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International variation in prevalence of rhinitis and its relation with sensitization to perennial and seasonal allergens.

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Short title: Atopy and variation in rhinitis prevalence

International Variations in Prevalence of Rhinitis and Relations with Sensitization to Perennial and Seasonal Allergens.

ABSTRACT

The relative importance of atopy in the etiology of rhinitis is largely unknown. We investigated geographical variations in rhinitis in relation to atopy.

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

The prevalence of rhinoconjunctivitis and rhinitis without conjunctivitis varied widely (from 1.5% to 24.5% and from 1.4% to 45.2%, respectively). For rhinoconjunctivitis, the population attributable fraction (PAF) varied from 0 to 71% for a positive prick test to one or more seasonal allergens and from 0 to 41% for perennial allergens. The PAF for sensitization to seasonal and perennial allergens was higher for affluent countries (36% and 25%, respectively) than for non-affluent countries (1.3% and 12.6%, respectively). For rhinitis without conjunctivitis, the PAF for perennial allergens was 8% for affluent countries and 4% for non-affluent countries. 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 have been underemphasized, particularly in less affluent countries. Atopy seems to be only marginally relevant for rhinitis without conjunctivitis, which seems mainly to reflect non-atopic rhinitis.

Keywords: ISAAC Phase Two, perennial, population attributable risk, rhinitis, seasonal, skin prick test

INTRODUCTION

Rhinitis is an important health problem affecting the quality of life of much 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 year ranged from 3.2 to 66.6% among 13-14 year old children. Furthermore, symptoms of allergic rhinitis seem to be increasing in some [2-5] but not in 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, we have shown that the importance of atopy as an etiologic factor for asthma varies considerably worldwide and is related to gross national income [10].

Until now research has focused on allergic rhinitis and the role of atopy. However, as early as 1988, Jones [11] reported on the importance of non-allergic perennial rhinitis and a recent review of the published literature [12] , that examined 22 population-based studies, indicated that indeed only half of the rhinitis cases (53%) was attributable to atopy. The question remains on 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 epidemiologic studies in European populations, the presence of a runny/blocked nose with conjunctivitis in absence of a cold proved to identify well those individuals with allergic rhinitis [1, 13, 14].

We investigated geographical variations in rhinitis in childhood. We defined two groups: “rhinoconjunctivitis”, likely to contain most of the individuals with allergic rhinitis, and “rhinitis without conjunctivitis”, expected to include both non-allergic and allergic rhinitis. We explored the importance of sensitization to seasonal and perennial allergens, and assessed the worldwide variation in the population attributable fractions (PAF) for the two categories of rhinitis. The work is based on Phase Two of ISAAC [15]. It is the first investigation that can compare standardized data from many different centres worldwide that have applied the same protocol for assessing rhinitis symptoms and, especially, to determine atopic sensitization. The interesting feature of ISAAC Phase Two is the possibility to make both ecological and individual comparisons.

METHODS

The methods used in the ISAAC Phase Two study are described in detail elsewhere [15] and in the online repository. Briefly, 30 study centres from 22 countries (Table1) drew random samples of approximately 1000 children from the classes where the majority of children had an age of 9-11 years. All studies and coordination have been approved by local ethics committees [15]. The parents were invited to fill in a standardized, self-administered questionnaire. The questions were identical to those used in the ISAAC Phase One for 6-7 year 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 where illiteracy was a problem (Ecuador, India, Brazil and Ghana) the questions were posed by trained interviewers.

In most centres, all children were invited to have a skin prick test. A few centres had drawn a random sub-sample [15] (see Table 1 and online depository).

Skin prick tests were done 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 from the centre PIs; for details see online repository). The skin prick test for sensitization to seasonal or perennial allergens was considered to be positive if at least one seasonal or perennial allergen, respectively, yielded a positive test result. A positive skin reaction was defined as a wheal diameter of $\geq$3 mm, after subtraction of the negative control.

Statistical analysis

Children aged 8-12 years were included in the analysis.

Spearman correlation coefficients were calculated for the correlation between prevalence rates of symptoms and of positive skin prick test reactivity. According to ISAAC policy, reported frequencies from study centres with less than 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 positive prick test was assessed with prevalence rate ratios (PRR) within centres [17]. Since children sensitized to perennial allergens are more likely to be sensitized to seasonal allergens, and vice versa, we calculated adjusted PRRs, considering the respective other group of allergens as adjustment variable. Initial models included also sex, number of siblings and parental allergy, but none of these variables influenced notably the obtained estimate and they were therefore omitted from the final model. Calculations were performed using SAS statistical software (version 9.1.3) and SUDAAN (version 9).

The population attributable fractions (PAF) (%) were calculated with STATA software (version 9) using the command "aflogit" which is equivalent to using the formula PAF = P_{ec} x (PRR-1)/PRR [18], 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].

Since asthma prevalence and the role of atopy may vary between affluent countries with a "Western" lifestyle and less affluent countries, we grouped the countries on the basis of gross national income (GNI) per capita, converted into U.S. dollars using the World Bank Atlas method [20]. The first group ("affluent countries") consists of high income countries [21] (GNI above 9200$ in 2001) and includes most European centres, essentially EU members before 2004, New Zealand and Hong Kong. The other group ("nonaffluent countries") comprises all other centres.

RESULTS

Questionnaire data on rhinitis symptoms for 54,178 children aged 8-12 years and skin prick data on allergen specific sensitization for 31,759 children were included in the analysis. Participation rates varied from 35% to 100% (median 83%) for the questionnaire, and from 24% to 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 (Table1).

The prevalence of sensitization 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 sensitization 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 sensitization to seasonal ($\rho = 0.5$, $p=0.019$), but not to perennial allergens ($\rho = 0.2$; $p=0.38$) (Fig.1). For rhinitis without conjunctivitis on the other hand, there was a significant correlation with sensitization to perennial ($\rho = 0.54$, $p = 0.007$) but not to seasonal allergens ($\rho = -0.05$, $p=0.84$).

Associations based on individuals and population attributable fractions

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

Rhinoconjunctivitis. The adjusted association between rhinoconjunctivitis and perennial allergens was positive in all but three centres (Ankara, Beijing and Ramallah). 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%CI:1.8-2.6), for non-affluent centres it was 1.5 (95%CI:1.1-2.1).

Adjusted PAFs varied from 0.9% in Tirana to 57.4% in Hong Kong (Table 4). For affluent centres the combined PAF was 25.0% (95%CI: 18.1%-31.4%), whereas among nonaffluent centres only 12.6% (95%CI: 2.7%-21.6%) were attributable to perennial allergens.

Sensitization to seasonal allergens was positively associated with rhinoconjunctivits in all centres except for Tirana and Bombay, and the remaining adjusted PRR ranged from 1.0 in Ankara and Almeria to 9.0 in Tromsø (Norway). The combined estimate was 3.6 (95%CI:2.6-5.0) for affluent centres and 1.6 (95%CI:1.1-2.4) for nonaffluent centres.

PAF ranged from around 0% in Almeria, Bombay and Tirana to 71.3 % in Tomsø. The PAF were highest in the Scandinavian centres and Dresden (Germany). The combined estimate for affluent centres was 35.9% (95%CI:23.6%-46.2%) and 1.3% (95%CI: 0%-2.8%) for nonaffluent centres.

When considering outdoor and indoor allergens together in all centres, the overall PAF is 56%

Rhinitis without conjunctivitis. _For the association with sensitization to perennial allergens, the adjusted PRR ranged from 0.3 in Linköping (not statistically significant) to 2.2 in Rome. The combined estimate for affluent centres was 1.5 (95%CI:1.3-1.7), and 1.2 (95%CI:1.1-1.4) for nonaffluent centres.

PAFs ranged from 0% in Bombay and Linköping to 24.9% in Hong Kong. Combined estimates give PAF of 8.0% (95%CI:5.5%-10.5%) for affluent countries and 4.0 (95%CI:1.2%-6.6%) for nonaffluent countries.

There was no association between sensitization 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 (95%CI:0.9-1.1) for affluent and 1.1 (95%CI:0.9-1.3) for nonaffluent centres.

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 sensitization to seasonal and perennial allergen for rhinitis, with and without conjunctivitis, was 33%.

Discussion

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

There are strengths and limitations of our study worth discussing. We have information on rhinitis and atopic sensitization for children in 29 centres worldwide, more than any previous study. All centres are 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, respective to the standard test set of six allergens, effect measures (OR, PAF) were only slightly changed by inclusion of local allergens. The countries analyzed had been selected based on the findings from ISAAC Phase One to ensure that the global variety of the disease's prevalence is captured. Our results therefore are likely to represent the worldwide variation in the relation between sensitization to allergens and rhinitis. On the other hand, 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 overrepresented. 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 be only minor as long as the selection factors have operated in the same manner for rhinitis and atopy. Indeed, the estimated OR and PAFs changed very little when these additional allergens were omitted from the analyses. Finally it can not be ruled out that there was a certain degree of misclassification , due to differential reporting of symptoms which may be related to cultural differences [1].

A strong variation in rhinitis symptom prevalence was already found in ISAAC Phase One [1]. Published estimates of population attributable fractions of atopy for rhinitis are limited and mostly based on studies conducted in industrialized affluent countries. Zacharasiewicz *et al.* [12]. analyzed the contribution of atopy to rhinitis, reviewing questionnaire data and skin prick test results from 20 studies including 57 centres. Only 5 non-affluent countries were included, however, and only 8 centres studied children under the age of 14. The estimated average PAF for any reported rhinitis symptoms or hay fever diagnosis was approximately 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 for adults [12, 13]. Our 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 this work [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 ISAAC Phase Two.

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 that reported rhinoconjunctivitis, was 64% in a Swiss population [13]. Our results show that atopy is an important risk factor for rhinoconjunctivitis but is only marginally relevant for rhinitis without conjunctivitis, which seems mainly to reflect non-atopic rhinitis. Seasonal and perennial allergens explained 36% and 25% of the prevalence of rhinoconjunctivitis in affluent countries, respectively, and 12.6 and 1.3 % in non-affluent countries. On the other hand, the PAF of rhinitis without conjunctivitis was much lower in both affluent (8% and 2.1%) and non-affluent countries (4% and 0.6%). This suggests that the role of sensitization is less important than has been previously assumed, even among children with symptoms considered generally to be characteristic for allergic rhinitis.

This conclusion holds even when considering a methodological limitation of our study, namely that we used skin prick tests alone 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 population attributable fractions based on skin prick test 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 when using these stricter definitions [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 epidemiologic studies [13, 22, 23]. In contrast, the PAFs for seasonal allergens are generally lower or equal to PAFs for perennial allergens among non-affluent centres. This may indicate that pollen does not play the major role in many of these countries.

Results of a previous study in China [24] are also in this direction: rhinitis was more strongly associated with sensitization to house dust mites than to the variety of pollen tested.

Results pointing to a dissociation of sensitization and supposedly allergic disease in non-affluent areas have previously been found for asthma. For example, in Ethiopia, no association between asthma and sensitization to house dust mites was found in a non-affluent rural area, in contrast to an urban more affluent environment [25]. The reasons for such a 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 [25]. and evidence in support of such a role stems from other investigations [26, 27].

One factor we did not consider is food allergy. However, sensitization to food allergens decreases whereas sensitization to aero-allergens increases with age between infancy and childhood [28-30]. Thus it seems unlikely that taking into account sensitization to food allergens would substantially alter our results. Hypersensitivity to food additives, such as preservatives and coloring agents, may also induce symptoms of rhinitis [31]. However, these agents may partly be triggering rather than etiological factors [32].

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

In many centres the proportion of rhinitis without conjunctivitis, i.e. of mainly non-allergic 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 non-affluent countries.

However, so far studies are relatively scarce on the influence of non-allergic risk factors on rhinitis and especially rhinoconjunctivitis. Risk factors that have been associated with non-infectious 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 mold at home and air pollution [24, 33-35]. Some of these factors have been investigated within the ISAAC Phase Two and their influence will be subject of future analyses.

In conclusion, our results highlight a high international variation in prevalence of rhinitis-related symptoms and atopic sensitization, and also in the underlying association between sensitization 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 emphasizes the need to investigate environmental risk factors for rhinitis.

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Phase Two he played a leading role in international studies of asthma and allergy and the crucial part in the conception of all work leading to this manuscript. He will be fondly remembered as a teacher and researcher of great warmth, enthusiasm and wisdom.

(***To the editor:*** *If necessary, the following list of members of the ISAAC Phase Two Study Group could go to the online data supplement.)*

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TABLE1. Participation and prevalence of symptoms by centre

		Participation rhinitis questionnaire		Prevalence of symptoms in the past year (%)		Participation skin prick test	
country	centre	number of children	participation rate (%)	rhinitis with conjunctivitis	rhinitis without conjunctivitis	number of children	participation rate (%)
Albania	Tirana‡	1045	94.3	6.7	14.6	929	84.0
Brasil	Uruguaiana‡	1971	96.3	21.0	9.9	1192	96.2
China	Beijing‡	4207	92.3	7.5	23.2	1044	90.8
China	Guangzhou‡	3502	93.1	7.0	29.1	1078	36.1
China	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
Germany	Munich	3271	86.7	12.8	8.3	2317	60.6
Ghana	Kintampo‡	1354	n.d.	n.d.	n.d.	1322	n.d.
Greece	Athens	985	85.3	4.8	12.9	985	85.3
Greece	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	n.d.	4.9	5.3	1556	n.d.
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	Tromso	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
Spain	Cartagena	1402	53.7	15.4	9.5	1030	39.6
Spain	Madrid	964	35.2	18.7	13.4	653	23.9
Spain	Valencia	1349	40.1	12.6	10.4	1023	30.5
Sweden	Linköping	904	81.4	13.8	5.1	857	77.0
Sweden	Östersund	1193	85.9	12.2	8.9	991	71.4
Turkey	Ankara‡	2966	87.3	11.8	17.7	2747	81.0
United Kingdom	West Sussex	1055	78.5	16.2	7.4	898	66.7

* the core standard allergens were not licensed in France (where allergens from Stallergènes were tested in 1451 children);
‡ centres in countries with a gross national income (GNI) per capita less than 9200$ in 2001 (“nonaffluent countries”)

TABLE 2. Prevalence of positive skin prick tests to perennial and seasonal allergens

		positive skin prick test to perennial allergens		positive skin prick test to seasonal allergens	
country	centre	prevalence (%)	number of positives	prevalence (%)	number of positives
Albania	Tirana	12.4	115	6.4*	59
Brasil	Uruguaiana	12.1	144	2.0	24
China	Beijing	22.9*	239	3.0	31
China	Guangzhou	31.5*	340	1.9	21
China	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
Germany	Munich	13.2	306	16.1	372
Ghana	Kintampo	1.6	21	0.1	1
Greece	Athens	9.2	91	8.2*	81
Greece	Thessaloniki	21.2	216	12.8*	130
India	Bombay	5.8	90	2.1	32
Island	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	Tromso	20.1	145	25.8	186
Palestine	Ramallah	10.3*	25	0.5*	1
Spain	Almeria	41.5	446	7.0	75
Spain	Cartagena	22.0	227	3.9*	40
Spain	Madrid	19.4	127	25.6*	167
Spain	Valencia	12.5	128	3.0*	31
Sweden	Linkoeping	11.8*	101	16.7	143
Sweden	Oestersund	18.6*	184	19.2	190
Turkey	Ankara	15.8*	433	15.2*	418
United Kingdom	West Sussex	10.6	95	11.1	100

* local allergens were tested in addition to standard set of six common allergens.

TABLE 3. Association between rhinitis with conjunctivitis and rhinitis without conjunctivitis with positive skin prick tests to perennial and seasonal allergens – adjusted prevalence rate ratios (95% confidence intervals). The prevalence rate ratio for perennial allergens is adjusted for seasonal allergens and vice versa.

		rhinitis with conjunctivitis		rhinitis without conjunctivitis	
		positive skin prick test to		positive skin prick test to	
Country	Centre	perennial allergens	seasonal allergens	perennial allergens	seasonal allergens
China	HongKong	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)
Germany	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)
Greece	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	Tromso	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)
Spain	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)
Spain	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)
Spain	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	Linkoeping	1.8* (1.3,2.7)	7.8 (4.9,12.4)	0.3* (0.1,1.6)	1.3 (0.5,3.5)
Sweden	Oestersund	1.9* (1.2,3.0)	8.8 (5.2,14.9)	1.3* (0.8,2.4)	0.9 (0.5,1.6)
U.K.	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)
Brasil	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)
China	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)	n.c. *	0.7* (0.2,2.4)	n.c. *
	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)

*local allergens were tested in addition to standard set of six common allergens.
‡ analysis does not include Tbilisi (see online depository)

TABLE 4. Population attributable fraction (PAF) of symptoms of rhinitis with and without conjunctivitis caused by sensitization to perennial allergens and seasonal allergens – adjusted PAF (95% confidence intervals). The PAF for perennial allergens is adjusted for seasonal allergens and vice versa.

		PAF of symptoms of rhinitis with conjunctivitis		PAF of symptoms of rhinitis without conjunctivitis	
		positive skin prick test to		positive skin prick test to	
Country	Centre	perennial allergens	seasonal allergens	perennial allergens	seasonal allergens
China	HongKong	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 †
Germany	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)
Greece	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	Tromso	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)
Spain	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)
Spain	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)
Spain	Valencia	18.7 (10.8,25.9)	1.6* (-1.9,5.1)	8.1 (0.2,15.4)	0.0* †
Sweden	Linkoeping	20.8* (9.0,31.1)	56.7 (44.0,66.6)	0.0* †	3.4 (-10.2,15.2)
Sweden	Oestersund	26.2* (11.8,38.3)	64.4 (52.4,73.4)	5.7* (-5.5,15.6)	0.0 †
U.K.	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* †
Brasil	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)
China	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)

*local allergens were tested in addition to standard set of six common allergens.
† not computed, as the prevalence rate ratio is smaller than 1 and the PAF would therefore have a non-interpretable value (PAF<0)
‡ analysis does not include Ramallah and Tbilisi (see online depository)

Figure legends

FIGURE 1.

Scatterplots of the prevalence of rhinitis symptoms versus the prevalence of a positive skin prick test to seasonal allergens (a,b) and a positive skin prick test to perennial allergens (c,d)

FIGURE 2.

Association between rhinitis symptoms and a positive skin prick test to seasonal and perennial allergens: rhinoconjunctivitis vs. seasonal allergens (a), rhinitis without conjunctivitis vs. seasonal allergens (b), rhinoconjunctivitis vs. perennial allergen (c) and rhinitis without conjunctivitis vs. perennial allergens (d). Crude prevalence rate ratios and the 95% confidence interval are presented.

*The combined estimate does not include Tbilisi (see online depository)

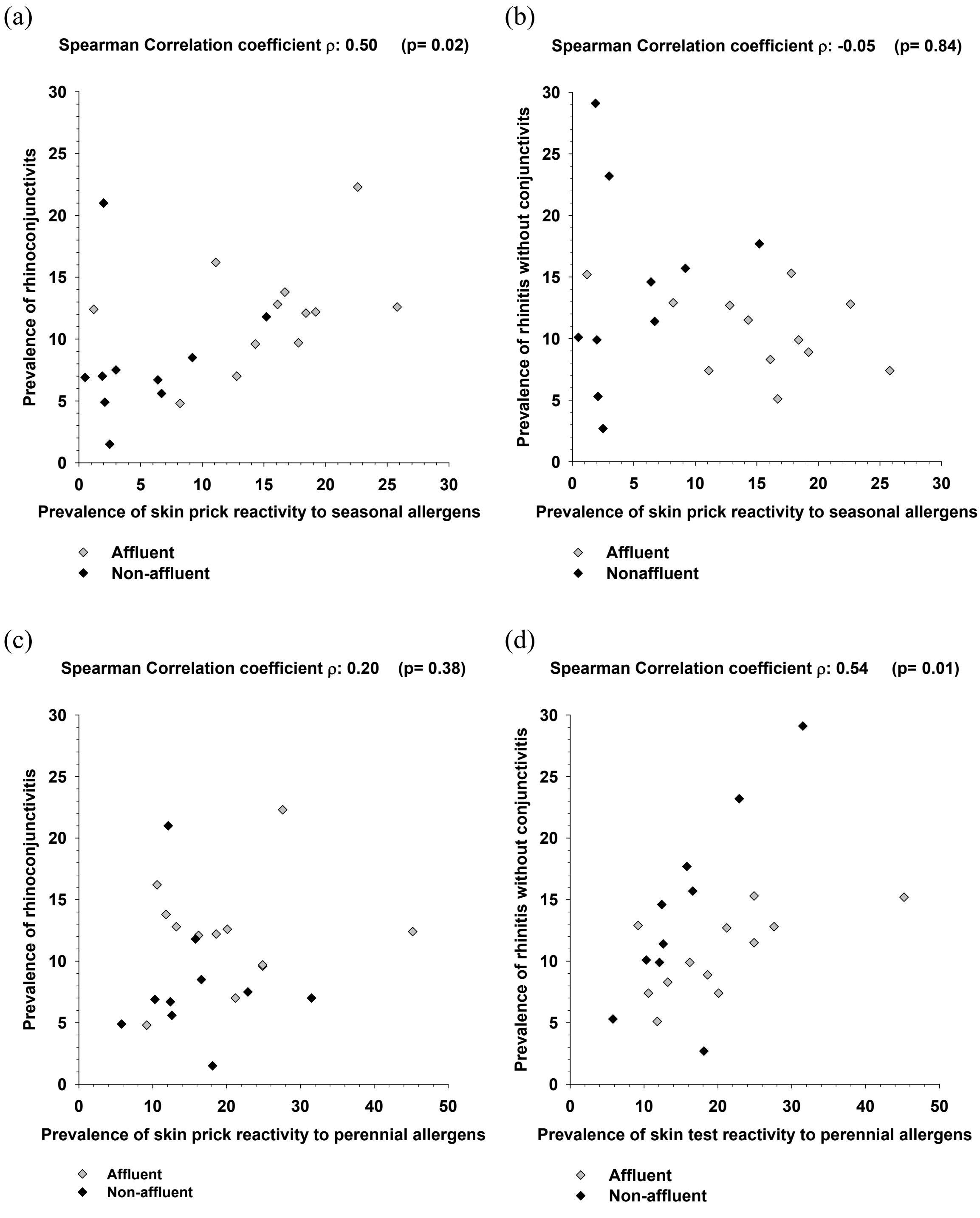
(a)
Spearman Correlation coefficient ρ: 0.50 (p= 0.02)
Prevalence of rhinoconjunctivits
Prevalence of skin prick reactivity to seasonal allergens
Affluent
Non-affluent
(b)
Spearman Correlation coefficient ρ: -0.05 (p= 0.84)
Prevalence of rhinitis without conjunctivits
Prevalence of skin prick reactivity to seasonal allergens
Affluent
Nonaffluent
(c)
Spearman Correlation coefficient ρ: 0.20 (p= 0.38)
Prevalence of rhinoconjunctivitis
Prevalence of skin prick reactivity to perennial allergens
Affluent
Non-affluent
(d)
Spearman Correlation coefficient ρ: 0.54 (p= 0.01)
Prevalence of rhinitis without conjunctivitis
Prevalence of skin test reactivity to perennial allergens
Affluent
Non-affluent

FIGURE 1.

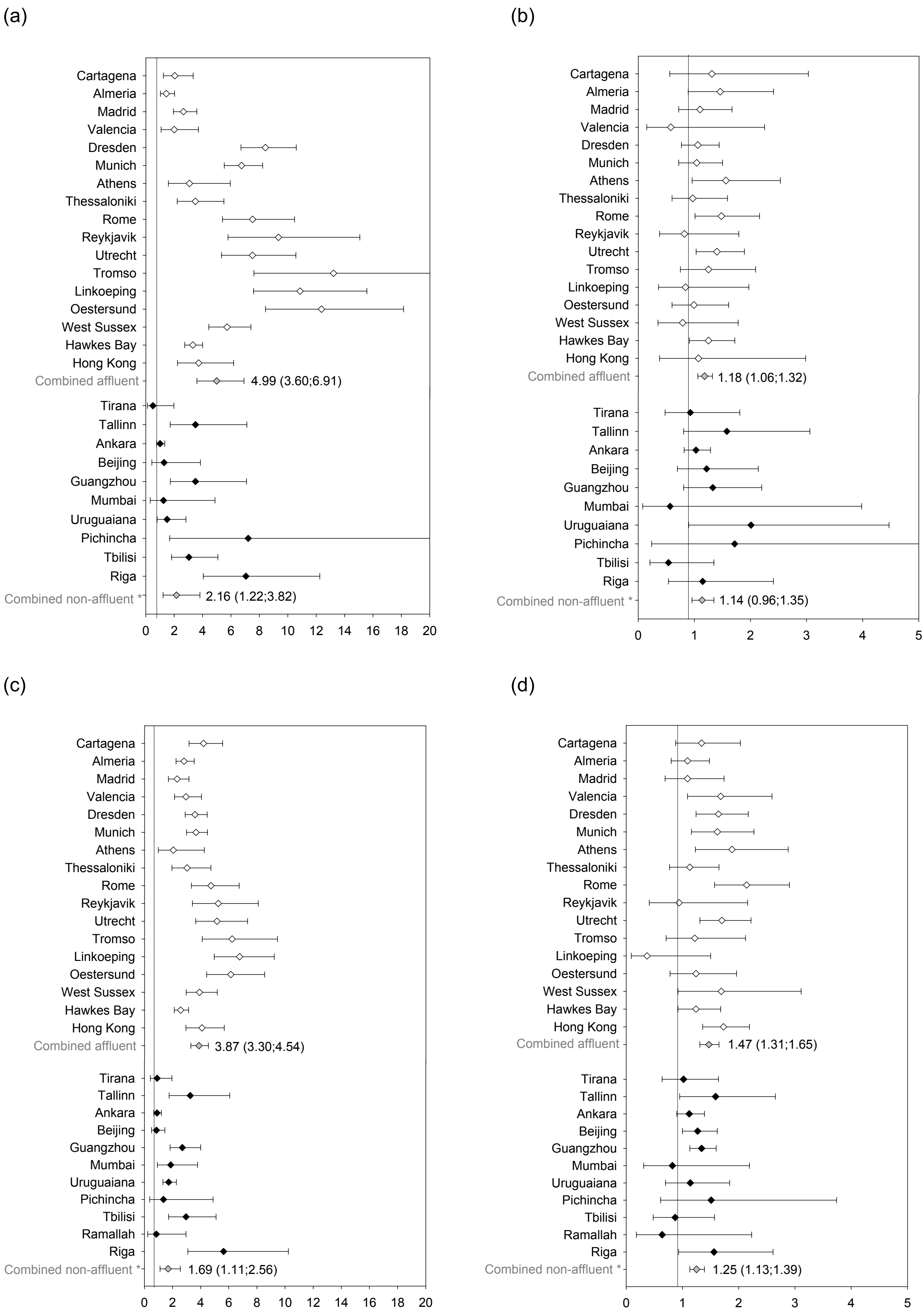
(a)
Cartagena
Almeria
Madrid
Valencia
Dresden
Munich
Athens
Thessaloniki
Rome
Reykjavik
Utrecht
Tromso
Linkoeping
Oestersund
West Sussex
Hawkes Bay
Hong Kong
Combined affluent
4.99 (3.60;6.91)
Tirana
Tallinn
Ankara
Beijing
Guangzhou
Mumbai
Uruguaiana
Pichincha
Tbilisi
Riga
Combined non-affluent *
2.16 (1.22;3.82)
0 2 4 6 8 10 12 14 16 18 20
(b)
1.18 (1.06;1.32)
1.14 (0.96;1.35)
0 1 2 3 4 5
(c)
Ramallah
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)

FIGURE 2.