

Prediction of atopic disease in the newborn: methodological aspects*

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Introduction

There appears to be general agreement that atopic manifestations depend upon genetic and environmental factors. The inheritance is believed to be either polygenic [1] or monogenic autosomal dominant [2,3]. Multiple additional factors have been suggested to influence the age of onset, type, severity, duration or recurrence of atopic illnesses.

Recent studies suggest that avoidance of alimentary allergens in early infancy and possibly during pregnancy may have favourable effects on the natural course of atopic disease [e.g. 4–7]. This seems to apply only to infants identified to be at risk because of family history and/or high cord-blood IgE [8–11].

Therefore, a great number of factors have to be considered if we want to predict disease. Most of them cannot be foreseen at all. Our on-going study focuses on the *risk* of developing atopic manifestations following exposure. However, justification for neonatal screening for the *risk* of atopic diseases is still under debate. Before establishing a general recommendation to screen all newborns for their risk of developing atopic illnesses it is necessary to scrutinize the available evidence.

Family history

In their review of 1990 [12], based on a paper by Kjellman [13], Björkstén and Gerrard estimate that 40% of infants and young children will present with some kind of allergic disease at any time and of any duration in early childhood if both parents are atopic. We are aware that the prevalence is highest during early adulthood but, so far, no prediction extends to that age.

The history is taken, usually by interview or questionnaire. The questionnaire of our on-going study contains 30 questions, each with a variable number of choices. By inclusion or exclusion of symptoms, signs or tests the proportion of atopic adults varies by a factor of at least two. According to our criteria, so far about 6.5% of the newborn infants have two atopic parents by history. However, even the way this information is being collected has an impact on the estimated proportion of infants at risk.

Figure 1 presents a profile on who qualifies to be non-atopic depending upon who answers the questions. The average percentage of parents free of atopy ranges between 74 and 90%, just by varying the person interviewed. Is this explained by level of education? Figure 2

presents the answer for hay-fever: mothers underrate the fathers at all levels of education.

Figure 3 shows (i) that we find this tendency in six regions of Germany, (ii) that there are regional differences, and (iii) that mothers alone tend to rate themselves higher with respect to atopy than if both parents answer.

Our questionnaire data also show a consistent increase of atopy with increasing level of education (Fig. 4). This could have three explanations: (i) the ability to comprehend and answer the questions correctly may depend on level of education; (ii) the true prevalence may differ according to educational level; (iii) a combination of (i) and (ii). This problem can only be solved by validating the questionnaire through objective parameters, e.g. Phadia-top®, which is presently in progress.

There are numerous additional problems involved in the collection of a valid history on atopic diseases in the family. At present it appears to be premature to stigmatize a newborn child as being a high risk candidate for atopy. In terms of research, a number of principles should be kept in mind.

- (i) Standardized, elemental questions that include relevant symptoms are essential and should substitute for unstructured medical histories.
- (ii) The persons answering and the circumstances need to be taken into account.

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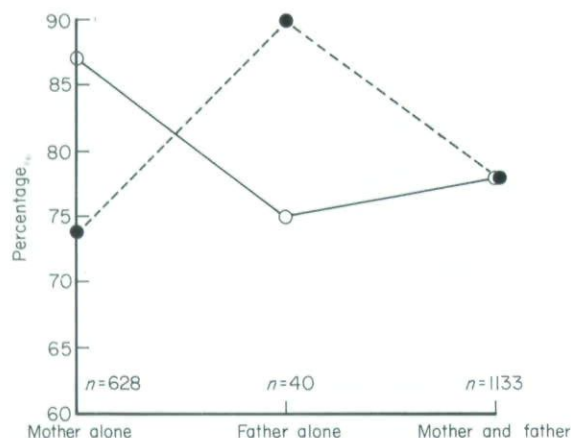


Fig. 1. Percentage of non-atopic mothers (●) and fathers (○) according to who answered the questionnaire.

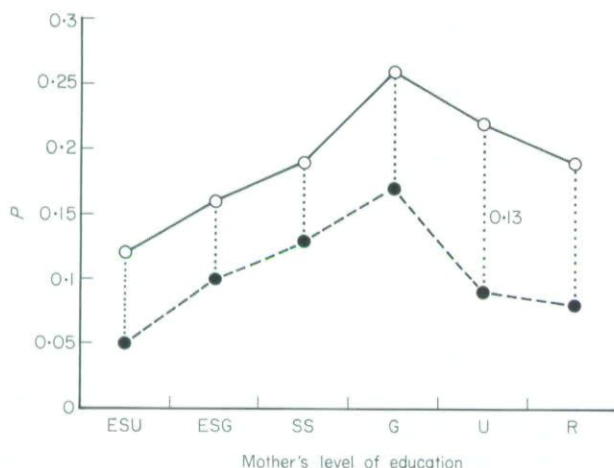


Fig. 2. Prevalence of hay-fever (in fathers) as rated by mothers (●, $n=594$) and fathers (○, $n=1127$) controlling for mother's level of education: ESU, elementary school (ungrad.); ESG, elementary school (grad.); SS, secondary school; G, gymnasium; U, university; R, answer refused.

- (iii) A retest evaluation is required (reliability).
- (iv) The questionnaire or interview has to be validated by external parameters, e.g. Phadiatop.

Retest reliability of our questionnaire—so far only in a subsample of 88 parents 6 months after delivery—demonstrates a 91% agreement with the first results (Fig. 5). Testing parental history of atopy against the results of the Phadiatop test in parents—again, very preliminary data—suggests a sensitivity of the questionnaire of about 80% and a specificity of about 90%. However, Phadiatop may not be the gold standard.

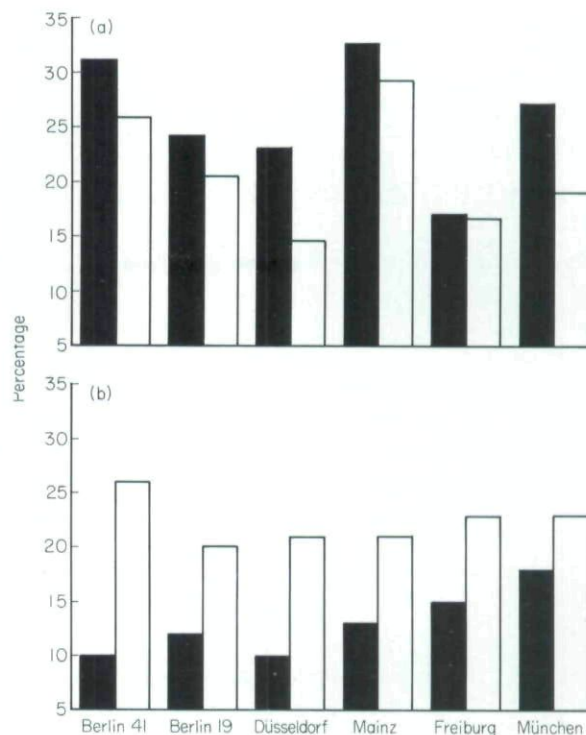


Fig. 3. Fluctuations in proportion of (a) atopic mothers and (b) atopic fathers according to region and who answered the questionnaire: ■ mother alone, or □ mother and father.

The combination of symptoms, signs and tests in the parents which predict later disease in their child should be identified on the basis of manifestations in carefully designed longitudinal studies, applying statistical modelling that takes into account other influential variables simultaneously.

Cord-blood IgE

According to several authors, elevated cord-blood IgE (>0.9 kU/l) accompanies a 3–50-fold rate of atopic manifestations in children [14, 15]. In their recent review [12], Björkstén and Gerrard suggest a very high sensitivity and specificity of neonatal IgE screening. However, from other sources and from our own preliminary results, only a small percentage (about 11%) of infants with a family history of atopy also have elevated values of cord-blood IgE, whereas the prevalence of such values in infants with no recognizable risk on the basis of family history was as high as about 8%. If, under these circumstances, IgE predicted about 94% of later atopy [12], a large overlap between family history and IgE would be expected. However, this is not the case. There is a large discrepancy between the prediction by cord-blood IgE and by family history (Fig. 6).

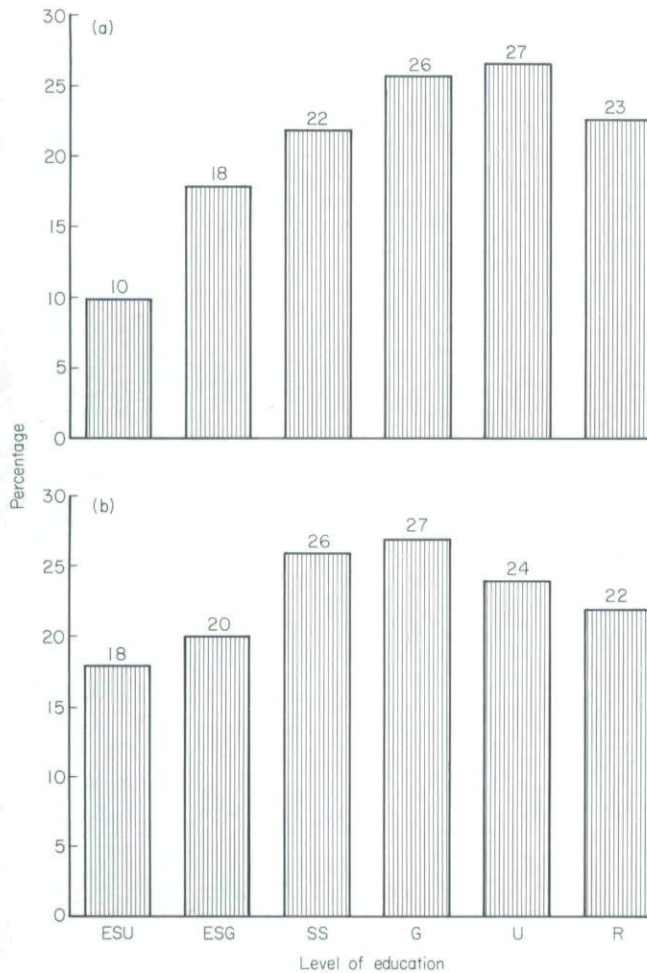


Fig. 4. Self-rated prevalence of atopic disease in (a) fathers ($n=1138$) and (b) mothers ($n=1921$) according to level of education (key as in Fig. 2).

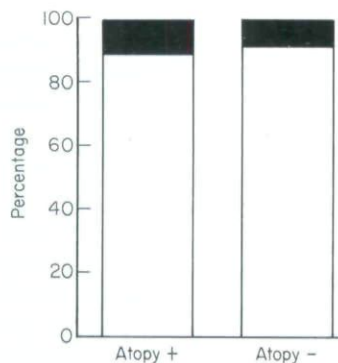


Fig. 5. Repeatability of screening of mothers ($n=88$, $t=6$ months): ■ disagreement; □ agreement. Proportion in agreement = 91%.

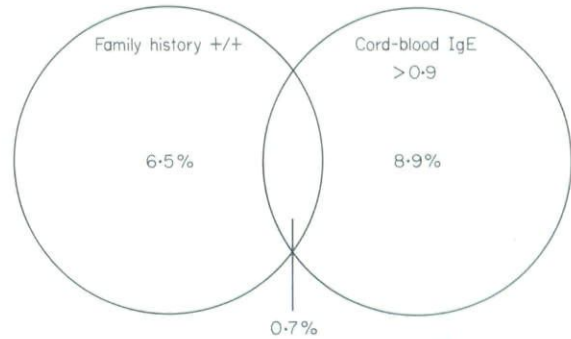


Fig. 6. Proportion of newborn infants estimated to be at risk of atopic disease on the basis of biparental history (6.5%) or elevated cord-blood IgE (8.9%) or both (0.7%).

Table 1. Factors influencing development of atopic disease

Factor	References
Cord-blood markers	[8,17,10,18]
Family history	[15]
Age	[19]
Gender	[19]
Race	[20]
Prematurity	[21]
Perinatal complications and surgery	[12]
Season of birth	[9,22,23]
Feeding habits	[7,5,24,4]
Housing conditions	[16]
Infections	[11,12]
Intensity of exposure to allergens	[25,26]
Early exposure to allergens	[24,26,27]
Tobacco smoke	[16]
Education and social status	[20]
Regionality	[28]

In consequence, the quality of IgE determination in cord blood has to be improved and contamination has to be carefully excluded, e.g. by IgA determination.

In future, a number of additional genetic, biochemical or immunological markers should be investigated for their capacity to predict atopic disease. Potential candidates for these parameters might be cell surface markers like the low-affinity Fc_ϵ -receptor II on lymphocytes or monocytes, its soluble fragment, the IgE-binding factor, lipid mediators in serum or histamine-releasing factors. In addition, DNA-analysis for markers of atopy may be useful as well as the ability of mononuclear cells to produce IgE *in vitro*.

As already mentioned, the predictive value of single cord-blood markers should not be analysed separately from other markers, including family history. Rather, its

relative contribution to the precision of the prediction should be determined.

Other factors besides heredity that are relevant for atopy manifestation

Table 1 compiles a number of factors that have been observed to influence the manifestation of atopy. Most of them have been discovered by one-sided analysis and testing. For example, according to Neuspiel *et al.* [16], atopic manifestations may be more prevalent in smokers than in non-smokers.

At the same time, smoking and atopy are influenced by age, gender, and level of education. In our preliminary data, and in a simple comparison, nearly all atopic criteria appear to be more prevalent in female and male non-smokers than in smokers (Fig. 7). Looking at the most frequent atopic problem, hay-fever, and including level of education as an additional variable, the prevalence of atopy in smokers is not always lower than in non-smokers (Fig. 8). But still we could end up with finding more non-smoking atopics than smoking ones. Before concluding that smoking prevents atopic manifestations, a study design has to include steps permitting causal inferences. We may be dealing here with a 'healthy smoker effect', i.e. atopic persons tend to refrain from smoking because their condition is worsened by smoking, and thus a greater proportion of persons not having any recognizable acute disadvantages from smoking tend to smoke. This would be the reverse conclusion to that which could have been drawn from crude simple analysis.

This is a simple example to explain why it is necessary to take into account all potential factors influencing the manifestation and course of atopic diseases simultaneously, to identify their independence and relative contribution to the whole process. Confounding and

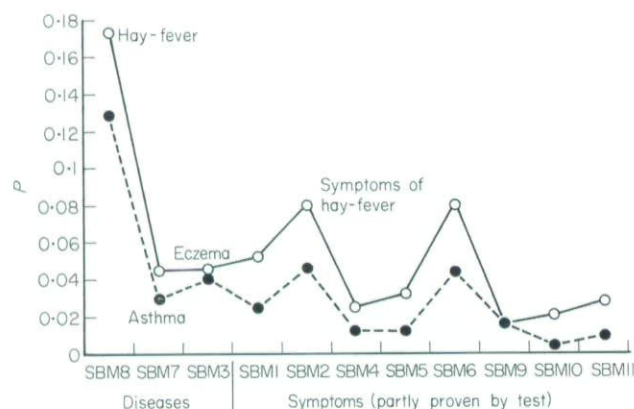


Fig. 7. Profile of atopic symptoms in smoking (●) and non-smoking (○) mothers.

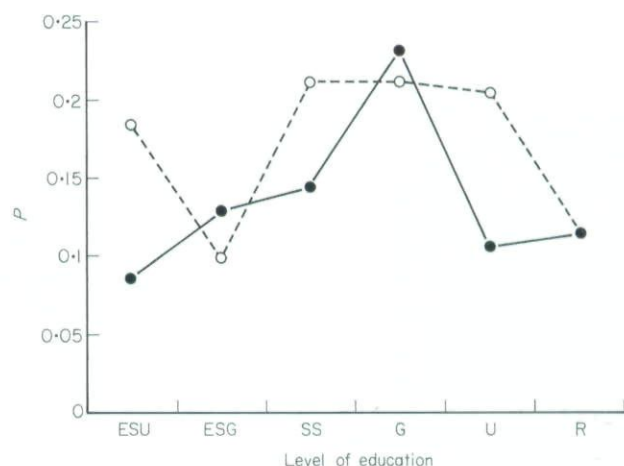


Fig. 8. Prevalence of hay-fever in mothers according to level of education (key as in Fig. 2) and whether smoking (●, $n=528$) or non-smoking (○, $n=1343$).

interaction of some of the factors will also become apparent by such an approach.

Similar principles apply to the outcome variables. Sensitivity and specificity have to be evaluated for symptoms, signs, and tests by retest and external validation. Data collection has to be systematic and elemental.

Conclusion and recommendations

In summary, we cannot yet predict with sufficient certainty who will develop atopic disease of what kind, severity, duration, recurrence and at what age. Also, we have insufficient knowledge of the influence of a number of factors besides genetics, and the kind of preventive measures to be applied. Like other groups in Europe, the U.S.A. and Canada, the authors are involved in specific intervention studies and, like others, they have drawn some conclusions about their study design.

- (i) It is necessary to collect important indicators describing the population from which the sample or cohort is derived. Any deviations from the population have to be taken into account before generalizations can be projected onto the population.
- (ii) If possible, randomization and observer blinding should be employed but, in any case, the observer, the region of investigation, and a number of circumstantial conditions of a study should be included in the statistical analysis.
- (iii) The sample size should be large enough for the number of variables to be considered simultaneously, and for the magnitude of effects that one wants to estimate with sufficient precision.
- (iv) Any drop-outs have to be assessed and the

resulting difference of a cohort or sample to the total population has to be taken into account. Dropping-out in a cohort can be measured continuously and be compensated for by projected oversampling.

- (v) The quality of data collection should be monitored throughout the study and only validated instruments should be applied.
- (vi) In allergic diseases, latency periods have to be considered. This is the domain of prospective studies.
- (vii) Enough time must be allowed for statistical data analysis. Statistical significance is an insufficient criterion to enter into the complex relationships between disposition, exposure and manifestation of allergic diseases.
- (viii) In experiments, random assignment does not guarantee that groups to be compared are identical with respect to variables other than the experimental ones. Confounding remains a problem, even in randomized studies. Therefore, all relevant information about the subjects should be included in the analysis which, in principle, should be a multivariate approach.
- (ix) Statistical analysis should go beyond the question of whether there is an effect or not. If factors other than the index ones are not taken into account, a statistically significant correlation or difference computed may, in reality, be non-existent, and vice versa. An appropriate epidemiological analysis, as already mentioned, puts all potential influences together and estimates the strength, the independence and interaction of all factors involved under '*ceteris paribus*' conditions. Although several software packages facilitate this approach, good epidemiological analyses may require as much time and effort as the collection of the data. This has to be explained as early as in a project application. But, with enough patience on the side of the researchers, the answers will be much more stable and dependable than any statistically significant correlations or differences in two-sided comparisons.

Although epidemiological analysis has been emphasized here in detail, the data analysis should not be handed over to the statisticians. Only a close cooperation between the researchers interested in the subject itself and the methodologists will achieve good results.

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