study, 114 did not give consent to be interviewed further, and 22 failed to provide enough questionnaire information. From the remaining sample of 1736 children, a "current asthma" case group ($n = 368$) was defined as those children with parent-reported asthma plus at least one symptom in the past 12 months ($n = 162$) or, in the absence of reported asthma, affirmative responses to four or more symptom questions referring to the past 12 months ($n = 206$). This resulted in a score with a scale of 0–10. Case status was based on a score of 4 or more (see Appendix 1).

Resources available to the study did not permit BHR testing of every child meeting the case definition. Accordingly, for BHR testing, the 368 case children were randomly ordered in lists by school and selected with the aim of achieving as large a sample as practicable, in

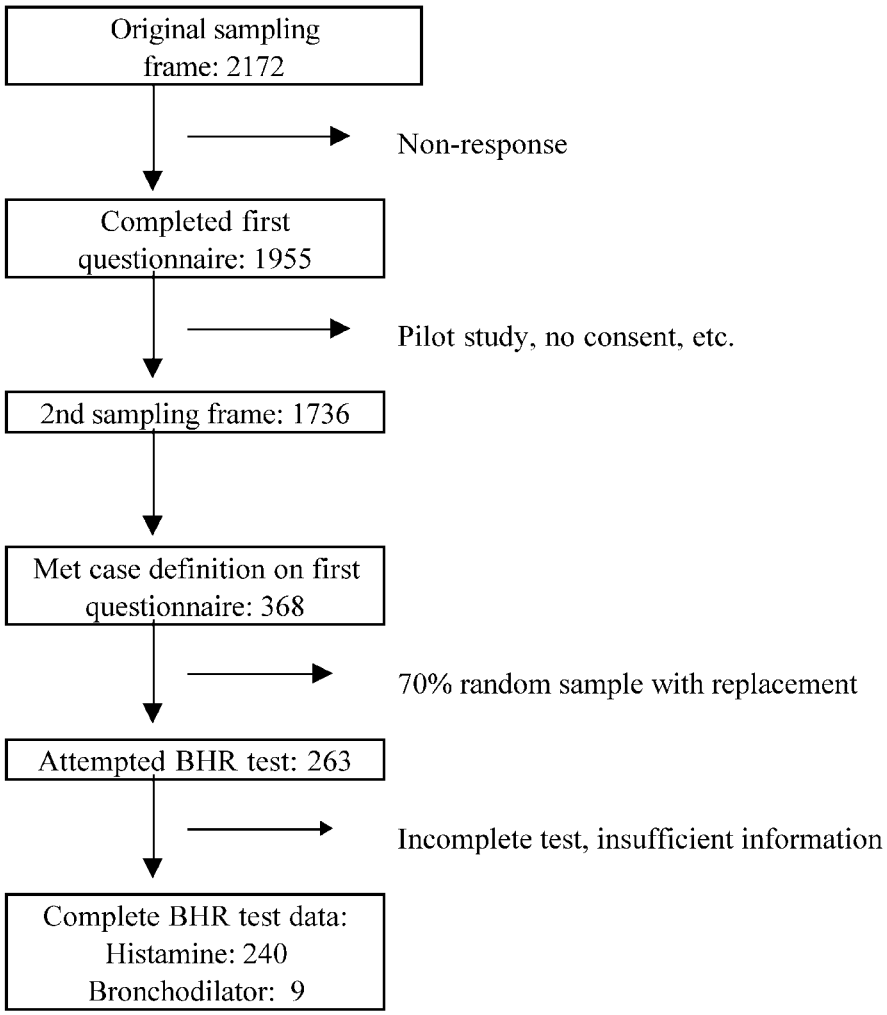

Figure 1. Sampling pathway to group that underwent bronchial hyperresponsiveness (BHR) testing.

this case a minimum of a 70% sample per school (n = approximately 258). Any unavailable subject was replaced by the child who was next on the random list for that school.

Smoking and Other Covariates

The parents of the children identified as cases were visited (in spring) by interviewers between 6 weeks and 3 months after the self-completed questionnaire survey. In the longer questionnaire used in the home interview, the asthma symptom questions were repeated, and further information was sought on sociodemographic features; the child's medical history; household smoking; household features such as pets, electricity/fuel use, visible dampness, and mold; and family history of asthma.

"Atopic history" was defined as a history of hay fever or eczema in the child. "Asthma recognition" was defined by a yes to the question "Has your child ever had asthma?" Symptom score was treated as a binary variable (7–10 vs. 4–6).

Urinary Cotinine

Urinary cotinine is a specific metabolite of nicotine with a half-life of approximately 20–40 hours and is a validated marker of exposure to environmental tobacco smoke (1). At the same time as the BHR testing, a specimen of urine was collected from the children at school.

These were frozen on the day of collection to -20°C and later analyzed by radioimmunoassay, adapted from a method by Knight et al. (21). This method uses polyclonal rabbit antiserum, I^{125}-labeled cotinine, with cotinine added to horse serum as a standard. The method has a detection sensitivity of 5 ng/mL and an interassay precision of $<10\%$. Quality control was exercised by measuring known standards from the supplying laboratory. To allow standardization for varying diuresis, urinary creatinine was measured by the Jaffe reaction on a Beckman CX5 discrete analyzer.

Bronchial Hyperresponsiveness Testing

Histamine challenge tests were carried out by using the long challenge protocol of Yan et al. (22). A Vitalograph S wedge-bellows spirometer was used, calibrated daily with a 3-L syringe. Any child who was judged clinically by the medical practitioner present to have a significant respiratory infection on the day was not tested. Parents were requested to withhold routine asthma medication on the morning of the test unless the child was ill, but it was not possible to evaluate compliance with this request. Each child was also asked privately at the time of the test whether he or she had ever tried cigarettes; none admitted to having done so. Temperature and humidity readings were obtained for each day of the study from the metropolitan weather station.

Each child carried out a standing forced expiratory maneuver without a noseclip until two reproducible tracings—that is, within 100 mL of each other—were obtained. The baseline measurement was repeated after an inhalation of normal saline. Any child who was found to have a presaline or postsaline forced expiratory volume in 1 second (FEV_1) of less than 75% of predicted for sex, age, and height was not challenged with histamine. Instead, the child inhaled 200 μg of salbutamol from a metered dose inhaler and repeated the expiratory maneuver after 10 minutes. A positive bronchodilator test was defined as one in which the FEV_1 increased by 15% or more postbronchodilator.

In the children whose baseline FEV_1 was 75% or more of predicted, the test consisted of inhaling doubling doses of histamine solution delivered with a series of De Vilbiss No. 40 handheld nebulizers, which dispense an average of 0.003 mL of solution with each squeeze. The exact amount per squeeze delivered by each of the nebulizers used in the study was measured at the beginning and again in the middle of the study to calculate the delivered dose for the coming phase of testing. The test was ended when a fall in FEV_1 of 20% or greater from the post-saline value was recorded (a positive test) or when a cumulative dose of approximately 7.8 μmol of histamine had been reached without such a fall (a negative test).

Any child who experienced a fall of 10% or more in the course of the challenge was given 200 μg of salbutamol at the end of the testing and was observed until the FEV_1 had returned to its baseline value.

Statistical Analysis

The principle of bronchoprovocation tests, such as histamine challenge, is to start with a very low inhaled dose, measure any fall in FEV_1 from baseline, and increase the dose until a 20% or greater fall in FEV_1 occurs or until the limit dose is reached. Different methods are available to analyze information obtained from such bronchoprovocation tests (23,24). For purposes of this report, the most familiar method was used, that is, analysis of BHR as a binary variable, with positive responders defined by a 20% or greater fall in their FEV_1 ("hyperresponsiveness") within the dose range of the test. Subjects who underwent a bronchodilator test because their baseline FEV_1 was less than 75% were included in the BHR group in the reported analysis. However, the analysis was repeated after excluding them. Because the design effect of sampling schools rather than individuals was found to be small, no adjustment for this effect was made.

The association between BHR and a range of covariates was first examined in bivariate analysis, expressed as the prevalence ratio (of a positive BHR test using one of the levels of exposure as the reference). These covariates included socioeconomic, medical history, and ETS exposure variables, as well as baseline FEV_1, asthma recognition, and symptom score (see above for definitions). The association between BHR and covariates of interest was then modeled in multivariate analysis using logistic regression, with the prevalence odds ratio as the measure of effect. The variables that were entered into multivariate analysis included ETS exposure variables of interest, covariates that were statistically significant in bivariate analysis, and potential confounders.

Effect modification, that is, variation of the ETS-BHR association across subgroups in the population, was tested by examining interaction terms in the model. Effect modifiers of interest were sex, atopic history, asthma recognition, and symptom score. Besides BHR, the other association of interest was that between baseline FEV_1 and ETS. FEV_1 was analyzed as a continuous variable, after adjustment for age, sex, and height, and mean adjusted FEV_1 was compared across different levels of the ETS exposure variables.

Ethics

The study was approved by the Ethics and Research Committee of the University of Cape Town Medical Faculty, and informed consent for histamine testing was obtained from parents of all participating children.

RESULTS

A total of 263 children attempted the BHR test. Of another 33 children who were invited to the testing, but were replaced by the child next on the list, 14 were absent on the day, 14 were judged at the test site to have a respiratory tract infection, and 5 were no longer at the school. Of those who attempted the test, eight were unable to perform an adequate test and two tests were curtailed because of time. There was insufficient or no questionnaire information on four of the children who completed the test, leaving 249 subjects for analysis. Of these, 240 successfully completed the histamine challenge test (115 positive, 125 negative). Of the positives, 23 responded by the fifth histamine dose of 0.49 μmol, 61 by the seventh dose of 1.95 μmol, and 115 by the last dose of 7.8 μmol. A further nine children had bronchodilator tests only (six with positive tests, three with negative tests).

CCR results were available for 248 children of these children. The median cotinine creatinine ratio (CCR) was 74.2 ng/mg (interquartile range: 33.9–137.7 ng/mg). The CCR increased with the number of smokers at home (Spearman's $r = 0.5$, $p = 0.0001$).

The symptom and maternal smoking profiles of the children who underwent BHR testing are listed in Table 1 and compared to those of children with asthma who were not tested ($n = 99$). There were no significant differences between the tested and untested group in symptoms, asthma recognition, hay fever, or maternal smoking prevalence. There was also no difference between the groups in a range of other demographic, socioeconomic, and domestic exposure variables (not shown).

Table 2 compares BHR with respect to a number of sociodemographic and medical history variables. There was no association between age or sex and BHR. There was a positive association between medical insurance and BHR (prevalence ratio (PR): 1.30, 95% confidence interval (CI): 1.03–1.66).

Of the medical history variables, children with an atopic history also showed greater BHR (PR: 1.46, 95% CI: 1.14–1.81). This was also the case for a history of hay fever or eczema separately. Symptom score was positively associated with BHR (PR: 1.45, 95% CI: 1.01–2.09), while asthma recognition was somewhat less so. Higher baseline FEV_1 was inversely associated with BHR (PR: 0.57, 95% CI: 0.39–0.81).

Table 3 compares BHR at different levels of a number of ETS exposure measures as well as reported household dampness or mold. In general, exposure to maternal smoking was associated with a lower frequency of BHR in the

Table 1

*Asthma Cases That Completed Bronchial Hyperresponsiveness Testing Compared to Untested Cases (*n = *348)*

Symptoms[a]/Diagnosis	Tested (%) ($n = 249$)[b]	Not tested (%) ($n = 99$)
Wheeze	97.4	93.8
Wheeze frequency ≥ 4	29.0	33.3
Sleep disturbance	85.6	87.5
Speech disturbance	40.3	47.9
Night cough without a cold	81.9	80.0
Post-exercise wheeze	81.0	78.4
Tight chest	85.5	89.6
Asthma ever	44.4	43.4
Hay fever ever	31.9	37.8
Selected exposure characteristics		
Mother smokes currently	57.8	60.4
Mother smoked in pregnancy	46.4	47.9
Mother smoked ever	69.0	66.3

[a]Past 12 months unless otherwise indicated.

[b]Includes nine children who underwent bronchodilator rather than histamine challenge test.

Table 2

Bronchial Hyperresponsiveness by Demographic, Socioeconomic, Medical History, and Lung Function Variables in Children with Asthma (n = 249)

Variable	Category	*N*	Positive BHR Test %	Prevalence Ratio (95% Confidence Interval)
Age, years	6–7	109	50.5	0.98 (0.76–1.26)
	8–11	124	51.6	
Sex	Female	119	52.9	0.94 (0.74–1.2)
	Male	130	50.0	
Medical insurance	No	172	47.1	1.30 (1.03–1.66)
	Yes	75	61.3	
Mother's education, years	0–8	152	53.3	0.91 (0.71–1.18)
	>8	96	49.0	
Mother contributes to income	No	153	49.7	1.11 (0.88–1.40)
	Yes	94	55.3	
Father's education, years	0–8	151	55.0	0.85 (0.66–1.10)
	>8	94	46.8	
Father contributes to income	No	95	53.7	0.94 (0.74–1.19)
	Yes	153	50.3	
Hay fever	No	169	45.6	1.44 (1.14–1.81)
	Yes	78	65.4	
Eczema	No	186	48.4	1.25 (0.97–1.60)
	Yes	63	60.3	
Atopic history	No	135	43.0	1.46 (1.14–1.85)
	Yes	112	62.5	
Parental asthma	No	170	50.6	1.08 (0.83–1.40)
	Yes	68	54.4	
Sibling asthma	No	191	51.8	1.04 (0.78–1.38)
	Yes	54	53.7	
Asthma recognition	No	142	45.8	1.28 (0.90–1.81)
	Yes	106	58.5	
Symptom score	4–7	183	45.9	1.45 (1.01–2.09)
	8–10	66	66.7	
Baseline FEV_1, mL	650–1420	125	65.6	0.57 (0.44–0.74)
	1420–2150	124	37.1	

BHR = bronchial hyperresponsiveness. FEV_1 = forced expiratory volume in 1 second.

children, though not reaching statistical significance (i.e., the confidence interval included 1).

The most suggestive effect was among children of mothers who smoked 15 or more cigarettes a day, who showed considerably less BHR compared to children whose mothers smoked none (PR: 0.60, 95% CI: 0.34–1.08). A similar pattern was evident for the number of smokers in the household, where the highest stratum (>3 smokers) showed a somewhat lower prevalence of BHR than the intermediate or unexposed stratum.

There was no association between paternal smoking and BHR. Although the higher quartiles of urinary CCR were associated with less BHR than the lowest stratum, there was no exposure response trend.

There was no association between reported household dampness and BHR. There was also no association between BHR and temperature or humidity on the test day (not shown).

To explore whether the child's symptoms or perception of the child's condition by parents might cause them to reduce the child's exposure to ETS, the relationships between urinary CCR and atopic history, asthma recognition, and asthma score were examined. This is shown in Table 4. Urinary cotinine was in fact lower among children with an atopic history and with asthma recognition than those without. Children with a higher symptom score showed a slightly lower level of urinary CCR.

Table 3

*Bronchial Hyperresponsiveness by Household Smoking and Other Environmental Variables in Children with Asthma (*n = *249)*

Variable	Category	*N*	Positive BHR Test (%)	Prevalence Ratio (95% CI)
Mother's smoking				
Current	Never	76	61.8	1.00
	Ex	27	44.4	0.72 (0.38–1.36)
	Current	144	47.9	0.78 (0.54–1.12)
Daily cigarettes	0	104	56.7	1.00
	1–14	102	53.9	0.95 (0.66–1.37)
	15–35	41	34.2	0.60 (0.34–1.08)
In pregnancy	No	114	53.5	
	Yes	133	49.6	0.93 (0.73–1.18)
In first year of child's life	No	109	54.1	
	Yes	140	49.3	0.91 (0.72–1.16)
Father's smoking				
Current	No	115	51.3	
	Yes	131	51.2	0.99 (0.78–1.27)
In first year of child's life	No	71	46.5	
	Yes	167	52.1	1.12 (0.84–1.50)
Number of smokers in house	0	41	53.7	1.00
	1–3	154	55.8	1.04 (0.76–1.43)
	>3	52	36.5	0.68 (0.43–1.08)
CCR, ng/mg	0–33.8	60	56.7	1.00
	33.9–74.2	64	48.4	0.86 (0.61–1.20)
	74.3–137.7	62	53.2	0.94 (0.68–1.30)
	>137.7	61	45.9	0.81 (0.57–1.15)
Household dampness or mold	No	161	49.1	
	Yes	88	55.7	1.14 (0.89–1.45)

BHR = bronchial hyperresponsiveness. CI = confidence interval. CCR = cotinine creatinine ratio.

Table 4

*Association of Urinary Cotinine with Various Features of Asthma or Atopic Status in Children with Asthma (*n = *249)*

Variable	Category	*N*	Cotinine Creatinine Ratio[a] (SE), ng/mg	*p*-Value for Difference
Atopic history	No	134	84.4 (2.70)	
	Yes	110	56.1 (2.91)	0.002
Asthma recognition	No	140	81.5 (2.64)	
	Yes	105	58.9 (3.00)	0.015
Symptom score	4–7	181	72.8 (2.58)	
	8–10	65	64.1 (2.58)	0.40

SE = standard error.
[a]Geometric mean.

Table 5

*Predictors of Bronchial Hyperresponsiveness in Multivariate Analysis in Children with Asthma (*n = *249)*

Variable	Categories	Odds Ratio (95% Confidence Interval)
Mother's daily cigarettes	0	1.00
	1–14	0.97 (0.67–1.41)
	15–35	0.62 (0.34–1.11)
Atopic history	No	
	Yes	1.27 (0.88–1.83)
Baseline FEV1 (mL)	650–1420	
	1420–2150	0.60 (0.42–0.86)
Asthma label	No	
	Yes	1.06 (0.72–1.58)
Symptom score	4–7	
	8–10	1.34 (0.89–2.01)
Medical insurance	No	
	Yes	1.32 (0.87–2.00)

FEV_1 = forced expiratory volume in 1 second.

Table 5 shows the results of multivariate analysis. Among the ETS variables, current smoking by the mother in the form of number of cigarettes smoked daily was entered into the model. This was adjusted for medical insurance, atopic history, baseline FEV_1, asthma recognition, and symptom score (treated as confounders) in multivariate analysis. There was no change in the negative association between maternal daily cigarette consumption and BHR compared to the bivariate analysis.

No significant effect modification was found. In particular, the associations (or lack of them) between BHR and maternal smoking, paternal smoking, number of household smokers, or CCR did not vary significantly by atopic history, asthma recognition, higher symptom score, parental or sibling history of asthma.

The analysis was repeated excluding the children who underwent the bronchodilator test only, with no change in the results.

ETS Exposure and FEV_1

Table 6 shows the mean baseline FEV_1 adjusted for age, sex, and height in relation to smoking exposure variables. The significant associations were a lower mean FEV_1 among children whose mothers currently smoked compared to children whose mothers did not, and similarly for children whose parents both smoked. Children whose fathers smoked had a higher mean FEV_1 than that of nonsmoking fathers, but this difference was not statistically significant. There was no association between FEV_1 and the cotinine creatinine ratio.

DISCUSSION

Bronchial hyperresponsiveness can be interpreted as a marker of current asthma severity, or, alternatively, susceptibility to acute asthmatic episodes in children identified as having asthma. BHR is not a fixed or defining characteristic of asthma, however. It may vary over time in the same child or vary considerably between asthmatic children; that is, it shows intraindividual and interindividual variability (25). In clinical settings a single measurement of BHR must be interpreted with caution. However, as long as this variability is distributed equally across the groups of interest, BHR remains useful as an objective outcome in epidemiological analysis of exposure factors contributing to asthma or its severity.

This study has failed to show that household ETS exposure is associated with a greater frequency of BHR in a population-based sample of children with recognised asthma or a history of recent asthma symptoms. This was so whether ETS exposure was defined in terms of urinary cotinine, reported parental smoking, or number of smokers in the house. Unexpectedly, the frequency of BHR was lowest in the highest stratum of both maternal smoking ($\geq$15 cigarettes smoked daily by the mother compared to

Table 6

*FEV_1[a] by Household Smoking Variables and CCR in Children with Asthma (*n = *247)*

Variable	Mean FEV_1 (SE), mL		Mean difference, mL	
	Yes	No	Yes − No	95% CI
Mother's smoking				
Current	1409 (19)	1641 (115)	−232	(−461, −2)
Ever	1526 (69)	1467 (48)	59	(107, 225)
In pregnancy	1464 (60)	1557 (83)	−93	(−296, 110)
In first year of child's life	1463 (57)	1560 (88)	−97	(−305, 110)
Father's smoking				
Current	1561 (91)	1449 (32)	112	(−78, 302)
In first year of child's life	1518 (72)	1502 (47)	16	(−154, 186)
Mother and father smoke	1385 (32)	1591 (62)	−150	(−286, −131)
Two or more smokers in household	1455 (53)	1591 (102)	−137	(−366, 92)

CCR (ng/mg)	Mean FEV_1 (SE), mL	Mean[a] Difference from Lowest Category, mL	
0–33.8	1467 (96)	—	
33.9–74.2	1466 (96)	2	(−320,325)
74.3–137.7	1653 (101)	190	(−139,520)
>137.7	1423 (97)	−40	(−363,282)

FEV_1 = forced expiratory volume in 1 second. SE = standard error. CI = confidence interval. CCR = cotinine creatinine ratio.

[a] Adjusted for age, sex, and height.

fewer or none), and number of household smokers (four or more compared to fewer or none).

The only expected association (11,15,16) that was demonstrated in this group of schoolchildren with asthma was an FEV_1 deficit among children whose mothers currently smoked or whose parents both smoked, compared to children whose mothers (or parents) were current nonsmokers.

The findings were also surprising in view of the robust association (odds ratio of the order of 1.7–2.0) between maternal and other household smoking and asthma when the whole population, that is, including the controls (scores 0–3), was analyzed (18). The results of the two studies suggest a model in which maternal smoking contributes to the induction of asthma and to its chronicity as measured by FEV_1 but not to the elevation of BHR in children with asthma.

Of other covariates examined, the known association between atopy and BHR from population studies (5,26) was confirmed. However, no significant variation in BHR by age, sex, reported household dampness or mold, or socioeconomic markers (other than medical insurance) could be demonstrated. The increased BHR among children with medical insurance is interesting but ambiguous, as medical insurance is both an indicator of better socioeconomic circumstances and greater access to private sector medical care.

Possible explanations for the unexpected findings include lack of power, bias, negative confounding, or effect modification. Lack of power is evident from the wide confidence intervals. However, the measures of effect estimates for the smoking variables were consistently either close to 1 or smaller than 1. While a larger study would have reduced the size of the confidence intervals, it is unlikely to have resulted in substantial reversal of the direction of the estimates.

Bias (due to the cross-sectional study design) away from finding an effect of current ETS exposure on BHR would occur if parents of children with correlates of BHR (such as more active or severe asthma or multiple manifestations of atopy such as rhinitis and eczema) avoided smoking around the children or reduced their smoking altogether. This was suggested by Frischer et al. (7), who found an association between ETS and peak expiratory flow variability (assumed to reflect BHR) in nonatopic asthmatic children but not in atopic asthmatic children,

and by Chen et al. (27), who found an association between ETS and diagnosed asthma in nonallergic but not in allergic children.

A seemingly protective effect of current smoking on current BHR among 8-year-old asthmatics was also found by Meinert et al. (28), in contrast to an adverse effect of smoking by the mother in pregnancy and during the child's first year of life on current BHR. This suggested that mothers reduced their smoking over time (or did not take it up) in response to having a child with BHR. The authors termed this the "healthy passive smoker" effect.

In this study, asthma recognition, atopic history, and higher symptom score were associated with increased BHR. In addition, urinary CCR was significantly lower in children with asthma recognition and atopic history than in those without and slightly lower in those with a higher asthma score. These covariates thus qualify as potential confounders. A strong selection effect based on these correlates of BHR could possibly produce a spurious inverse association between ETS and BHR, with the more bronchially responsive children having less ETS exposure. However, when these potential confounders were entered into multivariate analysis together with current maternal smoking activity, there was no change in the inverse association between maternal smoking and BHR.

Other forms of negative confounding were considered. Meijer et al. (13), measuring circadian peak flow variation in allergic asthmatic children, found an association of ETS with peak flow variation among children with mild to moderate BHR as measured by histamine challenge but not among those with severe BHR. Those authors postulated that the effect of ETS in the group of children with severe BHR was masked by the impact of other exogenous stimuli. The only marker of environmental allergen exposure measured in the current study was household mold or dampness, which was not associated with BHR. While sensitization to house dust mite is the most common form of atopy in this population (29), it is implausible that house dust mite exposure would be inversely related to ETS exposure.

Effect modification may result in an effect that occurs in a subgroup of the population being diluted if the whole population is studied. In this study, there was no effect modification by atopy, in contrast to the findings of Chen et al. (27) and Frischer et al. (7). Effect modification of the association between ETS and BHR among asthmatics by age, sex, and season has been noted in some studies. Murray and Morrison (11,12) found in their series that a positive association was demonstrable mainly in boys, among adolescents compared to the age group 7–11 years (the age range of our study), and during testing in the cold, wet season rather than in the warm, dry season. In the current study, there was no sex difference in the findings. All the testing was done in spring and early summer, when the child's household ETS exposure would conceivably be lower than in the wet winter months. Some authors have also suggested that there may be a susceptibility factor, as yet uncharacterized, making some asthmatics more sensitive to ETS than others (30–32).

The findings regarding ETS and BHR are in conflict with the results of a number of other studies of children with asthma, in which BHR was greater or more prevalent in the children of smokers (4,5,10–12). One of these study populations (10–12), in which histamine challenge was also used, consisted of diagnosed asthmatics attending a clinic and may have represented a selected group with more severe asthma. The sample in the current study was a group of children described as having symptomatic asthma or multiple symptoms of asthma in the previous 12 months. In this study, the spectrum of disease would be different from that in studies of clinic asthmatics, in that the sample included both children with current active asthma and those whose asthma might have been episodic, seasonal, or mild. However, the findings also contradict those of studies in which children in the asthma group were identified from population-based samples in a similar way (4,5), although the methods of BHR testing were different.

Chamber studies, in which asthmatic subjects are subjected to ETS under controlled conditions, have reproduced acute symptoms of upper and lower respiratory tract irritation but have produced conflicting results with regard to changes in BHR. Oldigs et al. (33) studied asthmatic children and found no consistent change in lung function or BHR after 1 hour of exposure to ETS. Some chamber studies of adult asthmatics have shown lung function decline and increased BHR on ETS challenge (32,34), although in the latter study subjects were preselected for previous "sensitivity" to ETS. Other chamber studies of asthmatic adults failed to show these responses to ETS (35,36). In general, these studies are able to reproduce only acute ETS exposures in small samples of mainly adult volunteers, and the relevance to chronic exposure of children in home environments is limited.

In conclusion, this study does not support the hypothesis that ETS aggravates asthma by increasing BHR. If anything, an inverse association between heavier maternal smoking and BHR was found. It is difficult to conceive of a biological basis for an inverse association. An attempt was made to adjust for factors that might induce

parents to modify their smoking in response to manifestations of asthma in their child, but the effectiveness of such adjustment is difficult to judge in a cross-sectional study. Further cross-sectional studies cannot solve this problem. Only prospective studies with measurement over appropriate time periods of both the child's ETS exposure and BHR are likely to be able to answer the question.

The findings of this study should be considered in the light of the conclusion of a recent systematic literature review by Cook and Strachan (9). Reviewing studies of passive smoking and BHR both in general populations and in asthmatic populations or subgroups, the authors concluded that there was insufficient evidence for an effect of ETS on BHR at the general population level. They cited selective reporting of results in published studies and publication bias in favor of positive studies as having produced a spurious positive association in the literature. In addition, the relatively few studies of asthmatic children were contradictory or inconclusive.

In contrast to the findings regarding BHR, the results of this study are consistent with an effect of maternal smoking, and combined maternal and paternal smoking, on lung function deficit (as reflected in FEV_1) among asthmatic children. ETS exposure may thus be an added risk factor for long-term lung function loss in wheezy children or children with asthma (15).

APPENDIX 1

Questions and scores (in parentheses) used in self-administered questionnaire as basis of case definition:

(minimum = 4, maximum = 10)

1. Has your child had *wheezing* or *whistling* in the chest in the last 12 months?

   1.1 *How many* attacks of wheezing or whistling in the chest has your child had in the last 12 months?

   None
   1–3 **(1)**
   4–12 **(2)**
   more than 12 **(2)**

2. In the last 12 months how often, on average, has your child *woken up* due to chest wheezing or whistling?

   Never
   Not every week **(1)**
   Every week **(1)**

3. In the last 12 months, has wheezing or whistling in the chest ever been so bad that your child *couldn't talk properly or had to whisper*? **(1)**

4. In the last 12 months, has your child's chest ever sounded wheezy or whistly *during or after running or* playing hard? **(1)**

5. In the last 12 months has the child had a troublesome *dry cough* in the night *that was not from* a cold or chest infection? **(1)**

6. In the last 12 months, has the child had a *tight chest*? **(1)**

7. Has the child ever had *asthma*? **(3)**

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