

Original article

Predictivity of allergic sensitization (RAST) for the onset of allergic diseases in adults

Background: Specific IgE antibodies are often detected without any clinical manifestation of allergies. We aimed to analyse the predictivity of allergic sensitization for incident symptoms of allergic diseases in adults during a 10-year follow-up.

Methods: In 1994/95 specific IgE antibodies against five common inhalant allergens (grass pollen, birch pollen, house dust mite, cat dander and *Cladosporium*) were diagnosed by radioallergosorbent test in 4178 adults aged 25–74 years. A subset of 2656 participants could be re-evaluated in 2004/05. Information on socio-economic factors and medical history, including data on atopic diseases, was assessed by a combination of a personal interview and a self-administered questionnaire. Logistic regression models were applied to study associations between allergic sensitization and incident allergic diseases.

Results: Allergic sensitization was an important predictor for incident hay fever (OR 7.95, CI 95% 4.64–13.62) and asthma (OR 1.82, CI 95% 1.29–2.57). Specific IgE antibodies were mainly related to outdoor allergens (grass and birch pollen) for hay fever and indoor allergens (mite and cat dander) for asthma, while for atopic dermatitis no specific IgE antibodies were identified as major predictors.

Conclusions: Allergic sensitization not only covers clinically apparent allergies, but indicates a prognostic factor for later allergies, even in adulthood.

Y. Schoefer¹, T. Schäfer², C. Meisinger¹, H.-E. Wichmann^{1,3}, J. Heinrich¹, for the KORA study group*

¹GSF - National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg; ²Institute of Social Medicine, Medical University Schleswig-Holstein, Campus Luebeck; ³Institute of Medical Data Management, Biometrics and Epidemiology, Ludwig Maximilians University, Munich, Germany

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Dr Yvonne Schoefer
GSF - National Research Center for Environment and Health
Institute of Epidemiology
Ingolstaedter Landstraße 1
D - 85764 Neuherberg
Germany

*The KORA study group consists of H.-E. Wichmann (speaker), A. Peters, C. Meisinger, T. Illig, R. Holle, J. John and co-workers who are responsible for the design and conduct of the KORA studies.

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Although allergic diseases are very common in both children and adults, epidemiological studies on atopic disorders in adults are less common. Prevalence rates vary between different regions and countries and affect up to 50% of the population (1). The development and severity of atopic diseases depend on a complex interaction between genetic factors, environmental exposure to allergens and nonspecific adjuvant factors such as life-style, tobacco smoke, air pollution and infections starting early in life (2). Besides clinical diagnosis of typical symptoms of hay fever, asthma or atopic dermatitis (AD), IgE antibodies as typical markers for atopic sensitization can be diagnosed by two main techniques, indirectly by skin prick test (SPT) and directly by radioallergosorbent test (RAST). Both tests were found to perform better in the negative than in the positive prediction of hay fever (3). RAST determines allergen-specific IgE antibodies in the serum and, in contrast with SPT, gives a quantitative result of detected IgE antibod-

ies. The validity of RAST as indicator for clinical allergy depends on used cut-off points for RAST-classes (3, 4). However, often high sensitization rates and RAST-classes are found without apparent allergies. We aimed to analyse the predictivity of allergic sensitization diagnosed by RAST regarding incident cases of hay fever, asthma and AD in adults in a 10-year follow-up study.

Methods

Study population and questionnaire

Study participants were evaluated in 1994/95 and 2004/05 in the framework of the KORA project (Cooperative Health Research in the Augsburg Region), a research platform for population based health research in the fields of epidemiology, health economics and health care research in the City of Augsburg and two adjacent counties (5). The study region has a population of about 600 000 of which 430 000 inhabitants were between 25 and 74 years of age in

1994/95. The sample was drawn in a two-stage procedure where first Augsburg city and 16 communities from the adjacent counties were selected by cluster sampling; then age-sex stratified random sampling was performed within each community (5, 6). The participants were sampled through the registration offices and invited to a specific, medically equipped study center. The KORA studies consist of a combination of extended health examinations and questionnaire-based (personal interview and self-administered) evaluations. Of the 4856 participants of the baseline study S3 in 1994/95, 3006 participated in the 10-year follow-up study F3 in 2004/05. Subjects were considered ineligible for F3 if they had died in the meantime ($n = 405$, 8%), lived too far outside the study region or were completely lost to follow-up ($n = 222$, 5%), or had demanded deletion of their address data ($n = 270$, 6%). Of the remaining 3959 eligible persons, 161 could not be contacted, 295 were unable to come because they were too ill or had no time, and 497 were not willing to participate in this follow-up, resulting in a response rate of 76%. For the present evaluation a subgroup of 4178 adults providing information on RAST-sensitization at baseline in 1994/95 with 2656 who could be re-approached 2004/05 was used. Study characteristics and data on baseline and follow-up are given in Table 1. Baseline information on socio-demographic variables, living conditions, risk factors (smoking, alcohol consumption, physical activity etc.), medical history and family history of chronic diseases, medication use and more was acquired by a standardized face to face interview by medical staff. An additional self-administered questionnaire collected data on present health conditions, including respiratory and allergic diseases. Data on atopic diseases in 2004/05 was assessed by self-administered questionnaire, asking: 'Did a doctor ever diagnose the following diseases?: asthma, atopic dermatitis, hay fever'.

Table 1. Baseline study characteristics and comparison of follow-up-participants and -nonparticipants

	Baseline study (S3) 1994/95	Follow-up participants (F3) 2004/05	Follow-up nonparticipants
Variables, % (n/N)	$N = 4178$	$N = 2656$	$N = 1522$
Age (years)	49.4 ± 14.0	47.3 ± 12.9	53.0 ± 15.2
Gender (female)	50.7 (2119/4178)	52.0 (1382/2656)	48.4 (737/1522)
Higher parental education*	43.4 (1815/4178)	48.4 (1285/2656)	34.8 (530/1522)
Smoking	24.8 (1036/4178)	23.5 (624/2656)	27.1 (412/1522)
Allergic sensitization†	31.6 (1305/4126)	32.4 (857/2645)	31.7 (480/1513)
Atopic diseases	30.7 (1127/3676)	30.5 (737/2416)	31.0 (390/1260)
Asthma	2.2 (86/3853)	2.2 (54/2504)	2.4 (32/1349)
Hay fever	14.5 (560/3866)	14.6 (367/2507)	14.2 (193/1359)
Allergies or eczema	23.2 (865/3730)	23.4 (575/2457)	22.8 (290/1273)

*10 years or more.

†IgE positive: at least one RAST $\geq$ class 1.

Allergen-specific IgE antibodies

During the first examination period in 1994/95, blood sample analyses included the detection of specific IgE antibodies against five common inhalant allergens (grass pollen, birch pollen, house dust mite (Der p1), cat dander (Fel d1) and *Cladosporium herbarum*). The standard laboratory procedures (RAST-CAP-FEIA; Pharmacia, Uppsala, Sweden) were performed by Pharmacia Diagnostics in Freiburg, Germany. The detection limit for RAST reactivity was set at 0.35 kU/l. Atopic sensitization was defined to be present if at least one of the five specific IgE antibodies was positive (RAST-class >0).

Statistical analyses

Descriptive statistical analyses and multivariate logistic regression modelling were carried out using SAS (SAS Institute Inc, Cary, NC, USA), version 9.13. Logistic regression analyses were performed to identify the predictivity of allergic sensitization adjusting for potential confounders such as age, gender, education and smoking. The logistic regression models were applied for incident health outcomes of hay fever, asthma and AD 10 years after evaluating the atopic baseline status by RAST and questionnaire. Afterwards the same models were applied to identify the predictivity of sensitization to single aeroallergens.

Results

A total of 4178 adults aged 25–74 years could be recruited for the baseline RAST-evaluation in 1994/95. Four thousand one hundred and twenty-six provided information on all five tested allergens (Table 2). About one-third of the participants were sensitized to any allergen with highest rates for house dust mite and grass pollen. The followed up study population of 2656 adults (Table 1) who were taken further analyses showed similar rates.

The incidence of hay fever from 1994/95 to 2004/05 was 3.9%, being highest among the youngest adults (Fig. 1). In contrast, for asthma, the incidence increased by age with an overall incidence of 6.5% for the 10-year-follow-up period. Allergic sensitization was an important predictor for existing (lifetime prevalence) and incident asthma and hay fever (Table 3, Fig. 2A–C). Rates of atopic diseases were slightly influenced by age and gender with all diseases being more frequent among female adults (Table 3). Hay fever and AD was more common in higher educated adults, while results for

Table 2. Data on allergic sensitization at Baseline (1994/95)

RAST-classes (IgE-levels)	House dust mite	Grass pollen	Birch pollen	Cat allergen	<i>Cladosporium</i>	Any allergen
1 (>0.35 kU/l)	5.0 (208/4175)	3.4 (140/4154)	2.2 (90/4128)	2.9 (121/4172)	1.0 (43/4144)	12.7 (522/4126)
2 (>0.7 kU/l)	6.6 (275/4175)	5.2 (214/4154)	3.9 (160/4128)	3.4 (141/4172)	0.5 (21/4144)	15.7 (648/4126)
3 (>3.5 kU/l)	3.1 (131/4175)	4.8 (201/4154)	3.6 (147/4128)	1.6 (68/4172)	0.1 (3/4144)	10.9 (450/4126)
≥ 4 (>17.5 kU/l)	1.1 (44/4175)	3.2 (132/4154)	3.4 (139/4128)	0.7 (27/4172)	0.1 (3/4144)	6.9 (285/4126)
Total	15.8 (658/4175)	16.5 (658/4154)	13.0 (536/4128)	8.6 (357/4172)	1.7 (70/4144)	31.6 (1305/4126)

Variables, % (n/N).

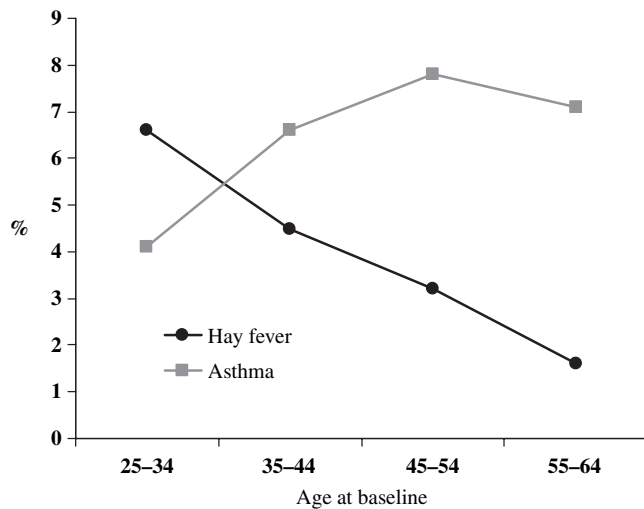


Figure 1. Age-dependent 10 year incidence of asthma and hay fever.

asthma were independent from the education. Rates for hay fever were higher among those living in the city of Augsburg.

When comparing single aeroallergens related to incident cases of hay fever, asthma and AD, clear pictures could be seen for all three diseases. Incident asthma was mainly associated with indoor allergens of house dust mite and cat dander (Fig. 2B), while allergic sensitization did not seem to play any important role for the prediction of AD later in adulthood (Fig. 2C). Incident hay fever was strongly associated with outdoor allergens tested by grass and birch pollen, but additionally seemed to be related to cat sensitization (Fig. 2A). When applying the same logistic regression models to the single aeroallergens as to sensitization in general, outdoor allergens for incident hay fever and indoor allergens for incident asthma remained relevant predictors (Table 4).

Discussion

Radioallergosorbent test-sensitization has an important impact on the predictivity of incident hay fever and asthma, even in adults. We could demonstrate a clear association of sensitization to outdoor allergens with the development of hay fever and a significantly increased risk of doctor-diagnosed asthma when sensitized to

Table 3. Logistic regression models for follow-up health outcomes

	Follow-up 2004/05							
	Lifetime prevalence				Incidence			
	Adjusted model 1*		Adjusted model 2†		Adjusted model 1*		Adjusted model 2†	
	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%
a) Hay fever (doctor-diagnosed)	<i>n/N</i> = 317/2294				<i>n/N</i> = 76/1960			
Sensitization	19.97	13.75–29.0	20.83	14.27–30.40	7.70	4.51–13.17	8.05	4.69–13.82
Covariates								
Age	0.75	0.66–0.85	0.73	0.64–0.84	0.68	0.54–0.85	0.65	0.51–0.83
Gender (female)	1.53	1.17–2.00	1.59	1.21–2.10	1.68	1.04–2.72	1.66	1.02–2.70
Higher education			2.00	1.48–2.66			1.39	0.84–2.31
Smoking			0.41	0.29–0.58			0.45	0.25–0.83
Place of residence (urban/rural)			1.58	1.20–2.08			1.92	1.18–3.12
b) Asthma (doctor-diagnosed)	<i>n/N</i> = 178/2294				<i>n/N</i> = 145/2245			
Sensitization	2.08	1.52–2.85	2.07	1.51–2.84	1.81	1.28–2.56	1.82	1.29–2.57
Covariates								
Age	1.26	1.09–1.46	1.27	1.09–1.48	1.23	1.05–1.44	1.21	1.02–1.44
Gender (female)	1.14	0.83–1.55	1.15	0.84–1.57	1.13	0.80–1.59	1.12	0.79–1.58
Higher education			1.02	0.74–1.40			0.87	0.61–1.23
Smoking			1.09	0.76–1.58			1.08	0.72–1.62
Place of residence (urban/rural)			1.22	0.89–1.66			1.18	0.84–1.65
c) AD (doctor-diagnosed)	<i>n/N</i> = 66/2253				<i>n/N</i> = 27/1774			
Sensitization	1.38	0.84–2.29	1.34	0.81–2.22	0.75	0.31–1.79	0.72	0.30–1.74
Covariates								
Age	0.75	0.59–0.95	0.78	0.61–1.00	0.87	0.62–1.24	0.92	0.63–1.33
Gender (female)	2.58	1.48–4.47	2.62	1.51–4.58	2.35	1.02–5.43	2.50	1.08–5.81
Higher education			1.95	1.12–3.38			2.19	0.94–5.11
Smoking			0.55	0.28–1.07			0.64	0.24–1.75
Place of residence (urban/rural)			1.30	0.79–2.14			1.47	0.68–3.19

*Age, gender.

†Age, gender, education, smoking, place of residence (urban vs rural).

AD, atopic dermatitis. Significant values are indicated in bold.

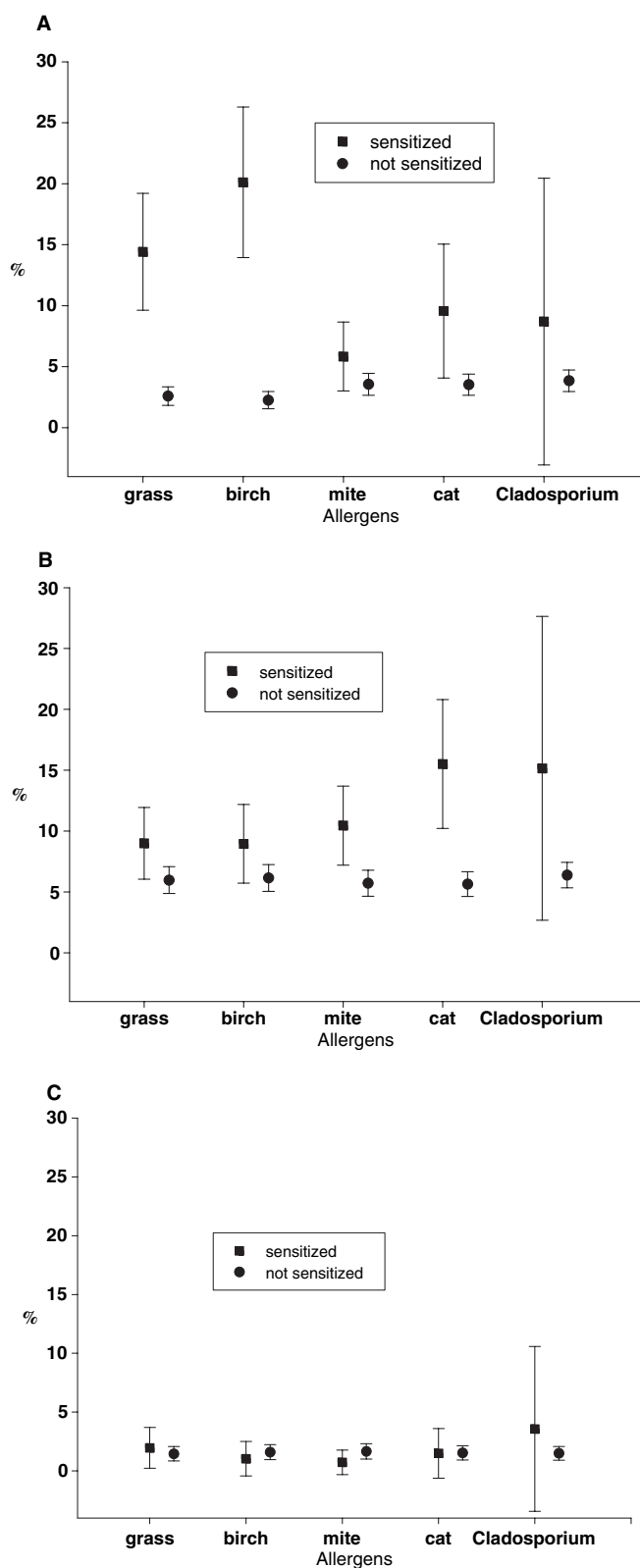


Figure 2. Incident cases of atopic diseases in adults within a 10-year follow-up. (A) Incident cases of hay fever; (B) incident cases of asthma; (C) incident cases of atopic dermatitis.

Table 4. Single aeroallergens related to incident health outcomes up to 2004/05

	Hay fever (doctor-diagnosed) <i>n/N</i> = 76/1960		Asthma (doctor-diagnosed) <i>n/N</i> = 145/2245		Atopic dermatitis (doctor-diagnosed) <i>n/N</i> = 27/1774	
	OR	CI 95%	OR	CI 95%	OR	CI 95%
Sensitization	8.05	4.69–13.82	1.82	1.29–2.57	0.72	0.30–1.74
Grass pollen	2.16	1.11–4.20	1.16	0.68–1.97	2.02	0.59–6.89
Birch pollen	7.84	4.16–14.76	0.99	0.57–1.71	0.42	0.08–2.24
House dust mite	0.72	0.35–1.46	1.64	1.05–2.55	0.43	0.09–1.97
Cat dander	1.34	0.59–3.03	2.63	1.59–4.35	1.19	0.25–5.59
<i>Cladosporium</i>	1.00	0.19–5.23	1.26	0.44–3.58	2.47	0.25–24.41

Logistic regression models adjusted for age, gender, education, smoking, place of residence (urban vs rural), specific allergens.

indoor allergens. For the incidence of asthma and hay fever, age-dependent but contrariwise trends can be seen with higher incidence of hay fever the younger and higher incidence of asthma the older the population is. Our results on incidence and age-trends are in line with other studies on incidence and remission of allergic rhinitis (7–9). However in our evaluation, we could not analyse remission rates as for analyses in 2004/05 we asked for ‘Did a doctor ever diagnose the following diseases?: (asthma, atopic dermatitis, hay fever)?’ and not whether the diseases resolved. Overall, longitudinal adult studies on allergic sensitization and outcomes are rare. Most research groups focus on children as in the prevalence and incidence of allergic diseases children still represent the biggest part (10–12). According to some evaluations, the epidemic may have reached a plateau by now (13, 14). Nevertheless, allergic illnesses especially asthma are common and costly diseases (10) and have a substantial impact on children’s and adults’ health.

In the clinical practice, the main method used to diagnose allergic sensitization is the SPT which is a test performed quickly and easily. In contrast with the RAST SPT is not able to give a clear quantitative result of allergen-specific IgE antibodies. Similar to RASTs the SPT can be positive without apparent allergies. In terms of predictivity for an onset of allergic diseases, RAST gives a more evident perspective with higher RAST-classes or IgE-values indicating higher risks for the development of allergic diseases. However, a study of Schäfer et al. (3) pointed out that the capability in predicting hay fever cases depended highly on chosen cut-off points for RAST reactivity with both tests (RAST and SPT) reaching similar power when using a cut-off point of 1.5 kU/l for RAST.

Allergic diseases have an important influence on the quality of life, social and economic aspects, working absence and mortality (10). A difficult point is to find adequate prevention strategies when knowing that someone is predisposed. Especially as studies are highly

discordant concerning influencing factors. In particular related to pet contact, no clear advice can be given as some studies promote the avoidance of pets while other studies indicate that children who grew up in homes with cats and/or dogs developed less atopic diseases as they grew older (11, 12, 15–19). In contrast, avoidance strategies for other allergens (e.g. house dust mite) have shown clinical benefits on preventing asthmatic symptoms (20). The prognostic factors seem to change by age. Overall, most frequently accounted factors are atopy in the family, gender, day-care attendance, siblings, birth weight, breastfeeding, early respiratory infections, living in damp houses, contact with pets, smoking in the family, own smoking, education, environmental conditions and allergenic sensitization (7, 12, 18, 19, 21–25). The effect of atopic family history is constant, while several risk factors known for early development of allergic diseases disappear later in childhood or adulthood and the effect of sensitization to specific allergens is leading (12). In line with other studies (26–33), in our study we could find that sensitivity to house dust mite and cat were significant risk factors for asthma. Hay fever not surprisingly was mainly associated with outdoor allergens (28). When looking at the crude association in Fig. 2, cat sensitization showed a strong influence too. These findings are similar to those of Bodtger et al. (8) who only found significant associations between outdoor allergens when looking at rhinitis symptoms to summer pollens (hay fever) while additionally finding associations to cat allergens and house dust mite when extending to associations to allergic rhinitis symptoms in total. For our multivariate analyses we adjusted for each tested allergen to avoid overestimations because of cross-reactivity. That however might have led to an underestimation of single allergens. Additionally, the possible influence of other allergens we did not test for has to be accounted for, e.g. food allergens, dog dander, other mites and cockroach. However, the RAST panel of five allergen-specific antibodies tested for is representative for the most common German allergens. Cockroaches for example are predominant allergens exposed to in the US

(27, 34) while they are not in Germany (27, 34–36). In a previous study on house-dust samples (35), cockroach allergens were below detection limit in 93% of the total samples. Similarly, sensitization to Ambrosia, mugwort and storage mite is not common in Germany, while specific IgE antibodies against *Cladosporium* is, but in <2%. Our study has further limitations. Information on atopic outcomes is exclusively questionnaire-based. Recall bias has to be accounted for. But as we asked for doctor-diagnosed asthma, hay fever and atopic dermatitis a potential overestimation of cases is reduced. Nevertheless, we do not know how much reported hay fever really is hay fever or how much asthma really is attributable to atopy. Some studies describing the association of asthma and atopy (defined by SPT or elevated IgE antibodies) concluded that an average of 30–40% of asthma cases would be attributable to atopy, in both adults and children (37, 38). Main strengths of our study are a considerable population-based sample size covering several adult age-groups, the enclosed broad measurement of the most common specific IgE antibodies and a long follow-up time of 10 years for calculating incidence rates in adults.

Conclusion

Radioallergosorbent test-sensitization not only covers clinically apparent allergies, but indicates a prognostic factor for later allergies, even in adulthood. The definition of RAST-classes should endorse and support risk assessment and prevention programmes for allergic diseases.

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