

Review article

Challenges in epidemiologic allergy research

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Epidemiologic studies indicate that the prevalence of asthma and allergic disease has increased in many countries in recent decades and that the occurrence differs between countries and regions (1). For example, there appears to be a higher prevalence of atopy and asthma in Western than in Eastern Europe (2, 3). Although hereditary factors are important for the risk of developing allergic disease, these results clearly show that nonhereditary risk factors must play a dominant role. Epidemiologic methodology is one of the key elements in elucidating the causes of time trends and geographic differences in the occurrence of allergy. A better understanding of these causes is crucial for adequate prevention.

In recent decades, a coherent epidemiologic methodology has evolved. This has centered on issues such as study design efficiency in chronic disease epidemiology, as well as understanding and controlling bias. Unfortunately, modern epidemiologic methodology has been employed in allergy research only to a limited extent, particularly in comparison with applications in cancer and cardiovascular research. The reasons behind this discrepancy remain obscure, but the result has been wasteful allocation of resources to inefficient and inappropriate studies, as well as delays in finding valid explanations for the descriptive data as a basis for preventive efforts.

There are several methodological challenges in epidemiologic allergy research. Here the focus will

be on issues related to analytic epidemiology; i.e., studies aimed at assessing causes or risk factors for disease. Primarily, three issues are discussed: disease classification, measurement of exposure, and estimation of etiologic fraction. The etiologic fraction, which is sometimes referred to as attributable proportion or attributable risk, denotes the proportion of disease in a population which is explicable by (or caused by) a certain risk factor (4). Consequently, it indicates the proportion of disease that would not have occurred had the risk factor been absent. This is a most useful measure for assessment of the public health impact of various risk factors and for prioritizing of preventive activities in different populations.

Classification of disease

Disease definition remains a particular problem in allergy research. Unlike many other fields, clear and uniform diagnostic criteria have long been lacking. Therefore, the successful efforts to coordinate multinational collaborative projects on asthma in children and adults constitute an important achievement (5, 6). Generally, it is not feasible to assess the occurrence of allergic disease from registers, such as hospital discharge registers, because many subjects with milder symptoms may not come into contact with a hospital or a doctor. Instead, population-based studies are required, often combining traditional questionnaire methodology with

laboratory tests. When time trends are evaluated, it is essential that the methods and criteria for diagnosis be identical on the different study occasions, even with regard to season (7). For example, questionnaire surveys performed several years apart indicate that the prevalence of respiratory symptoms in children consistent with asthma has increased in several parts of the world (8–10). Similar trends have been reported for hospital admissions (11–13), but the evidence is not consistent (14, 15). Changes in treatment and access to hospital care complicate the interpretation of data on hospital admissions (13, 16). Furthermore, modification of diagnostic criteria can be a problem for assessment of time trends (17). To enhance comparability between studies, authors have suggested that asthma be defined as symptomatic bronchial hyperresponsiveness (18). However, it is evident that many wheezing children do not show bronchial hyperresponsiveness to histamine, and some children do not wheeze but show histamine bronchial hyperresponsiveness (19).

In designing the instruments to define those with disease, it should be realized that the requirements may be quite different in descriptive and analytic studies. For example, in a descriptive study, it is often desirable to have a high sensitivity of the methods to identify subjects with disease. On the other hand, a poor sensitivity will have no major impact on the estimate of the association between exposure and disease, as described with the relative risk, provided the sensitivity in finding those with disease is independent of exposure. This is illustrated in Table 1, with a hypothetical example assuming different types of disease misclassification. The cumulative incidence is 5% in the unexposed group and 10% in the exposed group. Without disease misclassification, this gives a relative risk (rate ratio) of 2. An underdiagnosis (sensitivity 0.5) does not affect the risk estimate. Unfortunately, a high sensitivity of diagnostic tests is often accompanied by difficulties in obtaining high specificity, a situation which implies that false positives may appear. This will generally have severe dilution effects on the relative risk estimates. In the example, only a small drop in specificity to 0.95 results in an observed relative risk of 1.5, instead of the true risk of 2. Thus, in epidemiologic studies of etiologic relationships, the specificity of the methods to identify those with allergic disease is often more important than the sensitivity.

Exposure assessment

Epidemiologic studies of analytic type often suffer from problems in obtaining accurate information on exposure. Imprecise exposure data will generally

Table 1. Effects on relative risk by nondifferential misclassification of disease^a

	No. of cases		Relative risk
	Exposed	Unexposed	
No misclassification (sensitivity = 1.0, specificity = 1.0)	500	250	2.0
Underdiagnosis (sensitivity = 0.5, specificity = 1.0)	250	125	2.0
Overdiagnosis (sensitivity = 1.0, specificity = 0.95)	750	500	1.5

^a Cohort size of 10 000 is assumed, together with cumulative incidence of 5% among unexposed. Relative risk associated with exposure is 2, and 50% of cohort is exposed.

lead to dilution effects; i.e., the observed associations are weaker than the true (20). Particular problems arise when the exposure is variable and long time periods are of interest, as is often the case for studies on environmental causes of allergy. For example, most studies on environmental risk factors and asthma are of cross-sectional design. This is mainly explained by the high efficiency of this design for diseases with a low incidence but comparatively long duration, resulting in a high prevalence. If coupled with the ability to obtain information on exposure and disease at the same time, the cost-effectiveness is further enhanced. The evidence is not wholly consistent regarding an association between current allergen levels indoors and sensitization to house-dust mites and furred animals or symptoms of asthma on an individual basis (21–24). Dilution of the association because of difficulties in assessing long-term exposure may have contributed to these results. Obviously, effect modification by other factors, such as individual susceptibility and exposure to adjuvants, is also important and must be adequately controlled to determine the role of allergen exposure.

Biologic markers may sometimes be useful in estimating exposure. One advantage is the ability they offer to assess the total exposure from various sources and environments. For example, exposure to environmental tobacco smoke can be estimated via determination of cotinine in blood, saliva, or urine. Furthermore, this avoids bias from misreporting. A major disadvantage is the difficulty in assessing long-term exposure with biologic markers. The half-life of cotinine is only about 20 h (25), and this means that a single measurement represents exposure only during the last few days before sampling. Several studies have shown a clear association between urinary cotinine and wheezing bronchitis or asthma in children (26–29). However, it was also indicated that this biologic marker offered

no major advantage over the traditional questionnaire technique (29).

It may sometimes be useful to assess the quality of the method for acquisition of exposure information in a study. This is often feasible in a subsample of the whole study population. When the sensitivity and specificity of the exposure measure are known or may be estimated, it is possible to adjust the observed relative risk to account for nondifferential misclassification of exposure (30). Substantial efforts have been devoted to assessment of the quality of different methods for estimating dietary intake and exposure to ionizing radiation (31, 32). This information has also been used to adjust observed measures of association for random errors in the exposure assessment. With regard to indoor factors and allergy, the work on residential radon exposure is of particular interest. A recent report has suggested that the true risk estimates for lung cancer related to residential radon exposure were about 50–100% higher than the observed (33), although the original epidemiologic study used a very extensive methodology to estimate exposure, involving retrospective radon measurements in homes extending over several decades for more than 4000 study subjects (34). It is not clear whether adjustment for exposure misclassification has been attempted in any studies on environmental risk factors and allergy.

Misclassification of exposure is generally independent of disease status in cohort studies – so-called nondifferential misclassification – indicating that mainly attenuation of associations between exposure and health effects should be considered. However, in cross-sectional studies and case-control studies, the misclassification of exposure may be differential between those with and without disease. For example, subjects with allergy may overreport certain exposures, such as indoor mold growth (35). A particular problem may arise in studies on allergy because avoidance measures have been taken primarily by subjects with disease (36). Conscious or subconscious misreporting may also occur even without actual avoidance, such as misleading information on tobacco smoking and furred pets in the household, as a result of preventive pressures. Cross-sectional studies are of major concern in this respect. The information on exposure in such studies is often obtained long after the onset of disease, with ample time to modify exposure. For example, in one study, the reported prevalence of respiratory allergy and symptoms was lower among children of current pet owners than among children of parents who did not own pets (37). However, a different picture emerged when retrospective information was taken into account. The highest prevalence of pet allergy,

lower respiratory symptoms, and doctor-diagnosed asthma was found in children who had once had pets, particularly cats, but no longer had them. It may not be sufficient to ask about earlier exposure, as it has been shown that those who have changed their behavior tend to report earlier habits as being more similar to recent habits than had been reported earlier (38, 39).

It appears prudent to recommend that cross-sectional methodology be avoided in analytic allergy research unless longitudinal recall bias can be excluded, or exposure is constant and objective measurements are available. Caution is also necessary in case-control studies, although recall bias may be less pronounced than in cross-sectional studies because of a shorter time between acquisition of exposure information and disease onset. Although resource-consuming, prospective cohort studies are generally best suited for elucidation of risk factors for development of allergy (40, 41). A combination of cohort and case-control methodology may be feasible in certain situations, so-called nested case-control studies. In such studies, information on exposure is obtained for all study subjects before disease onset but is analyzed only for cases and controls. This is particularly efficient when the costs for analysis are high in comparison to those for storage, as is often the case for environmental and biologic samples.

Intervention studies are sometimes performed to elucidate causal relationships in allergy research (42–45). This has advantages in relation to control of certain types of bias. However, intervention studies are often characterized by poor efficiency, and application is primarily restricted to high-risk groups.

Etiologic fraction

A major advantage of epidemiologic studies is the opportunity to estimate the fraction of disease in the population that is caused by a certain exposure, the etiologic fraction. One prerequisite, however, is that the study be population-based. This is often not the case when high-risk groups, such as subjects with atopic heredity, are studied, or when the recruitment is hospital-based. High nonresponse rates may also compromise the ability to estimate exposure occurrence in the population, which is crucial for assessment of the etiologic fraction. On the other hand, nonresponse in recruitment of study subjects is of less concern in estimating relative risks; i.e., the risk of disease associated with a certain exposure in relation to the risk among the unexposed. This risk may be correctly ascertained in a study group even if the exposure is not representative of the whole population. An ana-

logy can be made with animal experiments. No one would claim that a group of rats under study must be representative of rats in general, but rather that the experimental conditions must be carefully controlled to avoid bias and that all included animals must be followed up in detail. The situation is similar in analytic epidemiology. It is more important to select a study group where bias can be minimized and all individuals followed up than to strive for representativeness. Obviously, the generalization of epidemiologic findings on disease etiology to other populations tends to be much less of a problem, even if special groups have been studied, than when the evidence is based on animal experiments. However, if the aim is to estimate the etiologic fraction, information on exposure occurrence in the relevant population must also be obtained. This may be done in a separate study based on a representative sample.

In a population-based epidemiologic study, it is possible to estimate both the exposure occurrence in the population and the risks associated with this exposure. For example, a recent study in Stockholm enabled estimation of the etiologic fraction associated with different risk factors for wheezing bronchitis or asthma in children up to 4 years of age (46). Table 2 shows that parental smoking, a brief period of breast-feeding, and pets in the household are important risk factors. The results are in general agreement with other similar studies from the same area (36, 47). This points to a substantial potential for primary prevention. It should be noted that the etiologic fraction for different risk factors cannot be summarized in a simple manner to get an overall estimate, primarily because interactions between risk factors have to be taken into consideration.

The concept of etiologic fraction clearly illustrates that risk factors associated with modestly elevated relative risks may also be important from a public health point of view if large population groups are exposed. In the interpretation of studies with modestly elevated relative risks, it is essential to distinguish between inconclusive and negative evidence (48). Several criteria have to be met if an

investigation is to be interpreted as negative. The observed relative risk should lie close to unity with a narrow confidence interval, a fact which necessitates a large study size. Furthermore, the exposure information must have a high precision, and negative confounding effects should be adequately controlled for. It is difficult to fulfill all these criteria simultaneously; therefore, conclusively negative epidemiologic studies are rare. Unfortunately, we still find that studies of limited size and/or using crude exposure measures are erroneously regarded as "negative", because the associations do not reach statistical significance, when the results should rather be considered "inconclusive".

Conclusion

There is a great potential for advances in the understanding of important determinants of allergy by modern epidemiologic methodology. However, clear and uniform diagnostic criteria with broad implementation are needed. In analytic epidemiology, more emphasis should be given to the specificity of the disease measures than to the sensitivity. Longitudinal studies are particularly useful for elucidation of etiologic relationships. The risks of differential misclassification of exposure in epidemiologic studies on allergy argue in favor of prospective designs. Population-based studies are required to assess the etiologic fraction, which is an important measure for setting priorities in prevention.

References

1. Woolcock AJ, Peat JK, Trevillion LM. Is the increase in asthma prevalence linked to increase in allergen load? *Allergy* 1995;50:935-40.
2. Bråbäck L, Brevorowics A, Dreborg S, Knutsson A, Pieklik H, Björkstén B. Atopic sensitization and respiratory symptoms among Polish and Swedish schoolchildren. *Clin Exp Allergy* 1994;24:826-35.
3. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64.
4. Miettinen OS. Theoretical epidemiology. Principles of occurrence research in medicine. New York: John Wiley, 1985.
5. Burney PGJ, Luczinska C, Chinn S, Jarvis D. European Community Respiratory Health Survey. *Eur Respir J* 1994; 7:954-60.
6. Asher HI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
7. Stewart AW, Asher MI, Clayton TO, et al. The effect of season-of-response to ISAAC questions about asthma, rhinitis and eczema in children. *Int J Epidemiol* 1997;26: 126-36.
8. Burney PGJ, Chinn S, Rona RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973-86. *BMJ* 1990;300:1306-10.

Table 2. Etiologic fraction associated with some risk factors for wheezing bronchitis or asthma in children up to 4 years of age from Stockholm^a

Risk factor	Prevalence of exposure (%)	Relative risk	Etiologic fraction (%)
Parental smoking	45	1.8	27
Short breast-feeding period (≤3 months)	34	1.6	16
Pets in household ^b	27	1.4	10

^a Modified from Rylander et al. (46).

^b Dog, cat, rodent, or bird.

9. Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ. Changing prevalence of asthma in Australian children. *BMJ* 1994;308:1591-6.
10. Skjøsberg OH, Clench-Aas J, Leegaard J, et al. Prevalence of bronchial asthma in schoolchildren in Oslo, Norway. Comparison of data obtained in 1993 and 1981. *Allergy* 1995;50:806-10.
11. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. *Thorax* 1989;44:614-19.
12. Carlsen K-H. Epidemiology of childhood asthma. *Eur Respir Rev* 1994;4:17,5-9.
13. Wickman M, Farahmand BY, Persson PG, Pershagen G. Hospitalization for lower respiratory disease during 20 years among children under 5 years of age in Stockholm County Report 27/95. Stockholm: Department of Environmental Health, Stockholm County Council, 1995.
14. Hill DJ, Hosking CS, Shelton MJ, Turner MW. Childhood asthma: clinical and immunological changes over a decade. *Clin Exp Allergy* 1991;21:343-9.
15. Strachan DP, Anderson HR. Trends in hospital admission rates for asthma in children. *BMJ* 1992;304:819-20.
16. Wennergren G, Kristjánsson S, Strannegård IL. Decrease in hospitalization for childhood asthma with increased use of anti-inflammatory treatment, despite an increase in the prevalence of asthma. *J Allergy Clin Immunol* 1996;97: 742-8.
17. Hill R, Williams J, Tattersfield A, Britton J. Change in use of asthma as a diagnostic label for wheezing illness in schoolchildren. *BMJ* 1989;299:898.
18. Toelle BGJ, Peat JK, Salome CM, Mellis CM, Woolcock AJ. Toward a definition of asthma for epidemiology. *Am Rev Respir Dis* 1992;146:633-7.
19. Patterson PK, Asher MI, Harrison AC, Mitchell EA, Rea HH, Stewart AW. The interrelationships among bronchial hyperresponsiveness, the diagnosis of asthma and asthma symptoms. *Am Rev Respir Dis* 1990;142:549-54.
20. Armstrong B. The effects of measurement errors on relative risk regressions. *Am J Epidemiol* 1990;132:1176-84.
21. Lau S, Falkenhurst G, Weber A, et al. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol* 1989;84: 718-25.
22. Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TAE. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. *J Allergy Clin Immunol* 1995;96: 449-56.
23. Marks GB, Tovey ER, Toelle BG, et al. Clinical aspects of allergic disease. Mite allergen (Der p 1) concentration in houses and its relation to the presence and severity of asthma in a population of Sydney schoolchildren. *J Allergy Clin Immunol* 1995;96:441-8.
24. Peat JK, Tovey E, Toelle BG, et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996;153:141-6.
25. Willers S, Skarping G, Dalene M, Skerfving S. Urinary cotinine in children and adults during and after semi-experimental exposure to environmental tobacco smoke. *Arch Environ Health* 1995;50:130-8.
26. Willers S, Svenonius E, Skarping G. Passive smoking and childhood asthma. Urinary cotinine levels in children with asthma and in referents. *Allergy* 1991;46:330-4.
27. Erlich R, Kattan M, Godbold J, et al. Childhood asthma and passive smoking. Urinary cotinine as a biomarker of exposure. *Am Rev Respir Dis* 1992;145:594-9.
28. Chilmonczyk BA, Salmun LM, Megathlin KN, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *N Engl J Med* 1993;328:1665-9.
29. Rylander E, Pershagen G, Eriksson M, Bermann G. Parental smoking, urinary cotinine, and wheezing bronchitis in children. *Epidemiology* 1995;6:289-93.
30. Flegal KM, Brownie C, Haas JD. The effects of exposure misclassification on estimates of relative risk. *Am J Epidemiol* 1986;123:736-51.
31. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat Med* 1989;8:1051-69.
32. Båverfält U, Swedjemark GA. Where are the errors when we estimate radon exposure in retrospect? *Radiat Prot Dosim* 1991;36:107-12.
33. Lagarde F, Pershagen G, Åkerblom G, et al. Residential radon and lung cancer in Sweden: risk analysis accounting for random error in the exposure assessment. *Health Phys* 1997;72:269-76.
34. Pershagen G, Åkerblom G, Axelson O, et al. Residential radon exposure and lung cancer in Sweden. *N Engl J Med* 1994;330:159-64.
35. Dales RE, Miller D, McMullen ED. Indoor air quality and health: validity and determinants of reported home dampness and moulds. *Int J Epidemiol* 1997;26:120-5.
36. Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall SL. Indoor environmental risk factors in young asthmatics: a case-control study. *Arch Dis Child* 1994;73:408-12.
37. Brunekreef B, Groot B, Hoek G. Pets, allergy and respiratory symptoms in children. *Int J Epidemiol* 1992;21:338-42.
38. Persson PG, Norell SE. Retrospective versus original information on cigarette smoking. Implications for epidemiologic studies. *Am J Epidemiol* 1989;130:705-12.
39. Hammar N, Norell S. Retrospective versus original information on diet among cases of colorectal cancer and controls. *Int J Epidemiol* 1991;20:621-7.
40. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;323:502-7.
41. Kuehr J, Frischer T, Meinert R, et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994;94:44-52.
42. Ziegler RS, Heller S, Mellon MH, et al. Effect of combined maternal and infant food allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989;84:72-89.
43. Hattevig G, Kjellman B, Sigurs N, Björkstén B, Kjellman N-IM. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989;19:27-32.
44. Chandra RK, Puri S, Hamed A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ* 1989;299:228-30.
45. Arshad SH, Matthews S, Gant C, Hide DW. Effects of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1493-7.
46. Rylander E, Pershagen G, Eriksson M, Nordvall L. Parental smoking and other risk factors for wheezing bronchitis in children. *Eur J Epidemiol* 1993;9:517-26.
47. Wickman M, Nordvall SL, Pershagen G. Risk factors in early childhood for sensitization to airborne allergens. *Pediatr Allergy Immunol* 1992;3:128-33.
48. Ahlbom A, Axelson O, Støttrup Hansen E, Hogstedt C, Jensen UJ, Olsen J. Interpretation of "negative" studies in occupational epidemiology. *Scand J Work Environ Health* 1990;16:153-7.

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