

What proportion of rhinitis symptoms is attributable to atopy?

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Abstract

The aim of this study was to assess what proportion of patients with rhinitis symptoms (unrelated to infection) in population-based studies is attributable to atopy. We assessed the relevance of atopy in rhinitis in different countries and populations and between different age groups by performing a Medline search from 1980 onward on population-based studies. In the 22 identified population-based studies found, the overall proportion of rhinitis cases that were atopic was 61%, the proportion of noncases that were atopic was 20%, and the proportion of rhinitis cases that were attributable to atopy was 53%. There is variation between studies but little evidence of systematic geographic variation. For future research on the prevalence and possible increase of atopic rhinitis, it seems to be of major importance to differentiate between atopic and other forms of rhinitis. © 2003 Elsevier Inc. All rights reserved.

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1. Introduction

The prevalence of rhinitis seems to be increasing world wide, along with the prevalence of other “atopic conditions,” such as asthma and atopic eczema [1,2]. The recent International Study of Asthma and Allergies in Childhood (ISAAC) [3] found striking international patterns of rhinitis prevalence: The lowest prevalences were found for 13- to 14-year-old patients in parts of eastern Europe and south and central Asia (as low as 1.4%); the highest prevalences (as high as 39.7%) were found in countries as diverse as Argentina, Australia, Brazil, Canada, Finland, France, Hong Kong, India, Malta, Nigeria, Paraguay, Peru, Spain, the United Kingdom, and the United States [3].

Rhinitis usually does not lead to severe medical conditions or hospital admissions. Nevertheless, it may lead to substantial physical discomfort and may significantly affect the quality of life [4]. An understanding of the etiology of rhinitis may lead to improved prevention and management of this condition. However, most treatment and prevention

strategies are focused on allergen-induced rhinitis and allergen avoidance measures, respectively, whereas other etiologic mechanisms may be important. For asthma, it has recently been shown that, at most, 40% of all cases are attributable to atopy [5]. It is not clear which mechanisms explain the other 60%, but nonallergic (antibody-independent) inflammatory mechanisms, as are often observed in occupational asthma, may be a plausible explanation [6,7]. Although there have always been controversial views on the definition of asthma and the importance of atopy in asthma, there has not been the same level of discussion concerning the role of atopy in upper respiratory tract symptoms such as rhinitis. It is assumed that nasal symptoms unrelated to infections are most often caused by atopy, possibly because hay fever (a classical allergic type of rhinitis) has been the most studied form of rhinitis. However, examples of nonallergic rhinitis (e.g., in occupational populations) and other types of rhinitis (e.g., vasomotor rhinitis, rhinitis medicamentosa [8], gravidity rhinitis [9], aspirin induced rhinitis [10]) are plentiful [11].

In this article we assess the relative importance of atopy in rhinitis unrelated to infection by estimating the proportion of rhinitis symptoms that are attributable to atopy in currently available population-based studies.

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2. Methods

2.1. Definition of atopy

Atopy has been characterized by the production of specific IgE in response to common environmental allergens, and skin prick testing provides a convenient test for atopy in epidemiologic studies [12]. In this article we focus on studies of skin prick test (SPT) positivity. SPTs are performed and interpreted differently between countries (e.g., the number of allergens tested varies between 2 and >15, and the definitions of a positive skin prick test differ, although in most studies a weal size of ≥ 3 mm is defined as a positive reaction). Total IgE measurements were not taken into account because they have shown to be an inadequate marker for allergic rhinitis [13]. In the current study, we estimate the overall proportion of rhinitis cases that are attributable to atopy. By implication, the remaining proportion of cases involves “nonatopic” rhinitis that has occurred due to non-atopic mechanisms.

2.2. Definition of rhinitis

Rhinitis can be considered an inflammatory disorder of the upper respiratory tract mucosae. It usually also affects the conjunctival mucosa and causes recurrent nasal symptoms including sneezing, rhinorrhea, or nasal congestion often accompanied by tears and itchy eyes. This is reflected in the ISAAC [14] definition of “symptoms of allergic rhinoconjunctivitis” as involving the combination of “sneezing or a runny or blocked nose” in the absence of a cold or flu and often combined with “itchy-watery eyes.” Rhinitis is caused by an inflammation of the nasal mucosa as a result of a specific (IgE-mediated or atopic) immune reaction or as a direct (nonatopic) irritant effect (see below) [15]. In the first case, symptoms occur as a classical allergic reaction where exposure to an allergen leads to symptoms in IgE-sensitized individuals. Skin prick testing to the appropriate allergens gives a positive result, and nasal swabs and lavages or biopsy of the mucosa reveals eosinophils, but neutrophils are usually also present [6]. In addition, some studies have suggested a local allergic reaction in the nasal mucosa reaction without evidence of a systemic reaction to allergens [16,17]. Seasonal symptoms in spring and summer only are often referred to as classical hay fever (pollinosis). Perennial allergic rhinitis is caused by an allergic response to allergens that are present throughout the year [18,19].

Irritants or toxins can directly influence the nasal mucosa and induce nasal symptoms, which are similar to allergic rhinitis and occur after exposure [20–22]. This so-called “irritant induced rhinitis” is characterized by a nonimmune (antibody-independent) mediated inflammation of the nasal mucosa that is dominated by neutrophils, as has been demonstrated after exposures to various irritants suggested to cause irritant rhinitis (e.g., ozone, grain dust, endotoxin, and fuel-oil ash) [23–25]. In addition to irritant-induced rhinitis, other types of rhinitis have been described in the literature that

do not seem to be associated with atopy: (1) vasomotor rhinitis [25,26], (2) rhinitis medicamentosa [8], (3) gravidity rhinitis [9], and (4) aspirin-induced rhinitis [10,11]. Furthermore, the non-eosinophilic rhinitis syndrome has been described by Leone [27]. Another minor cause for rhinitis symptoms, also suggested as a cause for vasomotor rhinitis, is a trauma to the nose [28].

2.3. Definition of rhinitis used in this article

The aim of the article is to assess the overall proportion of rhinitis cases that are attributable to mechanisms involving atopy. Therefore, it is important to consider all cases of rhinitis. We have considered any report of nasal symptoms unrelated to infection with or without obstruction, often with eye irritation or sneezing assessed by questionnaire or patient interview. We considered the proportions of rhinitis cases and nonrhinitic control subjects with atopy defined as a positive SPT. We assessed the proportion of rhinitis cases that are attributable to atopy (see below) and inferred that the remaining proportion of rhinitis cases occurs through nonatopic mechanisms. However, this is not meant to imply that nonatopic rhinitis constitutes a single coherent etiologic entity because there is a wide range of possible nonatopic mechanisms that may play a role.

2.4. Identification of studies

We performed a Medline search from 1980 onward for English language publications with the keywords “hypersensitivity,” “IgE,” or “skin tests.” From these, we selected epidemiologic studies on rhinitis (“hayfever” or “rhinitis” combined with “cross sectional studies,” “cohort,” “case-control studies,” “epidemiological studies,” “follow up studies,” “longitudinal,” or “prevalence”). Because the rationale was to analyze the importance of atopy in rhinitis patients on a population-based level, all studies with any pre-selected patient group (other than age) were excluded. Only studies using a true population-based approach were included in this study. Studies that had the presence of a positive SPT in the definition of the rhinitis symptoms were excluded from the analysis because we wanted to investigate the prevalence of SPT positivity in patients with symptoms of rhinitis. We excluded studies where no information on the proportion of atopy in rhinitis cases and nonrhinitic control subjects was given or where no unadjusted odds ratios (ORs) were available. Only studies with truly symptom-free control subjects (i.e., without nasal symptoms) were used in our analysis. Studies that appear twice in the tables due to the different outcome measures analyzed were used only once for the calculations of the weighted mean population-attributable risk (PAR). We used the broadest (or least specific) definition of rhinitis. We calculated the overall weighted (by study size) mean of the PARs of all the studies analyzed in this article. We stratified the analyses according to the definition of rhinitis used: First, we restricted the analysis to studies with a report of a medical diagnosis of hayfever;

this could introduce bias because this subgroup involves only symptomatic participants who sought medical advice. Second, we analyzed all articles where terms such as “allergic rhinitis,” “symptoms related to allergen exposure,” or “seasonal symptoms” were used. Third, we assessed the PAR in all studies with a broad definition of rhinitis as any report of occurrence of symptoms without specifically using the terms “allergic,” “seasonal,” or “exposure related” or without a diagnosis of hayfever.

2.5. PAR

The PAR was calculated as described previously [5]. Briefly, the proportion of rhinitis cases that are attributable to atopy can be assessed by the PAR. If exposure has an OR for “rhinitis” of R (the OR is the appropriate measure to use in prevalence studies and prevalence case-control

studies [12]), that is if R is the prevalence OR of atopy as a “cause” of rhinitis, then the proportion of exposed cases that are attributable to exposure is $(R - 1)/R$, and the proportion of all cases in the population that are attributable to exposure (i.e., PAR) is $P(R - 1)/R$, where P is the proportion of all cases that are exposed [5].

3. Results

We identified 22 population-based studies with all relevant information, from 16 countries, including one study involving 34 European centers. Table 1 shows the results of these studies. The proportion of cases attributable to atopy varied between 25.6% and 89.3%. Overall, 61.4% of rhinitis cases were atopic, compared with 19.5% of noncases, and

Table 1
Percentage of rhinitis cases attributable to atopy (defined as at least one positive skin prick test) in population-based studies

Definition of rhinitis	Country	Age group in years	No rhinitis		Rhinitis		Odds ratio	PAR (%)
			Number	% with atopy	Number	% with atopy		
Medical diagnosis								
Lombardi (1996) [34]	USA	6–7	396	33.3	221	57.9	2.8	37.3
Roemark (1998) [37]	Sweden	7–8	2009	21.3	140	75.0	11.1	68.3
Garcia Ramos Alonso (1992) [38]	Spain	15–22	309	35.3	192	87.5	12.8	80.7
Tschopp (1998) [13]	Switzerland	18–60	7968	12.3	1361	68.4	15.4	64.0
Total			10682	17.2%	1914	69.6%		62.9%
Rhinitis symptoms								
Sears (1993) [36]	New Zealand	13	481	50.1	181	76.8	3.3	53.6
Porro (1992) [33]	Italy	6–14	2114	10.5	190	44.2	6.7	37.6
Keles (1999) polluted area [30]	Turkey	15–17	145	7.6	43	51.2	12.8	47.2
Keles (1999) unpolluted area		15–17	186	16.1	12	75.0	15.6	70.2
Leynaert 1999 [39]		20–44	5198	26.0	1412	74.6	8.4	65.6
Özdemir 2000 [40]	Turkey	19	136	18	15	26	2.4	15.5
Ulrik 2000 [41]	Denmark	7–17	350	56	58	85	32.8	83.6
Soto-Quiros 2002 [42]	Costa Rica	13–14	65	71	105	81	1.8	34.8
Total			8124	22.7%	1838	71.1%		57.7%
Symptoms related to allergen exposure or seasonal symptoms								
Haahela (1980) [43]	Finland	15–17	630	18.9	78	83.3	21.5	79.5
Astarita (1988) [44]	Italy	9–15	809	31.3	121	61.2	3.5	43.5
Leung (1994) [29]	China	14–16	313	51.1	158	70.3	2.3	39.1
Hong Kong								
Kota Kinabalu	Malaysia		259	61.8	62	72.6	1.6	28.3
San Bu	China		627	49.6	20	60.0	1.5	20.6
Riijaerv (1995) [45]	Sweden	10–12	1143	7.9	91	90.1	116.5	89.3
Garcia-Gonzalez (1998) [46]	Spain	17–19	261	36.8	104	73.1	4.8	57.8
Roemark (1998) [37]	Sweden	7–8	1848	15.6	301	47.2	4.8	37.4
Wuethrich (1995) [47]	Switzerland	18–60	7347	17.2	1010	65.0	8.9	57.7
Droste (1997) [48]	Netherlands	20–70	1527	15.5	640	43.1	4.1	32.7
Indoor allergens								
Outdoor allergens		20–70	2025	11.7	142	43.7	5.8	36.2
Indoor & outdoor allergens		20–70	1945	12.2	222	55.4	9.0	49.2
Leynaert (1999) [39]	34 European centres	20–44	5198	26.0	1412	74.6	8.4	65.6
Tollerud (1999) [49] ^a	USA	41–86	867	17.3	204	40.7	3.3	28.3
Barbee (1999) [50]	USA	Adults 1st survey	620	12.6	489	38.4	4.4	29.6
		Adult 2nd survey	495	20.6	598	41.0	2.7	25.6
Total			25914	22.5%	5652	58.3%	Mean:	47.7%
Overall total			44720	19.5%	9404	61.4%	Overall mean:	52.5%

Abbreviation: PAR, population-attributable risk.

^a Estimates.

the overall weighted mean of the PAR of all the studies was 53%. Restricting the analysis to a report of a medical diagnosis of hayfever in the definition (four studies) produced the highest PAR estimate of 62.9% (95% confidence interval [CI] 62.1–63.6). Using a broad definition of rhinitis as any report of occurrence of symptoms without specifically using the terms “allergic,” “seasonal,” or “exposure related” or without a diagnosis of hayfever (nine studies) resulted in a PAR of 57.7% (95% CI 56.8–58.5). Studies using terms like “allergic rhinitis,” “symptoms related to allergen exposure,” or “seasonal symptoms” (11 studies) showed a PAR of 47.7% (95% CI 46.9–48.4).

4. Discussion

The aim of this study was to assess the importance of atopy in rhinitis symptoms overall and in different populations and countries based on currently available data. In the 22 identified population-based studies, the proportion of rhinitis cases that were attributable to atopy was assessed to be approximately 50%, suggesting that the other half was due to nonatopic mechanisms. Because data from different countries and populations were compared, biases due to differences in study setting and design should be considered. In addition, differences in health systems, health access, and diagnostic procedures may have biased our results (e.g., detection bias might have influenced our results, which is a limitation that can never be totally overcome and is present in the studies already published). We have attempted to summarize these results deriving from various countries, different populations, and different age groups. However, this kind of bias is unlikely to have seriously affected the results because the diagnosis of rhinitis based on a medical examination or a questionnaire is relatively straightforward and results in a small proportion of misclassification. In addition, in most studies a standardized and well-validated questionnaire was used, which minimizes potential biases. SPTs to assess atopy are well validated and standardized, and therefore no substantial biases are expected. Finally, even when we did calculate the PAR for studies using different definitions of rhinitis (Table 1), the estimated PARs were not substantially different from the overall PAR, indicating that the potential bias is only minor. It seems that the role of atopy in rhinitis symptoms differs greatly between countries and populations (Table 1). This is evident in a comparative study in three different regions in southeast Asia where Leung found large differences in the prevalence of allergic disease occurrence despite similarly high atopy rates (50% to 60%) [29]. The PAR of atopy, as a cause of rhinitis symptoms, was highest in Hong Kong (39%), lower in Kota Kinabalu (28%), and lowest in China (20%). The difference in PAR could not be explained by differences in sensitization to common aeroallergens, and therefore other factors, such as socioeconomic and lifestyle differences, may be more important. Results of the study by Keles et al.

showed that atopic subjects living in unpolluted areas are in general less likely to have rhinitis symptoms [30]. Furthermore, the PAR for atopy is lower in the more polluted area, suggesting that a larger proportion of rhinitis could be explained by nonallergic mechanisms in polluted areas. Thus, the relative importance of atopic and nonatopic mechanisms in rhinitis varies between countries [31] (Table 1). However, we found no obvious pattern in the geographic variation of the PAR of atopy in our analysis; further studies are needed to help explain the differences. When we analyzed diagnosed “hay fever” or clearly defined allergic rhinitis (possibly more severe cases of rhinitis because a doctor was consulted), we found a higher percentage of “cases” that were attributable to atopy as defined by SPT positivity, but there was still a significant proportion that were not. On the other hand, there was a large proportion of SPT-positive asymptomatics, which justifies the wider use of nasal provocation tests established by the International Rhinologist Society to differentiate between atopic rhinitis and other forms of rhinitis in the future [32].

We searched for obvious patterns concerning age to explain the variation of the PAR between the studies but found little overall difference between the weighted mean PAR for atopy in studies of rhinitis in children (46.3%) and studies in adults (53.4%). However, direct comparisons between adults and children are difficult to interpret when the populations compared do not derive from the same country, ethnic origin, etc. We found only one country where children and adults were analyzed separately by different authors. In Italy, Porro et al. [33] found a PAR of 37.6% in children, and Lombardi et al. [34] found a PAR of 37.3% in children, whereas the PAR for atopy in a general Italian population sample of adults was found to be 66.5% [35].

It might be argued that more severe definitions of atopy (e.g., based on the number of positive SPTs) would yield higher population-attributable estimates. However, the opposite is the case. Table 2 shows data adapted from Sears et al. [36] with the number of positive SPTs in relation to current hayfever symptoms. Using a stricter definition of atopy (by using an increasing number of positive SPTs) decreased the PAR because the proportion of positive subjects within each group decreased.

Table 2
Percentage of rhinitis cases attributable to atopy according to the number of positive skin prick tests^a

SPT	No rhinitis		Rhinitis		Odds ratio	PAR (%)
	Number	% with atopy	Number	% with atopy		
1+	481	31.39	181	76.80	7.23	66.18
2+	481	15.18	181	53.59	6.45	45.29
3+	481	7.07	181	36.46	7.55	31.63
4+	481	3.12	181	14.92	5.45	12.18

Abbreviations: SPT, skin prick test; PAR, population-attributable risk.

^a Adapted from Sears et al. [36].

Finally, it is interesting to contrast these findings with those for a previous analysis of asthma that used similar methodology [5]. The PAR estimates we obtained (53% in general and 63% in those with hay fever) were greater than we previously observed in asthma (38%) but were well below 100%. In conclusion, the PAR estimates for atopy as assessed in this study were 53% for rhinitis in general and 63% in those with hay fever. This indicates that the connection between atopy and rhinitis symptoms is far from straightforward. Although atopy is an important cause for allergic rhinitis, nasal symptoms can also appear in the absence of atopy. These cases are often regarded as minor exceptions, but our analyses indicate that nonatopic mechanisms may play a more important role than has previously been assumed. There are substantial differences in the PAR worldwide, and differentiating rhinitis subtypes is a priority for future research, especially when the prevalence of rhinitis symptoms is compared between populations and where conclusions on disease origin are drawn. Only a better differentiation and disease definition can provide new strategies for disease prevention and better treatment.

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