Mechanisms of Allergy – Short Communication

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2017;173:99–104
DOI: 10.1159/000475499

Received: January 19, 2017
Accepted after revision: April 5, 2017
Published online: June 28, 2017

Influence of Intrinsic and Lifestyle Factors on the Development of IgE Sensitization

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Keywords

Allergen sensitization · Antigens/allergens · Childhood · Environmental factors · Epidemiology · Farm environment · IgE antibodies · Microarray · Molecular diagnostics

Abstract

Background: IgE sensitization is a prerequisite for the development of allergic symptoms. The investigation of factors influencing the development of IgE is therefore crucial for understanding the onset of allergic diseases. ***Methods:*** This epidemiological study investigated personal, intrinsic, and lifestyle factors in a nonselected cohort of 501 Austrian adolescents (aged 12–21 years). IgE levels to 112 allergen molecules were analyzed in the serum of participants using the ImmunoCAP ISAC®. Allergic sensitization, IgE levels to single allergens, and ISAC score sums were correlated with results obtained from a questionnaire. ***Results:*** In this adolescent cohort, male participants showed a higher sensitization frequency (56.8%) compared to females (50.9%) and significantly increased IgE levels to profilins. Underweight subjects demonstrated a stronger IgE sensitization. Family size inversely correlated with IgE levels to PR-10 allergens, and predominately paternal allergies were a predictive factor for IgE sensitization in the children. Vaccination, breastfeeding, and delivery mode showed no influence, while a highly protective effect was observed for growing up on a farm. Of all of the investigated lifestyle factors, only smoking significantly influenced the risk for IgE development. Participants with moderate frequencies of colds showed increased sensitization levels. ***Conclusion:*** A hereditary predisposition and lifestyle factors such as a farming environment, smoking, family size, body weight, or frequency of colds significantly influenced the development of allergen-specific IgE in this cohort of adolescents.

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Introduction

The incidence of IgE sensitization and allergic diseases has been on the rise in the past decades [1]. Countries favoring a "westernized" lifestyle seem to be especially affected, and factors influencing this development are

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widely discussed in the literature [2]. Besides anamnesis, IgE sensitization represents a hallmark of allergy diagnosis using either extract-based tests or single, purified allergen molecules. The testing of defined allergen components allows a more precise diagnosis regarding symptom severity and discrimination of IgE cross-reactivity versus cosensitization [3]. In addition, multiplex technologies permit the simultaneous testing of allergen panels using minute amounts of serum. The onset of IgE sensitization has been linked to several factors, and the influences of a hereditary predisposition and a farming environment were identified in a number of studies [4–7]. The impacts of lifestyle on allergic disease is, however, frequently controversially discussed [1]. Therefore, epidemiologic investigations of well-defined study cohorts are needed to shed light on the development of allergic diseases and potentially contribute to the identification of preventive measures.

Methods

Serum samples from a cohort of 501 nonselected Austrian adolescents (aged 12–21 years) were analyzed for IgE to 112 single components using the ImmunoCAP ISAC® [8]. Personal data and lifestyle information were assessed by a questionnaire and correlated with sensitization data. In order to reflect the number of different sensitizations as well as IgE levels, we established the ISAC score sum for each individual, ranging from 0 (nonsensitized) to 39 (high IgE levels in all investigated allergen source families). Detailed information on study design, IgE sensitization, lifestyle data, and statistical analysis can be found in online supplementary Methods, Table E1, and Figure E1 (for all online suppl. material, see www.karger.com/doi/10.1159/000475499).

Results

Personal Data

In this cohort of 501 adolescents, a general sensitization rate of 53.5% was detected by means of ImmunoCAP ISAC® analysis [8]. Additional data regarding the study population is displayed in Figure 1a. A higher sensitization prevalence among males (56.8%) compared to females (50.9%), as well as a higher mean ISAC score sum (4.1 for male vs. 3.4 for female) was detected, but was not statistically significant. Significantly higher ISAC standardized units (ISU) were found for profilins Mer a 1, Bet v 2, and Hev b 8 among male participants ($p < 0.032$). No correlation of age and body height with IgE sensitization, ISAC score sum, or ISU levels to single allergens was observed. Only the height of girls correlated weakly, but significantly, with the ISAC score sum ($p = 0.020$, rho = 0.14). Negative correlations were identified between BMI-for-age percentiles and IgE levels to grass pollen allergens and Api g 1 ($p < 0.020$, rho <–0.10). Female and male participants showed no difference for BMI-for-age percentiles. In the pairwise comparison of ISAC score sum and categories of BMI-for-age percentiles, higher but not significantly different values were observed for participants <5th percentile compared to those in the 5th to 85th percentile ($p = 0.061$). However, a statistically significant difference was found between adolescents <5th percentile and those ≥85th percentile ($p = 0.046$; Fig. 1b). Significant differences among BMI-for-age percentile groups were observed for sensitization to Phl p 1, 4, 12, and profilins ($p < 0.040$).

Family Size and Hereditary Allergy Predisposition

Eighty-nine percent of participants had at least 1 sibling and family sizes were between 3 and 6 individuals for 89.4% of the participants. No differences in IgE sensitization were found between only children and those with siblings, or with regard to family size. However, slightly negative correlations were observed between the number of siblings and IgE to PR-10 allergens ($p < 0.0037$, rho <–0.13). Subjects with at least 1 allergic family member ($n = 245$) had a sensitization prevalence of 59.6%, while those without ($n = 222$) showed a significantly lower atopy rate of 47.7% ($p = 0.012$) as well as ISAC score sum ($p = 0.002$). Interestingly, this also holds true when exclusively the father but not when only the mother was allergic (Fig. 1c).

Early Life Influences and Lifestyle Factors

Participants reported whether they had been vaccinated with standard vaccines, were born by caesarean section, and breastfed as infants. No differences between the respective groups in terms of IgE sensitization were observed. Participants who grew up on a farm showed a reduced sensitization rate of 45.5% (vs. 55.7% for those who did not grow up on farms), which was not statistically significant ($p = 0.066$). However, farm exposure resulted in a significantly reduced ISAC score sum ($p = 0.004$), and reduced IgE levels to PR-10 and grass pollen allergens ($p < 0.007$).

No difference in IgE sensitization was found with regard to alcohol consumption. Among the 46 female participants using hormonal contraceptives, no disparity in IgE sensitization was observed. In our study cohort, diet, exposure to passive smoke or air pollution, time spent outside, physical activity, stress, or sleep were not subjec-

	Female	Male	Total
Study participants, *n* (%)	279 (55.7)	222 (44.3)	501 (100)
Atopic individuals, *n* (%)	142 (50.9)	126 (56.8)	268 (53.5)
Median ISAC score sum (interquartile range)	1.0 (0.0 – 5.0)	2.0 (0.0 – 6.0)	1.0 (0.0 – 6.0)
Mean age, years (range)	15.3 (150 – 184)	15.1 (12 – 20)	15.2 (12 – 21)
Mean height, cm (range)	166.2 (150 – 184)	172.4 (151 – 190)	169.4 (150 – 190)
Mean weight, kg (range)	54.7 (36 – 152)	60.6 (32 – 100)	57.4 (32 – 152)
Median BMI-for-age percentile (interquartile range)	41.2 (18.9 – 61.4)	46.0 (20.0 – 71.2)	43.4 (19.1 – 65.4)
Participants <5th percentile, *n* (%)	15 (5.5)	17 (7.9)	32 (6.6)
Participants 5th to 85th percentile, *n* (%)	237 (87.8)	174 (80.5)	411 (84.6)
Participants ≥85th percentile, *n* (%)	18 (6.7)	25 (11.6)	43 (8.8)

a

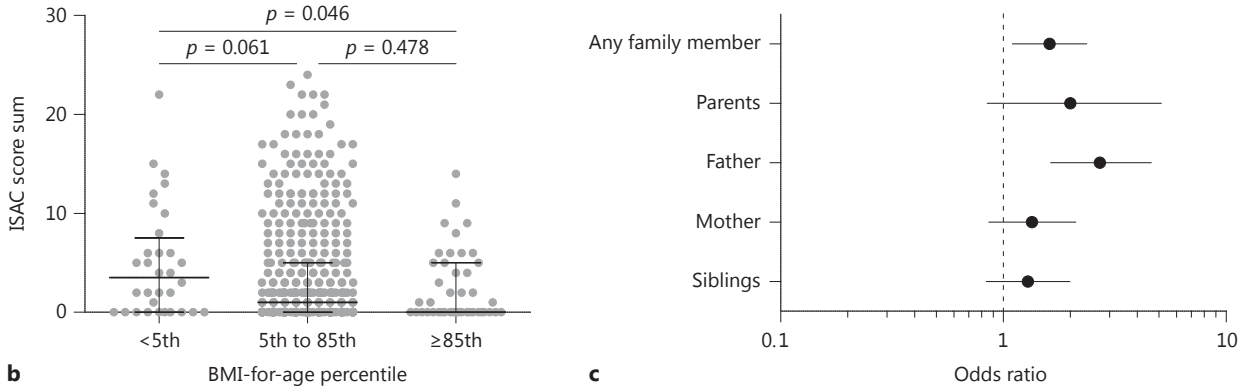

Fig. 1. Study population, BMI-for-age percentiles, and influence of allergic family history. **a** Personal data of the adolescent study cohort. **b** BMI-for-age percentiles according to Barlow [32] and ISAC score sums. Lines indicate the median with interquartile ranges; dots represent the ISAC score sums of individual participants. **c** Association of IgE sensitization of the study participants versus existing allergies among family members is given as the odds ratio with 95% confidence interval.

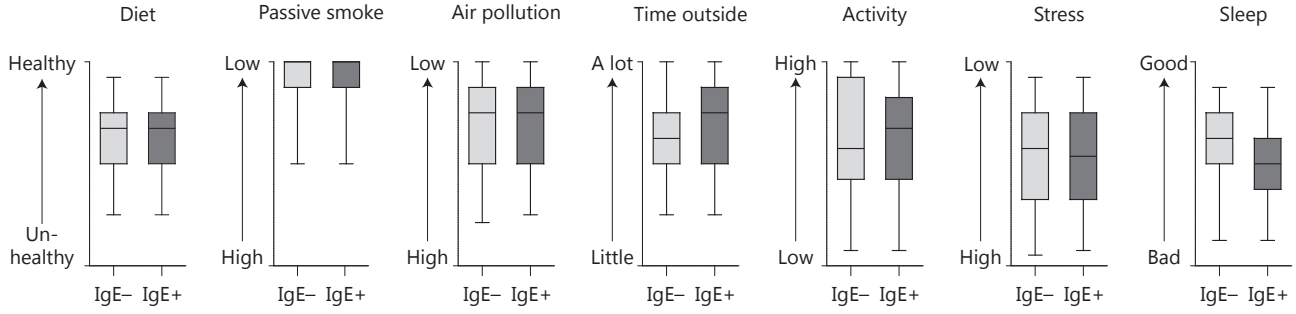

Fig. 2. Lifestyle factors reported from nonsensitized (IgE–) and sensitized participants (IgE+). The boxes indicate the 25th to 75th percentile; horizontal lines indicate the median; whiskers indicate the 5th and 95th percentiles.

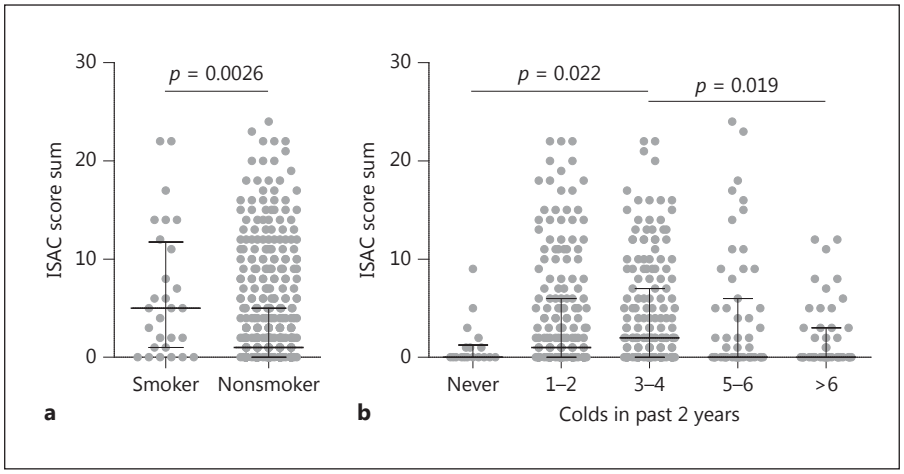

Fig. 3. Influence of smoking and having a cold. **a** Study participants were categorized into smokers and nonsmokers, and the respective ISAC score sum values are depicted. **b** The frequency of having a cold in the past 2 years (never to >6 times) plotted against the ISAC score sum.

tively ranked differently between sensitized and nonsensitized individuals (Fig. 2). The number of participants reporting that they are smokers was rather low (n = 28), yet this translated into an increased sensitization rate (78.6%) and an increased odds ratio for being sensitized (p = 0.006, OR = 3.38). Also, the ISAC score sum (Fig. 3a) and ISU levels were significantly higher among smokers. The frequency of having a cold revealed a difference in ISAC score sum. Interestingly, individuals stating that they had never had a cold within the preceding 2 years, as well as those with the highest frequency (>6×) showed significantly decreased IgE levels compared to those who indicated that they had been affected 3–4 times (Fig. 3b).

Discussion

As part of this study, the ISAC score sum was established to account for the number of sensitizations to single allergens and their ISU levels. Thus, a single value per subject was generated, allowing a more precise representation of the overall sensitization status compared to exclusive disjunction (yes/no judgement). In contrast to the evaluation of allergic symptoms, this study design allowed a detailed and specific measurement of IgE as a precursor of allergic diseases [9].

In line with previous studies [10–13], a higher sensitization frequency among male participants was noted. Interestingly, the preliminary data of Scala et al. [14] were confirmed, suggesting that male individuals have significantly higher IgE levels to profilin. The presented adolescent study cohort showed a trend towards gender discrepancies, which might become more pronounced with age as male IgE levels typically peak 10 years later [15]. We observed low correlations of female body height and ISAC score sum, as well as BMI-for-age percentiles and ISU values to predominately grass pollen allergens. An increased ISAC score sum for underweight participants was observed, which contrasts with the results from a Danish adult study, suggesting a decreased OR for IgE sensitization in underweight women but not men [12]. Other studies highlighted the relevance of an elevated body weight in childhood and increased allergy risk at a later stage [16–18]. While results indicate that body dimensions play a certain role in allergy, more detailed lifetime analyses are needed. Analogous to previous studies, lower IgE levels were found among participants with more siblings [2, 19]. While a hereditary component was clearly confirmed in our cohort [20–22], allergies of fathers, but not mothers, seemed to be the major confounding factor for IgE development in their offspring. Previous studies suggested that predominately maternal conditions play an important role in IgE production and asthma development in the offspring [23, 24]. To the best of our knowledge, this represents the first study showing that paternal allergies represent the most important hereditary impact for IgE sensitization.

Early life influences, such as standard vaccines, caesarean delivery, and breastfeeding, did not significantly affect IgE sensitization in our cohort. These observations should, however, be noted with caution, since the number of individuals per group was unbalanced. The German MAS-90 study reported decreased sensitization rates in vaccinated children [25], while in our cohort the few individuals (n = 24) who were not vaccinated also demonstrated a sensitization rate >50%. Earlier studies, includ-

ing higher numbers of participants born by cesarean, showed a significantly increased risk for atopy for this delivery mode [26]. A protective effect of breastfeeding on the development of allergic diseases has been suggested [27, 28]. In our study, the majority of participants were breastfed, however this did not translate into lower IgE levels. As another study also reported no association between exclusive breastfeeding and sensitization until 7 years [29], the finding could be explained by the fact that breastfeeding does not necessarily confine IgE development, but rather shows a protective effect regarding clinical symptoms. However, it should also be kept in mind that the information regarding breastfeeding was self-reported by the subjects, with the associated limitations in accuracy. In line with the "hygiene hypothesis," the beneficial effect of growing up on a farm was confirmed within this work [5–7]. The difference was particularly pronounced regarding sensitization to PR-10 and grass pollen allergens, which might relate to high pollen exposure among farm children and/or the general high sensitization rate towards these sources [8].

Among analyzed lifestyle aspects, only smoking showed a significant difference for IgE sensitization and frequently involved allergen molecules with very low sensitization rates [8]. An association of smoking and increased incidence of asthma and wheeze has been shown before [30], but an association between never smoking and a higher risk of atopy has also been reported [12, 13]. Despite the low number of smokers, we found a statistically significant effect, emphasizing the negative impact of smoking already in this age group. Previous studies have shown an association between atopy and alcohol intake, and passive smoke exposure and sensitization to some allergen sources as well as time spent outdoors contributing to the development of allergies [2, 12, 20, 31]. However, none of these factors caused statistically significant differences. Nevertheless, a trend was observed indicating that sensitized individuals spent more time outside, performed more sports, and reported poorer sleep than nonsensitized subjects. Participants stating to have a cold on a moderate basis had a significantly increased ISAC score sum compared to those that did not suffer from colds or individuals with a high frequency of episodes. This bimodal protection profile could be explained by a very robust immune system among those who very rarely experience a cold and have no allergies, or a favored Th1 response of the immune system among those frequently suffering from colds.

To conclude, this epidemiologic study investigated several intrinsic and environmental influences on the allergic sensitization of adolescents. IgE development could be linked to having an allergic father, not growing up in a farming environment, smoking, being underweight, and having a moderate frequency of colds.

Acknowledgements

This study was funded by Sparkling Science (www.sparkling-science.at), a program of the Federal Ministry of Science, Research and Economy of Austria (SPA 04/065-Alraune).

C. Wageneder-Schmid and the Biomedical Sciences team of the Salzburg University of Applied Sciences (K. Schwenoha, L. Helminger, J. Gmachl-Baumgartner, R. Wiltsche, U. Fötschl) are acknowledged for their support in this study. We thank the teachers E. Oberkofler (HBLA Ursprung), M. Hauer (BG Tamsweg), S. Fischinger (NMS Bürmoos), K. Schaffer (PdC BORG Radstadt), B. Wanzenböck (Musisches Gymnasium Salzburg), J. Pöttler (BG Seekirchen), R. Pilotto-Kofler and P. Paraschin-Wolfsberger (PG St. Rupert), M. Anderluch (BHAK/BHAS I Salzburg), G. Mussill and L. Mackner-Rath (BORG Nonntal), and the students of the participating schools for supporting the project.

Disclosure Statement

G.G. received lecture fees from Thermo Fisher Scientific. All other authors declare no conflicts of interest.

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