

Epidemiological evidence of the occurrence of rhinitis and sinusitis in asthmatics

Authors' affiliations:

I. Annesi-Maesano, INSERM Epidemiology and Biostatistics Unit, Viliejuif, France

Correspondence to:

Isabella Annesi-Maesano
INSERM Epidemiology and Biostatistics Unit 16
Ave. PV-Couturier
F94807 Viliejuif
France

Introduction

Since Galen's time, physicians have dealt with a syndrome in which asthma coexisted with disorders of the upper airways, such as rhinitis or sinusitis. This has been interpreted in two opposing ways. On one hand, there exist two distinct and separate entities, upper airway disease and asthma, respectively, and the former disease might be a risk factor for the latter. On the other hand, upper airway disease and asthma might be the expression of the same disease attacking simultaneously both upper and lower airways, probably because of a common risk factor. In this scheme, upper airway disease very often precedes asthma. However, the fact that geographical distribution and epidemiological associations of asthma and rhinitis or sinusitis differ indicates that neither of these explanations are exhaustive and that further investigations are needed.

The major difficulty in the study of the relationship between upper and lower airway disease comes from the fact that asthma, rhinitis and sinusitis constitute heterogeneous disorders for which no standardized definitions are available to be used in epidemiological settings. Asthma is both extrinsic (allergic) and intrinsic (nonallergic), for which no IgE-mediated process is proven; rhinitis is infectious, allergic (seasonal or perennial), or noninfectious, nonallergic; sinusitis is classified as acute or chronic. No consensus exists on the definition of these conditions. Furthermore, no gold standard has been assessed for diagnosing them. However, much progress has been achieved in both respects during recent years.

Epidemiology has contributed to the assessment of the relationship of rhinitis or sinusitis to asthma giving evidence of: 1) the relationship between the different conditions; 2) the determinants and risk factors; and partly 3) the natural history and prognosis of the conditions.

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Existing epidemiological data concern overall asthma and allergic rhinitis, which have been studied more often, since they can be diagnosed more easily than the other conditions. Data presented here are drawn mainly from population-based samples using either standardized questionnaires, mostly validated among patients, or objective clinical tests (see Appendix).

Evidence of the relationship

There are various pragmatic methods to define the different types of rhinitis, sinusitis as well as extrinsic and intrinsic asthma (Table 1), but questionnaires in particular have been used up to now in epidemiological surveys. Asthma affects between 5% and 30% of children and between 2% and 30% of adults globally. These figures are the synthesis of data not entirely comparable because of differences in populations and methods used. Recent epidemiological studies using standardized methodology have shown that the prevalence of asthma varies geographically in both children and in adults (1, 2). Almost all these studies have related to young people in order to avoid the problems of confounding asthma with the effects of cigarette smoking. The prevalence of active asthma is at its highest during childhood. No population-based studies distinguished between extrinsic and intrinsic asthma.

Prevalence figures have been published especially for allergic rhinitis (3). Allergic rhinitis affects up to 40% of individuals. Seasonal rhinitis was found in up to 30% of individuals, perennial rhinitis in up to 10%. Boys are more affected by allergic rhinitis than girls. Later in life, women are at higher risk than men. The mean age of onset of allergic rhinitis is between 8 and 11 years. The prevalence of allergic rhinitis decreases with age. Up to 21% of individuals might suffer from nonallergic rhinitis but figures do not differentiate between infectious and noninfectious rhinitis and in noninfectious rhinitis between nonallergic rhinitis with eosinophilia syndrome (NARES) and vasomotor rhinitis (VMR). The mean age of onset of nonallergic rhinitis is much later in life than in the case of allergic rhinitis. There is an equal incidence of nonallergic rhinitis in males and females.

Sinusitis is a complex disease (4). Sinusitis prevalence has been estimated as 10–30% but these estimates need to be confirmed in population studies, providing objective assessments. The true prevalence of polyposis is difficult to determine but can be inferred from the prevalence of

intrinsic asthma. Up to 4% of individuals of the general populations present nasal polyps (5).

It is well known that upper and lower airway diseases coexist in many patients. Classically, allergic rhinitis has been linked with extrinsic asthma and nonallergic rhinitis, with asthma beginning in adulthood and for which there is no provable atopy. Allergic rhinitis and extrinsic asthma occur together more often than expected by chance. According to the literature (3, 6), between 28 and 50% of asthmatic patients have allergic rhinitis compared to 10–20% in the general population. Conversely, 13–38% of allergic rhinitis patients have asthma against 5–15% in the general population. Thus, the probability for an asthmatic to have allergic rhinitis is higher than the probability for an individual with allergic rhinitis to have asthma, probably because of the natural history of the two conditions. Almost 75% of patients with extrinsic asthma have perennial rhinitis, whereas it is only reported in 40% of patients with intrinsic asthma (7, 8). Conversely, 20% of patients with perennial rhinitis have asthma. Hay fever has been related overall to seasonal asthma, whereas perennial rhinitis has been related to house dust mite asthma; this has been confirmed by skin-prick tests (9). The prevalence of both perennial rhinitis and asthma has risen in both adults and children over the last three decades. However, when interpreting such data it is important to consider that reported figures may be biased by differences in classification and diagnostic methods and increased awareness of the conditions.

A surrogate of the relationship between VMR and intrinsic asthma, which has never been studied in population samples, is given by the relationship between nasal polyposis and asthma, since the formation of polyps is often preceded by VMR. Up to 72% of individuals with polyps have asthma. It is worthwhile noting that men have nasal polyps twice as often as women but that women, who suffer less from asthma than men, have asthma with nasal polyps as often as men, so confirming the existence of the association between intrinsic asthma and polyposis.

The common association of sinus disease with asthma has been known many years (10). Sinusitis has been linked to allergic rhinitis, asthma and nasal polyps. Sinusitis is commonly associated with asthma and evidence is accumulating that there may be a cause-and-effect relationship; that is, that sinusitis triggers or aggravates asthma. Between 30 and 70% of patients with asthma present sinusitis as assessed using sinus X-rays. Conversely, 34% of patients with sinusitis have asthma. However, the relationship between sinusitis and asthma is debated because the

Table 1. Pragmatic methods to define asthma (A), rhinitis (R) and sinusitis (S)

Methods	Outcome	Comments
Clinical evaluation	All types of A, R, S	Not standardized but presently gold standard Largely used in epidemiology
Self-report of diagnosis	All types of A, R, S	Depending on health system Largely used in epidemiology
Self-report of the condition by questionnaire	All types of A, R, S but reliable only for A and AR	PPV high (rhinoconjunctivitis wheezing last year) Largely used in epidemiology
Allergy markers (IgE, SPT, eosinophils)	AR, EA vs IA	Depending on the type of marker Eosinophil count useful to diagnose NARES vs VMR
Function (nasal and lung)	Nasal patency (rhinometry, PNIF, rhinomanometry) PEF, FEV ₁	Depending on disease activity Few epidemiological data on R
Challenge	Nasal reactivity Bronchial reactivity	Depending on disease activity No epidemiological data on R
Endoscopy (nose, bronchi)	Various conditions of upper and lower airways	Difficult and not standardized Bronchoscopy never used in epidemiological studies for ethical reasons
Lavage	Inflammation (cells, mediators, cytokines)	No epidemiological data
Biopsy/smear	Cells (presence of eosinophils)	Few epidemiological data in the case of nasal biopsy Difficult to use for lungs
X-ray, CT-scan	Sinusitis, polyposis	Rarely used in epidemiology

AR: allergic rhinitis; NAR: nonallergic rhinitis; EA extrinsic asthma; IA: intrinsic asthma; NARES: nonallergic rhinitis with eosinophilia; VMR: vasomotor rhinitis; PPV: positive predictive value; PNIF: peak nasal inspiratory flow; PEF: oral peak expiratory flow.

investigations concerned were uncontrolled and were not adjusted for potential confounders.

Epidemiological studies conducted in population-based samples having taken age, sex, bronchitis, hay fever and parental asthma as well as other potential confounders into account failed to confirm the association in both adults (11) and children (12).

Experimentally, reflex bronchoconstriction can result from stimulation of receptors in the nose and nasopharynx. Indeed, substantial improvement in asthma is seen after appropriate medical or surgical treatment for sinusitis and nasal polyps in both children (13) and adults (14).

Determinants and risk factors

It has been said that a determinant is any individual characteristic (constitutional, environmental or behavioural) on which the study outcome, the comorbidity between upper and lower airway disease in our case, depend. A determinant can be causal or not and can increase or decrease the risk for the disease. As a risk factor, a determinant can affect the incidence of the relationship

(primary) or trigger symptoms, exacerbate disease or increase its severity (secondary).

Determinants of the association between upper and lower airway disease are useful in understanding underlying mechanisms. Concomitant occurrence of allergic rhinitis and extrinsic asthma is in favor of a common etiology. Atopy is the most important factor in enhancing the likelihood that both conditions will be expressed, but other factors will also participate (Table 2). Among host factors, the role of genetics, immunologic factors and bronchial hyperresponsiveness is highly likely. However, the fact that familial resemblance of the coexistence of rhinitis and asthma between parents and offspring (odds ratio=3.6; 95% confidence interval: 1.6–8.3) was lower than the resemblance between siblings (odds ratio=8.5; 95% confidence interval: 3.4–21.3) in a population-based study of 1773 Italian individuals supports the hypothesis that environmental factors also intervene (15).

Among environmental factors, irritants and active smoking may play a role but longitudinal studies, in order to assess causation, have been lacking. Cross-sectional observations of adolescents recruited in the frame of the International Study of Asthma and Allergies in Childhood (ISAAC) in the West Marne showed that active smoking was

significantly more common in individuals with both asthma and rhinitis (242/3941) than in others (odds ratio=1.61, 95% confidence interval: 1.02–2.55) (16). A smaller relationship also existed in the case of passive smoking. Other putative factors are temperature, including cold air, dampness, nutrition, lifestyle and socioeconomic disadvantages. Many of these factors are difficult to assess. Symptoms and exacerbations are triggered by allergenic exposure or infections, which are theoretically susceptible to intervention.

No population-based data exist on putative factors for the coexistence of sinusitis and asthma. The association of rhinosinusitis and asthma with or without atopy among family members of 130 English patients showed that 46% had a family history of rhinosinusitis, asthma or eczema, thus suggesting that common genetic factors are related to these upper and lower airway diseases (1, 7).

It is likely that various factors influence the relationship between upper and lower airways disease but little epidemiological evidence exists (Table 3). The first factor involved has been age, due to the age-dependent modifications in the airways and in the immune system (18). However, no population studies could confirm that the association between asthma and rhinitis depends on age and increases or decreases with advancing age. The relationship

might depend on family history of allergy, a marker of individual susceptibility to develop atopic disease.

In a large representative sample of 12 391 French adolescents, the relationship between hay fever and asthma as assessed by questionnaire was stronger among individuals with a familial history of asthma than in others (6). The underlying hypothesis was that both rhinitis and asthma were allergic because of the age range. Asthma phenotype appears also to be related to the relationship. Long-term asthma was more frequent in patients with hay fever than short-term asthma (odds ratio=2.70 vs 1.89, respectively, among French adolescents (19). It cannot be excluded that allergic rhinitis might exacerbate asthma (20). Furthermore, the measure of the association between hay fever and asthma became stronger when the type of asthma onset was taken into account in the large population of the NHAMES study (21). Those with late asthma onset had a higher risk of also having hay fever than those with medium and early onset (odds ratio=3.79 vs 3.06 and 2.71, respectively). Another factor which could affect the relationship between allergic rhinitis and asthma is allergenic exposure, but this has yet to be explored in population samples.

Perennial rhinitis is associated with a higher risk of the development of nonspecific bronchial hyperresponsiveness than seasonal rhinitis (22). Finally, no study has reported on the effect of behavioural factors, treatment or management of rhinitis on the subsequent development of asthma. The same factors are likely to intervene in the case of sinusitis and asthma.

Natural history

With regard to the timing of the relationship between allergic rhinitis and asthma, two patterns have been proposed: 1) simultaneous occurrence; and 2) different

Table 2. Putative factors and determinants contributing to the

Category	Determinants and factors	Type of relationship
Host	Genetic factors	Both AR & EA and NAR & IA (+)
	Familial history of allergy	Only AR & EA (+)
	Atopy	Only AR & EA (+)
	Airway hyperreactivity	Both (+)
	Immunologic factors	Both (?)
	Ethnic origin	Both (?)
Environment	Irritants (smoke, pollution)	Both (+)
	Active smoking	Both (+)
	Cold air	(?)
	Humidity	(?)
	Temperature	(?)
	Seasonal variations	(?)
	Nutrition	(?)
	Lifestyle	Only AR & EA (?)
	Socioeconomic disadvantages	(?)
Triggers	Allergens	Only AR & EA (+)
	Infections	Both (?)

AR & EA: allergic rhinitis and extrinsic asthma. NAR & IA: nonallergic rhinitis and intrinsic asthma. + = direct or indirect evidence; ? = lack of any evidence.

Table 3. Factors influencing the relationship between upper and lower airway disease

	Degree of certainty
Age	–
Asthma onset	±
Asthma severity	+
Environmental exposure (among which allergen exposure)	±
Treatment or management	?
Behavior	?

Table 4. The relationship between hay fever and asthma in population-based longitudinal studies

Population size (author) (ref.)	Outcome	Measurement of association*
n = 7225 (Anderson, UK) (27)	Asthma at 7 years	7.1
n = 770 (Sherman, USA) (11)	Asthma at 5–9 years	2.9
n = 8585 (Jenkins, Australia) (29)	Asthma at 7 years	3.9
n = 1021 (Settipane, USA) (26)	Asthma life (23 years follow-up)	3.0
*Odds ratio.		

timing with rhinitis preceding the development of asthma. The former pattern has been proposed by cross-sectional study in which patients have been observed by doctors; the latter by longitudinal studies in general population-based samples using epidemiological questionnaires (Table 4), even if this has not been observed consistently (23–25). Asthma was almost three times more likely to develop in patients who had allergic rhinitis and positive allergic skin tests than those who did not in a longitudinal study conducted in 1836 college students in the United States (26).

British data of 7225 individuals followed-up longitudinally showed that prior hay fever was associated with an increased risk of subsequent asthma or wheezing, and current hay fever was even more associated with asthma (27). Similarly, the risk of a history of asthma was higher if the child had a previous history of hay fever among 770 US children (28) or 8585 Tasmanian adults (29). Assessment of the two conditions in these surveys was based mainly on the diagnosis of the two conditions, so that it cannot be excluded that individuals with mild conditions not needing

medical management were excluded from the sample. Recall bias may also arise in longitudinal data using epidemiological questionnaires, since we found recently in a representative sample of 3941 French adolescents that most could not answer on the timing of occurrence of asthma and allergic rhinitis (6). Furthermore, because of bias in assumption, population-based investigations never explored whether asthma may be prior to allergic rhinitis. However, various elements appear to support that allergic rhinitis precedes asthma. Rhinitic subjects with nonspecific hyperresponsiveness develop asthma more frequently than those without (30, 31). The prognosis of rhinitis has also been explored among individuals with rhinitis followed-up carefully and for whom objective assessments of allergy were provided. There was a relevant number of new cases of asthma among them (32, 33), even if not always (34, 35) (Table 5), thus confirming population-based data according to which there are individuals with allergic rhinitis that are much more prone to asthma than others. The reason for this has yet to be elucidated. Probably, genetic studies will contribute to the understanding of underlying mechanisms.

Conclusions

During the past decade, our understanding of the coexistence of upper and lower airway diseases has evolved, slightly in part because of epidemiological studies. The historic perspective of these disorders as distinct and separate entities is being displaced by current thinking that they are described better as a continuum of inflammation involving one common airway (36), which occurs at different sites and at different periods of the life of the subject. Epidemiological research has provided increasingly

Table 5. Evolution of asthma among rhinitic patients

Author (ref.) (country)	Population	Follow-up length	Asthma incidence
Danielsson (32) (Sweden)	82 adults (6% with asthma)	1979–82	6% developed asthma 34% other lower airway symptoms
Linna (33) (Sweden)	154 children (110 seasonal and 44 perennial rhinitis)	8–11 years	20% overall among perennial rhinitis
Annesi (6) (France)	200 middle-aged men	5 years	None but few cases
Norman (35) (Sweden)	Adolescents	4 years	No report of data

meaningful information not only on the prevalence of the association but on the factors which impact upon the relationship. In spite of the evidence of heritability of upper and lower airway conditions, although no genetic component has yet been characterized, it is likely that the determinants of their coexistence are environmental. Epidemiology will be helpful in understanding the separate influences of either genetic or environmental factors in the association between asthma and rhinitis.

What can epidemiological studies contribute further? In the immediate future, epidemiology may help to improve diagnostic criteria in order to make a meaningful contribution

to the identification of the conditions for epidemiological purposes as well as for the general practitioner, who has to manage both upper and lower airway diseases. Due to epidemiology, investigation studies NMII use the same standardized methods to measure the prevalence and the incidence of the conditions at different points in time. Furthermore, prospective studies of community populations with repeated immunological and physiological measurements will extend our knowledge of the relationship and provide an approach of the additional factors that induce the relationship, and the mechanisms by which the link is maintained. Such studies are the only ones to prove causation.

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Appendix

Standardized questions to assess asthma in both children and adults have been provided. However, asthma is a complex disease difficult to define. The sensitivity and specificity of the questions used currently to assess asthma have been calculated taking indirect markers of asthma into account [37]. The situation is even worse in the case of rhinitis, which

covers a heterogeneous set of diseases. Standardized questionnaires have just begun to be proposed for allergic rhinitis only in ISAAC. Furthermore, new diagnostic criteria score for allergic rhinitis taking the history of the subject, a major tool in establishing the differential diagnosis of rhinitis, have recently been proposed [38]. Its sensibility and specificity taking the

medical diagnosis as a gold standard were high. Allergy skin tests are the definitive method for distinguishing allergic from nonallergic rhinitis and asthma, whereas total IgE are not indicated because of the overlap existing between values in allergic and nonallergic individuals [39]. No standardized definition of sinusitis exists.