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Original article

Rhinitis in Swiss adults is associated with asthma and early life factors, but not second hand tobacco smoke or obesity

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ARIA, Allergic rhinitis in asthma; BMI, Body mass index; ECHRS, European community respiratory health survey;
IgE, Immunoglobulin E; RRR, Relative risk ratio; SAPALDIA, Swiss cohort study on air pollution and lung and heart diseases in adults; SHS, Second hand tobacco smoke; TAHS, Tasmanian longitudinal health study; 95%CI, 95% Confidence interval

ABSTRACT

Background: Second hand tobacco smoke (SHS) and overweight/obesity are risk factors for asthma and lower airway respiratory symptoms. We investigated whether SHS or overweight/obesity were also associated with allergic or non-allergic rhinitis.
Methods: Cross-sectional data were obtained during the second SAPALDIA Study. Interviewer administered questionnaires were completed by 8047 participants from 8 communities in Switzerland. Blood was collected from 5841 participants and tested for allergen specific IgE. Allergic rhinitis was defined as nasal symptoms with detectable IgE. Data were analysed by multinomial logistic regression with four outcome categories defined according to the presence or absence of rhinitis and/or atopy.
Results: The prevalence of allergic rhinitis was 885 (15.2%) and non-allergic rhinitis 323 (5.5%). The risk of allergic rhinitis was increased in subjects with physician diagnosed asthma (Relative Risk Ratio 6.81; 95%CI 5.39, 8.6), maternal atopy (1.56; 1.27, 1.92) and paternal atopy (1.41; 1.11, 1.79). Older subjects were at lower risk (0.96; 0.95,0.97 per year), as were those raised on a farm (0.64; 0.49,0.84), with older siblings (0.92; 0.86,0.97 per sib) or from rural areas. The risk of non-allergic rhinitis was also increased in subjects with physician diagnosed asthma (4.02; 2.86, 5.67), reduced in males (0.59; 0.46, 0.77), but not associated with upbringing on a farm or older siblings. There were no significant associations of SHS or overweight/obesity with either form of rhinitis.
Conclusions: Allergic and non-allergic rhinitis have different risk factors apart from asthma. There are significant regional variations within Switzerland, which are not explained by the factors examined.

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Introduction

Rhinitis is characterised by nasal symptoms such as rhinorrhoea, post-nasal drip, sneezing, obstruction and/or pruritus. The ARIA (Allergic Rhinitis in Asthma) classification[1] includes infectious, allergic, occupational, drug induced and hormonal rhinitis. There are also other rarer causes including the non-allergic rhinitis with eosinophilia syndrome, irritant, food-related and atrophic rhinitis. Epidemiological studies to date have focussed on allergic rhinitis,[2–4] which is highly prevalent in many Western countries[5] and causes considerable impairment of quality of life.[6] The median fraction attributable to atopy (population attributable risk) was 27%,[5] which means that other risk factors for rhinitis must also be important.

Second hand (or environmental tobacco) smoke (SHS) exposure is associated with lower respiratory symptoms, asthma and decrements in lung function. Both active smoking and SHS may increase the risk of chronic rhinitis.[7,8] However the results of studies of active and passive smoking on allergic rhinitis have been conflicting. Obesity and overweight are associated with lower respiratory symptoms and several studies have suggested that this increasingly common condition is associated with asthma, particularly non-allergic asthma.[9] This could provide a partial explanation for the increase in the prevalence of asthma that has been observed in Western countries over the last 50 years. Longitudinal analysis of data from the Tasmanian longitudinal Health Study (TAHS) found that adiposity at 7 years was associated with current asthma at 32 years of age, particularly in women.[10] However much less is known about the possible role of obesity/overweight in rhinitis.

The aims of the present analysis of data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) were to address the following questions:

1. Does second hand smoke (SHS) increase the risk of allergic or non-allergic rhinitis?
2. Does obesity/overweight increase the risk of allergic or non-allergic rhinitis?
3. Are any associations independent of demographic factors, family history, asthma, occupational and early life exposures?

Methods

Subjects

SAPALDIA enrolled 9651 Swiss adults aged between 18 and 60 years at baseline in 1991. Subjects in the present analysis were participants in the second SAPALDIA study conducted from 2001 to 2003, when weight was measured and blood collected for allergic and other markers. The detailed methods and characteristics of participants have been described elsewhere.[11] However briefly, an interviewer administered questionnaire similar to that used in the European Community Respiratory Health Survey (ECHRS)[12] was completed by 8047 participants from 8 communities around Switzerland (Basel, Wald, Davos, Lugano, Montana, Payerne, Aarau and Geneva) (Fig. 1). A health examination was agreed to by 6528 participants and 5973 completed the entire protocol. The study was approved by the Swiss Academy of Medical Sciences and ethics committees of all regional study sites. Written informed consent was obtained from all study participants.

Definitions

Exposure to second hand smoke (SHS) was defined as a positive response to the following question: Have you been regularly exposed to tobacco smoke in the last 12 months? This definition has been previously used in SAPALDIA.[13] Overweight was defined as $25 \leq$ Body Mass Index (BMI) < 30 kg/m^2 and obesity as BMI ≥ 30 kg/m^2.[14]

The ***outcome*** of rhinitis was defined as a positive response to the question: Do you have any nasal allergies including hay fever? Asthma was defined as positive responses to: Have you ever had asthma? and Was this confirmed by a doctor?

Atopy was considered an effect modifier. Blood was taken from 5841 participants and assayed for total and allergen specific IgE *in vitro*. The polyvalent Phadiatop™ assay detected allergen specific IgE ≥ 0.35 kU$_A$/L to any of 11 allergens [*Cladosporium*, *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cat, dog, horse, birch, timothy, olive, mugwort, *Parietaria judaica*].

Allergic rhinitis was defined as a positive answer to the rhinitis question together with a positive Phadiatop™. ***Non-allergic rhinitis*** was defined as a positive answer to the rhinitis question, with a negative Phadiatop™.

Parental atopy was defined as a positive response to either of the following questions: Did your mother ever have eczema, skin or nasal allergy or hay fever? Did your father ever have eczema, skin or nasal allergy or hay fever?

Statistical analysis

This commenced with a cross-sectional analysis of the data on rhinitis from SAPALDIA2. Univariate associations with the extent of participation or type of rhinitis were assessed in contingency tables with χ^2 tests. Comparisons between groups were made by analysis of variance or non-parametric equivalents if distributional assumptions were not satisfied. Multinomial logistic regression models were then fitted with four outcome categories defined according to the presence or absence of rhinitis and/or atopy. Forward entry was used with stepwise selection based on the likelihood ratio test. Initial selection of covariates was guided by the literature and prior knowledge. Covariates included: demographic – age, sex, level of education, nationality (Swiss/other); family history – maternal or paternal asthma or atopy; occupation – self reported exposure to vapours, gas, dust or fumes; early childhood "hygiene" – number of older siblings, early respiratory infections, farm residence and day care attendance; and active smoking – non-smoker, ex-smoker or current smoker. Sensitivity analyses were conducted and covariates retained in the models if they altered the OR by 10%. Doctor diagnosed asthma was initially fitted as a covariate, and subsequently examined as a stratification variable. The effect estimates from the multinomial logistic models were expressed as Relative Risk Ratios (RRR) and 95% confidence intervals (95%CI), relative to the group with no rhinitis or atopy. RRR can be interpreted as odds ratios conditional on having observed either the reference outcome or the outcome in question. Analyses were conducted in SPSS (version 19, IBM, Armonk NY 2010) and SAS (version 9.3, SAS Institute Inc., Cary NC, USA, 2011).

Results

Description of subjects

Of the 8047 participants in this follow-up study, 4180 (51.9%) were female and 3867 (48.1%) male. The mean (SD) age at this examination was 52.1 (11.6) years. Mean BMI was 25.9 (4.45) kg/m^2, thus 2494 (25.8%) were classified as overweight and 1068 (11.1%) obese. The educational level of 2082 (25.9%) participants was considered high (University or technical college), 5257 (65.4%) intermediate (middle school or apprenticeship) and 702 (8.7%) low (primary and/or secondary school). Doctor diagnosed asthma was

Fig. 1. SAPALDIA study regions.

reported by 775 (9.6%) of participants. There were 3394 (42.2%) never smokers, 2537 (26.3%) former and 2116 (26.3%) current smokers. Over a quarter (1953 or 25.6%) had been exposed to SHS in the last 12 months, but only 6.4% reported exposure at work and mean (SD) daily hours exposed to SHS were 0.78 (2.1). A similar proportion (1801 or 27.4% of respondents) reported current occupational exposure to vapours, gas, dust or fumes.

A family history of maternal asthma was reported by 369 (4.6%), maternal atopy by 1102 (13.7%), paternal asthma by 465 (5.8%) and paternal atopy by 793 (9.9%) participants in SAPALDIA2. Early life hygiene factors included 3660 (45.5%) sharing a bedroom in early childhood, 1831 (22.8%) attending day care, 638 (7.9%) had a severe respiratory infection before the age of 5 years, 979 (12.2%) were exposed to maternal smoking and 1038 (15.8%) lived on a farm up to the age of 5.

Compared to those who only completed the questionnaire, those who provided blood to be tested for IgE were slightly younger; were more likely to be Swiss nationals, highly educated, never smokers and living on a farm up to the age of 5 years. Conversely they were less likely to be currently exposed to SHS or maternal smoking during childhood. There were also significant variations in the full participation rate between communities ($p < 0.001$). There were no significant differences in sex, BMI, overweight/obese, doctor diagnosed asthma, occupational exposures, number of older siblings or family history (Table 1).

Allergic and non-allergic rhinitis

The prevalence of allergic rhinitis was 885 (15.2%) and non-allergic rhinitis 323 (5.5%) in 5834 subjects with complete data. A further 874 (9.1%) were atopic but did not report symptoms of rhinitis. However a clear majority of subjects did not have rhinitis or atopy. Key unadjusted differences between these 4 groups are summarised in Table 2. Females were significantly more likely than males to have non-allergic rhinitis. Allergic rhinitis was more prevalent in Basel and Geneva than Wald or Payerne. Those with allergic rhinitis were significantly younger, had a lower BMI and were less likely to be overweight/obese. They were also significantly more likely to have higher education. The mean [SD] age of onset of allergic rhinitis was 22.5 [14.2] years which was significantly younger than non-allergic rhinitis (35.2 [17.3] years, $p < 0.0001$). Doctor diagnosed asthma was significantly more likely among both allergic and non-allergic rhinitis than the other groups. Those with allergic rhinitis were significantly less likely to be current or former smokers. However there were no significant differences between groups in exposure to SHS in the previous 12 months, exposure to SHS at work, daily hours exposed to SHS or occupational exposure to vapours, gas, dust or fumes.

A family history of maternal or paternal atopy was significantly more likely among those with allergic rhinitis. Maternal asthma was slightly more common among those with allergic rhinitis, but

Table 1
Differences between participants who only completed the questionnaire and those who also provided blood to be tested for IgE.

	Questionnaire only (n = 2212)	Full participation (n = 5835)	*P* value
Male sex (%)	1028 (46.5)	2839 (48.7)	0.08
Age – mean (SD) years	51.7 (11.9)	52.2 (11.4)	0.05
BMI – median [IQR] kg/m^2	25.5 [22.5, 28.8]	25.4 [22.8, 28.3]	0.45
Overweight/obese (%)	426 (54.6)[†]	3068 (52.7)	0.32
Education – high (%)	479 (21.7)	1603 (27.5)	
Intermediate (%)	1403 (63.5)	3, 854 (66.1)	<0.001
Asthma (%)	232 (10.5)	543 (9.3)	0.11
Smoking – current (%)	691 (31.2)	1425 (24.4)	
Former (%)	676 (30.6)	1861 (31.9)	<0.001
Exposed to SHS (%)	515 (28.4)	1438 (24.7)	0.002
Occupational exposure to vapours, gas, dust or fumes (%)	194 (24.8)[†]	1607 (27.8)	0.08
Maternal atopy (%)	297 (13.5)	805 (13.8)	0.68
Paternal atopy (%)	231 (10.5)	562 (9.6)	0.27
Childhood on farm	98 (12.6)[†]	940 (16.3)	0.008
Maternal smoking	310 (14.1)	669 (11.5)	0.002

[†] n = 780.

Table 2
Description of participants by type of rhinitis. *P* values relate to comparisons between the four categories (n < 5834 for some analyses because of missing data).

	No rhinitis or atopy (n = 3752)	Atopic only (n = 874)	Non-allergic rhinitis (n = 323)	Allergic rhinitis (n = 885)	*P* value
Male sex (%)	1774 (47.3)	509 (58.2)	112 (34.7)	444 (50.2)	<0.001†
Area – Geneva	181 (58.0)	47 (15.1)	30 (9.6)	54 (17.3)	
Aarau	638 (65.6)	134 (13.8)	47 (4.8)	154 (15.8)	
Payerne	589 (69.8)	131 (15.5)	54 (6.4)	70 (8.3)	
Montana	395 (66.7)	81 (13.7)	23 (3.9)	93 (15.7)	
Lugano	536 (62.1)	153 (17.7)	30 (3.5)	144 (16.7)	
Davos	260 (63.4)	58 (14.1)	26 (6.3)	66 (16.1)	
Wald	751 (66.8)	154 (13.7)	66 (5.9)	153 (13.6)	
Basel	402 (56.1)	116 (16.2)	47 (6.6)	151 (21.1)	<0.001†
Age – mean (SD) yrs	53.6 (11.2)	51.2 (11.1)	52.8 (10.8)	47.6 (11.5)	<0.001‡
BMI – median [IQR] kg/m^2	25.5 [22.9, 28.4)	25.6 [23.1, 28.7]	25.4 [22.4, 28.9]	24.8 [22.5, 27.4]	<0.001§
Overweight/obese (%)	2015(53.8)	481 (55.3)	167 (52.0)	405 (45.9)	<0.001†
Education – high (%)	933 (24.9)	248 (28.4)	82 (25.5)	340 (38.5)	
Intermediate	2565 (68.4)	566 (64.8)	207 (64.3)	516 (58.4)	<0.001†
Asthma (%)	168 (4.5)	115 (13.2)	53 (16.4)	207 (23.4)	<0.001†
Smoking – current (%)	933 (24.9)	248 (28.4)	81 (25.1)	163 (18.4)	
Former	1237 (33.0)	257 (29.4)	112 (34.7)	255 (28.8)	<0.001†
Exposed to SHS (%)	909 (24.2)	241 (27.7)	82 (25.5)	206 (23.4)	0.14†
Occupational exposure to vapours, gas, dust or fumes (%)	1018 (27.4)	241 (27.8)	87 (27.4)	261 (29.8)	0.53†
Maternal atopy (%)	445 (11.9)	121 (13.8)	50 (15.5)	189 (21.4)	<0.001†
Paternal atopy (%)	312 (8.3)	87 (10.0)	36 (11.1)	127 (14.4)	<0.001†
Childhood on farm	697 (18.8)	111 (12.8)	55 (17.5)	77 (8.8)	<0.001†
Maternal smoking	396 (10.6)	119 (13.7)	38 (11.8)	116 (13.3)	0.022†

† χ^2 test for comparison of proportions.
‡ Analysis of variance.
§ Kruskal Wallis test.

there was no significant difference in paternal asthma (data not shown). Those without rhinitis or atopy were significantly more likely to have spent the first five years of their lives on a farm. Maternal smoking during childhood was more likely among those with allergic rhinitis or atopy alone. There were no significant differences in severe early respiratory infections or day care attendance between participants with rhinitis or atopy and those without these conditions.

Multinomial logistic models of allergic and non-allergic rhinitis are summarised in Table 3. The risk of allergic rhinitis was significantly increased in subjects with doctor diagnosed asthma (RRR 6.81; 95%CI 5.39, 8.6), maternal atopy (1.56; 1.27, 1.92) and paternal atopy (1.41; 1.11, 1.79). Older subjects were at lower risk (0.96; 0.95, 0.97 per year), as were those raised on a farm (0.64; 0.49, 0.84), with older siblings (0.92; 0.86, 0.97 per sib) or from Aarau, Payerne, Montana or Wald. The risk of non-allergic rhinitis was also significantly increased in subjects with doctor diagnosed asthma (4.02; 2.86, 5.67), but reduced in males (0.59; 0.46, 0.77) and those from Aarau, Montana or Lugano.

There was no significant independent association of SHS with either form of rhinitis. Maternal smoking was not selected to enter the model. When current smoking was selected by the stepwise procedure, non-smokers appeared to be at an increased risk of allergic rhinitis (1.88; 1.51, 2.34), as did former smokers (1.43; 1.12, 1.82). However exposure to SHS was still not significantly associated with either form of rhinitis. This finding did not change when the data were stratified by asthma.

Similarly there was no significant independent association of overweight/obesity with either form of rhinitis. The distributions of all four outcome groups as a function of BMI in those without or with asthma are given in Fig. 2a,b respectively.

When the analysis was stratified by asthma status, BMI in the non-extreme range was not associated with either form of rhinitis in non-asthmatics (Fig. 2a). In asthmatics, there was a tendency for persons with allergic rhinitis to have BMI at the lower end (Fig. 2b).

Discussion

This large population based study has confirmed that allergic and non-allergic rhinitis have different risk factors, apart from asthma. However second hand tobacco smoke and overweight/obesity did not appear to be independent risk factors for either form of rhinitis. The strongest risk factors for allergic rhinitis were asthma and a family history of atopy. The risk was lower among older subjects, which could be due to atopy declining with age or a cohort effect. The protective effects of older siblings and being raised on a farm are consistent with the "hygiene" hypothesis.[15] The apparent association with higher education as a proxy for socio-

Table 3
Multinomial logistic models of allergic and non-allergic rhinitis.

	Allergic rhinitis		Non-allergic rhinitis	
	RRR	95%CI	RRR	95%CI
Male sex	1.08	(0.91, 1.27)	0.59	(0.46, 0.77)
Area† – Geneva	0.78	(0.54, 1.17)	1.30	(0.78, 2.16)
Aarau	0.63	(0.48, 0.83)	0.61	(0.40, 0.94)
Payerne	0.36	(0.26, 0.50)	0.74	(0.48, 1.13)
Montana	0.65	(0.47, 0.89)	0.47	(0.27, 0.80)
Lugano	0.86	(0.65, 1.15)	0.47	(0.29, 0.77)
Davos	0.88	(0.62, 1.24)	0.89	(0.53, 1.50)
Wald	0.70	(0.53, 0.92)	0.75	(0.50, 1.13)
Age (/year)	0.96	(0.95, 0.97)	0.99	(0.98, 1.003)
SHS	0.86	(0.71, 1.03)	1.04	(0.79, 1.37)
Overweight/obese	0.96	(0.81, 1.13)	1.02	(0.80, 1.31)
Older sibs number	0.92	(0.86, 0.97)	0.96	(0.89, 1.04)
Paternal atopy	1.41	(1.11, 1.79)	1.22	(0.84, 1.78)
Maternal atopy	1.56	(1.27, 1.92)	1.18	(0.85, 1.64)
Education‡ – high	1.48	(0.94, 2.32)	0.68	(0.42, 1.10)
intermediate	1.02	(0.66, 1.57)	0.57	(0.38, 0.87)
Asthma	6.81	(5.39, 8.60)	4.02	(2.86, 5.67)
Childhood on farm	0.64	(0.49, 0.84)	0.91	(0.66, 1.27)

RRR, Relative Risk Ratio (relative to group with no rhinitis or atopy); SHS, Second Hand Smoke.
† Basel is reference community.
‡ Low education is reference category.

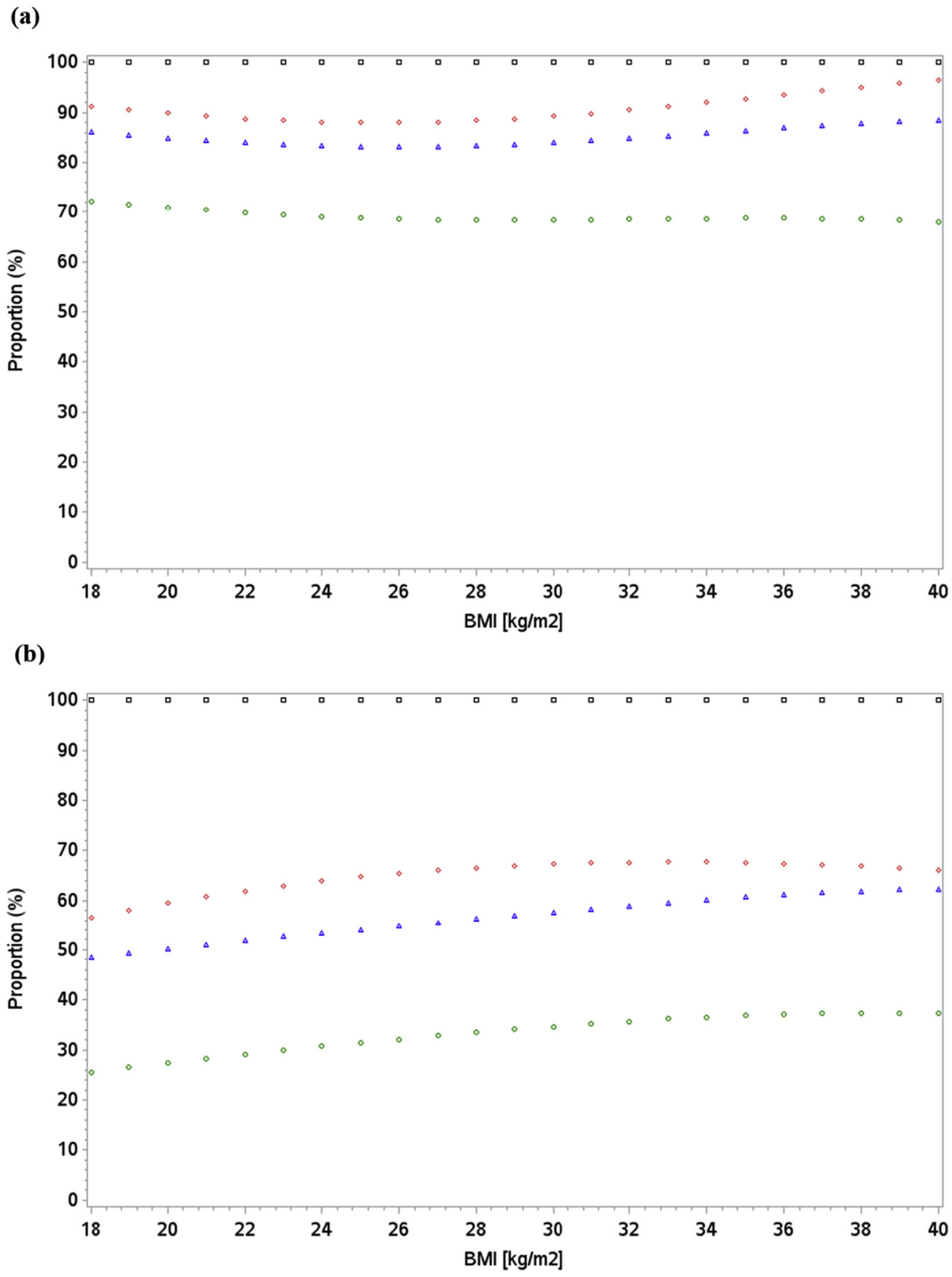

Fig. 2. Distribution of rhinitis/atopy outcomes as a function of BMI in subjects **(a)** without **(b)** with doctor diagnosed asthma. The lowest curve (green circles) gives the proportion of subjects without rhinitis symptoms or atopy. Second band (between green circles and blue triangles) proportion of subjects with atopy but no rhinitis symptoms. Third band (between blue triangles and red diamonds) proportion of subjects with rhinitis symptoms but no atopy. Fourth band (between red diamonds and black squares) proportion of subjects with rhinitis symptoms and atopy.

economic status was probably due to confounding by other factors. Non-allergic rhinitis appeared to be more common in females than males, similar to non-allergic asthma. Symptoms also appeared to commence at an older age than in allergic rhinitis.

Striking regional variations in the prevalence of rhinitis and atopy both within Switzerland[16] and around Europe and beyond have been noted previously.[5] The prevalence of allergic and non-allergic rhinitis was generally lower in the rural communities, consistent with the hygiene hypothesis. However the variation remained even after accounting for the early life environment, suggesting that other factors might be responsible. The prevalence was not consistently lower in alpine communities (Davos, Montana), suggesting that allergen exposures might be less relevant. However this is likely to be confounded by selection effects as it is

conceivable that some asthmatics moved to Davos to reduce allergen exposures.

Second hand smoke (SHS) exposure during childhood was associated with lower respiratory symptoms, asthma and decrements in lung function among young adults participating in the European Community Respiratory Health Survey (ECRHS).[17] Occupational SHS exposure was also associated with any respiratory symptom and current asthma in adults.[17] Both active smoking and SHS may increase the risk of chronic rhinitis.[7,8] However the results of studies of smoking on allergic rhinitis have been conflicting, perhaps due to self report bias or "healthy smoker" effects. We think that avoidance is the most likely explanation for the apparent protective effect that we observed of current or former smoking on allergic rhinitis.

The literature to date on overweight/obesity and rhinitis has been inconclusive. Such a relationship is biologically plausible and similar to asthma might be mediated through inflammatory pathways involving cytokines including tumour necrosis factor (TNF).[18] One case-control study from China found that obesity was associated with a 3 fold increase in the risk of allergic rhinitis.[19] On the other hand, a large cross-sectional study of Japanese adults found that obesity and active smoking were associated with a reduced risk of rhinitis without asthma,[20] which could be due to reverse causation. An earlier study of Japanese children found that obesity was associated with a reduced risk of allergic conjunctivitis with or without allergic rhinitis.[21] However there was no overall association of BMI with allergic rhinitis per se. So our inability to demonstrate a simple linear association in Swiss adults is not altogether surprising. The suggestive evidence of an interaction between BMI, asthma and allergic rhinitis needs to be studied further in the context of longitudinal data. In our cross-sectional analyses, we cannot differentiate whether obesity is protective against allergic rhinitis in asthmatics or whether persons with asthma and allergic rhinitis are more likely to adapt a lifestyle and diet to avoid obesity.

The main strengths of SAPALDIA are the sampling of a nationally representative population and a high retention rate on follow-up (86% of living persons).[11] The use of an objective *in vitro* test of allergen specific IgE to classify atopy is a further strength. Weight and height were measured, allowing accurate estimation of BMI. Weaknesses are similar to other previous studies. The diagnosis of rhinitis or hay fever relied on self report and was subject to misclassification. However this question has been widely used in the ECRHS.[22,5] We concede that the combination of this question with allergen specific IgE cannot identify mixed rhinitis.[23] Furthermore exposure to SHS and the diagnosis of parental atopy were also based on self report. Not all subjects who completed questionnaires provided blood potentially introducing further selection bias. In particular smokers and those exposed to SHS were less likely to fully participate. However further analysis of propensity scores suggested that this did not explain the differences in the prevalence of allergic or non-allergic rhinitis between communities. The present analysis is cross-sectional and apart from early life exposures cannot clearly establish the sequence of events.

The major clinical implication of our findings flows from the strong association between asthma and rhinitis. We would encourage clinicians to ask about nasal symptoms in their patients with asthma. Treating allergic rhinitis can improve asthma control.[1] Whilst avoidance of SHS and weight loss are clearly desirable for individual patients and public health purposes, we would not expect these measures to have much effect on the risk of rhinitis. Although this study adds to the evidence supporting the hygiene hypothesis, there is currently no feasible intervention for primary prevention of allergies. The significant regional variations of rhinitis within Switzerland remain unexplained and require further research.

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(a) Allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics.
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Conflicts of interest

MJA has received conference travel support from Boehringer Ingelheim and Sanofi and an unrelated consultancy from AstraZeneca. He holds investigator initiated grants from Pfizer and Boehringer Ingelheim for unrelated research. He was previously chair of the COPD guidelines committee of the Lung Foundation of Australia. The rest of the authors have no conflict of interest.

Authors' contributions

NK, EZ and NPH designed the study. MJA, CS, TS and NPH wrote the manuscript. AJB, LB, MWG, MI, TR, PSG and AJT contributed to data collection in the field and in the laboratory. MJA and CS performed the statistical analysis and interpretation of the results. All authors read and approved the final manuscript.

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