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Article type : Original Article: Airway Diseases

Editor : Thomas Bieber

19.4.2017

ALL-2016-00784, Birth decade affects the sensitization pattern and asthma-risk in Finnish adult population

Dear Editor of Allergy,

We have revised and checked the English of the manuscript entitled “Birth decade affects the sensitization pattern and asthma-risk in Finnish adult population”. It has now been submitted online to Allergy. Please find both the revisions in red –version and the original version. Please find below a point-by-point response to the Reviewer comments. We would kindly enquire if the manuscript is now suitable for publication in Allergy.

Comments from Reviewer # 1

1. line 35 please further describe previous results

RESPONSE: We thank the reviewer for this kind comment. We have now described in more detail the previous results.

2. was rhinitis investigated in patients and controls?

RESPONSE:

We are sorry for leaving out this information. We acknowledge that we were not able to study the potential confounding effect of allergic rhinitis due to small sample size. However, we have previously demonstrated in this study population that self-reported allergic rhinitis associates with asthma, with younger age and with a multiple sensitizations pattern (8, 21). Further studies with increased sample size are needed to study the pathomechanisms of this putative asthma phenotype. This and the new reference (number 21) have been added to the discussion section.

References:

(8) Toppila-Salmi S. et al. Sensitization pattern affects the asthma risk in Finnish adult population. Allergy. 70 (2015) 1112–1120.

(21) Ådjers K. et al. Self-Reported Allergic Rhinitis and/or Allergic Conjunctivitis Associate with IL13 rs20541 Polymorphism in Finnish Adult Asthma Patients. Int Arch Allergy Immunol. 172 (2017) 123-128.

3. table s2: what “only other” means?

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13194

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RESPONSE: Thank you for the important remark. “Only other” means sensitization to allergen(s) out of the index allergen type, for example in the table “poll. +other” means sensitization both within the pollen allergen type and out of the pollen allergen type. Similarly were formed the “anim. +other” “mite +other”, and “mould +other” groups. We have clarified this in the Results section and in the footnote of Table S2.

4. tables are interesting but figures would help to summarise results

RESPONSE: We agree that a figure would be informative for readers and have now provided Figure 1. Thank you.

Additional note from the Authors:

Page 7, Results section; 2nd paragraph: The number of positive skin prick test reactions

We also wanted to provide the OR, CI values for the “data not shown” spot (shown in red; page 8, row 1). We performed further statistics by using the continuous sum of the SPT positive values. This OR value did not change by more than 10 %. Thus the sentence has therefore been crossed out (as shown in revised manuscript).

ALL-2016-00784 Manuscript revised in red

Brief communication

Birth decade affects the sensitization pattern and asthma-risk in Finnish adult population

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The study was supported by the ethical committee of the Pirkanmaa Hospital District

Running title: Age affects sensitization pattern and asthma risk

Key words: asthma, epidemiology, sensitization, skin prick test

Abbreviations

SPT skin-prick test

Abstract

Background: We have previously shown that sensitizations to several types of allergens distinguishes subjects with and without adult-onset asthma in Finland. The aim was to analyze how age affects sensitization and asthma-risk.

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Methods: We used previous population-based case-control data (N=523) from Finnish adult asthma patients with one or two matched controls. Asthma was diagnosed based on a typical history of asthmatic symptoms and lung function tests. Allergic sensitization was determined by skin prick test (SPT) to 17 aeroallergens. Information on demographics was obtained by a questionnaire.

Results: Sensitization to more than one allergen type and the number of positive SPT reactions associated with younger age and asthma. Atopic subjects aged 65 or over were characterized by sensitization to only 1-2 allergens, with very few animal danders and without an association with asthma.

Conclusions: Multiple sensitizations and animal dander sensitization are more common among Finnish asthmatic adults aged under 56 than among older asthmatics. Cohort studies are needed to understand timing of host-environmental interactions behind this.

Introduction

The increased prevalence of asthma and allergic diseases is a major public health problem worldwide. The prevalence of adult asthma has increased during the past decades and is around 9 % in Northern Europe (1). Atopy, family history, smoking and exposure to inhaled irritants are known risk factors of asthma (2). In Finland, sensitization rates to birch pollen and cat have increased during the past 10 years (3). The risk factors of asthma diverge by several factors, such as between different environments, populations, and decade of birth (4,5).

Change in the pattern of sensitization to different aeroallergens in adult populations with atopy has been detected in several countries undergoing westernization (6). During the last century, Finland has gone through a strong westernization, increasing strongly in the 1930s, as observed by the strong reduction in infant mortality (7).

We recently showed within this study population that 6-17 positive skin prick test (SPT) reactions, or sensitization to several types of allergens distinguishes subjects with adult-onset asthma in Finland ~~that an increased number of positive skin prick test (SPT) reactions and polysensitization pattern characterize Finnish adult-onset asthma population~~ (8). We also demonstrated that mite sensitization was not independently associated with asthma (8). Our aim was to observe the association of subject age to the sensitization pattern and asthma within this population. We hypothesized that sensitization to several allergens characterizes a younger age group with asthma.

Methods

The data was obtained as previously described (8). Briefly, the asthma sample (N=245) was Finnish population-based subjects (age over 30 years) with entitlement to special reimbursement for asthma medication from the Social Insurance Institution of Finland (requiring lung-function-test confirmed physician-diagnosed asthma and regular use of asthma medication). Age-, gender- and area-of-residence matched controls (N=405) without asthma were initially selected from a population register. SPT were performed in 1997 as previously described (8). SPT responses were considered positive if the allergen caused a wheal with a diameter of at least 3 mm. The following patients were withdrawn from the final analyses: subjects with SPT saline > 0 mm; subjects with SPT histamine < 3 mm; cases without at least one control. 456 subjects (193 494 patients with asthma and 263 262

controls) were included in the study. Demographics and assessment of environmental exposure were collected through a questionnaire as previously described (8).

Statistics were performed with SPSS Base 18 Statistical Software Package (SPSS, Chicago, IL, USA) and STATA (Release 13.1 software, StataCorp, Texas, USA). We formed age groups based on the age of the patient when SPT and other tests were performed in 1997. The age groups were: 31-55 years, 55-65 years and 66-89 years. The comparison between asthmatics and non-asthmatics were performed separately in the three age groups by conditional logistic regression and were reported as odds ratios (OR) with 95% confidence intervals. Two-tailed P-values less than ~~inferior to~~ 0.05 were considered statistically significant.

Results

Individual allergens

When analyzing the prevalence of sensitization to each allergen in each age group and its association to asthma, we found that sensitization to dog, cat, horse or cow dander was more frequent in the younger age groups of 31-55 years and 56-65 years; and these sensitizations were also associated with asthma in the younger age groups (Table S1). Sensitization to birch, timothy grass, smooth meadow grass or mugwort pollen was also more prevalent in the younger age groups of 31-55 years and 56-65 years; yet they associated with asthma only in the middle age group of 56-65 years (Table S1). The prevalences of sensitization to mite and mould allergens were lower and/or did not remarkably associate with asthma, except *Aspergillus fumigatus* in the age group of 56-65 years (Table S1).

The number of positive skin prick test reactions

In the age group 31-55 years, the number of positive SPT reactions increased statistically significantly asthma-risk ($p=0.015$, $OR=1.17$, $CI=1.03-1.34$, by continuous conditional logistic regression). Similar findings were detected in the age group of 56-65 years ($p=0.010$, $OR=1.27$, $CI=1.06-1.52$). In contrast in the age group of 66-89 years, the number of positive SPT reactions did not increase the risk for asthma ($p=0.66$, $OR=1.05$, $CI=0.84-1.31$). In the four categories of positive SPT reactions, sensitization to 6-7 allergens was clearly more prevalent in the youngest age group (31-55 years) and it associated strongly with asthma (Figure 1, Table 1). The models were adjusted for ~~by~~ two potential confounding factors: reported childhood environment in the countryside and reported childhood environment in the farm. None of the OR values change more than 10 % after adjustment of these variables

The patterns of sensitization

There were four types of allergens tested by SPT: pollen, animal, mite and mould. We formed four different patterns of sensitization within these indexed types as previously described (8). In brief, “no” means no skin prick test positive values, “only” means sensitization only within the index allergen type, “only other” means sensitization to allergen(s) out of the index allergen type, for example “poll. +other” means sensitization both within the pollen allergen type and out of the pollen allergen type. Similarly were formed the “anim. +other” “mite +other”, and “mould +other” groups. We detected that the sensitization pattern “Animal type + other” was clearly more prevalent in younger age groups of 31-55 years and 56-65 years, and it associated with asthma only in these younger age groups (Table S2).

Discussion

This case-control study in Finnish adults showed that multiple sensitizations are more frequent in adult asthmatics than in control subjects mainly in the younger age groups, ~~but~~. Overall, sensitization to more than one allergen type was more prevalent in our study population in younger age groups. Thus, it could be speculated that in the Finnish population, there are differences between the pathomechanisms of sensitization to one or several allergen types in different age groups, and that the pathogenesis of polysensitization is putatively associated to asthma in subjects born in 1932 or after.

We previously demonstrated that polysensitization predominates in Finnish adult-onset asthma (8). It has been shown that polysensitization in adults increased during the last 15 years and that a polysensitization cluster can already be identified in infants of 18 months of age (9,10).

We demonstrated that the number of positive SPT reactions increased the risk of adult asthma in a dose-dependent pattern, but only in subjects born in 1932 or after. Subjects having 6-17 positive SPT reactions carried about a six-fold risk for asthma in the youngest age group of 31-55 years. It could be suggested that counting positive SPT reactions might be an easy tool for estimating asthma risk in Finnish adults born after 1942. Yet, clinical significance and the pathogenetic background need to be studied with a bigger population. Dose-dependent association between sensitization and adult asthma has previously also been detected by others (11).

In our population, sensitization to any mite was not associated with asthma in any of the age groups, which is in line with previous studies of ours and other groups (8,12). Sensitization to mould allergens was not associated with asthma except sensitization to *Aspergillus fumigatus*, although the overall prevalence of sensitization to *Aspergillus* was low. Interestingly in another study, the authors found no decline in sensitization to mould between 55-73 year olds to 18-34 year olds (13).

Of individual allergens, we found that sensitization to animal danders was more prevalent in both asthma and control groups in younger age groups in contrast to the oldest age group. Moreover, animal dander sensitization associated with asthma only in the younger age groups. Interestingly, in a USA population-based study, asthma in patients aged 55 or over was associated with sensitization to indoor allergen levels whereas in subjects between 20 to 40 years of age, asthma was associated with sensitization to both indoor and outdoor allergens (14). It would be important to evaluate with increased sample size whether the development of animal dander sensitization in subjects born 1932 or after, has a role in the atopy and asthma epidemic.

The childhood environment (farm and countryside) were selected as confounding factors. They were selected as they might associate both with birth decade and with sensitization. After adjustment by these variables, the results remained similar. In a recent study, it was shown that traditional farming methods and higher microbial exposure protected children from asthma and reduced sensitization (15). In light of this, significantly more of the patients aged over 65 have spent their childhood in the countryside or on a farm, in comparison to the younger generations who live in an urban environment, which could protect from development of polysensitization. Yet further studies to prove this are needed.

Previously, others have shown that number of positive SPT and serum IgE levels decrease in parallel with age, however asthma affects still between 3.5-7.5% of people aged 65 or over (16, 17). Nevertheless, other studies have shown that IgE production is not impaired in the elderly whereby immunosenescence is an unlikely explanation for the difference in sensitization rate (18). Exposure to relatively low levels of traffic related air pollution in middle age was found to associate with increased risk of sensitization and asthma (19). Immigrants have been shown to develop multiple sensitizations more frequently than native-born people and ethnical background seems to influence this (20). Younger generations with polysensitization and asthma may be carrying the epigenetic changes of their previous generations, which have lived in the countryside and farm and once facing the urban environment, the immune system may aberrantly react to lack of high microbial exposure.

The limitations of our study include small sample size representing only one adult population. We were not able to separate the effects of age, period and cohort on the risk of sensitization and asthma due to the cross-sectional nature of our study. We acknowledge that we were not fully able to study the potential confounding factors such as allergic rhinitis. We have previously demonstrated in this study population that self-reported allergic rhinitis associate with asthma, with younger age and with multiple sensitizations pattern (8, 21). Further studies with increased sample size are needed to study the pathomechanisms of this asthma phenotype in adults.

The strengths are the population basis of the asthmatics, and that the case-control set up was adjusted by age, gender and region of living. The effect of immunotherapy was not investigated, however at the time of data collection allergen immunotherapy was rarely given in Finland.

To conclude, multiple sensitizations and animal dander sensitization might characterize Finnish asthmatic adults who are 31-65 years of age and were born in 1930's or after. Further observations of other reasons for the beginning of the atopic epidemic in the 1930's would be important. Nonetheless, further studies with a cohort setup are needed to study cohort-effect.

Acknowledgements

This study was supported in part by the grants from the Finnish Medical Foundation, The Finnish Society of Allergology and Immunology, Jane and Aatos Erkko Foundation, the Finnish Cultural Foundation, the Tampere Tuberculosis Association, Väinö and Laina Kivi Foundation, Yrjö Jahnsson Foundation. The authors thank MD Auli Hakulinen for providing valuable comments.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Figure 1

Prevalence of the number of SPT positive reactions in asthma group and control group, presented in the three different age groups.

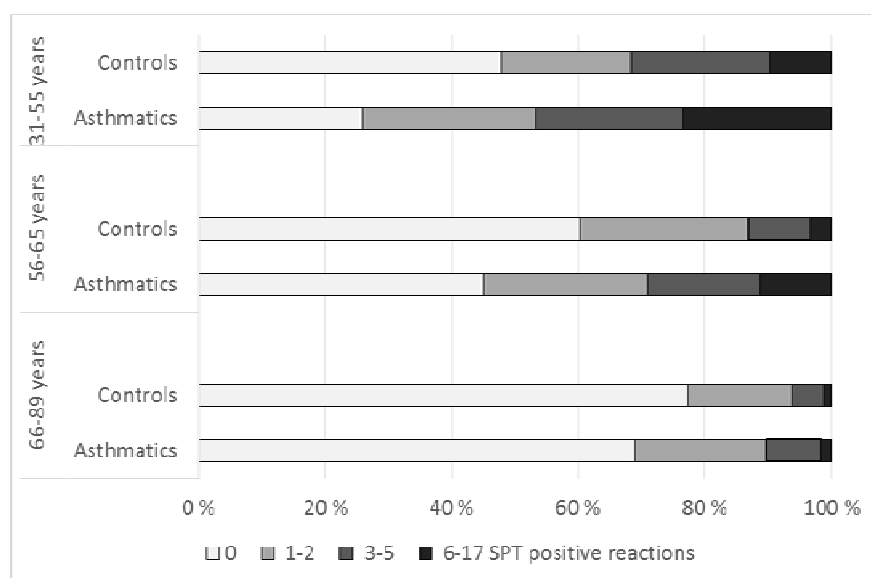


Table 1

Association between the numbers of positive skin prick test (SPT) reactions and asthma diagnosis in three age groups by conditional logistic regression.

Age group years	Positive SPT reactions number	Controls with sensitization		Asthmatics with sensitization		OR _{raw}	95% CI		p-value
		n	%	n	%		lower	upper	
31-55	0	44	47.8	19	26.0	1			
	1-2	19	20.7	20	27.4	3.26	1.10	9.62	.032
	3-5	20	21.7	17	23.3	2.10	0.82	5.33	.12
	6-17	9	9.8	17	23.3	6.50	1.89	22.41	.003
	total	92	100.0	73	100.0				
56-65	0	55	60.4	28	45.2	1			
	1-2	24	26.4	16	25.8	1.27	0.57	2.84	.56
	3-5	9	9.9	11	17.7	4.09	1.02	16.47	.047
	6-17	3	3.3	7	11.3	3.49	0.86	14.18	.081
	total	91	100.0	62	100.0				
66-89	0	62	77.5	40	69.0	1			
	1-2	13	16.3	12	20.7	1.34	0.52	3.45	.55
	3-5	4	5.0	5	8.6	1.66	0.43	6.38	.46
	6-17	1	1.3	1	1.7	1.64	0.10	27.61	.73
	total	80	100.0	58	100.0				

The age groups are based on the age of the patient when the SPT and other tests were performed in 1997. CI = confidence interval, low. = lower, upp. = upper; OR = odds ratio adjusted. Cases (n=193) and controls (n=263) are matched for gender, age and region.