International variation in prevalence of rhinitis and its relationship with sensitisation to perennial and seasonal allergens

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ABSTRACT: **The relative importance of atopy in the aetiology of rhinitis is largely unknown. The present study investigated the geographical variations in rhinitis in relation to atopy.**

The cross-sectional study involved 54,178 children (aged 8–12 yrs) from 30 study centres in 22 countries worldwide. Symptoms of rhinoconjunctivitis and rhinitis without conjunctivitis in the last 12 months were reported in parental questionnaires and children were skin-prick tested.

The prevalence of rhinoconjunctivitis and rhinitis without conjunctivitis varied widely (1.5–24.5% and 1.4–45.2%, respectively). For rhinoconjunctivitis, the population attributable fraction (PAF) varied 0–71% for a positive skin-prick test to one or more seasonal allergens and 0–41% for perennial allergens. The PAF for sensitisation to seasonal and perennial allergens was higher in affluent countries (36 and 25%, respectively) than nonaffluent countries (1.3 and 12.6%, respectively). For rhinitis without conjunctivitis, the PAF for perennial allergens was 8 and 4% for affluent and nonaffluent countries, respectively. No significant PAF was found for seasonal allergens.

Overall, atopy explained only a limited proportion of rhinitis symptoms, suggesting that the importance of other environmental factors has been under emphasised, particularly in less affluent countries. Atopy seems to be only marginally relevant for rhinitis without conjunctivitis, which seems mainly to reflect nonatopic rhinitis.

Rhinitis is an important health problem affecting the quality of life of a large part of the child population. In Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC) [1] the prevalence of rhinitis symptoms in the past 12 months ranged 3.2–66.6% among 13–14-yr-old children. Furthermore, symptoms of allergic rhinitis seem to be increasing in some [2–5] but not all countries [6–9]. As for childhood asthma, the international differences in prevalence and the time trends for rhinitis are still not well understood. Recently, it has been shown that the importance of atopy as an aetiological factor for asthma varies considerably worldwide and is related to gross national income (GNI) [10].

Until recently research has focused on allergic rhinitis and the role of atopy. However, as early as 1988, JONES [11] reported on the importance of nonallergic perennial rhinitis and a more recent review of the published literature [12], which examined 22 population-based studies, indicated that indeed only half of all rhinitis cases (53%) were attributable to atopy. The question remains as to how frequently rhinitis is attributable to atopy and how often symptoms that have been classically regarded as typical of allergic rhinitis are really attributable to atopy.

Traditionally, allergic rhinitis has been subdivided into seasonal and perennial types based on time and duration of symptom occurrence. For these two forms, perennial and seasonal allergens (house dust mites, animal dander and pollens) have been held responsible. In epidemiological studies in European populations, the presence of a runny/

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blocked nose with conjunctivitis in the absence of a cold proved to identify those individuals with allergic rhinitis [1, 13, 14].

The present authors investigated geographical variations in rhinitis in childhood. The following two groups were defined: 1) rhinoconjunctivitis, likely to contain most of the individuals with allergic rhinitis; and 2) rhinitis without conjunctivitis, expected to include both nonallergic and allergic rhinitis. The importance of sensitisation to seasonal and perennial allergens was explored, and the worldwide variation in the population attributable fractions (PAF) was assessed for the two categories of rhinitis. The present study is based on Phase Two of ISAAC [15]. It is the first investigation to compare standardised data from several different centres worldwide which have applied the same protocol for assessing rhinitis symptoms and particularly, for determining atopic sensitisation. An interesting feature of ISAAC Phase Two is the possibility to carry out both ecological and individual comparisons.

MATERIALS AND METHODS

The methods used in the ISAAC Phase Two study are described in detail elsewhere [15] and in the online supplementary data. Briefly, 30 study centres from 22 countries (table 1) drew random samples of ~1,000 children from the classes in which the majority were aged 9–11 yrs. All studies and coordination were approved by local ethics committees [15]. The parents were invited to fill in a standardised, self-administered questionnaire. The questions were identical to those used in the ISAAC Phase One study for 6–7-yr-old children [1, 15, 16]. The question ''In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose, when he/she did not have a cold or the flu?'' (Yes/No) was followed by (if Yes) ''In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'' In countries in which illiteracy is a problem (Ecuador, India, Brazil and Ghana) the questions were posed by trained interviewers. In most centres, all children were invited to undergo a skin-prick test. Several centres drew a random sub-sample (table 1 and online supplementary data) [15].

Skin-prick tests were performed with six common aeroallergens and, in addition, centres were encouraged to test allergens of local relevance. Seasonal allergens comprised mixed tree pollen and mixed grass pollen, perennial allergens were *Dermatophagoides pteronyssinus*, *D. farinae* and cat hair. *Alternaria* and local allergens were classified as either perennial or seasonal depending on the location (information obtained from the centre principle investigator; see online supplementary data). The skin-prick test for sensitisation to seasonal or perennial allergens was considered to be positive if at least one seasonal or perennial allergen yielded a positive test result. A positive skin-reaction was defined as a wheal diameter of $\geqslant 3$ mm, after subtraction of the negative control.

Statistical analysis

Children aged 8–12 yrs were included in the analysis. Spearman correlation coefficients were calculated for the correlation between prevalence rates of symptoms and positive skin-prick test reactivity. According to ISAAC policy, reported frequencies from study centres with <60% participation for parental questionnaires should not be interpreted as

prevalence estimates and were, therefore, not included in the ecological comparisons.

At the individual level, the association between specific symptoms and a positive skin-prick test was assessed with prevalence rate ratios (PRR) within centres [17]. Since children sensitised to perennial allergens are more likely to be sensitised to seasonal allergens, and *vice versa*, adjusted PRRs were calculated with the other group of allergens considered as the adjustment variable. Initial models also included sex, number of siblings and parental allergy, but none of these variables notably influenced the obtained estimate and were therefore omitted from the final model.

The PAFs (%) were calculated using the following formula [18]:

$$PAF = P_{ec} \times (PRR\text{-}1)/PRR \qquad (1)$$

where P_{ec} is the prevalence of exposure among the cases (*i.e.* children with rhinitis). Combined estimates of the PRR and PAF across several study centres were calculated using random effects meta-analysis models [19].

As asthma prevalence and the role of atopy may vary between affluent countries with a ''Western'' lifestyle and less affluent countries, the countries were grouped on the basis of GNI per capita, converted into US dollars using the World Bank Atlas method [20]. The first group (affluent countries) consisted of high-income countries (GNI >US$9,200 in 2001) [21] and included most European centres, essentially EU members before 2004, New Zealand and Hong Kong (China). The other group (nonaffluent countries) comprised all other centres.

RESULTS

Questionnaire data on rhinitis symptoms for 54,178 children aged 8–12 yrs and skin-prick data on allergen-specific sensitisation for 31,759 children were included in the analysis. Participation rates varied 35–100% (median 83%) for the questionnaire, and 24–99.9% (median 67%) for the skin-prick test (table 1).

Prevalence of symptoms

The prevalence of rhinoconjunctivitis symptoms ranged from 1.5% in Pichincha province (Ecuador) to 24.5% in Almeria (Spain), and the prevalence of rhinitis without conjunctivitis ranged from 2.7% in Pichincha province to 29.1% in Guangzhou (China; table 1).

The prevalence of sensitisation to any of the perennial airborne allergens tested also varied widely between centres, from 1.4% in Ghana to 45.2% in Hong Kong (table 2). The prevalence of skin-prick test sensitisation to any of the seasonal allergens varied from 0.1% in Ghana to 25.8% in Tromsø (Norway).

Ecological correlations

There was a significant correlation between rhinoconjunctivitis and sensitisation to seasonal (ρ=0.5, p=0.019) but not perennial allergens (ρ=0.2, p=0.38; fig. 1). However, for rhinitis without conjunctivitis, there was a significant correlation with sensitisation to perennial (ρ=0.54, p=0.007) but not with seasonal allergens (ρ= -0.05, p=0.84).

TABLE 1 Participation and prevalence of symptoms by centre

| Country and centre	Participation rhinitis questionnaire		Prevalence of symptoms in the past year		Participation skin-prick test	
	Children n	Participation rate	Rhinitis with conjunctivitis	Rhinitis without conjunctivitis	Children n	Participation rate
Albania						
Tirana[#]	1045	94.3	6.7	14.6	929	84.0
Brazil						
Uruguaiana[#]	1971	96.3	21.0	9.9	1192	96.2
China						
Beijing[#]	4207	92.3	7.5	23.2	1044	90.8
Guangzhou[#]	3502	93.1	7.0	29.1	1078	36.1
Hong Kong	3010	96.7	12.4	15.2	1324	63.8
Ecuador						
Pichincha province[#]	894	100.0	1.5	2.7	894	99.9
Estonia						
Tallinn[#]	966	83.4	5.6	11.4	642	55.5
France[¶]						
Créteil	1373	64.8	14.6	15.4		
Georgia						
Tbilisi[#]	951	82.7	7.0	9.6	173	75.9
Germany						
Dresden	3013	82.5	12.1	9.9	2259	61.6
Munich	3271	86.7	12.8	8.3	2317	60.6
Ghana						
Kintampo[#]	1354	ND	ND	ND	1322	ND
Greece						
Athens	985	85.3	4.8	12.9	985	85.3
Thessaloniki	1018	63.0	7.1	12.7	1018	63.0
Iceland						
Reykjavik	935	46.5	11.2	6.3	633	38.0
India						
Bombay[#]	1656	ND	4.9	5.3	1556	ND
Italy						
Rome	1346	82.9	9.6	11.5	1307	62.3
Latvia						
Riga[#]	906	87.3	8.6	15.7	295	30.8
Netherlands						
Utrecht	3527	64.4	9.7	15.3	1286	43.3
New Zealand						
Hawkes Bay	1320	84.3	22.3	12.8	1288	82.2
Norway						
Tromsø	3675	81.5	12.6	7.4	722	60.2
Palestine						
Ramallah[#]	2293	84.8	6.9	10.1	221	65.0
Spain						
Almeria	1127	49.9	24.5	13.4	1075	47.7
Cartagena	1402	53.7	15.4	9.5	1030	39.6
Madrid	964	35.2	18.7	13.4	653	23.9
Valencia	1349	40.1	12.6	10.4	1023	30.5
Sweden						
Linköping	904	81.4	13.8	5.1	857	77.0
Östersund	1193	85.9	12.2	8.9	991	71.4
Turkey						
Ankara[#]	2966	87.3	11.8	17.7	2747	81.0
UK						
West Sussex	1055	78.5	16.2	7.4	898	66.7

Data are presented as %, unless otherwise stated. ND: no data available. [#]: centres in countries with a gross national income per capita <US$9,200 in 2001 (nonaffluent countries); [¶]: the core standard allergens were not licensed in France, where allergens from Stallergènes (Antony, France) were tested in 1,451 children.

TABLE 2	Prevalence of positive skin-prick tests (SPT) to perennial and seasonal allergens			
Country and centre	**Positive SPT to perennial allergens**		**Positive SPT to seasonal allergens**	
	Prevalence %	Positives n	Prevalence %	Positives n
Albania				
Tirana	12.4	115	6.4[#]	59
Brazil				
Uruguaiana	12.1	144	2.0	24
China				
Beijing	22.9[#]	239	3.0	31
Guangzhou	31.5[#]	340	1.9	21
Hong Kong	45.2[#]	599	1.2	16
Ecuador				
Ecuador	18.1[#]	162	2.5	22
Estonia				
Tallinn	12.6[#]	81	6.7	43
Georgia				
Tbilisi	27.4[#]	50	18.1	28
Germany				
Dresden	16.2	365	18.4	415
Munich	13.2	306	16.1	372
Ghana				
Kintampo	1.6	21	0.1	1
Greece				
Athens	9.2	91	8.2[#]	81
Thessaloniki	21.2	216	12.8[#]	130
India				
Bombay	5.8	90	2.1	32
Iceland				
Reykjavik	13.9	88	17.9	113
Italy				
Rome	24.9	326	14.3[#]	187
Latvia				
Riga	16.6	49	9.2	27
Netherlands				
Utrecht	24.9[#]	320	17.8	229
New Zealand				
Hawkes Bay	27.6	355	22.6	291
Norway				
Tromsø	20.1	145	25.8	186
Palestine				
Ramallah	10.3[#]	25	0.5[#]	1
Spain				
Almeria	41.5	446	7.0	75
Cartagena	22.0	227	3.9[#]	40
Madrid	19.4	127	25.6[#]	167
Valencia	12.5	128	3.0[#]	31
Sweden				
Linköping	11.8[#]	101	16.7	143
Öestersund	18.6[#]	184	19.2	190
Turkey				
Ankara	15.8[#]	433	15.2[#]	418
UK				
West Sussex	10.6	95	11.1	100

[#]: local allergens were tested in addition to a standard set of six common allergens.
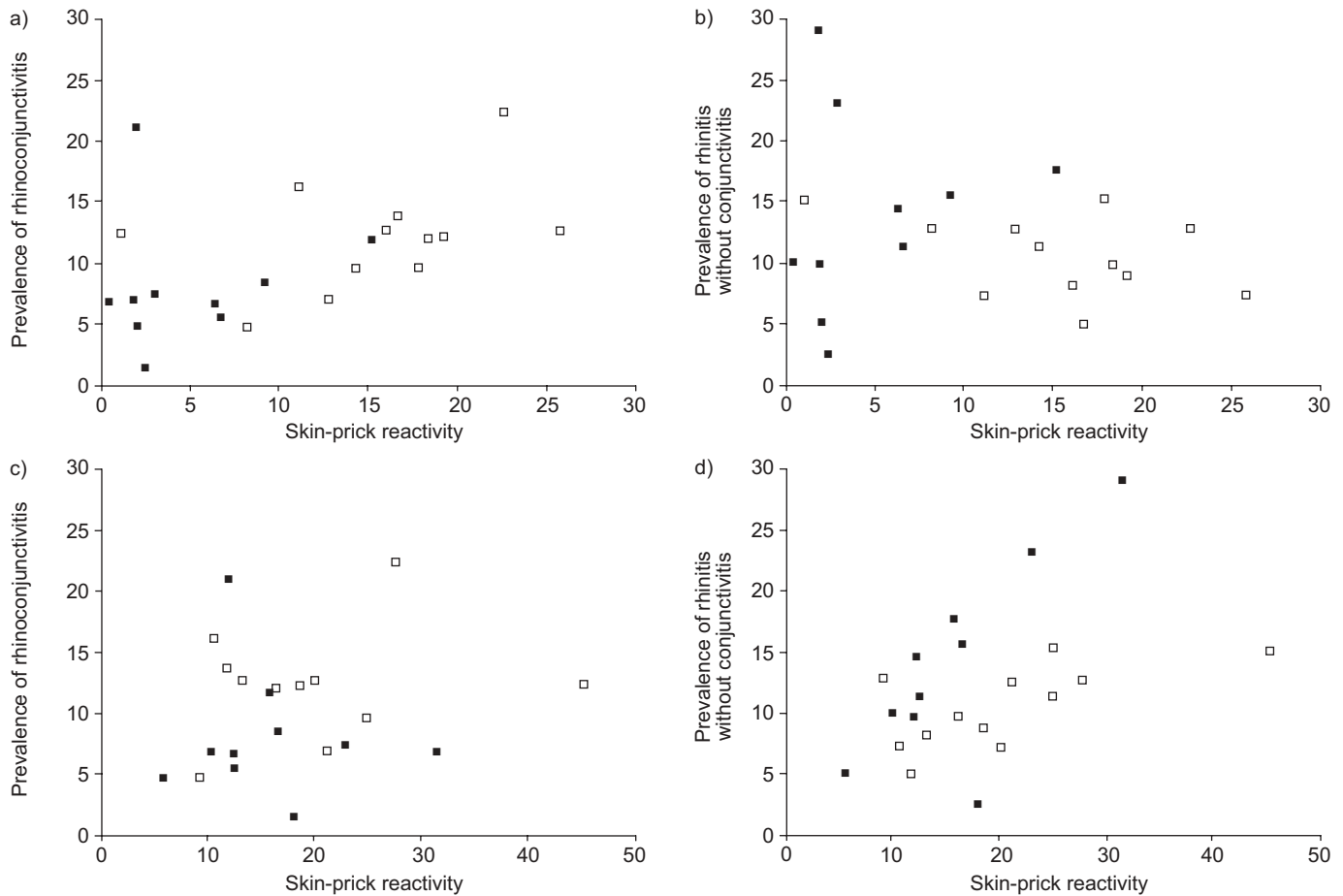
FIGURE 1. Scatter plots of the prevalence of rhinitis symptoms *versus* the prevalence of a positive skin-prick test to a and b) seasonal allergens, and c and d) perennial allergens. □: affluent countries; ■: nonaffluent countries. a) Spearman correlation coefficient 0.50, p=0.02; b) Spearman correlation coefficient 0.05, p=0.84; c) Spearman correlation coefficient 0.20, p=0.38; d) Spearman correlation coefficient 0.54, p=0.01.

Associations based on individuals and PAFs

The association between rhinitis and sensitisation to perennial/seasonal allergens is presented in figure 2 (crude PRR) and table 3 (PRR adjusted for seasonal/perennial allergens).

Rhinoconjunctivitis

The adjusted association between rhinoconjunctivitis and perennial allergens was positive in all but three centres (Ankara, Turkey; Beijing, China; and Ramallah, Palestine). The remaining adjusted PRR ranged from 1.1 in Tirana (Albania) to 4.1 in Cartagena (Spain). For affluent centres, the combined estimate was 2.2 (95% confidence interval 1.8–2.6) and for nonaffluent centres it was 1.5 (1.1–2.1).

Adjusted PAFs varied from 0.9% in Tirana (Albania) to 57.4% in Hong Kong (table 4). For affluent centres the combined PAF was 25.0% (18.1–31.4%), whereas among nonaffluent centres, only 12.6% (2.7–21.6%) were attributable to perennial allergens.

Sensitisation to seasonal allergens was positively associated with rhinoconjunctivits in all centres except Tirana (Albania) and Bombay (India), and the remaining adjusted PRR ranged from 1.0 in Ankara (Turkey) and Almeria (Spain) to 9.0 in Tromsø (Norway). The combined estimate was 3.6 (2.6–5.0) for affluent centres and 1.6 (1.1–2.4) for nonaffluent centres.

PAF ranged from ∼0% in Almeria (Spain), Bombay (India) and Tirana (Albania) to 71.3% in Tromsø (Norway). The PAF were highest in the Scandinavian centres and Dresden (Germany). The combined estimate was 35.9% (23.6–46.2%) and 1.3% (0–2.8%) for affluent and nonaffluent centres, respectively. When considering outdoor and indoor allergens together in all centres, the overall PAF was 56%.

Rhinitis without conjunctivitis

For the association between sensitisation to perennial allergens, the adjusted PRR ranged from 0.3 in Linköping (Sweden; not statistically significant) to 2.2 in Rome (Italy). The combined estimate for affluent centres was 1.5 (1.3–1.7) and 1.2 (1.1–1.4) for nonaffluent centres.

PAFs ranged from 0% in Bombay (India) and Linköping (Sweden) to 24.9% in Hong Kong. Combined estimates gave a PAF of 8.0% (5.5–10.5%) for affluent countries and 4.0% (1.2–6.6%) for nonaffluent countries.

There was no association between sensitisation to seasonal allergens and rhinitis without conjunctivitis. The PRR estimates were not statistically significant in any centre. The estimates for the combined PRR were 1.0 (0.9–1.1) for affluent and 1.1 (0.9–1.3) for nonaffluent centres.
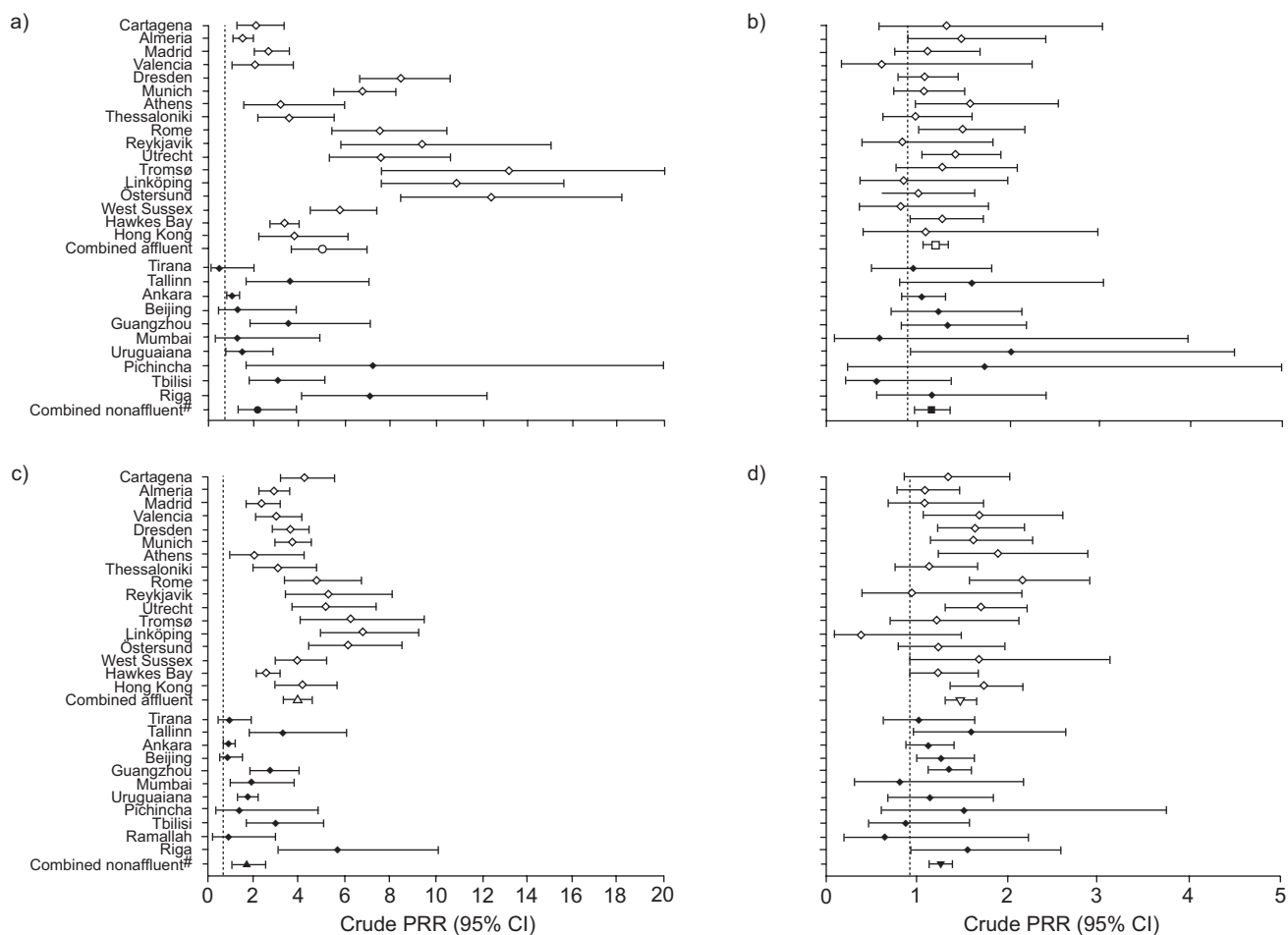
FIGURE 2. Association between rhinitis symptoms and a positive skin-prick test to seasonal and perennial allergens. a) Rhinoconjunctivitis *versus* seasonal allergens, b) rhinitis without conjunctivitis *versus* seasonal allergens, c) rhinoconjunctivitis *versus* perennial allergen and d) rhinitis without conjunctivitis *versus* perennial allergen. a) ○: 4.99 (3.60–6.91); ●: 2.16 (1.22–3.82); b) □: 1.18 (1.06–1.32); ■: 1.14 (0.96–1.35); c) △: 3.87 (3.30–4.54); ▲: 1.69 (1.11–2.56); d) ▽: 1.47 (1.31–1.65); ▼: 1.25 (1.13–1.39). PRR: prevalence rate ratios. #: does not include Tbilisi, Georgia (see online supplementary data).

Combined estimates of PAF were 2.1% (95% CI -0.3–4.5%) for affluent countries and 0.6% (95% CI -0.5–1.6%) for nonaffluent countries. The overall PAF of the sensitisation to seasonal and perennial allergen for rhinitis, with and without conjunctivitis, was 33%.

DISCUSSION

The present study indicates great variation in rhinitis symptom prevalence and its relationship to atopic sensitisation. Generally, both the ecological and the individual-based analyses showed a strong association of rhinoconjunctivitis with sensitisation to perennial and seasonal allergens, whereas for rhinitis without conjunctivitis a relationship could only be seen with perennial allergens. The PAFs due to atopy varied greatly and were considerably higher among affluent than nonaffluent centres.

There are strengths and limitations of the current study that are worth discussing. The present authors obtained information on rhinitis and atopic sensitisation for children in 29 centres worldwide, more than any previous study. All centres were comparable methodologically. In particular, the skin-prick

test was performed according to the same protocol using the same extracts and the same staff-training procedures [15]. In addition, allergens of local relevance were also included. However, with respect to the standard test set of six allergens, effect measures (odds ratios and PAF) were only slightly changed by inclusion of local allergens. The countries analysed were selected based on the findings from the ISAAC Phase One study to ensure that the global variety of the disease prevalence was captured. Therefore, the current results are likely to represent the worldwide variation in the relationship between sensitisation to allergens and rhinitis. However, one clear limitation of the present study is that, in some centres, response rates were low and it cannot be fully excluded that sick children are over-represented. This may have increased the prevalence estimate for rhinitis symptoms and the considered risk factors. However, the influence on the association between rhinitis and skin-prick tests will probably only be minor as long as the selection factors have operated in the same manner for rhinitis and atopy. Indeed, the estimated odds ratio and PAFs changed very little when these additional allergens were omitted from the analyses. Finally, it cannot be ruled out that there was a certain degree of misclassification

TABLE 3	Association of rhinitis with conjunctivitis and rhinitis without conjunctivitis with positive skin-prick tests to perennial and seasonal allergens			
	Rhinitis with conjunctivitis		**Rhinitis without conjunctivitis**	
Country and centre	**Perennial allergens**	**Seasonal allergens**	**Perennial allergens**	**Seasonal allergens**
China				
Hong Kong	4.0 (2.9–5.5)[#]	2.3 (1.4–3.8)	1.7 (1.4–2.2)[#]	0.8 (0.3–2.3)
Germany				
Dresden	1.4 (1.1–1.8)	7.3 (5.6–9.6)	1.8 (1.3–2.4)	0.8 (0.6–1.2)
Munich	1.6 (1.2–2.0)	5.6 (4.4–7.2)	1.8 (1.2–2.5)	0.8 (0.6–1.2)
Greece				
Athens	1.4 (0.7–3.1)	2.7 (1.4–5.5)[#]	1.8 (1.1–2.7)	1.3 (0.8–2.1)[#]
Thessaloniki	2.3 (1.3–3.8)	2.5 (1.4–4.3)[#]	1.2 (0.8–1.7)	0.9 (0.6–1.5)[#]
Iceland				
Reykjavik	1.9 (1.2–3.0)	7.0 (4.0–12.1)	1.0 (0.4–2.5)	0.8 (0.4–1.8)
Italy				
Rome	2.2 (1.3–3.7)	4.8 (3.0–7.9)[#]	2.2 (1.5–3.1)	1.0 (0.6–1.5)[#]
Netherlands				
Utrecht	2.4 (1.5–3.9)[#]	4.8 (3.0–7.6)	1.7 (1.2–2.2)[#]	1.1 (0.8–1.5)
New Zealand				
Hawkes Bay	1.6 (1.2–2.0)	2.6 (2.0–3.3)	1.2 (0.8–1.6)	1.2 (0.8–1.6)
Norway				
Tromsø	2.3 (1.4–3.6)	9.0 (4.7–17.3)	1.1 (0.6–2.2)	1.2 (0.6–2.3)
Spain				
Almeria	2.8 (2.2–3.5)	1.0 (0.7–1.4)	1.0 (0.8–1.4)	1.4 (0.9–2.4)
Cartagena	4.1 (3.1–5.5)	1.2 (0.8–1.9)[#]	1.3 (0.9–2.0)	1.2 (0.5–2.7)[#]
Madrid	1.7 (1.2–2.4)	2.2 (1.6–3.1)[#]	1.1 (0.6–1.8)	1.1 (0.7–1.7)[#]
Valencia	2.9 (2.1–4.0)	1.4 (0.7–2.6)[#]	1.8 (1.1–2.7)	0.5 (0.1–2.0)[#]
Sweden				
Linköping	1.8 (1.3–2.7)[#]	7.8 (4.9–12.4)	0.3 (0.1–1.6)[#]	1.3 (0.5–3.5)
Öestersund	1.9 (1.2–3.0)[#]	8.8 (5.2–14.9)	1.3 (0.8–2.4)[#]	0.9 (0.5–1.6)
UK				
West Sussex	2.1 (1.5–3.0)	4.4 (3.1–6.1)	1.9 (1.0,3.7)	0.6 (0.3–1.5)
Affluent	2.2 (1.8–2.6)	3.6 (2.6–5.0)	1.5 (1.3–1.8)	1.0 (0.9–1.1)
Albania				
Tirana	1.1 (0.5–2.3)	0.5 (0.1–1.8)[#]	1.1 (0.6–1.8)	0.9 (0.4–2.0)[#]
Brazil				
Porto Alegre	1.7 (1.3–2.3)	1.3 (0.7–2.4)	1.1 (0.7–1.8)	2.0 (0.9–4.5)
China				
Beijing	0.8 (0.5–1.4)[#]	1.4 (0.5–4.3)	1.3 (1.0–1.6)[#]	1.1 (0.6–2.0)
Guangzhou	2.6 (1.7–3.8)[#]	2.4 (1.2–4.7)	1.3 (1.1–1.6)[#]	1.2 (0.7–2.0)
Ecuador				
Pichincha province	1.2 (0.3–4.2)[#]	7.0 (1.7–30.0)	1.5 (0.6–3.8)[#]	1.6 (0.2–12.1)
Estonia				
Tallinn	2.5 (1.1–5.7)[#]	1.9 (0.7–5.0)	1.5 (0.8–2.6)[#]	1.2 (0.6–2.6)
Georgia				
Tbilisi	2.2 (1.2–4.2)[#]	2.1 (1.1–3.8)	1.1 (0.5–2.1)[#]	0.5 (0.2–1.5)
India				
Bombay	2.0 (1.0–4.1)	0.8 (0.2–3.1)	0.9 (0.3–2.4)	0.6 (0.1–4.2)
Latvia				
Riga	3.1 (1.4–7.0)	3.6 (1.6–7.8)	1.7 (0.9–3.1)	0.9 (0.3–2.1)
Turkey				
Ankara	0.9 (0.7–1.2)[#]	1.0 (0.8–1.4)[#]	1.1 (0.9–1.4)[#]	1.0 (0.8–1.3)[#]
West Bank				
Ramallah	0.9 (0.3–3.1)[#]	NC[#]	0.7 (0.2–2.4)[#]	NC[#]
Nonaffluent[¶]	1.5 (1.1–2.1)	1.6 (1.1–2.4)	1.2 (1.1–1.4)	1.1 (0.9–1.3)

Data are presented as adjusted prevalence rate ratios (95% confidence interval). The prevalence rate ratio for perennial allergens is adjusted for seasonal allergens and *vice versa*. NC: not calculated due to no observations. [#]: local allergens were tested in addition to a standard set of six common allergens; [¶]: analysis does not include Tbilisi, Georgia (see online supplementary data).

TABLE 4 Population attributable fraction (PAF) of symptoms of rhinitis with and without conjunctivitis caused by sensitisation to perennial allergens and seasonal allergens

Country and centre	PAF of symptoms of rhinitis with conjunctivitis		PAF of symptoms of rhinitis without conjunctivitis	
	Perennial allergens	Seasonal allergens	Perennial allergens	Seasonal allergens
China				
Hong Kong	57.4 (45.1–66.9)[#]	2.4 (0.3–4.6)	24.9 (13.6–34.7)[#]	0.0[¶]
Germany				
Dresden	11.1 (3.5–18.1)	55.9 (48.6–62.1)	10.5 (4.0–16.7)	0.0[¶]
Munich	12.6 (6.5–18.3)	45.6 (39.0–51.5)	8.6 (2.0–14.8)	0.0[¶]
Greece				
Athens	5.1 (-7.8–16.5)	13.4 (0.2–24.9)[#]	6.8 (0.1–13.0)	2.6 (-3.5–8.2)[#]
Thessaloniki	24.6 (7.5–38.5)	20.0 (6.4–31.5)[#]	3.1 (-6.3–11.8)	0.0[#,¶]
Iceland				
Reykjavik	21.0 (4.5–34.6)	56.6 (39.7–68.7)	0.6 (-12.3–12.0)	0.0[¶]
Italy				
Rome	31.3 (14.5–44.8)	43.2 (31.6–52.8)[#]	22.3 (11.3–31.9)	0.0[#,¶]
Netherlands				
Utrecht	35.1 (19.1–48.0)[#]	48.0 (35.5–58.0)	14.0 (4.8–22.2)[#]	1.7 (-6.1–8.9)
New Zealand				
Hawkes Bay	16.2 (7.4–24.1)	29.2 (21.8–35.9)	4.5 (-6.7–14.5)	3.4 (-6.4–12.4)
Norway				
Tromsø	33.4 (15.1–47.7)	71.3 (54.7–81.9)	2.5 (-12.7–15.7)	4.9 (-12.7–20.0)
Spain				
Almeria	42.7 (33.2–50.8)	0.1 (-3.2–3.3)	1.6 (-12.8–14.2)	3.0 (-2.0–7.8)
Cartagena	40.5 (30.9–48.8)	1.3 (-2.4–4.8)[#]	6.6 (-4.8–16.7)	0.8 (-3.6–4.9)[#]
Madrid	14.4 (4.3–23.3)	25.2 (13.5–35.3)[#]	1.2 (-9.3–10.7)	1.9 (-10.7–13.1)[#]
Valencia	18.7 (10.8–25.9)	1.6 (-1.9–5.1)[#]	8.1 (0.2–15.4)	0.0[#,¶]
Sweden				
Linköping	20.8 (9.0–31.1)[#]	56.7 (44.0–66.6)	0.0[#,¶]	3.4 (-10.2–15.2)
Öestersund	26.2 (11.8–38.3)[#]	64.4 (52.4–73.4)	5.7 (-5.5–15.6)[#]	0.0[¶]
UK				
West Sussex	14.8 (7.9–21.1)	30.4 (22.6–37.4)	8.0 (-1.9–16.9)	0.0[¶]
Affluent	25.0 (18.1–31.4)	35.9 (23.6–46.2)	8.0 (5.5–10.5)	2.1 (-0.3–4.5)
Albania				
Tirana	0.9 (-8.6–9.6)	0.0[#,¶]	0.7 (-6.0–6.8)	0.0[#,¶]
Brazil				
Porto Alegre	8.0 (2.9–12.7)	0.6 (-1.3–2.5)	1.0 (-5.7–7.2)	2.0 (-1.2–5.0)
China				
Beijing	0.0[#,¶]	1.1 (-3.2–5.2)	5.7 (-0.7–11.7)[#]	0.3 (-1.8–2.3)
Guangzhou	33.6 (17.5–46.5)[#]	3.8 (-0.7–8.0)	9.6 (3.3–15.4)[#]	0.4 (-0.9–1.7)
Ecuador				
Pichincha province	3.3 (-30.0–28.0)[#]	13.2 (-8.5–30.5)	8.1 (-15.4–26.8)[#]	1.6 (-6.8–9.3)
Estonia				
Tallinn	19.1 (-0.2–34.6)[#]	9.5 (-5.3–22.2)	6.0 (-4.5–15.5)[#]	1.9 (-5.7–8.9)
India				
Bombay	5.1 (-2.2–11.8)	0.0[¶]	0.0[¶]	0.0[¶]
Latvia				
Riga	32.1 (6.9–50.4)	28.6 (10.3–43.1)	9.4 (-3.1–20.4)	0.0[¶]
Turkey				
Ankara	0.0[#,¶]	0.6 (-4.0–5.1)[#]	1.9 (-2.0–5.7)[#]	0.0[#,¶]
Nonaffluent[+]	12.6 (2.7–21.6)	1.3 (-0.2–2.8)	4.0 (1.2–6.6)	0.6 (-0.5–1.6)

Data are presented as adjusted PAF in % (95% confidence interval). The PAF for perennial allergens is adjusted for seasonal allergens and *vice versa*. [#]: local allergens were tested in addition to a standard set of six common allergens; [¶]: not computed as the prevalence rate ratio was <1 and the PAF would, therefore, have a noninterpretable value (PAF <0); [+]: analysis does not include Ramallah (Palestine) and Tbilisi (Georgia; see online supplementary data).

due to differential reporting of symptoms, which may be related to cultural differences [1].

A strong variation in rhinitis symptom prevalence has been previously found in ISAAC Phase One [1]. Published estimates of PAFs of atopy for rhinitis are limited and mostly based on studies conducted in industrialised affluent countries. ZACHARASIEWICZ et al. [12] analysed the contribution of atopy to rhinitis, reviewing questionnaire data and skin-prick test results from 20 studies including 57 centres. However, only five nonaffluent countries were included and only eight centres studied children aged <14 yrs. The estimated average PAF for any reported rhinitis symptoms or hay fever diagnosis was ~53%. For the subgroup ''symptoms related to allergen exposure'' (or ''seasonal symptoms''), the PAF was 48%. In addition, there seems to be some indication that the PAF are lower for children than adults [12, 13]. The present result for rhinoconjunctivitis in affluent countries is similar (56%) but when considering rhinitis without any further distinction the PAF is only 33%. However, any comparison with the study by ZACHARASIEWICZ et al. [12] has to be considered with caution, due to the variety of definitions used for rhinitis in different studies and the fact that the subjects in most studies were outside the age range investigated in the ISAAC Phase Two study.

The combination of the two ISAAC questions on rhinitis (rhinitis symptoms accompanied by itchy-watery eyes) is a useful epidemiological instrument to measure mainly the occurrence of allergic rhinitis, at least in European populations [13, 14]. For example, the positive predictive value for detecting atopy, i.e. the proportion of children with a positive skin-prick test among those who reported rhinoconjunctivitis, was 64% in a Swiss population [13]. The current results show that atopy is an important risk factor for rhinoconjunctivitis but is only marginally relevant for rhinitis without conjunctivitis, which mainly seems to reflect nonatopic rhinitis. Seasonal and perennial allergens accounted for 36 and 25% of the prevalence of rhinoconjunctivitis in affluent countries, respectively, and 12.6 and 1.3% in nonaffluent countries, respectively. The PAF of rhinitis without conjunctivitis was much lower for seasonal and perennial allergens in both affluent (8 and 2.1%, respectively) and nonaffluent countries (4 and 0.6%, respectively). This suggests that the role of sensitisation is less important than has been previously assumed, even among children with symptoms generally considered to be characteristic of allergic rhinitis.

This conclusion is true even when considering a methodological limitation of the present study, namely that skin-prick tests alone were used to define atopy. Positive skin-prick tests are not a perfect measure of an allergy of the nasal mucosa, and nasal provocation with allergen extracts may be more specific when investigating allergic rhinitis. However, this does not necessarily imply that the PAFs based on skin-prick tests underestimate the real value. Indeed, while the PRR may increase when using a more specific exposure measure, the prevalence of the measured exposure may decrease. For example, when examining PAFs for asthma due to atopy with a stricter definition (reaction to at least two or three allergens as opposed to at least one allergen) the PAF for asthma proved to be lower [18].

The predominant role of seasonal allergens, in particular pollen, for rhinoconjunctivitis (measuring the classic ''hay fever'') among affluent centres is in line with conventional wisdom and several epidemiological studies [13, 22, 23]. In contrast, the PAFs for seasonal allergens were generally lower or equal to PAFs for perennial allergens among nonaffluent centres. This may indicate that pollen does not play the major role in many of these countries. Results from a previous study in China [24] also follow in this direction; rhinitis was more strongly associated with sensitisation to house dust mites than to the variety of pollen tested.

Results pointing towards a dissociation of sensitisation and supposedly allergic disease in nonaffluent areas have previously been found for asthma. For example, in Ethiopia, no association was found between asthma and sensitisation to house dust mites in a nonaffluent rural area, in contrast to an urban more affluent area [25]. The reasons for such dissociation are not clear and have not been specifically addressed. The role of infection with parasites or other microbial agents and their influence on allergies has been discussed previously [25]. Evidence in support of such a role stems from other investigations [26, 27].

One factor the present authors did not consider was food allergy. However, sensitisation to food allergens decreases with age between infancy and childhood, whereas sensitisation to aero-allergens increases [28–30]. Thus, it seems unlikely that taking into account sensitisation to food allergens would substantially alter the current results. Hypersensitivity to food additives, such as preservatives and colouring agents, may also induce symptoms of rhinitis [31]. However, these agents may partly be trigger factors rather than aetiological factors [32].

Traditionally, it has been recognised that there are allergic and nonallergic forms of noninfectious rhinitis. In children, certain forms of nonallergic rhinitis linked to occupational exposures or certain medications are presumably of little importance, other mechanisms implying an autonomic dysfunction leading to vasomotor rhinitis may play a role.

In many centres, the proportion of rhinitis without conjunctivitis, i.e. mainly nonallergic forms of rhinitis, relative to rhinoconjunctivitis is considerable or even higher. This and the relatively low fraction of rhinitis that could be attributed to atopy in the present study strongly suggest that risk factors not related to allergy are also of great importance, especially in nonaffluent countries.

However, to date, studies on the influence of nonallergic risk factors on rhinitis and, especially, rhinoconjunctivitis are relatively scarce. Risk factors that have been associated with noninfectious rhinitis include parental smoking, smoking during pregnancy/breastfeeding, high birth weight, early introduction of foods or formula, respiratory infections, central heating with gas and space heating, synthetic bedding, dampness or mould at home, and air pollution [24, 33–35]. Some of these factors have been investigated within the Phase Two ISAAC study and their influence will be the subject of future analyses.

In conclusion, the present results highlight a high international variation in prevalence of rhinitis-related symptoms and atopic

sensitisation, and also in the underlying association between sensitisation and rhinitis. The strength of this association varies strongly between countries and is lower overall than has been previously suspected. In particular, mechanisms unrelated to atopy seem to play a major role in nonaffluent countries. This emphasises the need to investigate environmental risk factors for rhinitis.

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