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Prediction of new-onset asthma and nasal allergy by skin prick test and RAST in a cohort of adults.

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Abstract

Background: Limited information exists regarding the incidence and predictors of asthma and nasal allergy in adulthood. We determined the incidence rate of asthma and nasal allergy in adults and assessed the predictive value of skin prick tests (SPT) and radioallergosorbent tests (RAST) on these two outcomes.

Methods: Two German centres involved in the European Community Respiratory Health Survey conducted a follow-up assessment in 2012 of the baseline participants (1185 adults aged 21 to 47 assessed in 1990). The predictive value of SPT and RAST on new-onset asthma and nasal allergy was assessed by cox regression and by calculating the positive/ negative predictive value (PPV/NPV).

Results: During the 20 years between baseline and follow-up, 3.1 and 4.4 per 1000 person-years new-onset asthma and nasal allergy cases were recorded, respectively. The hazard ratios for SPT of any specific and of all aeroallergens combined were slightly higher than those of RAST for asthma and nasal allergy. The NPVs of both SPT and RAST were very high and similar (0.94-0.96) whereas the PPVs were low (0.09-0.20).

Conclusion: Positive SPT results showed a better association with new onset asthma and nasal allergy than positive RAST to any specific aeroallergens or to all combined.

Key words: incidence rate, skin prick test, radioallergosorbent test, ECRHS

Introduction

Asthma and nasal allergy are common chronic disorders affecting 2.0%-8.4% and 12.1%-34.4% of Europeans, respectively [1]. The prevalence for both conditions was increasing but appears to have more recently plateaued. Worldwide data indicate heterogeneity in asthma prevalence trends, whereas the prevalence of nasal allergy continues to increase in most countries [2]. Therefore, allergic diseases pose a serious public health problem with a substantial impact.

A few studies have prospectively assessed the incidence of asthma and/or nasal allergy in adulthood using a ten year follow-up [3-6]. Most of these papers have utilized data from the European Respiratory Health Survey (ECRHS). No study has yet reported on the onset of asthma and nasal allergies in adulthood using a follow-up of 15 years or more. While the prevalence for asthma and nasal allergy have been reported previously in adult German populations [7, 8], there are no studies providing incidence rates for Germany utilizing a long-term follow-up of 20 years. Previous studies [3, 4, 9, 10] have identified sex, smoking, atopy, body mass index, brochial hyperresponsiveness (BHR), exposure to mould and early acute respiratory infection as risk factors for asthma and nasal allergy. However, no study has considered the potential predictive value of skin prick tests (SPT) or radioallergosorbent tests (RAST) as determinants for new asthma and nasal allergy onset in adults. The longitudinal predictive power of these factors should be examined.

Our study presents prevalence and incidence data for asthma and nasal allergy in a German prospective cohort followed for 20 years. We also examined potential long-term predictors for

new-onset asthma and nasal allergy, with a special emphasis on the role of SPT and RAST positivity.

Material and Methods

Study population and design

The European Respiratory Health Survey (ECRHS) is a population-based multi-centre cohort study of respiratory health among adults. Study design and methods have been described previously [11] and the full protocol is available at http://www.ecrhs.org/. Two German centres, located in Hamburg and Erfurt, were included in this study. Briefly, the ECRHS I (baseline study) was performed between 1990 and 1992 on random samples of the general population. In stage one, each participant was sent a screening questionnaire. From the responders, a random sample was invited to take part in a clinical examination (stage two). The ECRHS II (2000-2002) and ECRHS III (2010-2012) are follow-up studies of the population included in ECRHS I stage 2. Data presented in this study were collected between 1990 and 2012 in the German centres in Hamburg and Erfurt, as part of the framework of ECRHS. In ECRHS I, 1282 and 1251 individuals participated in the Erfurt and Hamburg cohorts, respectively (figure 1). In Erfurt, 16 individuals did not consent to address storage and thus only 1266 individuals were contacted for ECRHS III. In Hamburg, a randomly drawn subsample of 900 individuals were invited to participate in ECRHS III. Of the contacted individuals in Erfurt and Hamburg, 767 and 518, respectively, were between 21-47 years at baseline in ECRHS I. Therefore, our study population consists of 1185 men and women aged 21 to 47 years who participated in the medical examination at baseline. Of those,

924 subjects (Erfurt 540; Hamburg 384) participated in the ECRHS III (responders) and 261 persons did not (non responders). To identify a population at risk of new-onset asthma and or nasal allergy, those who reported a history of asthma or nasal allergy in ECRHS I were excluded (asthma: 17/23 in Erfurt/Hamburg; nasal allergy: 68/89 in Erfurt/Hamburg). Within the remaining population, new-onset asthma and nasal allergy were defined as a positive response to the questions: ’Have you ever had asthma?’ and ‘Do you have any nasal allergies, including hay fever?’, respectively. The age of new-onset asthma and nasal allergy was lower than the age at baseline (ECRHS I) for 29 and 26 participants, respectively. When this difference was not more than two years, the age of new-onset of disease was set equal to the age at baseline. For individuals for whom this difference was greater than two years, the midpoint of the age of reported new-onset of disease and age at ECRHS III was set as the age of new-onset. In case the midpoint was still lower than the age at baseline or that no age of new-onset of disease was reported , the subject was excluded. The final study population consisted of 874 subjects (Erfurt: 517; Hamburg 357) with no indication for asthma at baseline and 754 subjects (Erfurt 465; Hamburg 289) with no indication of nasal allergies at baseline (see figure 1).

The study protocol was approved (ethical approval for baseline: 1989 (Medical Association of Schleswig-Holstein in Bad Segeberg, Hamburg) and 1991 (Erfurt) and for follow-up in 2009 (regarding both substudies)) by the Local Ethics Committee of the Bayerische Landesärztekammer and of the Medical Association of Schleswig-Holstein in Bad Segeberg. Written informed consent was obtained from all participants.

Assessment of allergic sensitization in ECHRS I

SPT were performed using Phazets (Pharmacia Diagnostics AB, Uppsala, Sweden), which are individual antigen-coated lancets, and two control lancets (histamine and uncoated). The lancets were applied to the volar surface of the forearm. After 15 minutes, the outline of the wheal was drawn on a strip of adhesive transparent tape, that was subsequently transferred to the data sheet. Wheal diameters were read at the widest point and at an angle of 90 degrees to the diameter at the midpoint. A skin test for a specific allergen was considered positive if a mean wheal diameter to the allergen was $\leq$ 3 mm, and the wheal diameter to histamine was $\geq$3 mm and to uncoated Phazets <3 mm. Cat, *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), *Cladosporium herbarum* and birch allergens were selected for this analysis. Specific IgE against these same four allergens were also measured in serum samples in a central laboratory by RAST (CAP-RAST, Pharmacia Diagnostics, Uppsala, Sweden). Values >0.35 kU/L for an allergen were considered positive. Specific IgE against *Timothy grass* was not assessed as we wanted a similar allergen spectrum for both the SPT and RAST. Of the individuals with single RAST positivity for *Timothy grass,* 8.5% (5/59) and 27.8% (10/36) had new-onset asthma and nasal allergy, respectively.

Lung function measurements and BHR in ECHRS I

In ECRHS I, forced expiratory volume in the first second (FEV1) was determined using pneumatograph-based electronic spirometers (Compact Pneumo Lab, and PSC-PC, Jaeger, Würzburg, Germany). BHR was obtained using the metacholine challenge (Mefar MB3 dosimeter, Mefar srl Bovezzo, Italy) and was defined as a fall of at least 20% in FEV1 associated with a cumulative dose of $\leq$ 2mg methacholine.

Analysis of data

Characteristics of responders and non responders at baseline were compared using Chi-squared tests.

Asthma and nasal allergy incidence rates were calculated as the number of new cases of asthma and nasal allergy, respectively, divided by the person-years at risk during the observation period.

Relative risks (RR) with 95% confidence intervals (CIs) are given for potential determinants of new-onset asthma and nasal allergy. The following potential determinants were considered: sex, centre, asthma (for new-onset nasal allergy), nasal allergy (for new-onset asthma), eczema, BHR, family history (considered positive in the case of an affirmative answer to any of the following questions : 'Did your mother ever have asthma?', 'Did your mother ever have eczema, skin or nasal allergy or hay fever?', Did your father ever have asthma?', and 'Did your father ever have eczema, skin or nasal allergy or hay fever?'), pet ownership (considered positive in the case of an affirmative answer to any of the following questions: 'Do you keep a cat?', 'Do you keep a dog?', and 'Do you keep any birds?'), mould exposure ('Has there ever been any mould or mildew on any surface, other than food, inside the home?'), job exposure ('Have you ever worked in a job which exposed you to vapours, gas, dust or fumes?'), current smoking, contact to older children in early life (considered positive in the case of reported older siblings or an affirmative answer to the question 'Did you go to school, play school or nursery with older children before the age of five years?'), any positive SPT (Cat, *D. pteronyssinus*, *Cladosporium herbarum*, birch), and any positive RAST (Cat, *D. pteronyssinus*, *Cladosporium herbarum*, birch). Atopic status was determined using SPT and

RAST. The social status of individuals was assessed using the reported age at which fulltime education was completed and was categorized into three groups: age≤16 years, 16 years<age≤ 23 years, 23 years<age. The population attributable fraction was calculated as the risk difference divided by the risk in exposed (atopic) individuals multiplied by the proportion of all cases in the exposed (atopic) population.

Cox regression analyses were performed with person-years under observation as the dependent variable and asthma or nasal allergy as the event. Hazard ratios (HR) with 95% CIs are given for predictive variables in crude models and in models adjusted for gender, centre, social status, family history and smoking.

Measures of diagnostic accuracy of SPT and RAST (positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity) were calculated for individuals who developed asthma or nasal allergies between 1990 and 2012.

Positive likelihood ratio (LR+) was determined by the calculation of sensitivity/(1-specificity) and negative likelihood ratio (LR-) by the calculation of (1-sensitivity)/specificity.

The significance level was set to 5%.

Kaplan-Meier curves were obtained with SigmaPlot 12.0 (Systat Software, Inc., San Jose. CA).

Venn diagrams were plotted using the Venn Diagram Plotter Program originally written by Kyle Littlefield for the Department of Energy (PNNL, Richland, WA).

All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Descriptive Data

Of the 1185 adults asked to participate in ECRHS III, 924 responded (response rate 78.0 %). In general, responders and non responders did not differ in their basic characteristics, as assessed in 1990-1992 during ECRHS I (table 1). However, responders were more likely to be female, from Erfurt and be of higher social status compared to non responders. In contrast, responders were less likely to own pets and currently smoke.

Outcome data

In total, 50 cases of new-onset asthma and 60 cases of new-onset nasal allergy occurred during the 20 year observation period (1990/1992-2010/12), which corresponds to 16072 and 13668 person-years under risk, respectively.

Main results

The incidence rates for asthma and nasal allergy are presented in Table 2. The asthma crude incidence rate was 3.11/1000 person-years and that for nasal allergy was 4.39/1000 person-years. In Hamburg, the incidence rate was higher than in Erfurt for both outcomes. Rates were also higher for females than males. At the end of the follow-up period, 44% of the new asthma cases and 10.3% of subjects without asthma stated that they had suffered from wheeze in the last 12 months. Additionally, 28 (56%) of the incident asthma cases reported current treatment with asthma medication and thus might have been free of symptoms. Of those not undergoing current treatment with asthma medication, 33.3% of the subjects with new-onset asthma and 9.7% without asthma reported wheeze symptoms in the last 12 months. The RR and 95% CIs for the relationship between each risk factor with new-onset asthma and nasal allergy are given in table 3. These findings differ slightly when the analyses are stratified by centre (see tables 1a-2b in supplement).

The HRs obtained by cox-regression, which were adjusted for gender, centre, social status, family history and smoking, were higher for each SPT compared to the corresponding RAST for both new-onset asthma and nasal allergy (table 4). A significantly increased hazard for new-onset asthma showed a positive RAST for cat, as well as positive SPTs for cat, *D. pteronyssinus* and birch. Positive SPTs for cat and birch, as well as a positive RAST for birch were significantly associated with an increased hazard for new-onset nasal allergy. The highest HR was observed between a positive SPT for cat and new-onset asthma as well as between a positive SPT for birch and new-onset nasal allergy. Any positive SPT and any positive RAST significantly increased the hazard for new-onset asthma and nasal allergy. Thus, for both outcomes, the HR was stronger for any positive SPT than for any positive RAST. When the analysis was stratified by centre, this trend was similar in Hamburg but reversed in Erfurt. However, the numbers in both of these stratified analyses are small and there is a substantial overlap in the CI (see tables 1a – 4b in supplement).

As seen in figure 2, there is partial overlap between individuals with new-onset asthma and nasal allergy who were positive to any SPT and any RAST. Among those with either new-onset asthma or nasal allergy, more individuals tested positive for any RAST than for any SPT. In total, 31 of 50 (62%) individuals with new-onset asthma and 38 of 60 (63%) individuals with new-onset nasal allergy tested positive for at least one SPT and/or at least one RAST at baseline, and therefore were atopic. The population attributable fraction for asthma and nasal allergy was 36% and 44%, respectively.

Of the 874 non asthmatic individuals at baseline, 196 were positive to at least one SPT, 21 of which developed asthma during the 20 year observation period. Similarly, 293 (of the 874

non-asthmatics) were positive to at least one RAST, 25 of which developed asthma. With regard to nasal allergy, 754 individuals were without nasal allergies at baseline, 123 of which were positive to at least one SPT and 24 of which subsequently developed nasal allergies during the follow-up period. Finally, 216 (of the 754 individuals without nasal allergies) were positive to at least one RAST, 31 of which developed nasal allergies during follow-up. Sensitivity was higher for RAST than for SPT for both asthma (50.0, CI 36.1-63.9 vs. 42.0, CI 28.3-55.7) and nasal allergy (51.6, CI 39.0-64.3 vs. 40.0, CI 27.6-52.4). Although the CIs are overlapping, Conversely, specificity was higher for SPT than for RAST for asthma (78.8, CI 76.0-81.6 vs. 67.5, 64.3-70.7) and for nasal allergy (85.7, CI83.1-88.3 vs. 73.3, CI 70.1-76.6). As seen in table 5, the PPVs for SPT and RAST for asthma were very low and similar and the CI overlapped (0.11, CI 0.07-0.16 versus 0.9, CI 0.06-0.12). For nasal allergy, the PPV for SPT and RAST were low and differed more substantially, although again the CI overlapped (0.2, CI 0.13-0.28 versus 0.14, CI 0.10-0.20). The NPV for SPT and RAST were high and similar for asthma and nearly identical for nasal allergy.

LR+ and LR- for SPT and RAST are rather weak, as LR+ is (with exception of SPT in nasal allergy: LR+ = 2.8) below 2 and LR- is between 0.5 and 1.0 for both tests (see table 5).

The relationship between time to onset of asthma/nasal allergy and new-onset asthma/nasal allergy for subjects with any positive SPT and subjects with any positive RAST at baseline is shown in figure 3. Two years after the baseline survey (ECRHS I), the probability of new-onset asthma was greater for individuals with at least one positive SPT than for those with at least one positive RAST. For all time points, the probability of new-onset nasal allergy was

higher for individuals with at least one positive SPT than for individuals with at least one positive RAST.

Discussion

Key results

The present study provides information about the incidence, risk factors and prediction by SPT and RAST of new-onset asthma and nasal allergy in a population of German adults followed for 20 years.

The incidence rates for asthma and nasal allergy were higher in Hamburg than in Erfurt. Women had a higher incidence rate than men for both conditions. The incidence of asthma was related to sex, BHR, nasal allergy, social status, any positive SPT and any positive RAST. The incidence of nasal allergy was associated with eczema, any positive SPT and any positive RAST. SPT was a slightly better predictor for the new-onset of asthma and nasal allergy than RAST. An analysis of allergen specific SPT and RAST identified a positive reaction to the cat allergen as the strongest predictor for new-onset asthma and a positive reaction to the birch allergen as the strongest predictor for new-onset nasal allergy.

Limitations

The main limitation of long-term prospective cohort studies is a loss to follow-up. However, the response rate of our study in ECRHS III can be regarded as high (78% when only eligible subjects are considered). Responders did not differ from non responders in many potential risk factors such as age, nasal allergy, eczema, SPT or RAST. Nevertheless, our sample can not be considered as completely unbiased. The long observation period of our study, with time intervals of approximately 10 years between follow-ups, might lead to recall bias,

especially in terms of age of new-onset of disease. We used self-reported data from questionnaires to assign asthma and nasal allergy status, which may lead to misclassification, especially with regard to asthma given the potential confounding influence of chronic obstructive pulmonary disease (COPD). We think asthma medication, as an outcome, is likely less subject to recall bias than self-reported physician diagnosis of asthma or nasal allergy. Including more self-reported respiratory symptoms as outcomes would have similar limitations. More 'objective' data, such as lung function measurements and BHR testing or a clinical case ascertainment, would diminish the misclassification bias of this study. Unfortunately, this information was not available. Also, it is possible that some of the new-onset asthma cases are attributable to a change in diagnostic labelling.

Fourteen and 46 individuals, respectively, reported that they ever had asthma and nasal allergy in ECRHS I but did not report these symptoms in ECRHS III. These inconsistencies could be due to a true remission in individuals who have had asthma or nasal allergy years ago, but that the disease did not persist. Considering the long observation period of this study, it is plausible that some individuals with new-onset asthma or nasal allergy who had negative SPT and RAST at baseline became sensitized during the observation period. Furthermore, a lower cut off point for the tests might lead to a higher sensitivity.

The large sample size, international standardised methods of data collection following ECRHS protocols, and population-based setting of this study are unique and important strengths. Moreover, the design of a prospective cohort with a long (20 years) follow-up time, which includes a question on new onset, allows incidence rates to be calculated. The detailed

information on health behaviours and risk factors, gained through questionnaires and medical examinations, permits analyses to be adjusted for a large number of potential confounders.

Interpretation

Incidence rates of asthma (crude 3.1; men 2.2; women 4.1) were within the range of those observed in previous cohort studies (crude 2.2-4.5, men 1.0-4.5, women 1.3-4.9) [12-14]. As reported by most other studies, a higher incidence rate was found for females than for males [9, 10]. One study reported that only the risk of developing non allergic asthma differed by gender [15].

In the current study, incidence rates of nasal allergy (crude 4.4; men 3.6, women 5.3) are below the lifelong incidence reported by Matheson et al. in all 48 centres of the ECRHS study (7.0 men; 7.9 women) [4]. This difference might be due to the fact that our study does not report lifelong incidence but rather the incidence of nasal allergy between 1990/1992 and 2010/2012 only. This shorter timeframe likely leads to less recall and misclassification bias. Although risk factors for asthma and nasal allergy have been assessed previously, this is the first cohort study to show the effect of potential determinants on new-onset of disease over a 20 year follow-up.

The association between low social status and new-onset asthma found in the present study confirms the results of previous publications which have reported similar associations with the prevalence of asthma [16], with the exception of the study by Montnemery et al [17]. The association between socioeconomic status and asthma in children is complex [18] and likely depends on asthma severity, poverty, many life-style factors and potentially also country of

residence. While asthma (probably severe) prevalence is higher in children from less privileged families in inner cities, we previously found that asthma is more prevalent in the upper social class in a large cohort of German children, which is consistent with other German studies [19].

The impact of atopy on asthma remains unclear. Twenty years ago, Burrows et al. [20] stated that asthma almost always has an allergic basis in children and adults. However, Anto et al. [3] and Zacharasiewicz et al. [21] found an attributable fraction of atopy on the development of asthma to be in the range of 12% and 30% in adults. The attributable fraction we report (36%) is higher.

Among subjects with new onset of nasal allergy, 63% were atopic (at least one positive SPT or RAST) at baseline. This finding is consistent with data published by Zacharasiewicz et al. [21] who reported that 61% of rhinitis cases were atopic. However, their attributable fraction (53%) is higher than that of the current study (44%). The non atopic cases may represent rhinitis without an allergic base or may represent cases who were not atopic at baseline but who developed atopy during the observation period. Furthermore, including *Timothy grass* in the RAST would probably have lead to higher attributable fractions for new-onset asthma and nasal allergy.

SPT and RAST are both significant predictors for new-onset asthma and nasal allergy. The calculation of PPV and NPV demonstrated that positivity to at least one SPT is a better predictor for both conditions than positivity to at least one RAST. However, the overlapping CI of these point estimates indicate that this potential superiority is likely minor. The negative prediction of at least one positive SPT and at least one positive RAST were (nearly) equal and

performed better than the positive predictions. The sensitivity of RAST for new onset was stronger than of SPT, while specificity showed better results for SPT. Similar results were reported for both conditions for adults by Tschopp et al. [22] using Phadiatop instead of RAST and for children by Schäfer et al. [23] with regard to hay fever .

The LR indicates the value of a diagnostic test by comparing the likelihood that a certain test result would be expected in a patient with the definite disorder compared to the likelihood of the same result expected in a patient without the definite disorder. Here a distinction is drawn between LR+ concerning positive test results and LR- concerning negative test results. The classification of the test value given by LR is determined as excellent (LR+>10, LR-<0.10), good (LR+ 5-10, LR- 0.1-0.2), moderate (LR+2-5, LR- 0.2-0.5) or weak (LR+ 1-2, LR- 0.5-1.0) [24]. Therefore, the value of SPT and RAST in terms of prediction of new- onset asthma and nasal allergy is poor. When interpreting the test values of SPT and RAST for new-onset asthma, it must be acknowledged that only a part of all asthma cases are atopic. Furthermore, the much lower rate of SPT positivity than RAST positivity might have an effect on these estimates. Sensitization to cat allergen was most strongly associated with new-onset asthma, followed by mite. Considering the allergens tested in this study, for new-onset nasal allergy, sensitization to birch allergen was the strongest predictor, followed by cat. Positive SPT of every single allergen was more strongly related to new-onset of both asthma and nasal allergy than a positive RAST. This association might even increase with the use of a lower cut-off value for SPT [23, 25]. Previous studies have stated that the results of SPT and RAST are not interchangeable and that a positive SPT not accompanied by a positive RAST might be due to IgE antibodies that are not detectable by any RAST procedures [26, 27]. As previously

shown, there are differences in the prevalence of atopic diseases between East and West Germany [7, 28]. Therefore, as anticipated, the current results differ between Hamburg and Erfurt when the analyses are stratified by centre. This observation supports the hypothesis of site-specific influences on risk factors for the new onset of asthma and nasal allergy. Although the sample sizes are small, there seems to be a generally higher risk of specific allergic sensitization for asthma onset in Hamburg compared to Erfurt. Similar differences were not found for nasal allergies. As suggested by the ISAAC studies in children [29], there might be substantial variation in the dependency between asthma and atopy which could explain the differences in the associations between SPT and RAST with new onset of asthma and nasal allergy in Erfurt and Hamburg.

Conclusion

We report that SPT and RAST are both unpromising tests for prediction of new onset of asthma and nasal allergy in a cohort of German adults followed for 20 years, although, a positive SPT seems to present a slightly better predictor than any detectable specific IgE . However, the role of atopy on these diseases remains ambiguous, especially with regard to asthma. Further prospective longitudinal studies are needed to determine long-term predictors for new-onset asthma and nasal allergy.

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Table 1. Characteristics of the ECRHS study population, aged 21-47 years, at baseline(1990-92), stratified by participation in ECRHS III

	Participants of follow-up N = 924		*Non participants of follow-up N = 261*		*P-value*
	n/N	%	n/N	%	
Sex (female)	464/924	50.2	113/261	43.3	0.05
Age	34.6*/924		33.9*/261		0.18**
Centre (Erfurt)	540/924	58.4	127/261	48.7	0.01
Asthma at baseline	40/924	4.3	6/261	2.3	0.13
Nasal allergy at baseline	157/924	17.0	43/261	16.5	0.84
Eczema at baseline	329/924	35.6	93261	35.6	0.99
BHR at baseline	153/778	19.7	44/185	23.8	0.21
Family history[§]	245/914	26.8	68/255	26.7	0.96
Social status[§§]					0.02
Age≤16	18/856	2.1	12/233	5.1	
16<Age≤23	650/856	75.9	179/233	76.8	
23<Age	188/856	22.0	42/233	18.0	
Pet ownership at baseline	276/924	29.9	99/259	38.2	0.01
Mould exposure ever	208/916	22.7	59/259	22.8	0.98
Job exposure[$] ever	396/923	42.9	120/261	46.0	0.38
Current smoking[$$] at baseline	352/924	38.1	117/261	44.8	0.05
Any positive SPT	93/924	10.1	25/261	9.6	0.82
SPT cat	27/924	2.9	10/261	3.8	0.46
SPT *D. Pteronyssinus*	46/924	5.0	16/261	6.1	0.46
SPT *Cladosporium*	1/924	0.1	0/291	0.0	0.60
SPT birch	56/924	6.1	14/261	5.4	0.67
Any positive RAST	318/924	34.4	107/261	41.0	0.05
RAST cat	63/840	7.5	11/212	5.2	0.24
RAST *D. Pteronyssinus*	127/823	15.4	30/205	14.6	0.78
RAST *Cladosporium*	50/838	6.0	7/213	3.3	0.12
RAST birch	80/826	9.7	18/208	8.7	0.65
Contact with older children in early life	709/924	76.7	203/261	77.8	0.72

[§]Family history: parental history of asthma, nasal or skin allergy, or eczema; [§§]Social status: age in years at the end of full time education; [$]Job exposure: in job exposed to vapours, gas, dust or fumes; [$$]Current smoking at baseline; SPT: skin prick test; BHR: bronchial hyperresponsiveness; RAST: radioallergosorbent test; Any positive SPT: at least one positive skin prick test ; Any positive RAST: at least one positive radioallergosorbent test
*mean **unpaired t-test, α=5%

Table 2. New-onset asthma in subjects without asthma and new-onset nasal allergy in subjects without nasal allergy during the 20 years follow-up period

	New onset asthma *Subjects without asthma* *at ECRHS I* *N = 874*	*New onset nasal allergy* *Subjects without nasal Allergy* *at ECRHS I* *N = 754*
	IR/1000 person-years	IR/1000 person-years
Overall	3.11	4.39
Hamburg	3.65	5.14
Erfurt	2.74	3.92
Male	2.20	3.57
Female	4.06	5.26

IR: incidence rate

Table 3. Unadjusted predictors for the new-onset of asthma and nasal allergy in German adults during a 20 year follow-up

	New- onset asthma Subjects without asthma at ECRHS I N = 874		*New-onset nasal allergy Subjects without nasal allergy at ECRHS I N = 754*	
	RR	CI (95%)	RR	CI (95%)
Sex				
Female	1.79	1.02-3.15	1.44	0.88-2.35
Male	1		1	
Centre				
Erfurt	0.75	0.44-1.28	0.76	0.47-1.24
Hamburg	1		1	
Asthma at baseline	-		1.75	0.59-5.16
No asthma at baseline			1	
Nasal allergy at baseline	2.51	1.43-4.42	-	
No nasal allergy at baseline	1			
Eczema at baseline	1.62	0.95-2.78	1.76	1.09-2.86
No eczema at baseline	1		1	
BHR at baseline	4.14	2.29-7.48	1.69	0.96-2.99
No BHR at baseline	1		1	
Family history[§]				
negative	1		1	
positive	1.32	0.74-2.34	1.29	0.75-2.07
Social status[§§]				
Age≤16	1		1	
16<Age≤23	0.33	0.11-0.98	1.23	0.18-8.37
23<Age	0.19	0.05-0.69	1.20	0.17-8.60
Pet ownership at baseline	0.91	0.50-1.66	0.85	0.49-1.47
No pet ownership at baseline	1		1	
Mould exposure ever	0.77	0.38-1.57	1.49	0.88-2.52
No mould exposure ever	1		1	
Job exposure[$] ever	1.05	0.61-1.80	0.89	0.54-1.47
No job exposure ever	1		1	
Current smoking at baseline[$$]	0.71	0.39-1.27	0.63	0.37-1.07
No current smoking at baseline	1		1	
Any positive SPT	2.51	1.46-4.29	3.42	2.12-5.52
No positive SPT	1		1	
Any positive RAST	1.98	1.16-3.39	2.66	1.65-4.31
No positive RAST	1		1	

Contact to older children in early life	0.87	0.47-1.60	0.72	0.42-1.09
No Contact to older children in early life	1		1	

RR: relative risk; CI: confidence interval; BHR: bronchial hyperresponsiveness; [§]Family history: parental history of asthma, nasal or skin allergy, or eczema; [§§]Social status: age in years at the end of full time education; Job exposure: in job exposed to vapours, gas, dust or fumes; [$$]Current smoking at baseline; SPT: skin prick test; RAST: radioallergosorbent test; Any positive SPT: at least one positive skin prick test; Any positive RAST: at least one positive radioallergosorbent test

Table 4. Adjusted associations between SPT and RAST and the new-onset of asthma and nasal allergy during a 20 year follow-up

	New-onset asthma Subjects without asthma at ECRHS I N = 874		*New-onset nasal allergy Subjects without nasal allergy at ECRHS I N = 754*	
	HR*	CI (95%)	HR*	CI (95%)
SPT cat	5.46	2.59-11.49	6.60	2.94-14.84
RAST cat	2.52	1.04-6.08	2.01	0.79-5.10
SPT D. Pteronyssinus	2.23	1.02-4.88	1.82	0.85-3.88
RAST D. Pteronyssinus	1.62	0.70-3.73	1.37	0.64-2.95
SPT Cladosporium	3.63	0.86-15.37	1.34	0.18-9.88
RAST Cladosporium	0.93	0.22-3.90	1.18	0.37-3.79
SPT birch	2.19	1.08-4.44	7.24	3.91-13.39
RAST birch	1.16	0.41-3.30	5.41	2.72-10.76
Any positive SPT	2.65	1.40-5.01	4.00	2.21-7.25
Any positive RAST	1.90	1.01-3.58	3.43	1.90-6.19

HR: hazard ratio; CI: confidence intervals; SPT: skin prick test; RAST: radioallergosorbent test; Any positive SPT: at least one positive skin prick test; Any positive RAST: at least one positive radioallergosorbent test

*Hazard ratio adjusted for gender, centre, social status, family history and smoking

Table 5. Measures of diagnostic accuracy regarding SPT and RAST as predictors of new-onset asthma and nasal allergy

	Asthma *N = 874*		*Nasal Allergy* *N = 754*	
	SPT	RAST	SPT	RAST
LR+	1.98	1.54	2.80	1.94
LR-	0.73	0.74	0.69	0.66
PPV	0.11 (0.07-0.16)*	0.09 (0.06-0.12)*	0.20 (0.13-0.28)*	0.14 (0.10-0.20)*
NPV	0.96 (0.94-0.97)*	0.96 (0.94-0.97)*	0.94 (0.92-0.96)*	0.95 (0.92-0.96)*

SPT: skin prick test; RAST: radioallergosorbent test; LR+: positive likelihood ratio; LR-: negative likelihood ratio; *: confidence intervals

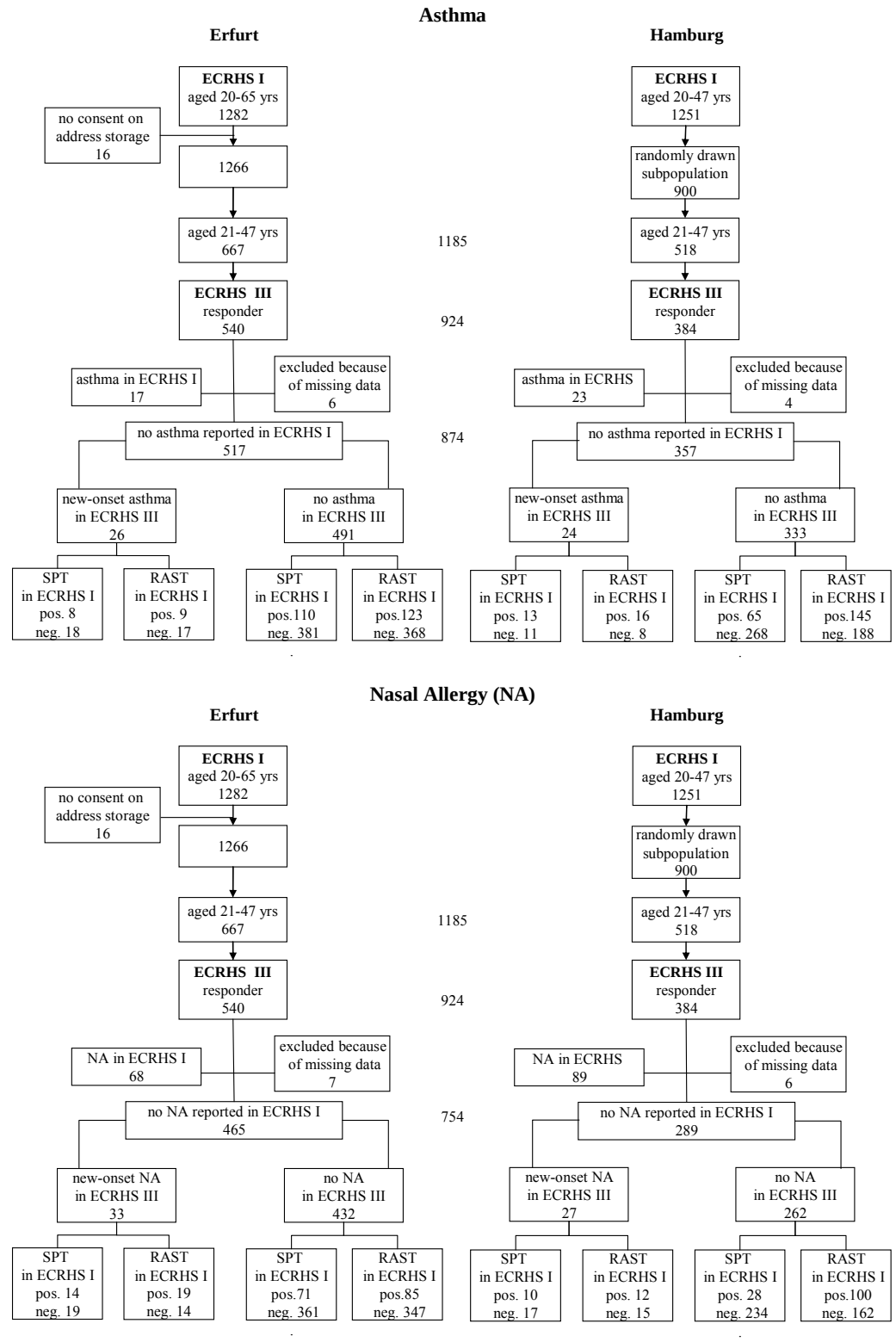

Fig. 1 Flow chart for statistical analysis plan

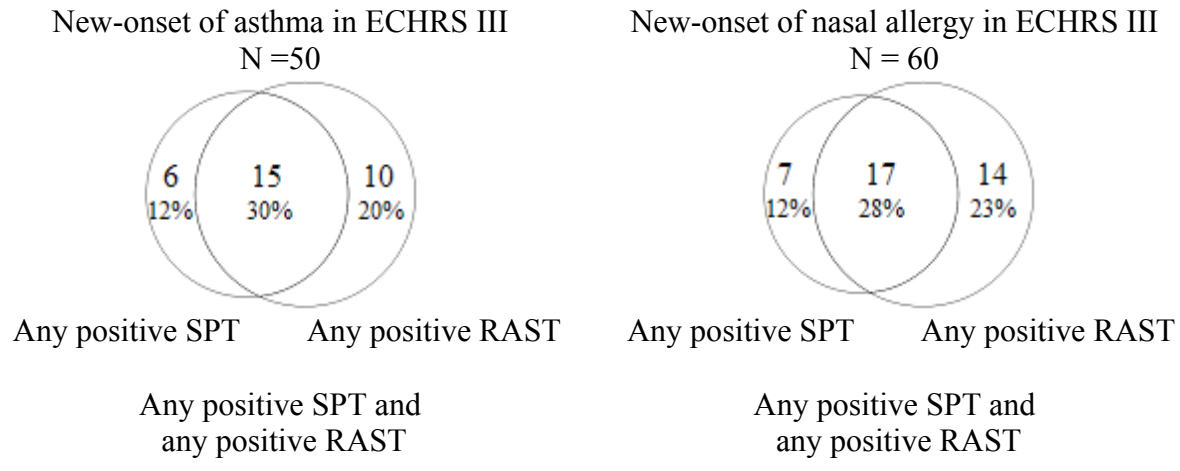

Fig. 2. Venn diagram depicting the overlap between any positive SPT and any positive RAST at baseline (1990-92) in patients with a new onset of asthma or nasal allergy in ECHRS III

Any positive SPT: at least one positive skin prick test; Any positive RAST: at least one positive radioallergosorbent test

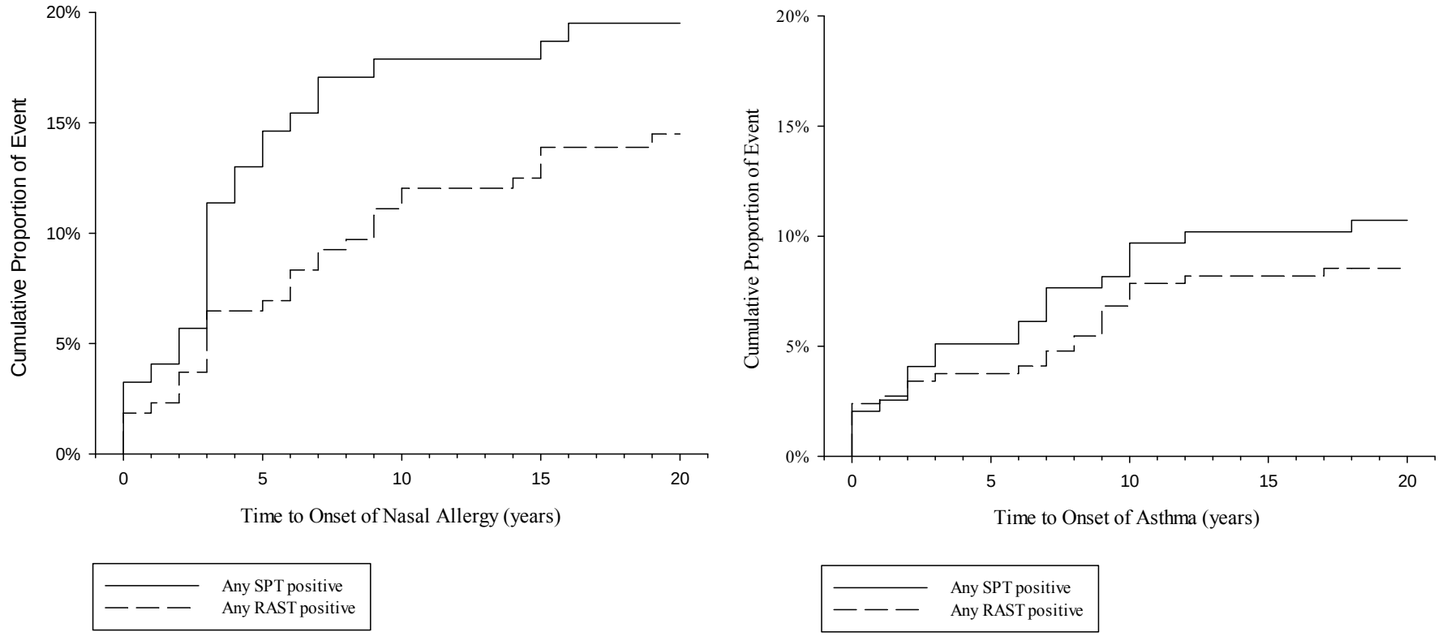

Fig. 3. Kaplan-Meier curves for new-onset of asthma and nasal allergy
Cumulative Proportion of Events: Cumulative proportion of new-onset asthma/nasal allergy at certain times under control; SPT: skin prick test; RAST: radioallergosorbent test; Any SPT positive: at least one positive skin prick test; Any RAST positive: at least one positive radioallergosorbent test;
Participants from Erfurt and Hamburg, aged 21 to 47 years at baseline