

Does allergy in parents depend on allergy in their children?

Recall bias in parental questioning of atopic diseases

Michael Kulig, MD, MPH,^a Renate Bergmann, MD,^b Gunther Edenharter, PhD,^c
Ulrich Wahn, MD,^b and the Multicenter Allergy Study Group,* Berlin, Germany

Background: A positive atopic family history has proved to be one important risk factor for the development of atopic diseases in offspring. However, many epidemiologists are concerned about the accuracy and reliability of data because responses to questionnaires can be biased for many reasons. **Objective:** The study investigated whether responses of parents questioned about their atopic diseases change depending on the development of atopic symptoms in their children. **Methods:** During a prospective birth cohort study on atopy in children (the Multicenter Allergy Study) parents filled out questionnaires twice within 2 years about their atopic diseases. Differences between the 2 responses were examined by log-linear and logistic regression models depending on the diagnosed atopy status of the study children. **Results:** Mothers tended to report more atopic diseases in the second questioning than in the first, indicating a nondifferential misclassification. Fathers were influenced by the development of atopic diseases in their children: they reported significantly more atopic diseases if the child developed atopic illness with atopic dermatitis. **Conclusion:** In parental questioning about atopic diseases, a recall bias must be considered for the association of atopic family history and atopy in children. Especially in case-control and cross-sectional studies, such misclassifications can result in biased estimates of prognosis and risk factors. (*J Allergy Clin Immunol* 2000;105:274-8.)

Key words: Atopic diseases, atopic family history, questioning of parents, children, recall bias

A positive family history for atopy has proved to be an important risk factor for development of atopic diseases in offspring.¹⁻⁴ Atopic parents can be regarded as the phenotype of a genetic disposition for atopy in a subject.⁵ Many studies have focused on the familial association of atopy.⁶⁻⁸ Atopic family history is mostly included as a

Abbreviation used
AD: Atopic dermatitis

possible risk factor in studies on atopic diseases. Information about the familial disease pattern is mainly obtained by history taking. However, many epidemiologists regard the accuracy and reliability of the data as a point of concern, particularly if it is obtained by interview or questionnaire.^{9,10} Harlow and Linet¹¹ and Linet et al,¹² in reviewing the accuracy of recall of anamnestic data and comparing interview data with medical records, showed that the accuracy of recall should remain a point of concern in epidemiologic studies. In the case of allergic illnesses (hay fever and asthma) the percentage of positive reports in interviews matched by medical records ranged from 66% to 49%, with decreasing percentages for longer recall periods.

Accuracy of responses to questionnaires can be biased for many reasons.¹³ In studies on atopy in childhood, mainly the mothers respond or it is not even exactly specified who completed the questionnaire.^{8,14-16} Also the time period between the presence of symptoms and the history taking varies from study to study. Parents may be asked at birth of as-yet unaffected babies or may be questioned shortly after the diagnosis of an atopic disease in their children. The knowledge of the disease status may increase recall among relatives of newly diagnosed subjects.

In some studies the atopic family history is only summarized into the 2 relatively rough categories "present" and "absent." In this case the atopic family status depends on the respective family size and the number of family members questioned. Other investigators perform the analysis considering atopic histories of mothers and fathers separately. These divergent approaches result in different estimates of the familial disease association. Often a stronger influence of maternal than paternal atopy is reported when the development of atopic conditions is examined in children.^{6,17,18} Only rarely are higher risk ratios for a paternal association described.^{7,16} The phenomenon of a stronger maternal influence is also called the "Carter effect" and it is partly explained by the multifactorial mode of inheritance.¹⁹ Another explanation could be that the environmental conditions of the child correspond to a higher degree to those of the mother than to the paternal conditions because as a rule the mother is the primary caregiver. But the significance of

From the ^aInstitute of Social Medicine and Epidemiology, Charité Hospital, Humboldt University of Berlin, the ^bDepartment of Pediatric Pneumology and Immunology, Humboldt University of Berlin, and the ^cRobert Koch Institute, Berlin, Germany.

The Multicenter Allergy Study (MAS-90) has been supported by German Ministry of Research and Technology grant No. 01EE9406.

Received for publication May 10, 1999; revised Oct 27, 1999; accepted for publication Oct 28, 1999.

Reprint requests: Michael Kulig, MD, MPH, Institut für Arbeitsmedizin, Sozialmedizin, und Epidemiologie, Universitätsklinikum Charité, 10098 Berlin, Germany.

* V. Wahn, J. Forster, C. P. Bauer, and F. Zepp for the Multicenter Allergy Study Group.

Copyright © 2000 by Mosby, Inc.

0091-6749/2000 \$12.00 + 0 1/1/104105

TABLE I. Comparison of frequencies of reported parental atopic diseases at two time points (n = 500 mothers and fathers)

	Second questioning					
	Mothers			Fathers		
	-	+ No AD	+ With AD	-	+ No AD	+ With AD
First questioning						
-	302*	21	5	297*	12	7
+ No AD	14	119*	12	18	128*	12
+ With AD	6	2	19*	4	5	17*
			(P = .068†)			(P = .79†)

-, No atopic disease; + atopic disease present.

*Symmetric responses.

†Test for symmetric responses at the two time points.

that possible influence still remains unclear: is the supposed stronger influence of the mother a true biologic effect or should bias be considered for that association?

In this study the parental atopy was assessed for the same mothers and fathers at 2 different time points. By comparing the parental response patterns, we could investigate whether there is an information bias in parental questioning regarding atopic diseases.

METHODS

Patients

For a prospective multicenter birth cohort study on atopy in children (the Multicenter Allergy Study), 1314 newborn infants were recruited in 5 German cities during 1990. The details of the study are described elsewhere.²⁰ Briefly, the cohort infants were followed-up at the ages 3, 6, 12, 18, and 24 months. Atopic diseases of the study children were diagnosed by a pediatric allergist. The participation rate at the second birthday of the children was 83%. Informed consent was given by all parents before entering the study.

At birth of the children, the parents filled out a standardized questionnaire about their own atopic diseases and relevant symptoms. Two years later, parents were sent the same atopy questionnaire. At birth 1280 mothers and 912 fathers responded personally. Because our aim was to analyze the response pattern in mothers and fathers and to compare the patterns, we included only families where both parents responded personally. This resulted in an initial 874 parents with both the mothers and the fathers filling out the questionnaire for themselves. Of these 874 parents, 670 parents responded again 2 years later. Some of the parents decided to undergo allergy testing procedures after the start of the study. It can be assumed that their awareness of their own diseases changed, possibly by participation in the study. Those families were excluded from the analysis because the test results could have influenced the parental answers. The remaining 500 mothers and 500 fathers who responded at both time points were included in the analysis.

Prevalences of atopic dermatitis (AD), allergic rhinitis and wheezing, and allergy against food, mite, and cat allergens in parents were determined by the questionnaire. The questions and definitions of the diseases had been described previously.^{20,21} The atopic diseases of the children and parents were summarized into 3 categories: (1) no atopy at all, (2) any of the above-mentioned diseases but not AD, and (3) AD (with or without other atopic diseases). The categories were chosen because AD is the most frequent and most symptomatic manifestation during the first years of life. In this article the term "atopic diseases" refers to these 3 categories.

Statistics

The observed asymmetry of the parental responses regarding the 2 time points was examined by log-linear models with use of GLIM4.²² The overall agreement of the parental responses can be considered as partitioned into a symmetric and an asymmetric part. The agreement of the table is examined for these 2 parts. The symmetry of parental responses was coded by an indicator variable X with 6 levels, as proposed by Agresti²³ and Lindsey²⁴: $\delta_k X(ij = ji)$, where $X(\cdot)$ is the indicator function $X(ij) = X(ji)$ for the i disease categories at the first questioning and the j disease categories at the second questioning. Under the hypothesis of a consistent response pattern, the answers would be symmetric. In the log-linear model this theoretic symmetry is fixed by the variable X . For the examination of the asymmetry (ie, a change above [respectively below] the diagonal of the table) another dummy variable, U , was used.²⁵ It was coded 1 if the parental report classified the child in a higher atopic disease category at the second questioning than at the first. Study center and parental educational level were included as possible factors influencing the symmetry of parental responses. Educational level was defined as highest schooling level of the 2 parents (middle school, high school, higher education). In the analysis the following models were used: basic model, which fixes the theoretic symmetry of the table, $X*CHILD$; model 1, which tests for the asymmetry of the table, $X*CHILD + U$; and model 2, which tests whether the asymmetry of the table is influenced by atopic diseases of the study child, $X*CHILD + U*CHILD$, where "*" specifies main effects and interaction. To examine whether the reliability of parental responses depends on the development of atopic symptoms in the children, the analysis was stratified according to the atopic disease status of the children. The agreement of the responses was tested in each of the 3 strata. The goodness of fit (as change in deviance) of the hierarchical log-linear models was compared and the differences in deviance were tested for significance.²²

The presence of a potential recall bias was also evaluated by means of a logistic regression model: the occurrence of AD in the study child depended on the parental atopy status. Because the purpose of the study was to demonstrate a potential recall bias in parental questioning and not to determine the true effect of parental atopy on the development of atopic disorders in childhood, the effect estimators in the regression analysis were not adjusted for possible covariates or confounders.

RESULTS

Parental responses at the two time points are shown in Table I. The maternal responses at the two questionings tended not to agree ($P = .068$). The differing maternal response pattern was not attributable to the development

TABLE II. Comparison of frequencies of reported parental atopic diseases at two time points (n = 500 mothers and fathers) stratified according to atopic conditions of study child

	Second questioning					
	Mothers			Fathers		
	-	+ No AD	+ With AD	-	+ No AD	+ With AD
First questioning						
Nonatopic study child (n = 181)						
-	107*	11	1	107*	3	3
+ No AD	4	43*	7	6	46*	4
+ With AD	2	2	4* (NS)†	2	4	6* (NS)†
Atopic study child (without AD, n = 217)						
-	137*	8	2	129*	6	-
+ No AD	9	47*	4	12	61*	1
+ With AD	3	-	7* (NS)†	1	1	6* (NS)†
Atopic study child (with AD, n = 102)						
-	58*	2	2	61*	3	4
+ No AD	1	29*	1	-	21*	7
+ With AD	1	-	8* (NS)†	1	-	5* (P = .0002)†

-, No atopic disease; +, atopic disease present.

*Symmetric responses.

†Test for symmetric responses at two time points. NS, No significant asymmetry ($P > .05$).**TABLE III.** Odds ratios of effect of maternal and paternal atopy for development of AD in their children

	Analyzed sample of 500 families (102 children with AD)		Total study sample (231 children with AD)*	
	First questioning	Second questioning	First questioning	Second questioning
Mother nonatopic†	1.0	1.0	1.0	1.0
Mother atopic without AD	1.2	1.3	1.2	1.2
Mother atopic with AD	2.1	2.1	2.5	2.2
Father nonatopic†	1.0	1.0	1.0	1.0
Father atopic without AD	0.7	0.8	1.0	1.1
Father atopic with AD	1.1	3.4	1.6	3.5

*Data about parental symptoms and atopic disorders in their children were available from 1149 mothers and 1146 fathers at first questioning and from 1026 mothers and 963 fathers at second questioning.

†Reference category.

of an atopic disease in the children (Table II, $P = .27$). In contrast, the answers of the fathers were affected by the atopic conditions of the study children. If the child did not have an atopic disease or symptoms except AD, paternal responses were consistent. However, if the child had an atopic illness with marked symptoms (ie, AD in early childhood), fathers gave positive answers significantly more frequently about own atopic diseases at the second questioning (Table II, $P = .0002$). Any association could be excluded between the asymmetric responses and the study center or the parental educational level as possible confounders. The diagnosis of the children was given to parents at the time it was made at any of the follow-up visits. To investigate whether the time between diagnosis and the second questionnaire could influence the responses, we compared the time periods of parents who gave symmetric responses with the periods of parents who gave asymmetric responses (ie, possible recall bias). We observed slightly greater time intervals in mothers and fathers who gave asymmetric responses. However, the difference was not statistically significant (chi-square test: mothers, $P = .41$; fathers, $P = .76$).

The discordance of the responses can also be demonstrated on the basis of effect measures in a logistic regression model. The odds ratios of the effects of parental atopy as risk for the development of an AD in the study child were compared at the two questionings (Table III, modeled separately for the included 500 pairs of parents and the total Multicenter Allergy Study sample, irrespective of whether the questionnaire was filled out personally or by a proxy). In the logistic regression analysis the effects of maternal atopy as a risk factor of atopic disease in the child are similar for the maternal answers at both time points. Regarding the responses of the fathers, however, the odds ratio of paternal atopy was three times higher if the responses of the second questioning were used instead of the first, indicating a substantial recall bias.

DISCUSSION

Atopic family history is regarded as possible risk factor or predictor for atopic disorders, representing a genetic disposition. Statements of family members are gath-

ered but the accuracy and reliability of the data is rarely evaluated, for example, by a retest with an identical questionnaire among the same individuals. In the current study mothers as well as fathers were requested and asked separately about their own atopic diseases within 2 years. The analysis of the parental response pattern revealed no clear evidence for an information bias in maternal statements (ie, mothers reported only slightly more atopic symptoms at the second questioning independently of the atopy status of their children). In contrast, paternal answers were biased by differential misclassification: fathers reported more atopic symptoms at the second questioning if the child had atopic illness with marked symptoms. This indicates an increased sensitivity among fathers after the development of atopic diseases in their children. Fathers of affected children seemed to think more about their disease history than did fathers of unaffected children. This could result in an overestimation²⁶ of the association between paternal atopy and atopic symptoms in their children, as indicated by the much higher effect measures in the logistic regression analysis at the second questioning.

In the literature, the genetic influence of the mother is reported to be stronger than that of the father.^{18,27,28} Analogously, our analysis resulted in a higher odds ratio for maternal than paternal atopy when the first questionnaire data were used. The opposite was found if we used the second questionnaire data. Our aim, however, was not the determination of the true effect of parental atopy on the development of atopic illness in children. The contradictory result reflects the changing responses at the two questionings and may be partly explained by overestimation because of recall bias.

Our results were based on parents who filled out both questionnaires personally. If the remaining parents were also considered, the data indicated an information bias of about the same direction and magnitude (as shown in Table III). The prevalence of atopic diseases in all questioned cohort parents differed to a greater extent both between mothers and fathers and also between the two time points than in the analyzed subgroup. According to the responses to the first questionnaire, 35% of all cohort mothers and 30% of the fathers were atopic at the beginning of the study, but 39% of the mothers and 35% of the fathers were classified as atopic 2 years later. One explanation for the discrepancy between mothers and fathers may be that at the first questioning only 70% of the fathers of the total cohort filled out the questionnaire themselves (of whom 34% reported atopic symptoms), whereas the remaining 30% of paternal responses were given by the mothers (with only 20% of the fathers reported as atopic). In contrast, 98% of the mothers responded personally. The situation that questionnaires are filled out by proxies will probably often occur. This may lead to an underreporting of disorders comparable to our findings when the mothers responded instead of the fathers. It can also be speculated whether the higher prevalence of parental atopy at the second questioning may be a result of the participation in the study, favoring a better recall. A

real increase in the prevalence of atopic diseases in adults within only 2 years seems very improbable.

To evaluate such associations, the valid parental atopic conditions must be ascertained. The parental atopy status is used to predict whether a child is at risk for development of an atopic disease. When such criteria are applied to select children for intervention studies and for inconvenient and expensive preventive measures, a bias as described in this article must be taken into account.

On which survey responses should future analysis be based? Our findings indicate that the occurrence and the magnitude of the recall bias described seem to depend on the questioning context (eg, the relationship among the relatives and the time point of assessment). At the birth of the child, parents are still unaware of the child's future atopy status. At that time parental responses are obviously less influenced in a certain direction. Some nondifferential underreporting must be assumed, which can result in conservative effect estimation. But, if parents are asked after the child has developed atopic symptoms, a recall bias must be considered. The results may be distorted toward an overestimation of the effect, especially among fathers. The knowledge of the diagnosis may increase recall among the parents of the affected children, whereas parents of unaffected children may not recall their disease history well. Especially in case-control and cross-sectional studies a recall bias must be considered for the association of family history and atopy in children when relative disease risks are estimated. In prospective studies such as ours in which parents are asked several times, the estimation of relative disease risks can be allowed for the changes in the parental response pattern. But it must be considered thoroughly which questioning data is used in the analysis to avoid substantial information bias.

REFERENCES

1. Bousquet J, Michel F-B. Predictors of risk for allergy. *Intest Immunol Food Allergy* 1995;34:93-104.
2. Croner S, Kjellman N-IM. Development of atopic disease in relation to family history and cord blood IgE levels: eleven-year follow-up in 1654 children. *Pediatr Allergy Immunol* 1990;1:14-20.
3. Odelram H, Björkstén B, Leander E, Kjellman N-IM. Predictors of atopy in newborn babies. *Allergy* 1995;50:585-92.
4. Bergmann KE, Bergmann RL, Schulz J, Graß T, Wahn U. Prediction of atopic disease in the newborn: methodological aspects. *Clin Exp Allergy* 1990;20(3 Suppl):21-6.
5. Marsh DG, Meyers DA, Bias W. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981;305:1551-9.
6. Diepgen TL, Blettner M. Analysis of familial aggregation of atopic eczema and other atopic diseases by odds ratio regression models. *J Invest Dermatol* 1996;106:977-81.
7. Abdulrazzaq YM, Bener A, Debuse P. Association of allergic symptoms in children with those in their parents. *Allergy* 1994;49:737-43.
8. Åberg N. Familial occurrence of atopic disease: genetic versus environmental factors. *Clin Exp Allergy* 1993;23:829-34.
9. Phillips PH, Linet MS, Harris EL. Assessment of family history information in case-control cancer studies. *Am J Epidemiol* 1991;133:757-65.
10. Khoury MJ, Flanders WD. Bias in using family history as a risk factor in case-control studies of disease. *Epidemiology* 1995;6:511-9.
11. Harlow SD, Linet MS. Agreement between questionnaire data and medical records: the evidence for accuracy of recall. *Am J Epidemiol* 1989;129:233-48.
12. Linet MS, Harlow SD, McLaughlin JK, McCaffrey LD. A comparison of

- interview data and medical records for previous medical conditions and surgery. *J Clin Epidemiol* 1989;42:1207-13.
13. Vervloet D, Haddi E, Tafforeau M, Lanteaume A, Kulling G, Charpin D. Reliability of respiratory symptoms to diagnose atopy. *Clin Exp Allergy* 1991;21:733-7.
 14. Kuehr J, Frischer T, Karmaus W, Meinert R, Barth R, Herrman-Kunz E, et al. Early childhood risk factors for sensitization at school age. *J Allergy Clin Immunol* 1992;90:358-63.
 15. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;23:504-11.
 16. Infante-Rivard C. Childhood asthma and indoor environmental risk factors. *Am J Epidemiol* 1993;137:834-44.
 17. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94:895-901.
 18. Ruiz RGG, Kemeny DM, Price JF. Higher risks of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy* 1991;22:762-6.
 19. Happle R, Schnyder UW. Evidence for the Carter effect in atopy. *Int Arch allergy Appl Immunol* 1982;68:90-9.
 20. Bergmann RL, Bergmann KE, Lau-Schadensdorf S, Luck W, Danne-mann A, Bauer CP, et al. Atopic diseases in infancy: the German Multi-center Atopy Study (MAS-90). *Pediatr Allergy Immunol* 1994;5(1 Suppl):19-25.
 21. Bergmann RL, Forster J, Schulz J, Bergmann KEB, Bauer CP, Wahn U. Validation of instruments in a multicenter cohort study. *Pediatr Allergy Immunol* 1993;4:130-5.
 22. Francis B, Green M, Payne C, editors. The Glim system: release 4 manual. Oxford: Oxford University Press; 1993.
 23. Agresti A. Categorical data analysis. New York: John Wiley; 1990.
 24. Lindsey JK. Modelling frequency and count data. Oxford: Clarendon Press; 1995.
 25. May SM. Modelling observer agreement—an alternative to kappa. *J Clin Epidemiol* 1994;47:1315-24.
 26. Mertens TE. Estimating the effects of misclassification. *Lancet* 1993;342:418-21.
 27. Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp Allergy* 1996;26:624-9.
 28. Hourihane JOB, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996;313:518-21.

Availability of Journal Back Issues

As a service to our subscribers, copies of back issues of *The Journal of Allergy and Clinical Immunology* for the preceding 5 years are maintained and are available for purchase until inventory is depleted. The following quantity discounts are available: 25% off on quantities of 12 to 23, and one third off quantities of 24 or more. Please write to Mosby, Inc, Subscription Services, 11830 Westline Industrial Dr, St Louis, MO 63146-3318, or call (800) 453-4351 or (314) 453-4351 for information on availability of particular issues and prices. If unavailable from the publisher, photocopies of complete issues may be purchased from Bell & Howell Information and Learning, 300 N. Zeeb Rd., Ann Arbor, MI 48106, (313) 761-4700.