Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature

Jessica P. Rajan, MD,[a] Nathan E. Wineinger, PhD,[b] Donald D. Stevenson, MD,[a] and Andrew A. White, MD[a]
San Diego, Calif

Background: Aspirin-exacerbated respiratory disease (AERD) is manifested by adult-onset asthma, nasal polyposis, chronic rhinosinusitis, and aspirin sensitivity. Previously reported prevalence rates have been widely variable based on the population studied, method of diagnosis, and definition of aspirin sensitivity.
Objective: We sought to determine the prevalence of AERD among asthmatic adults.
Methods: A systematic review of databases was performed to identify all clinical trials published on or before June 16, 2013, that evaluated the prevalence of AERD. The studies were clustered into 7 different groups based on underlying disease (asthma, nasal polyps or chronic rhinosinusitis, or both), as well as on the methodology of prevalence determination.
Results: A total of 1770 articles were identified, with 27 considered appropriate for inclusion. Prevalence rates of AERD ranged from 5.5% to 12.4% based on study type. Among all studies in asthmatic patients, regardless of method, the prevalence of AERD was 7.15% (95% CI, 5.26% to 9.03%). The prevalence of AERD was highest among patients with severe asthma (14.89% [95% CI, 6.48% to 23.29%]). Among patients with nasal polyps and chronic rhinosinusitis, the prevalence was 9.69% (95% CI, 2.16% to 17.22%) and 8.7% (95% CI, −1.02% to 18.34%), respectively.
Conclusion: AERD is a distinct and important subtype of asthma and polypoid sinus disease. The prevalence of AERD is 7% in typical adult asthmatic patients and twice that number in patients with severe asthma, which underscores the importance of recognizing this disorder. Early identification of this syndrome is critical in view of the increased morbidity and costs associated with asthma exacerbations and the option to treat patients with AERD with long-term aspirin treatment after desensitization. (J Allergy Clin Immunol 2015;135:676-81.)

Key words: *Aspirin-exacerbated respiratory disease, Samter triad, aspirin-induced asthma, prevalence*

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
NSAID: Nonsteroidal anti-inflammatory drug

Aspirin-exacerbated respiratory disease (AERD) is a complex syndrome typified by underlying inflammation of the respiratory tract in which patients experience adult-onset asthma, nasal polyposis/chronic rhinosinusitis, and aspirin/nonsteroidal anti-inflammatory drug (NSAID) sensitivity. This syndrome has also been previously referred to as Samter triad (asthma, nasal polyposis, and aspirin/NSAID intolerance). Patients with AERD have greater morbidity characterized by more emergency department visits, hospitalizations, and corticosteroid bursts when compared with those seen in patients with aspirin-tolerant asthma.[1] Identifying this syndrome is critical because asthma exacerbations secondary to aspirin sensitivity have significant morbidity and can be costly. Additionally, long-term daily aspirin treatment after aspirin desensitization can be an effective treatment for patients with AERD.

The widely variable reported prevalence rates of AERD have discordantly led to speculation that this syndrome is either very rare or much more common than generally appreciated. Previously reported rates have ranged from 1.2%[2] to 44%[3] depending on the population studied, method of diagnosis, and definition of aspirin sensitivity. Prior studies might have been limited by bias and should be re-evaluated for usable homogeneous data. For instance, Spector et al[4] excluded patients with a prior history of clinical intolerance to aspirin, whereas Dursun et al[5] looked at patients who were all referred for evaluation of AERD. Thus inclusion/exclusion criteria, as well as referral patterns, can introduce bias and therefore need to be critically evaluated. Studies also vary on whether concurrent medications that could potentially affect the outcome of aspirin oral challenges were continued, held, or simply not mentioned at all.

The difficulty in determining the prevalence of AERD is illustrated in a meta-analysis that reported the widely divergent prevalence rates of 21% among asthmatic adults based on oral aspirin challenge and 2.7% based on patients' histories.[6] This analysis of 21 studies included some clinically heterogeneous groups. Although a meta-analysis of oral challenge studies should provide an accurate rate of AERD among asthmatic patients, it does not seem reasonable to conclude, as this study would suggest, that 1 of every 5 asthmatic patients has AERD. Anecdotally, this is a much higher rate than seen in our tertiary referral center.

To clarify the prevalence of AERD, we performed a meta-analysis of publications among asthmatic adults, as well as among those with nasal polyposis and chronic rhinosinusitis.

From [a]the Department of Allergy, Asthma and Immunology, Scripps Clinic and [b]the Scripps Translational Science Institute.
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Corresponding author: Jessica P. Rajan, MD, Scripps Clinic, 3811 Valley Centre Dr, S99, San Diego, CA 92130. E-mail: jessicarajan@gmail.com.
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METHODS

Data sources and searches

A systematic review of PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials databases was performed by using a prespecified protocol (Table I) and search strategy to identify all clinical trials published on or before June 16, 2013, that evaluated the prevalence of AERD (see Fig E1 in this article's Online Repository at www.jacionline.org). Additionally, manual searches were performed from reference lists of included studies to identify additional trials. Studies were included if they contained published data and were written in the English language. We also only included studies that were performed in adults (age >18 years) given that AERD tends to have onset during early adulthood and has been studied more extensively in this age group. The PRISMA method was used to exclude duplicate and irrelevant records based on abstracts. Full-text articles (n = 159) were then assessed for eligibility, and 27 were included in quantitative synthesis (Fig 1). The Cochrane collaboration tool for assessing risk of bias was used to evaluate each trial.[7]

Study selection and data extraction

The inclusion criteria were as follows: (1) adults older than 18 years; (2) patients with asthma and/or rhinosinusitis or nasal polyps; (3) primary data gathered by means of either questionnaire, retrospective medical chart review, or history gathered by a physician and diagnosis by means of oral challenge. Studies were excluded if they contained no primary data (ie, case reports, review articles, editorials, and letters to the editor), if they were performed in children, if they did not have enough data presented to calculate prevalence (ie, not all of the details of the study were disclosed), if the selection of patients was biased, or if the study was performed in a tertiary referral center for AERD with known referral bias.

Data were abstracted from published articles. Two authors reviewed all selected publications independently. Each author independently abstracted data from selected articles using standardized data collection forms. Any discrepancies in data abstraction were resolved by means of consensus.

Statistical analysis

AERD prevalence rate analysis was conducted based on the following types of studies: studies assessing AERD (1) among asthmatic patients through questionnaires, (2) among asthmatic patients through retrospective chart review/history gathered by a physician, (3) among asthmatic patients by using a combined approach of history gathered by a physician and oral challenge, (4) among all asthmatic patients regardless of study method, (5) among patients with severe asthma, (6) among patients with nasal polyps, and (7) among patients with chronic rhinosinusitis. In all cases we observed a significant deviation in the homogeneity of prevalence rates across studies (maximum $P = .0045$). Thus inverse variance–weighted random effects meta-analyses were performed. Additionally, prevalence rates were regressed on method of diagnosis, year, country in which the study was conducted, and sample size. Conditional significance testing was performed. All statistical analyses were performed with R version 2.15.2 software.[8]

RESULTS

Study characteristics

After database search and removal of duplicates, a total of 159 articles were identified for full-text review (Fig 1). These were assessed on the basis of inclusion/exclusion criteria, and a manual search was performed on all references of chosen studies, resulting in a total of 27 studies; the characteristics of these studies are listed in Table II.[1-3,9-32] Of those in which oral challenges were performed (n = 6), 3 were single blind, 1 was open, and in 2 the blinding was not specified. Three of the studies were placebo controlled, 2 were not, and 1 did not specify whether placebo challenges were used. Dates of publication of all studies ranged from 1968 to 2012.

TABLE I. Search strategy—PICOS (Population, Intervention, Comparator, Outcomes, Study Design) approach used for the systematic review: Among adult patients with AERD, what is the prevalence of those with asthma?

Population	Included	Adults
	Excluded	Children
Intervention	Included	Patients with asthma
Comparator/control	Included	Patients with AERD
Outcomes	Included	Prevalence
Studies	Included	Controlled clinical trials in human subjects
	Excluded	Flawed study design Selection bias No primary data

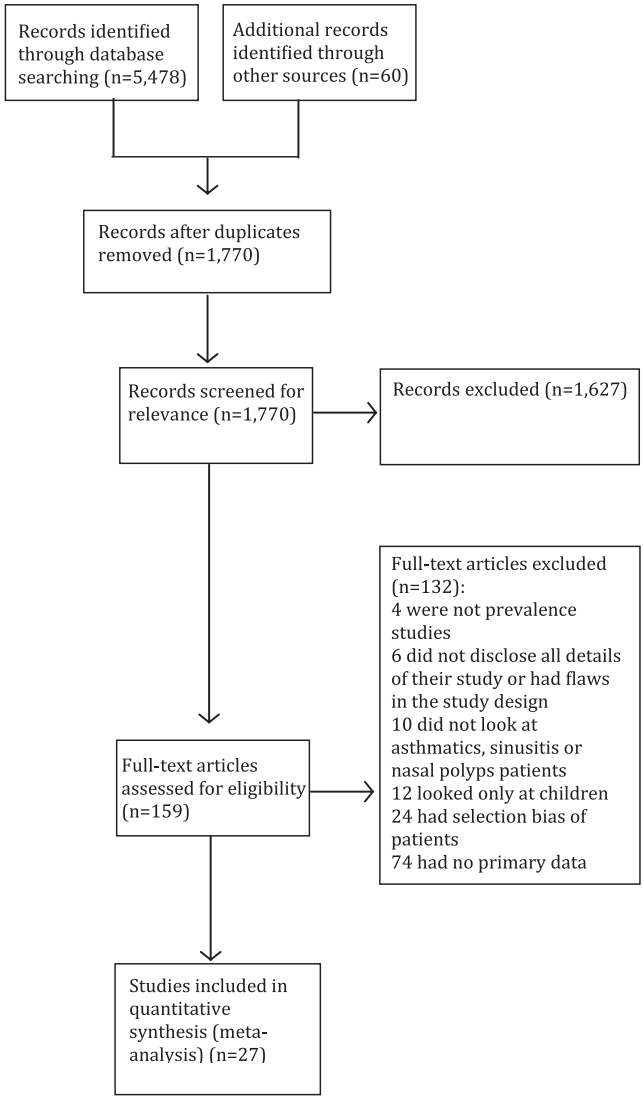

FIG 1. PRISMA flow diagram for study selection.

Prevalence

Among studies in asthmatic patients in which a questionnaire format was used to determine prevalence, the calculated inverse variance–weighted prevalence rate was 7.3% (95% CI, 5.14% to

TABLE II. Prevalence rates of AERD among each study analyzed by test method

Study/location	Disease	No. of patients	Questionnaire	Retrospective chart review/physician-patient interview	Oral challenge	Patients with AERD/total no. of patients	Prevalence
Among asthmatic patients using questionnaires							
Charpin et al, 2003/United States[9]	Asthma	205	31			31/205	15.1%
Hedman et al, 1999/Finland[2]	Asthma	136	12			12/136	8.8%
Kasper et al, 2003/Poland[10]	Asthma	703	30			30/703	4.3%
Kasper et al, 2009/Poland[11]	Asthma	582	38			38/582	6.5%
Moon et al, 2013/South Korea[12]	Asthma	1173	68			68/1173	5.8%
Vally et al, 2002/Australia[13]	Asthma	644	79			79/644	12.3%
Yoshimine et al, 2005/Japan[14]	Asthma	2637	233			233/2637	8.8%
Among asthmatics using retrospective chart review or physician interview							
Chafee et al, 1974/United States[15]	Asthma	1775		75		75/1775	4.2%
Lee, 1968/United States[16]	Asthma	550		38		38/550	6.9%
Moloney, 1977/England[17]	Asthma	95		9		9/95	9.5%
Picado et al, 1989/Spain[18]	Asthma	92		13		13/92	14.1%
Sabry, 2010/Saudi Arabia[19]	Asthma	365		46		46/365	12.6%
Stevenson et al, 1975/United States[20]	Asthma	234		21		21/234	9.0%
Among asthmatic patients using combined methods							
Bavbek et al, 2012/Turkey[21]	Asthma	1344	145		35	180/1344	13.4%
McDonald et al, 1972/United States[22]	Asthma	282		14	8	22/282	7.8%
Weber et al, 1979/United States[3]	Asthma	45		7	13	20/45	44.4%
Among patients with severe asthma							
Mascia et al, 2005/United States[1]	Severe asthma	3307	459			459/3307	13.9%
Marquette et al, 1992/United States[23]	Severe asthma	147		35		35/147	23.8%
Castillo and Picado, 1986/Spain[24]	Severe asthma	74			14	14/74	18.9%
Yoshimine et al, 2005/Japan[14]	Severe asthma	282	80			80/282	28.4%
Among patients with nasal polyps							
Bavbek et al, 2011/Turkey[25]	Nasal polyps	53			12	12/53	22.6%
Dufour et al, 2004/England[26]	Nasal polyps	60		10		10/60	16.7%
Johansson et al, 2004/Sweden[27]	Nasal polyps	82	6			6/82	7.3%
Patriarca et al, 1986/Italy[28]	Nasal polyps	154		54		54/154	35.1%
Moloney 1977/England[17]	Nasal polyps	445		25		25/445	5.6%
Settipane and Chafee, 1977/United States[29]	Nasal polyps	211		30		30/211	14.2%
Staikuniene et al, 2008/Lithuania[30]	Nasal polyps	84		16		16/84	19.1%
Among patients with chronic rhinosinusitis							
Celejewska-Wojcik, 2012/Poland[31]	Chronic rhinosinusitis	24			8	8/24	33.3%
Kim and Kountakis, 2007/United States[32]	Chronic rhinosinusitis	152		9		9/152	5.9%
Staikuniene et al, 2008/Lithuania[30]	Chronic rhinosinusitis	121		16		16/121	13.2%

9.53%; Tables III and Fig 2). The prevalence of AERD among studies of asthmatic patients in which a physician either reviewed the medical record or obtained a clinical history from the patient was 5.5% (95% CI, 2.36% to 8.66%). There were also studies in which combined methods were used to obtain a prevalence rate, and among these, the combined prevalence rate was 12.4% (95% CI, 4.04% to 20.67%). We then combined all studies evaluating asthmatic patients regardless of the method of AERD assessment and found the combined prevalence rate was 7.2% (95% CI, 5.26% to 9.03%). In evaluation of studies involving patients with severe asthma, the combined prevalence rate was 14.89% (95% CI, 6.48% to 23.29%). We then assessed prevalence rates among patients with nasal polyps and chronic rhinosinusitis, which were 9.7% (95% CI, 2.16% to 17.22%) and 8.7% (95% CI, −1.02% to 18.34%), respectively. We also found that for asthmatic patients, the method of diagnosis ($P = .45$), country in which the study was performed ($P = .91$), year of publication ($P = .36$), and sample size ($P = .66$) were not conditionally associated with the reported prevalence.

DISCUSSION

AERD is a complex disease process that requires clinician intuition to suspect the diagnosis. Patients with AERD typically have adult-onset asthma, nasal polyposis, chronic rhinosinusitis, and NSAID sensitivity. It is only on specifically querying reactions to other NSAIDS or aspirin that a provisional diagnosis can be rendered. Yet history is not enough, and 15% of patients with AERD might not be aware of their diagnosis before undergoing aspirin provocation challenges.[33] It has also been noted that up to 15% of patients who report a history of an NSAID- or aspirin-induced respiratory reaction will go on to have negative

TABLE III. Prevalence rates among each of the groups studied

	Prevalence rate	95% CI
Among asthmatic patients based on questionnaires	7.3%	5.14% to 9.53%
Among asthmatic patients based on retrospective chart review or physician-patient interview	5.5%	2.36% to 8.66%
Among asthmatic patients based on combined methods	12.4%	4.04% to 20.67%
Among patients with severe asthma	14.9%	6.48% to 23.29%
Among patients with nasal polyps	9.7%	2.16% to 17.22%
Among patients with chronic rhinosinusitis	8.7%	−1.02% to 18.34%

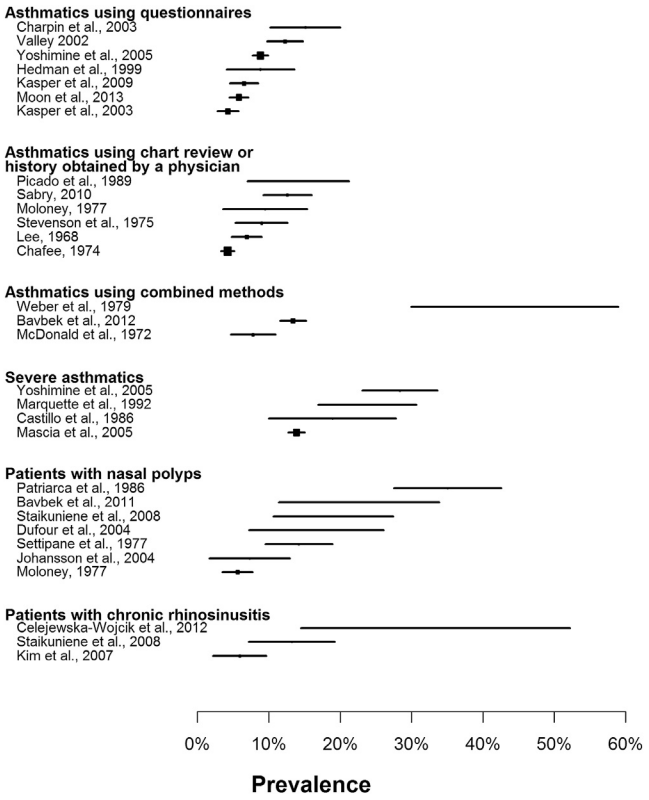

FIG 2. Prevalence rates among studies analyzed. *Blocks* represent point estimates, whereas *lines* represent corresponding 95% CIs.

aspirin provocation test results.[33] This demonstrates that in patients with asthma and a history of "aspirin allergy," a diagnosis of AERD still is questionable. However, the diagnosis is much more likely if the aspirin reaction led to hospitalization or intubation for asthma exacerbation.[5,23,24] The standard diagnostic test is a double-blind, placebo-controlled oral challenge with aspirin in increasing doses. This can be an expensive and time-consuming procedure and understandably provides a barrier to enroll a large enough population of patients to adequately power an epidemiologic study. Double-blind challenges are more often supplanted by a single-blind or nonblind oral aspirin challenge. In addition, inhalation challenges, nasal challenges, and intravenous protocols have all been described as alternative tests for the diagnosis of aspirin hypersensitivity.[34,35] Among studies evaluating prevalence among patients with nasal polyps and those with chronic rhinosinusitis, none confirmed positive reactions with nasal or inhalation challenge. A positive challenge result should be defined in terms of what is commonly seen in patients with AERD, namely nasal-ocular allergy–type symptoms (with a decrease in nasal inspiratory flow) and asthma symptoms with a 15% or greater decrease in FEV_1. Laryngospasm, urticaria, flushing, and gastrointestinal upset can accompany the respiratory symptoms but do not occur in isolation. Cutaneous eruptions alone without any other accompanying symptom are far more likely to represent COX-1–mediated urticaria, a well-described clinical entity that is distinct from AERD. Ideally, a positive diagnostic challenge result in patients with AERD will include both subjective symptoms and objective data (a significant decrease in nasal inspiratory flow rate and a decrease in FEV_1).

We found that prevalence rates of AERD were similar in asthmatic patients assessed by means of either questionnaire or review by a physician (either retrospective chart review or clinical history; ie, 7.3% and 5.5%, respectively). Given that asthmatic patients might not associate their symptoms with aspirin ingestion and the historical diagnosis depends on patient memory, studies based on questionnaires alone are likely to be the most unreliable.[12] In addition, questionnaires filled out by patients often do not distinguish between reactions to aspirin or NSAIDs and many times do not distinguish between the presence of solely cutaneous symptoms versus respiratory symptoms.[11,36] As previously reported, prevalence rates with questionnaires are typically found to be higher than in studies in which a face-to-face interview was conducted.[10] Studies based on a physician's diagnosis either through interview with patients or retrospective chart review are likely to be more reliable than patient-completed questionnaires.

Given that oral aspirin challenge is the current diagnostic standard, studies based on oral aspirin challenge are likely to be the most reliable.[37] However, when reviewing these studies, there are variations in patient selection. Some only challenged patients with a prior history of symptoms after aspirin ingestion, whereas others exclude patients with any history of prior reactions.[4,38] We excluded studies with a selection bias, favoring either patients with or those without AERD. One study was performed with an oral challenge model. However, the diagnosis of AERD was made based on change in pulmonary function test results regardless of symptoms and therefore had to be excluded.[39]

It is clear that leukotriene receptor antagonists, 5-lipoxygenase inhibitors, and antihistamines can potentially mask what would otherwise have been a positive challenge result.[40-42] Ideally, all premedications in any challenge study should be eliminated. However, the safety of the oral challenge is significantly enhanced by addition of leukotriene inhibitors. This means that some patients can be so well protected by leukotriene receptor antagonism that patients with true AERD have negative challenge results, a phenomenon termed silent desensitization.[42] Therefore disclosure of the pretreatment program is a minimal requirement because no agreed upon, standardized oral challenge protocol is available. Unfortunately, we did not find any oral challenge studies that met these strict inclusion criteria.

We conclude that prevalence rates of AERD are similar among populations of asthmatic patients when compared with those of patients with nasal polyps. Patients with severe asthma are twice as likely to have AERD. Because AERD is characterized by severe

and aggressive nasal polyposis, it is not surprising that in the larger population of patients with chronic sinusitis, which frequently is not associated with nasal polyposis, the prevalence of AERD is much lower. There did not appear to be any specific ethnic or regional variation in the prevalence of AERD, with one notable exception.

In a large series of regional Chinese patients with nasal polyps, a rigorous challenge study identified only 0.57% with positive oral aspirin challenge results.[43] This is far lower than what would have been expected based on the available corroborating data. This specific population is associated with polyps that are much more neutrophilic in general, a polyp population in which AERD would not be expected to be highly represented.[44,45] Because this specific population might be different, this study was not included in overall prevalence calculations. This variant phenomenon is worthy of ongoing study.

After reviewing all of these studies and looking carefully at our referral patterns in a tertiary referral center for aspirin desensitization, it is difficult to escape the conclusion that a perfect epidemiologic study with a large population of patients with typical AERD not biased on referral for an intervention in the disease is impossible. Therefore we conclude that a review such as ours is likely to be the best available estimate of the prevalence of AERD. It is suspected that although the prevalence of AERD in asthmatic patients reported in this study is in the 5% to 7% range, much less than the greater than 20% reported in some other studies, it is still more common than most clinicians would suspect. Physicians who routinely treat asthmatic patients should be aware that up to 15% of their patients with severe asthma might have this syndrome and would have an improved clinical course through treatment with leukotriene modifiers and aspirin desensitization. AERD continues to be an important phenotype of inflammatory airways disease that requires a high degree of suspicion to synthesize the various aspects of this syndrome and proceed to making an accurate diagnosis.

Key messages

- **In a meta-analysis of prevalence studies, AERD occurs in approximately 7% of adult asthmatic patients.**
- **AERD should be considered in all patients with severe asthma and comorbid nasal polyposis.**

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Search (asthma, aspirin-induced [MeSH Terms]) OR ((((AERD) OR aspirin exacerbated respiratory disease)) AND asthma)

Search NSAID-induced asthma

Search NSAID-induced asthma Filters: Clinical Trial

Search aspirin-intolerant asthma

Search Samter's

Search samter's triad

Search aspirin intolerance

Search (asthma, aspirin-induced [MeSH Terms]) AND ((((AERD) OR aspirin exacerbated respiratory disease)) AND asthma)

Search (((AERD) OR aspirin exacerbated respiratory disease)) AND asthma

Search (((asthma) AND AERD)) OR asthma, aspirin-induced [MeSH Terms]

Search (asthma) AND aspirin exacerbated respiratory disease

Search (asthma) AND AERD

Search asthma, aspirin-induced [MeSH Terms]

Search (AERD) OR aspirin exacerbated respiratory disease

Search aspirin exacerbated respiratory disease

Search AERD

FIG E1. Example PubMed search strategy.