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Smoking, environmental tobacco smoke, and aspirin-exacerbated respiratory disease

Jinny E. Chang, MD ^{*}; Ding Ding, MPH [†]; Joaquin Martin-Lazaro, MD [‡]; Andrew White, MD ^{*}; Donald D. Stevenson, MD ^{*}

^{*} Scripps Clinic, La Jolla, California

[†] University of California, San Diego

[‡] Arquitecto Marcide Hospital, Ferrol, Spain

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ABSTRACT

Background: Tobacco smoke is a widely recognized environmental pollutant and is a major public health hazard worldwide. Although environmental tobacco smoke (ETS) has a clear link with many conditions, including asthma, ear infections, and sinus cancer, evidence related to aspirin-exacerbated respiratory disease (AERD) requires further investigation.

Objective: To investigate whether active smoke or ETS exposures are associated with an increased risk of developing AERD.

Methods: A total of 260 patients with AERD were enrolled in a case-control study with their respective asymptomatic spouses serving as matched controls. Multiple logistic regression analysis was used to examine the association of AERD with active smoking and ETS, adjusted for age, sex, and location of childhood residence.

Results: The AERD case patients were more likely to have ever smoked actively when compared with controls (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.04-2.28). A significant association (OR, 3.46; 95% CI, 2.22-5.39) was found between childhood ETS exposure and AERD. If a patient was exposed to ETS during both childhood and adulthood, results showed an OR of 5.09 for developing AERD (95% CI, 2.75-9.43). However, no statistically significant association between AERD and ETS only during adulthood was found (OR, 1.60; 95% CI, 0.75-3.40), suggesting that the combined effect of childhood and adulthood ETS may be augmented by the prior childhood exposure.

Conclusions: Active smoking and childhood ETS exposure are associated with increased odds of developing AERD. In particular, combined childhood and adulthood exposure had major effects. This study suggests that ETS is at least one contributor to the syndrome of AERD.

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Introduction

Cigarette smoke is a widely recognized environmental pollutant and health hazard. Environmental tobacco smoke (ETS) is an involuntary exposure to smoke released from the burning end of a cigarette or exhaled mainstream smoke from other smokers.¹ The 2006 US Surgeon General report stated that ETS is a major health threat and there is no safe level of exposure.¹ Increasing evidence has linked ETS to various diseases, including lung cancer,^{2,3} heart disease,⁴ childhood cancers,⁵ and lower respiratory tract infections.⁶ However, few studies have examined the association between ETS and chronic sinusitis and nasal polyp formation. No study, to our knowledge, has linked ETS with the syndrome of aspirin-exacerbated respiratory disease (AERD). AERD is characterized by adult onset of pansinusitis and nasal polyps, asthma, and

then respiratory reactions to ingestion of aspirin or any nonsteroidal anti-inflammatory drug (NSAID) that blocks cyclooxygenase 1.⁷ In a large survey of prevalence studies, AERD occurred in 21% of all asthmatic patients with a range of 4% to 44%.⁸ In patients with pansinusitis with nasal polyps, approximately a third of patients had AERD.⁹

Previous epidemiologic research on ETS and chronic sinusitis revealed mixed findings,¹⁰ so no definitive conclusions could be drawn. Despite the association between ETS with acute and chronic nasal symptoms in adults and children, no direct associations between active or passive cigarette smoke and chronic sinusitis were found in one study.¹¹ Another study found increased prevalence of both acute and recurrent or chronic sinusitis with active cigarette and other tobacco use.¹² However, a study based on the National Health and Nutrition Examination Survey found no associations between chronic sinusitis and ETS.¹³ The most recent case-control study has linked 5 years of ETS with chronic sinusitis in adults.¹⁴

Requests: Jinny E. Chang, MD Scripps Clinic San Diego, California E-mail: Chang.Jinny@scrippshealth.org.

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Evidence exists that both active smoking and ETS have direct putative effects on airway epithelium, including increased mucous secretion,¹⁵ decreased ciliary movement, transport,¹⁶ ciliogenesis,¹⁷ and increased mucosal permeability to allergens.¹⁸ ETS is associated with increased levels of total IgE in adults^{19,20} and children.²¹ Allergic sensitization to specific antigen in mice exposed to ETS demonstrated that ETS enhanced formation of specific IgE antibodies.²² Children in households with ETS exposure were more likely than controls with nonsmoking parents to have decreased interferon γ production in their peripheral monocytes.²³ By contrast, cigarette smoke stimulates eosinophilia,^{24,25} an invasive cell found in chronic hyperplastic eosinophilic sinusitis.²⁶ Therefore, based on direct and indirect pathogenic effects of ETS in humans and mice, it is reasonable to suspect that chronic hyperplastic eosinophilic sinusitis with or without nasal polyps could be the pathological consequence of ETS.

Children are especially susceptible to ETS-induced respiratory diseases. The 2007 US Surgeon General report indicated that 60% of children aged 3 to 11 years in the United States were exposed to ETS.²⁷ Maternal smoking before and after delivery is associated with delayed development of bronchial airways.^{28,29} A strong epidemiologic link between childhood ETS exposure and development of asthma has been demonstrated.³⁰ However, it is now generally accepted that multiple factors (eg, cigarette smoke, stress, obesity, allergen exposure, viral respiratory infections, dietary patterns, air pollution) all conspire in varying degrees to induce asthma in children.³¹ The purpose of this study was to investigate whether active smoking and childhood and adulthood ETS exposures are associated with an increased risk of developing AERD.

Methods

Study participants

All study patients were diagnosed as having AERD by confirming pansinusitis, nasal polyps, asthma, and respiratory reactions to aspirin.^{7,32} Patients had radiographs and/or computed tomograms that showed pansinusitis. Patients experienced a mean of 5 infectious sinusitis episodes with asthma exacerbations in the prior year. On average, patients had undergone 3 prior polypectomy or sinus operations before this study. All had asthma of varying degrees of severity. Seventy percent had positive wheal-and-flare skin test results to relevant aeroallergens. All were taking controller medications for asthma, including inhaled corticosteroids, long-acting bronchodilators, and montelukast or occasionally zafirlukast or zileuton, as well as topical nasal corticosteroids. Patients were referred to our center at the Allergy, Asthma, and Immunology Division of Scripps Clinic and had positive oral aspirin challenge results with respiratory reactions, followed by aspirin desensitization and daily treatment with aspirin. Patients tended to be self-selected for greater severity because they were referred for aspirin desensitization followed by daily aspirin treatment.³³

Study design

The study used a matched case-control design. All cases had AERD.^{7,32} Controls were patients' asymptomatic spouses who did not have allergic rhinitis or sinusitis by history. Spouses were selected as matched controls because of their similarity in age, socioeconomic status, and living environment, a previously validated method.³⁴ If the patient had been previously divorced or widowed and remarried, the current spouse was enrolled. The current spouse's history of smoking exposure was elicited directly from the spouse, who usually accompanied the patient to the clinic. If the spouse was not with the patient, information was obtained from the patient. Occasionally, patients could not provide complete information; in this case, spouses were surveyed by telephone.

Spouses with any history of allergic rhinitis or sinusitis were excluded from the study, as were their live-in patient partner.

Questionnaires and enrollment procedure

Aspirin challenge followed by desensitization is a proven treatment intervention³⁵ and was provided as a service to referred patients. While undergoing aspirin desensitization, patients were invited to participate in ancillary research studies, including donation of blood samples for basic research projects and questionnaires. All study projects were approved by the institutional review board of Scripps Health. Patients provided written informed consent before completing self-administered questionnaire on active cigarette smoking, ETS history, and primary location of residence during childhood. These study questions were combined with other questions, which included medications, sinus infections, and lifestyle changes. The purpose of this study was not revealed to participants to minimize report bias.

Measures

Active smoking.

Participants reported lifetime smoking status, duration of smoking (in years), and the average number of packs of cigarettes smoked per day. The number of years of smoking and the number of packs of cigarettes smoked per day were multiplied to calculate pack-year, a composite number that takes into account both duration and dose. One pack-year was defined as smoking 20 cigarettes a day for a year. The retrospective method of calculating pack-years was previously validated.³⁶ Both duration of smoking and pack-year had a skewed distribution and were categorized for data analyses.

Environmental tobacco smoke.

Participants were asked whether they were exposed to ETS during childhood (<18 years of age) and adulthood (≥ 18 years of age). Duration of exposure (years) was reported for both childhood and adulthood exposure. Both childhood and adulthood exposures were categorized because of skewed distributions. The number of smokers in the home during childhood was recorded.

Location of Residence.

Participants were asked to report the primary location of residence during childhood: urban, suburban, or rural. If they lived in more than one place, the location with the longest duration of exposure was recorded.

Statistical analyses

Statistical analyses were conducted with SPSS statistical software, version 17.0 (SPSS Inc, Chicago, Illinois). *t* tests and χ^2 tests compared age, sex, and primary location of residence between cases and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) for AERD were calculated using multiple logistic regression. Adjusted variables included age, sex, and place of residence. Trend test used continuous independent variables in logistic regression. Analyses of ETS were restricted to never-smokers only. All tests were 2-sided, with an α level of .05.

Results

Study participants

Between 2003 and 2009, 311 patients with AERD completed smoking questionnaires. Of 311 patients, 32 were excluded because they were single (no control); 19 were excluded because their spouses had a history of sinusitis or allergic rhinitis and could not serve as asymptomatic controls. The final sample for data analysis on active smoking included 260 patient-spouse pairs ($n = 520$). The study sample for data analysis on ETS included 371 never-smokers (175 cases and 196 controls).

Table 1
Demographic characteristics, smoking status and environmental tobacco smoke (ETS) history of cases and controls^a

	Case (n = 260) n (%)	Control (n = 260) n (%)	P
Age (categorical)			.920
18-29	13 (5.0)	14 (5.4)	
30-39	52 (20.0)	44 (16.9)	
40-49	83 (31.9)	79 (30.4)	
50-59	71 (27.3)	77 (29.6)	
60-69	29 (11.2)	34 (13.1)	
70+	12 (4.6)	12 (4.6)	
Age (continuous, Mean $\pm$ SD)	47.7 $\pm$ 11.9	48.4 $\pm$ 12.2	.527
Gender			.001
Male	112 (43.1)	150 (57.7)	
Female	148 (56.9)	110 (42.3)	
Primary location of childhood residence			.096
Urban	82 (25.0)	94 (29.6)	
Sub-urban	113 (43.5)	89 (34.2)	
Rural	65 (31.5)	77 (36.2)	

^aData are presented as number (percentage) of study participants unless otherwise indicated.

Descriptive statistics

The mean (SD) age of the study participant was 48.0 (12.0) years. Cases and controls had similar distributions of age (Table 1). However, cases were more likely to be female than controls (56.9% vs 42.3%, $P < .001$), an observation similar to previous epidemiologic surveys.³⁷ There was no statistical difference in the primary location of childhood residence (urban, suburban, rural) between cases and controls.

Prevalence for lifetime active smoking was 28.6%. For smokers ($n = 149$), the mean (SD) duration of smoking was 13.2 (9.6) years, and the mean number of pack-years was 14.4 (14.6). Among non-smokers, 38.3% were not exposed to any ETS, 30.7% were exposed to ETS during childhood only, 10.2% were exposed during adulthood only, and 20.8% were exposed both during childhood and adulthood. There were no missing data on demographic information, smoking, and ETS history.

Active smoking and AERD

Table 2 presents unadjusted and adjusted ORs and 95% CIs for active smoking and AERD. Adjusting for age, sex, and location of childhood residence, AERD cases were more likely to have ever smoked actively when compared with controls (OR, 1.54; 95% CI,

1.04-2.28). Further subanalyses among smokers indicated a trend for the associations between smoking duration and AERD ($P = .004$), in which cases were more likely to have smoked for a longer period. A similar trend was found with pack-years ($P = .003$).

ETS and AERD

Analyses of ETS and AERD were limited to those who had not actively smoked (never-smokers). Significant associations were found between AERD and childhood ETS exposure (Table 3). Adjusting for age, sex, and location of childhood residence, AERD cases were more likely to be exposed to ETS during childhood than controls (OR, 3.46; 95% CI, 2.22-5.39). Among individuals who were exposed during childhood, a dose-response trend was not readily observed. AERD cases were more likely than controls to have been exposed for 10 to 17 years vs 9 years or less throughout childhood (OR, 2.85; 95% CI, 1.01-8.07); however, for those exposed during the entirety of their childhood (18 years), the ratio lost statistical significance. No association was found between number of smokers in the home and AERD.

A significant association between adulthood ETS exposure and AERD among never-smokers was also found (OR, 1.98; 95% CI, 1.25-3.12). However, the association between ETS duration and AERD was not significant. Considering that a large proportion of individuals (67%) who were exposed during adulthood were also exposed during childhood, we created a new variable (no ETS exposure, childhood exposure only, adulthood exposure only, both childhood and adulthood exposure) to disentangle the effects from childhood and adulthood ETS exposure. Results suggested AERD cases were more than 3 times as likely to have been exposed to ETS during childhood only (OR, 3.21; 95% CI, 1.89-5.46). Cases had an OR of 5.09 (95% CI, 2.75-9.43) for having been exposed during both childhood and adulthood. No statistically significant association was found between AERD and adulthood ETS only (OR, 1.60; 95% CI, 0.75-3.40).

Discussion

Our study found an association between lifetime active smoking and AERD. Among never-smokers, a strong association was found between ETS during childhood and AERD (OR, 3.21). ETS during adulthood was not associated with increased odds for AERD if individuals were not exposed during childhood. However, individuals had the highest odds for AERD when exposed during childhood and adulthood (OR, 5.09). No dose-response association was found between ETS during childhood and ETS during adulthood with AERD.

Table 2
Associations between aspirin exacerbated respiratory disease and active smoking

	Cases (n = 260) n (%)	Controls (n = 260) n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	P ^b
Cigarette smoking					.031
Never smoker	175 (67.3)	196 (75.4)	1.00	1.00	
Ever smoker	85 (32.7)	64 (24.6)	1.49 (1.02, 2.18)	1.54 (1.04, 2.28)	
Smoking duration (years) ^c					.004 ^d
<1-10	52 (61.2)	22 (34.4)	1.00	1.00	
11-20	22 (25.9)	28 (43.8)	3.01 (1.18, 7.65)	4.33 (1.48, 12.67)	
21+	11 (4.2)	14 (21.9)	1.00 (0.38, 2.63)	1.23 (0.44, 3.44)	
Dose + duration (pack-years) ^c					.003 ^d
<1-10	54 (63.5)	21 (32.8)	1.00	1.00	
11-20	18 (21.2)	26 (40.6)	3.36 (1.39, 8.11)	4.43 (1.59, 12.31)	
21+	13 (15.3)	17 (26.6)	0.91 (0.35, 2.32)	0.98 (0.35, 2.75)	

^aAnalyses conducted among 149 active smokers (85 cases and 64 controls).

^bAdjusting for age, gender, and primary location of childhood residence.

^cP for logistic regression analyses adjusting for covariates.

^dP for trend test in logistic regression.

Table 3

Associations between aspirin-exacerbated respiratory disease and childhood and adulthood environmental tobacco smoke among nonactive smokers

Variable	Cases, No. (%) (n = 175)	Controls, No. (%) (n = 196)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	P value ^b
Exposed to ETS during childhood					<.001
No	60 (34.3)	120 (61.2)	1.00	1.00	
Yes	115 (65.7)	76 (38.8)	3.03 (1.98-4.63)	3.46 (2.22-5.39)	
Childhood ETS exposure duration, y ^c					.02
<1-9	13 (11.3)	11 (14.5)	1.00	1.00	
10-17	39 (33.9)	13 (17.1)	2.54 (0.92-7.03)	2.85 (1.01-8.07)	
18	63 (54.8)	52 (68.4)	1.03 (0.42-2.48)	0.99 (0.40-2.44)	
No. of smokers in the household during childhood ^c					.75
1	53 (46.1)	39 (51.3)	1.00	1.00	
2	46 (40.0)	28 (36.8)	1.21 (0.65-2.26)	1.21 (0.64-2.28)	
≥3	16 (13.9)	9 (11.8)	1.31 (0.52-3.28)	1.35 (0.53-3.41)	
Exposed to ETS during adulthood					.004
No	108 (61.7)	148 (75.5)	1.00	1.00	
Yes	67 (38.3)	48 (24.5)	1.91 (1.23-2.99)	1.98 (1.25-3.12)	
Adulthood ETS exposure duration, y ^d					.40
<1-10	34 (50.7)	24 (50.0)	1.00	1.00	
11-20	16 (23.9)	15 (31.3)	1.33 (0.55-3.19)	1.04 (0.41-2.62)	
≥21	17 (25.4)	9 (18.8)	1.77 (0.61-5.17)	2.07 (0.65-6.56)	
Childhood or adulthood exposure					<.001
No exposure		98 (50.0)	1.00	1.00	
Exposure only as a child	44 (25.1)	50 (25.5)	2.85 (1.71-4.76)	3.21 (1.89-5.46)	
Exposure only as an adult	16 (9.1)	22 (11.2)	1.62 (0.78-3.38)	1.60 (0.75-3.40)	
Exposure both as a child and an adult	51 (29.1)	26 (13.3)	4.37 (2.42-7.89)	5.09 (2.75-9.43)	

Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio.

^aAdjusting for age, sex, and primary location of childhood residence.^bP value for logistic regression analyses adjusting for covariates.^cData analyses conducted among 191 nonsmokers who were exposed to secondhand smoke during childhood (n=115 cases and 76 controls).^dData analyses conducted among 115 nonsmokers who were exposed to secondhand smoke during adulthood (n=67 cases and 48 controls).

Because there were no prior studies of passive or active smoking and AERD, no comparisons can be made. However, epidemiologic studies of patients with chronic sinusitis, a major but not exclusive hallmark of AERD, have been conducted. The recent matched case-control study by Tammemagi et al¹⁴ showed an association between ETS and chronic rhinosinusitis. A strong dose-response relationship between risk of chronic rhinosinusitis and the number of exposure venues during adulthood was found. However, the study by Tammemagi et al only examined ETS in adulthood. Given that the mean age of patients was 54 years, it was likely that the onset of rhinosinusitis occurred before reported ETS exposure in the past 5 years. Because 60% of children in the United States were exposed to ETS during childhood, it is likely that most cases in the study by Tammemagi et al were also exposed in their childhood. Therefore, their results may have been an augmentation of prior childhood ETS effect rather than an adult de novo association. In our study, more than 76% of the cases and 54% of the controls who were exposed during adulthood were also exposed during childhood, and after separating out childhood and adulthood exposures, the effects from adulthood exposure were attenuated.

Because the mean onset of AERD is at approximately 30 years of age, how could childhood ETS exposure contribute to the pathogenesis of disease? This is a perplexing question, and a definitive answer is not apparent. However, there are potential explanations. First, childhood ETS exposure is likely to have cumulative effects on respiratory membranes with persistent damage and inflammation well after ETS ceases. Second, many AERD patients have documented pansinusitis in their late teens or 20s, even though reported mean onset of disease is in the late 20s. Third, studies concerning onset of AERD have all focused on historical events, such as aspirin- and NSAID-induced asthma attacks. No study has established the precise onset of inflammation of sinuses, nasal membranes, or

bronchi in AERD patients. Although clinical symptoms precede the first aspirin- or NSAID-induced asthma attack,³⁵ no one knows precisely when asymptomatic inflammation actually begins. Therefore, predicting who will have AERD and who should undergo an initial biopsy is impossible. Fourth, early life influences adult-onset disease in asthma,³⁸ which may extend to AERD. Barker's hypothesis of plasticity in development theorizes that an environmental disruption can establish an altered phenotype that inadvertently increases the risk of disease.^{39,40} Environmental signals during childhood may prime the patient via an epigenetic pathway^{41,42}; thus, childhood ETS may have a greater effect than adult exposure.

Many but not all AERD patients describe a viral respiratory infection at the beginning of their symptomatic respiratory disease somewhere in their late teens to middle age.⁴³ In fact, a major hypothesis to onset and perpetuation of AERD is that a rhinovirus infection begins the disease and is never cleared because of defects in immune regulators. With the use of reverse transcription polymerase chain reaction, the results of bronchial biopsies of 7 of 7 AERD patients were positive for rhinovirus RNA.⁴⁴ However, this finding was not limited to asthmatic patients with AERD. In fact, the consensus is that viral respiratory infections are the most common provoking factors of acute asthma exacerbations in both children and adults with all varieties of asthma.⁴⁵ This finding further suggests that asthmatic patients lack important antiviral protective responses in airway epithelium, innate immune responses (interferon secretion, macrophage, and T_H1 cell dysfunction), poorly functioning mucociliary clearance, and airway remodeling. All of these systems, which are designed to prevent or limit virus infection, can be destroyed or altered by known effects of cigarette smoke on membranes and resident cells of the respiratory mucosa. Epithelial cells exposed to cigarette smoke have altered response to

rhinovirus infection with increased viral RNA, thus possibly putting the asthmatic patient at increased risk for AERD.⁴⁶

Because 70% of our patients and 66% of a large series of AERD patients had positive wheal-and-flare skin test results to relevant environmental allergens,³³ the role of atopy in the years preceding the onset of the first NSAID-induced respiratory reaction may be important in some patients with AERD. Therefore, ETS may provide an altered environment that drives naive T cells toward a T_H2 phenotype after exposure to antigen. In genetically susceptible patients who eventually will develop recognized AERD, early cigarette exposure may be a key initiating factor in the disease pathogenesis. The combination of cigarette smoke, atopy, and viral infections is difficult to untangle, but all are thought to be major factors in the asthma pathogenesis.³¹ Because of these observations, it seems likely that multiple triggering exposures are important in the pathogenesis of AERD. Genetics undoubtedly play some role in susceptibility to ETS or virus infections and the drive toward T_H2 cells. However, family prevalence of AERD is quite low, suggesting that environmental assaults are the most important factors in the pathogenesis of AERD.

In this study, we adjusted for childhood residence as a potential confounding variable. Air pollution and particulate matter have been associated with respiratory diseases.⁴⁷ Small respirable particulate matter that can penetrate the alveoli (<2.5 μ m) and deposit in larger airways (<10 μ m) are higher in urban sites than suburban and rural locales because of motor vehicle traffic and associated hydrocarbons.⁴⁸ Because we were unable to obtain retrospective data on air pollution levels during childhood, we used urban, suburban, or rural as a marker for air pollution levels. However, no significant associations between location of childhood residence and AERD were found.

One of the limitations of the current study is its retrospective design, which is inherently associated with recall bias. In this study, smoking and ETS-related questions were administered with other questions regarding multiple health conditions and exposures. To avoid differential recall or report between cases and controls, research objectives were not provided. Another limitation is lack of comprehensive measures of potential confounders because the cause of AERD is likely to be multifactorial. This can include items not asked in our questionnaire, such as use of specific medications (eg, topical decongestants) that have been implicated in slowing mucociliary transport with long-term use.⁴⁹ Overall, we tried to minimize differences between cases and controls by enrolling patient-spouse pairs because they tend to have similar ages, socioeconomic status, and living environments.

From surveying a large group of adult AERD patients and their asymptomatic spouses, we have found associations among active smoking, childhood ETS exposure, and adult onset of AERD. Active smokers had an OR of 1.54 (95% CI, 1.04–2.28) for having AERD. ETS exposure in never-smokers had a significant association (OR, 3.46; 95% CI, 2.22–5.39) between childhood ETS exposure and AERD. If an individual was exposed to ETS during both childhood and adulthood, results showed an OR of 5.09 for developing AERD (95% CI, 2.75–9.43). However, no statistically significant association between AERD and ETS during adulthood only was found (OR, 1.60; 95% CI, 0.75–3.40), suggesting that the combined effect of childhood and adulthood ETS may be augmented by the prior childhood exposure. Given the high prevalence of ETS exposure among children in the United States, more research and tobacco control efforts should focus on prolonged risks of ETS, such as AERD and other respiratory diseases. This study suggests that ETS is at least one contributor to chronic sinusitis, asthma, and nasal polyps in patients with AERD.

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