Ann Allergy Asthma Immunol 113 (2014) 386–392

Contents lists available at ScienceDirect

Childhood intermittent and persistent rhinitis prevalence and climate and vegetation: a global ecologic analysis

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A R T I C L E I N F O

Article history:
Received for publication March 19, 2014.
Received in revised form June 17, 2014.
Accepted for publication June 25, 2014.

A B S T R A C T

Background: The effect of climate change and its effects on vegetation growth, and consequently on rhinitis, are uncertain.

Objective: To examine between- and within-country associations of climate measures and the normalized difference vegetation index with intermittent and persistent rhinitis symptoms in a global context.

Methods: Questionnaire data from 6- to 7-year-olds and 13- to 14-year-olds were collected in phase 3 of the International Study of Asthma and Allergies in Childhood. Associations of intermittent (>1 symptom report but not for 2 consecutive months) and persistent (symptoms for ≥2 consecutive months) rhinitis symptom prevalences with temperature, precipitation, vapor pressure, and the normalized difference vegetation index were assessed in linear mixed-effects regression models adjusted for gross national income and population density. The mean difference in prevalence per 100 children (with 95% confidence intervals [CIs]) per interquartile range increase of exposure is reported.

Results: The country-level intermittent symptom prevalence was associated with several country-level climatic measures, including the country-level mean monthly temperature (6.09°C; 95% CI, 2.06–10.11°C per 10.4°C), precipitation (3.10 mm; 95% CI, 0.46–5.73 mm; per 67.0 mm), and vapor pressure (6.21 hPa; 95% CI, 2.17–10.24 hPa; per 10.4 hPa) among 13- to 14-year-olds (222 center in 94 countries). The center-level persistent symptom prevalence was positively associated with several center-level climatic measures. Associations with climate were also found for the 6- to 7-year-olds (132 center in 57 countries).

Conclusion: Several between- and within-country spatial associations between climatic factors and intermittent and persistent rhinitis symptom prevalences were observed. These results provide suggestive evidence that climate (and future changes in climate) may influence rhinitis symptom prevalence.

Introduction

The prevalence of allergic rhinitis is increasing in most countries.[1] Environmental factors are suspected of being important contributing influences. There is now considerable evidence that climate change is measurably altering the timing, distribution, quality, and quantity of allergenic plants and aeroallergens,[2,3] the primary risk factors for allergic rhinitis. Such changes are occurring via meteorologic factors and through interactions with greenhouse gases. For example, ragweed in an urban site with higher temperature and carbon dioxide concentrations, similar to those associated with projected climate change, grew faster, flowered earlier, and produced significantly greater above-ground biomass and ragweed pollen compared with ragweed grown in a rural area.[4] Allergic responses may also be heightened by air pollutants acting directly on the individual and/or through interactions with allergens.[5]

Previously, allergic rhinitis symptoms were classified as seasonal or perennial based on the timing of allergen exposure.

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Disclosures: Ms Fuertes received support from the Canadian Institutes of Health Research (Sir Frederick Banting and Charles Best Canada Graduate Scholarship). Ms Butland received support from the Department of Health and the Natural Environment Research Council.

http://dx.doi.org/10.1016/j.anai.2014.06.021
1081-1206/

However, this classification is not universally applicable and poorly reflects a patient's true experiences.[6] An improved classification system, which categorizes rhinitis symptoms as intermittent or persistent, is applicable worldwide, better suits a patient's needs, and is now being recommended.[7] Intermittent and persistent rhinitis are not synonymous with seasonal and perennial rhinitis and may be differentially associated with risk factors.[8] Studies that assess how climatic factors may influence these 2 types of rhinitis and associated diseases are of interest[9] and may provide indications as to the potential effects of future climate change.

One way to examine such associations is through the use of temporal data, as has been done in limited-area studies.[10−13] However, this approach is not currently feasible on a global scale. Alternatively, spatial associations can be examined. The International Study of Asthma and Allergies in Childhood (ISAAC) is unique in its global scope and is well suited to assess spatial associations between disease and ecologic measures of exposure, such as climate. ISAAC Phase One reported a suggestive role for long-term climatic conditions on asthma and atopic eczema symptom prevalences in Western Europe (57 centers in 12 countries).[14] No significant associations were found with allergic rhinitis symptom prevalence. The current study extends this work by taking advantage of the substantially larger ISAAC Phase Three data set and the newly adopted rhinitis classifications. Specifically, we aimed to assess spatial associations between the prevalence of intermittent and persistent rhinitis symptoms with climate and vegetation in a global context.

Methods

Study Population

The rationale and methods for ISAAC Phase Three have been previously published.[15] The current analysis is limited to ISAAC centers that collected valid data on monthly rhinitis symptoms: 222 centers in 94 countries for 13- to 14-year-olds and 135 centers in 59 countries for 6- to 7-year-olds. A diagram summarizing data availability is provided in eFigure 1. All collaborating centers obtained ethical approval from their local ethics committee or board. Letters describing the survey were sent to parents of all children. Parental completion of the questionnaire for the 6-to 7-year-olds implied consent. For the older age group, passive consent for the teenager to complete their own questionnaire at school was used by most centers.

Health Outcomes

Monthly data on rhinitis symptoms were collected via standardized parent-completed (for children 6−7 years of age) or child-completed (for children 13−14 years of age) ISAAC questionnaires (protocols available on the ISAAC website; http://isaac.auckland.ac.nz/). Individuals were asked to indicate if in the last 12 months they (or their child) had experienced a problem with sneezing or a runny or blocked nose when they (or their child) did not have a cold or flu. Subsequent questions asked whether this nose problem was accompanied by itchy eyes (at any time in the last 12 months) and in which of the past 12 months this nose problem occurred. Using the monthly data collected from the last of these questions, we calculated the prevalences of intermittent (at least 1 symptom report but not for 2 consecutive months) and persistent (symptoms for at least 2 consecutive months) rhinitis symptoms per center. Any apparent inconsistencies between stem and subsequent branch questions were accepted and not changed.

Environmental Factors and Covariates

Data on monthly mean daily temperature, total precipitation, and vapor pressure, averaged for 1991−2000 for $0.5^\circ \times 0.5^\circ$ grids (approximately 3,025 km^2), were obtained from the Intergovernmental Panel on Climate Change Data Distribution center.[16,17] Normalized difference vegetation index (NDVI) data for 2005 were obtained from the Global Land Cover Facility at a resolution of 0.07° on a 16-day basis and averaged per month.[18,19] NDVI data range from -1 (water) to $+1$ (dense vegetation), with values close to 0 indicating barren areas of rock, sand, or snow. Using the monthly data on temperature, precipitation, vapor pressure, and NDVI, we calculated the mean, maximum, minimum, SD, and maximal difference (difference between the monthly maximum and minimum) of monthly measurements for each factor. Data on gross national income (GNI) per capita were obtained from the World Bank (Atlas Method 2003).[20] When missing, GNI data were imputed using information from the Central Intelligence Agency World Fact Book (2003) (7 countries).[21] Population density data for 2005 were obtained from the Socioeconomic Data and Applications center.[22] Centers were classified into 5 climate types according to the Köppen climate classification system (snow/polar, equatorial, arid, warm temperate with dry winter, and warm temperate fully humid).[23]

The assignment of environmental variables to the centers has been previously described.[24] Briefly, coordinates for the study population were assigned to a $0.1^\circ \times 0.1^\circ$ square and compared with the 8 surrounding $0.1^\circ \times 0.1^\circ$ squares (each square covers approximately 121 km^2). Of these 9 squares, the one with the highest population density was considered the center grid and used for mapping. Climate data were mapped to this single coordinate. For population density and NDVI, the mean values of the center grid and 8 surrounding grids (each sized $0.07^\circ \times 0.07^\circ$, approximately 59 km^2) were used. Because the resolution of the NDVI data ($0.07^\circ \times 0.07^\circ$) is not the same as used during the original geocoding of the centers ($0.1^\circ \times 0.1^\circ$), the sizes of the grids used for mapping the environmental factors differ. For climate, population density, and NDVI data, which were available at the center level, country-level means were calculated,[25] which may not necessarily represent the true mean of a country. Data on GNI per capita were only available at the country level.

Analytic Strategy

Correlations between center-level variables were assessed using Spearman correlation coefficients because not all variables were normally distributed. Linear regression mixed models, which allow consideration of the hierarchical structure of the data, were used to assess associations between the prevalence of intermittent and persistent rhinitis symptoms with the mean, maximum, minimum, SD, and maximal difference of monthly measurements of temperature, precipitation, vapor pressure, and NDVI (as implemented in the lme4 package[26] in the statistical program R, version 3.0.1).[27] Fully adjusted models included the exposure of interest, GNI per capita, population density, and climate type. Furthermore, all models included country as a random intercept and fixed effects for both the center- and country-level representation of each explanatory variable, except for GNI per capita, which was available only at the country level. GNI per capita was included in the models because it was associated with the prevalence of atopic symptoms in worldwide analyses.[28] Including a random intercept for country, to allow the prevalence rates in countries to deviate from the estimated overall prevalence to avoid spurious results, is important.[14]

In sensitivity analyses, models were further adjusted for air pollution (particulate matter with aerodynamic diameters $<2.5\ \mu/m$ and nitrogen dioxide; data sources and assignment to centers have been previously described)[24] and mutually adjusted for mean vegetation in the models estimating the effects of the climatic factors and mean temperature, precipitation, and vapor pressure in the models estimating the effects of vegetation.

Between-country effects are presented as the mean difference in country-level prevalence (per 100 children) associated with a 1-unit increase in country-level exposure, with corresponding 95% confidence intervals (CIs). For countries with more than 1 participating center, the mean difference in center-level prevalence (per 100 children) associated with a 1-unit increase in center-level exposure were also estimated (within-country effects). All analyses were conducted using the statistical program R, version 3.0.1.[27]

Results

Distribution of Intermittent and Persistent Rhinitis Prevalences

For the centers with 13- to 14-year-olds, the mean center prevalence for intermittent rhinitis was highest in equatorial regions (mean prevalence, 20.0), was lowest in centers with snow/polar climates (mean prevalence, 8.9), and varied significantly by climate type (analysis of variance $P < .01$; Table 1). There was less variation by climate type for persistent symptoms (highest in warm temperate fully humid regions [mean prevalence, 16.1] and lowest in arid climates [mean prevalence, 11.9]; analysis of variance $P = .04$).

Center-specific sample sizes and intermittent and persistent symptom prevalences are reported in eTables 1 and 2 for the 13- to 14-year-olds and 6- to 7-year-olds, respectively. Figures 1 and 2 depict the global distribution of intermittent and persistent symptom prevalence, respectively, for the centers with older age groups.

Distribution and Correlation of Environmental Factors

Characteristics of modeled variables for the 13- to 14-year-olds are given in Table 2. All 3 measures of mean climatic variables were positively correlated with intermittent rhinitis prevalence. The prevalence of persistent rhinitis was negatively correlated with mean temperature. GNI per capita was negatively correlated with intermittent rhinitis prevalence, mean temperature, and vapor pressure and positively correlated with persistent rhinitis prevalence and mean NDVI. Population density was negatively correlated with mean NDVI and positively correlated with mean temperature and vapor pressure. Positive correlations were observed among all climatic factors. Mean precipitation was positively correlated with mean vegetation. Correlations were similar for the centers with younger age groups, although for persistent rhinitis there was a positive association with precipitation and no evidence of an association with mean temperature. Correlations among different measures of the same climatic factor were also examined. For the centers with older age groups, mean temperature was positively correlated with minimum and maximum temperature and negatively correlated with measures of variability. Mean vapor pressure was positively correlated with the minimum, maximum, and SD and negatively correlated with the maximal difference. Mean precipitation and vegetation were positively correlated with all other measures of precipitation and vegetation, respectively.

Table 1
Intermittent and persistent rhinitis symptom prevalence by climate type for the centers with 13- to 14-year-olds (222 centers)

Climate type	No. of centers	Intermittent rhinitis		Persistent rhinitis	
		Mean (SD)	Range	Mean (SD)	Range
Snow/polar	12	8.9 (8.0)	0.4–22.4	14.0 (9.3)	3.4–28.3
Arid	23	13.3 (10.3)	0.1–45.4	11.9 (6.0)	1.4–25.6
Equatorial	64	20.0 (11.0)	0.0–49.5	12.9 (8.5)	0–33.8
Warm temperate with dry winter	21	9.5 (4.0)	3.5–18.6	14.6 (7.0)	3.1–26.8
Warm temperate fully humid	102	15.4 (7.8)	0.0–44.9	16.1 (7.1)	1.1–32.1

Associations Between Rhinitis Symptoms and Environmental Factors

Between-country associations (mean differences in country-level prevalence per 100 children associated with a 1-unit increase in country-level exposure) for the fully adjusted models for the centers with 13- to 14-year-olds are presented in Table 3. Intermittent symptom prevalence was positively associated with the mean and minimum monthly temperature and negatively associated with the maximal difference in monthly temperature. Intermittent symptom prevalence was also positively associated with the mean, maximum, SD, and maximal difference of monthly precipitation measurements and the mean, maximum, and minimum monthly vapor pressure measurements. Four of the 10 significant associations observed for the centers with older age groups were also significant for the centers with younger age groups (eTable 3). Persistent symptom prevalence was not associated with any climatic variable in the fully adjusted models. Confounder-adjusted risk estimates for vegetation were elevated but nonsignificant for both outcomes.

For the 13- to 14-year-old age group, 37 countries had more than 1 participating center (165 centers in total). These centers were used to assess the mean difference in center-level prevalence per 100 children associated with a 1-unit increase in center-level exposure (Table 4). Within-country positive associations were observed between intermittent symptom prevalence and mean monthly temperature and the SD of monthly vapor pressure measurements. Further positive associations were also observed between persistent symptom prevalence and mean and maximum monthly temperature and the mean, maximum, minimum, and SD of monthly vapor pressure measurements. When the within-country analyses were replicated in the 6- to 7-year-old age groups (98 centers in 23 countries), only the associations between persistent symptoms and mean, maximum, and minimum monthly vapor pressure were significant. A positive within-country association was also observed between the maximum monthly vegetation measurements and persistent symptom prevalence but only among the 6- to 7-year-old age groups.

When the analysis was restricted to children with intermittent or persistent rhinitis symptoms who also reported itchy-eye symptoms in the last 12 months, risk estimates remained in the same direction but were generally smaller and were not significant for 1 of the 10 between-country associations and 5 of the 8 within-country associations observed for the 13- to 14-year-old age groups (eTable 5). Within-country associations were robust to the adjustment for air pollution (ie, particulate matter with aerodynamic diameters $<2.5\ \mu$/m and nitrogen dioxide) and mutual adjustment for meteorologic and vegetation factors. Estimates for the between-country associations were also generally similar, although a loss of statistical significance was occasionally observed (data not shown).

Discussion

Several spatial associations between climatic factors and the prevalence of intermittent and persistent rhinitis symptoms were observed in a nonrandomly selected group of centers and countries that participated in ISAAC Phase Three. Our results suggest a general positive association of mean monthly temperature and vapor pressure (which were highly correlated, $r_s = 0.925$) and precipitation, with symptom prevalence. This cross-sectional global study is a first step in assessing how climate change can affect allergic rhinitis symptoms. However, the generalizability of the observed associations and the influence of other factors not accounted for in this analysis on the association between climate and rhinitis remain unknown.

To account for the hierarchical nature of the data, we examined between- and within-county effects (country- and center-level associations, respectively). Associations with intermittent rhinitis

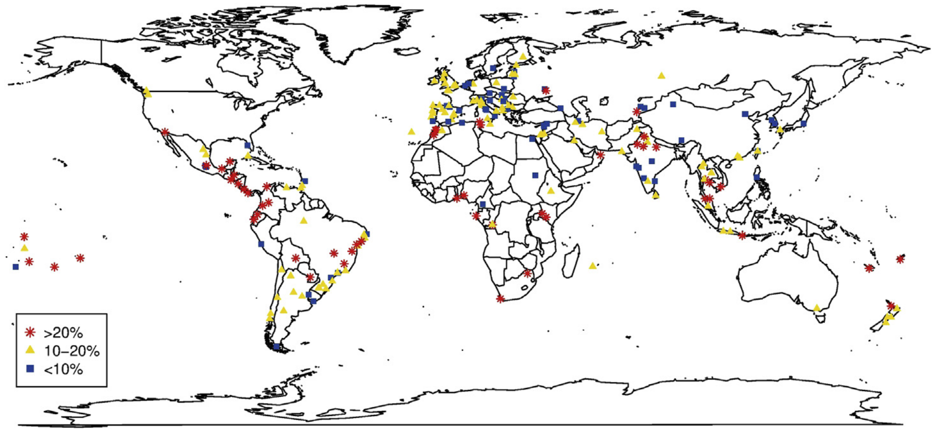

Figure 1. World map showing the center prevalence of intermittent rhinitis symptoms for the centers with 13- to 14-year-olds.

prevalence were most consistent at the country level, and only limited evidence was observed at the center level. Persistent rhinitis prevalence was only associated with climatic factors at the center level. One explanation for these findings may be that intermittent symptoms are more strongly associated with temporal changes in certain allergens affected by climate (eg, pollens and molds), whereas lifestyle factors have a greater influence on persistent symptoms. Thus, we were able to detect the relatively strong between-country associations for climate with intermittent symptom prevalence but not with persistent symptom prevalence because this latter association may be confounded by more important causal lifestyle factors that differ by country. Differences in sensitization patterns across areas are also likely to exist. Because these factors are less likely to differ within countries, the potentially weaker association for persistent symptom prevalence with climatic factors may only be detectable in the within-country analyses, which are less likely influenced by unmeasured confounding.

Our finding of a positive association of temperature, vapor pressure, and precipitation with rhinitis symptoms has been in part observed in previous single- or limited-area studies,[10,11,13] but others report null findings.[12,29–31] It is challenging to reconcile these previous studies with the current one because the effect of climate on allergen distribution (and thus presumably rhinitis) likely varies with local vegetation and geographical area.[32] Furthermore, these studies are based on data collected from adults, whereas the current study focuses on children and teenagers. To the best of our knowledge, there are only 2 multiarea studies on rhinitis. A study of 48 European centers conducted on adults concluded that climate can account for significant variability in (mostly asthma-related) respiratory symptom prevalence, although hay fever was only associated with temperature during the hottest month.[33] Another study, and the only one to include centers outside Europe and to study children, uses data from ISAAC Phase One.[14] In this study, climatic factors and allergic rhinitis symptoms were not associated, although suggestive evidence for asthma and atopic eczema was reported for Western European centers. In general, worldwide associations were inconsistent. By contrast, the current study is based on a substantially larger number of centers (222 centers in 94 countries and 144 centers in 81 countries were used in the current and previous worldwide analyses for the 13- to 14-year-olds, respectively) and examines intermittent and persistent rhinitis prevalences as outcomes rather than any report of rhinitis in the last 12 months. As the prevalence of rhinitis symptoms has increased in most centers between the timing of the ISAAC Phase One (1992–1997) and ISAAC Phase Three (2000–2003) surveys,[34] associations with intermittent and persistent rhinitis symptoms may be easier to detect in the ISAAC Phase Three data. The current study is also the first, to our knowledge, to examine associations between vegetation and rhinitis prevalence in a global context.

The mechanisms by which climatic factors may influence rhinitis are unclear but may be indirect via changes in indoor factors, such as dampness, which are likely to affect the distribution of indoor allergens, or via changes in pollen types, distributions, and concentrations, a phenomenon well documented in previous

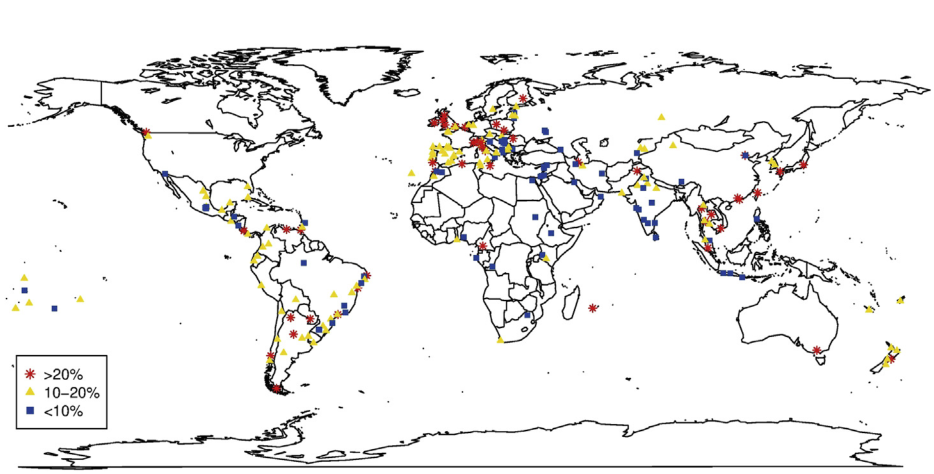

Figure 2. World map showing the center prevalence of persistent rhinitis symptoms for the centers with 13- to 14-year-olds.

Table 2
Correlations between modeled variables for the centers with 13- to 14-year-olds (222 centers)

Variable	Period	Median (IQR)	Spearman correlation					
			Intermittent rhinitis	Persistent rhinitis	Mean NDVI	Mean temperature	Mean precipitation	Mean vapor pressure
Health outcome								
Intermittent rhinitis	~2000–2003	14.1 (9.7–20.0)	–	–	0.074	0.361[a]	0.223[a]	0.332[a]
Persistent rhinitis	~2000–2003	13.7 (8.6–19.5)	–	–	0.105	−0.195[a]	0.054	−0.084
Economic/population								
GNI per capita[b]	2003	2950 (1,483–13,070)	−0.202[a]	0.526[a]	0.303[a]	−0.441[a]	−0.021	−0.318[a]
Population density	2005	809 (297–2,779)	−0.025	0.048	−0.310[a]	0.222[a]	0.062	0.183[a]
Environmental factors								
Mean NDVI,[c] NDVI units	2005	0.4 (0.3–0.5)	–	–	–	−0.058	0.422[a]	0.084
Mean temperature, °C	1991–2000	17.9 (12.1–24.4)	–	–	–	–	0.407[a]	0.925[a]
Mean precipitation, mm	1991–2000	81.7 (50.4–124.5)	–	–	–	–	–	0.568[a]
Mean vapor pressure, hPa	1991–2000	14.1 (10.7–21.7)	–	–	–	–	–	–

Abbreviations: GNI, gross national income; IQR, interquartile range; NDVI, normalized difference vegetation index.
[a]$P < .05$.
[b]Correlations with GNI per capita are with country-level variables (94 countries).
[c]Only 215 centers had information on NDVI.

studies covering smaller geographic areas.[2] Because an NDVI estimate assigned to one geographic coordinate is unlikely to accurately reflect the vegetation of a whole area, we used the mean of 9 NDVI estimates, each assigned to a 0.07° × 0.07° square (area coverage of approximately 59 km^2). Most risk estimates obtained were elevated, although all but one were nonsignificant, despite moderate variation in NDVI units among countries (range of mean country vegetation estimates was 0.44) and within countries (eg, range of mean center vegetation estimates was 0.68 in Chile with 5 participating centers and 0.49 in Spain with 12 participating centers). Inclusion of interaction terms between vegetation and temperature exposures yielded some significant associations for intermittent rhinitis (data not shown). We also examined whether associations may be stronger among smaller countries where the NDVI estimate is more likely to reflect exposures throughout the country. Only when the analysis was restricted to countries smaller than 50,000 km^2 (21 centers in 17 countries) was a positive between-country association found between intermittent symptom prevalence and the maximal difference and SD of monthly vegetation estimates. Because it is well established that pollen can disperse over large distances,[35] it is possible that our ecologic study design may not be ideal for assessing associations with vegetation, which may be more heterogeneous over small areas. Furthermore, using NDVI as a surrogate for vegetation did not allow us to distinguish plant species of differing allergenicity.

An important strength of this study is the ability to examine associations between and within countries using a multilevel modeling approach. Examining between-country associations allows the use of the entire data set, thereby taking full advantage of the large number and exposure contrasts of the countries

Table 3
Between-country associations for intermittent and persistent rhinitis prevalence with environmental factors for the centers with 13- to 14-year-olds (222 centers in 94 countries)[a]

Country-level environmental factor	Mean difference in country-level prevalence (95% CI) per 100 children per 1-U increase in country-level exposure	
	Intermittent rhinitis	Persistent rhinitis
Temperature		
Mean (10.4°C)	0.59 (0.20 to 0.98)[b]	−0.02 (−0.34 to 0.29)
Maximum (4.6°C)	0.33 (−0.15 to 0.82)	−0.10 (−0.47 to 0.27)
Minimum (16.1°C)	0.43 (0.15 to 0.71)[b]	−0.02 (−0.25 to 0.21)
SD (2.1°C)	−0.56 (−1.62 to 0.49)	0.05 (−0.78 to 0.88)
Maximal difference (12.5°C)	−0.36 (−0.67 to -0.05)[c]	0.07 (−0.18 to 0.32)
Precipitation		
Mean (67.0 mm)	0.05 (0.01 to 0.09)[c]	0.01 (−0.02 to 0.04)
Maximum (166.1 mm)	0.02 (0.01 to 0.04)[c]	0 (−0.01 to 0.02)
Minimum (42.7 mm)	0 (−0.07 to 0.07)	0 (−0.06 to 0.05)
SD (51.5 mm)	0.09 (0.03 to 0.14)[b]	0.01 (−0.04 to 0.05)
Maximal difference (137.8 mm)	0.03 (0.01 to 0.05)[a]	0 (−0.02 to 0.02)
Vapor pressure		
Mean (10.4 hPa)	0.60 (0.21 to 0.99)[b]	0.17 (−0.15 to 0.48)
Maximum (8.6 hPa)	0.44 (0.07 to 0.81)[c]	0.18 (−0.11 to 0.47)
Minimum (10.8 hPa)	0.55 (0.17 to 0.93)[b]	0.12 (−0.19 to 0.44)
SD (2.0 hPa)	0.25 (−1.24 to 1.74)	0.75 (−0.38 to 1.87)
Maximal difference (4.9 hPa)	−0.23 (−0.69 to 0.23)	0.23 (−0.12 to 0.58)
Vegetation[d]		
Mean (0.1)	8.03 (−8.75 to 24.81)	9.45 (−3.84 to 22.75)
Maximum (0.1)	6.33 (−8.54 to 21.20)	7.98 (−3.91 to 19.87)
Minimum (0.1)	4.31 (−13.52 to 22.14)	8.48 (−5.57 to 22.53)
SD (0.02)	11.57 (−41.84 to 64.98)	19.32 (−23.92 to 62.56)
Maximal difference (0.1)	5.48 (−13.14 to 24.11)	3.51 (−11.51 to 18.53)

Abbreviation: CI, confidence interval.
[a]All models adjusted for center mean exposure of interest, center, and country mean population density, country gross national income per capita, and climate type.
[b]$P < .01$.
[c]$P < .05$.
[d]Vegetation data only available for 215 centers in 87 countries.

Table 4
Within-country associations for intermittent and persistent rhinitis prevalence with environmental factors among countries with 2 or more centers per country for the centers with 13- to 14-year-olds (165 centers in 37 countries)[a]

Center-level environmental factor	Mean difference in center-level prevalence (95% CI) per 100 children per 1-U increase in center-level exposure	
	Intermittent rhinitis	Persistent rhinitis
Temperature		
Mean (10.7°C)	0.43 (0.02 to 0.84)[b]	0.39 (0.03 to 0.76)[b]
Maximum (6.8°C)	0.32 (−0.05 to 0.68)	0.37 (0.05 to 0.70)[b]
Minimum (11.9°C)	0.26 (−0.10 to 0.62)	0.16 (−0.16 to 0.49)
SD (2.6°C)	0.63 (−0.50 to 1.75)	0.71 (−0.30 to 1.72)
Maximal difference (12.1°C)	0.12 (−0.28 to 0.52)	0.22 (−0.13 to 0.58)
Precipitation		
Mean (68.7 mm)	−0.03 (−0.06 to 0.01)	−0.01 (−0.04 to 0.03)
Maximum (162.9 mm)	−0.01 (−0.02 to 0.01)	−0.01 (−0.03 to 0)
Minimum (35.1 mm)	−0.05 (−0.11 to 0.01)	0 (−0.05 to 0.06)
SD (58.5 mm)	−0.01 (−0.06 to 0.04)	−0.04 (−0.08 to 0)
Maximal difference (161.5 mm)	0 (−0.02 to 0.02)	−0.01 (−0.03 to 0)
Vapor pressure		
Mean (8.4 hPa)	0.22 (−0.15 to 0.59)	0.37 (0.04 to 0.70)[b]
Maximum (10.1 hPa)	0.20 (−0.08 to 0.49)	0.31 (0.06 to 0.56)[b]
Minimum (6.2 hPa)	0.25 (−0.17 to 0.67)	0.39 (0.02 to 0.76)[b]
SD (2.4 hPa)	1.14 (0.06 to 2.21)[b]	1.32 (0.37 to 2.27)[c]
Maximal difference (5.7 hPa)	0.30 (−0.10 to 0.71)	0.28 (−0.09 to 0.64)
Vegetation		
Mean (0.2)	−1.25 (−10.81 to 8.31)	−2.89 (−11.42 to 5.64)
Maximum (0.2)	−0.40 (−8.82 to 8.02)	−0.25 (−7.79 to 7.29)
Minimum (0.2)	−2.93 (−13.61 to 7.76)	−5.47 (−14.98 to 4.04)
SD (0.05)	0.75 (−36.50 to 37.99)	7.53 (−25.95 to 41.02)
Maximal difference (0.2)	3.19 (−9.41 to 15.78)	6.94 (−4.31 to 18.20)

Abbreviation: CI, confidence interval.
[a]All models adjusted for the country mean exposure of interest, center and country mean population density, country gross national income per capita, and climate type.
[b]$P < .05$.
[c]$P < .01$.

participating in ISAAC Phase Three. However, it is likely that substantial between-country differences were not captured by model adjustments for GNI per capita, climate type, or air pollution, and thus we cannot exclude the possibility that residual confounding may be affecting the between-country associations. The differentiation between intermittent and persistent symptoms is however less likely to be affected by translation or awareness artifacts attributable to language and culture, which often hinder international comparisons of prevalence in ISAAC (and other questionnaire-based studies). Nevertheless, it remains possible that there may be some variation in the way the questionnaires were completed or administered. Confounding, although still possible, is less of a concern for the within-country associations because causal factors are less likely to differ to the same degree within countries as between countries. However, we did not account for individual risk factors, a limitation common to all ecologic studies. Given that only countries with 2 or more participating centers per country can contribute to the within-country analysis, these results are hindered by a lack of statistical power in terms of fewer centers and smaller exposure variation. Finally, a possible limitation of this study is that associations were not adjusted for multiple testing because it is not clear that the different exposure metrics (eg, the mean, maximum, minimum, SD, and maximal difference of temperature) represent the same exposure, especially not worldwide, and correcting for multiple testing can lead to conservative results when exposures are highly correlated.

ISAAC, given its size and worldwide coverage, which spans several different climate zones, is unique in its ability to assess the associations considered in this report. The collection of data from both 13- to 14-year-olds and 6- to 7-year-olds, using the standardized and validated ISAAC protocol and questionnaire, allowed for replication of analyses. The direction of estimates was the same for all significant between-country associations with intermittent symptoms and all but one within-country associations with persistent symptoms. Given that symptom data were collected for each month and therefore the period in days and weeks of each rhinitis episode was not available, our persistent rhinitis definition differs slightly from that proposed by the Allergic Rhinitis and Its Impact on Asthma workshop group, which requires symptoms to persist for more than 4 days per week and for more than 4 consecutive weeks.[7] The outcome definitions used in this report also deviate from those commonly used by ISAAC for allergic rhinitis (rhinoconjunctivitis), which requires a positive report of both nose symptoms and itchy eyes.[1] Information on itchy eyes was only collected for one time point covering anytime in the last 12 months. A sensitivity analysis that considered intermittent or persistent symptoms and itchy eyes anytime in the last 12 months as alternate outcomes yielded similar results, especially for the between-country associations. Associations for both intermittent and persistent symptoms were stronger for children who reported that their nose problems interfered with daily activities “a moderate amount” and a “lot” compared with those who answered “not at all” or “no answer provided,” which may suggest that climate not only influences the prevalence of disease but also the severity of symptoms (data not shown). However, we were unable to replicate this finding using the more stringent severe symptom definition normally used by ISAAC (which identifies severe symptoms as those that interfere with daily activities “a lot”) because the center prevalences of severe symptoms were quite low. As with all questionnaire-based data, recall bias is possible. Symptom reports were highest in the months before and after the month the surveys were administered. We do not anticipate that this would affect the results because the outcomes considered were not month specific. Caution should be applied in interpretation of these data as representative of world prevalence because the centers and countries participating in ISAAC were not randomly selected. Finally, although during the design of this analysis we attempted to use data from the same period, not all data sets overlap temporally.

In conclusion, several between- and within-country spatial associations between climatic factors (temperature, vapor pressure, and precipitation) and the prevalence of intermittent and persistent rhinitis symptoms were observed in this cross-sectional global analysis. These results provide suggestive evidence that climate influences the prevalence of rhinitis symptoms. Although not conclusive, our results represent a first step in investigating how future climate change may affect rhinitis symptom prevalence.

Acknowledgments

We thank all children, parents, and school teachers for their cooperation and participation. We also thank the many unnamed fieldworkers and funding agencies that supported ISAAC in their localities, as well as Mary Field-Smith for her assistance with the preparation of this article. All investigators in ISAAC Phase Three are listed in the eAppendix.

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eAppendix. International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and Phase Three Study Groups

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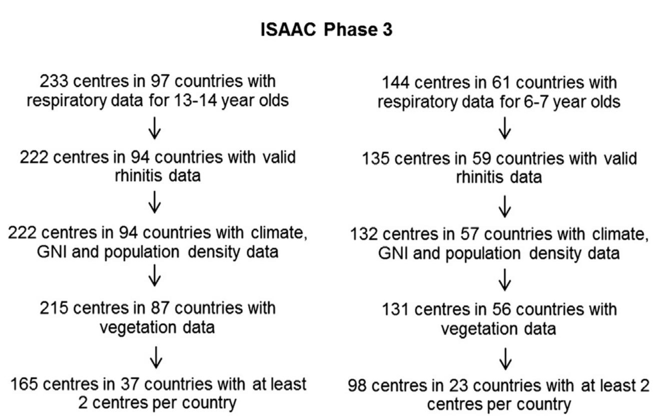

eFigure 1. Data availability for the study population.

eTable 1
Descriptive statistics for the centers with 13- to 14-year-olds

Country	Center	No. of children	Intermittent rhinitis prevalence	Persistent rhinitis prevalence
Africa				
Algeria	West Algiers	4,203	0.07	27.96
Cameroon	Yaounde	2,983	0.07	25.54
Congo	Brazzaville	1,012	49.51	6.42
Ethiopia	Addis Ababa	3,195	19.69	5.67
Gabon	Port-Gentil	3,166	36.13	0
Kenya	Eldoret	3,289	27.79	5.66
	Nairobi	3,023	21.63	12.44
Morocco	Casablanca	1,777	21.72	28.59
	Marrakech	1,689	20.07	11.84
	Benslimane	1,254	14.51	7.89
	Boulmene	1,008	32.04	5.85
Nigeria	Ibadan	3,142	35.65	0
République Democratique du Congo	Kinshasa	2,930	14.71	3.72
Reunion Island	Reunion Island	2,362	19.26	20.58
South Africa	Cape Town	5,037	25.99	18.60
	Polokwane	4,660	39.94	8.71
Sudan	Khartoum	2,896	8.91	4.39
Togo	Lome	3,090	21.17	11.62
Tunisia	Grand Tunis	6,119	40.42	18.35
	Sousse	3,042	45.40	18.28
Asia-Pacific				
China	Beijing	3,530	0.48	28.33
	Guangzhou	3,514	14.34	29.00
	Tibet	2,878	0.87	3.41
	Tong Zhou	3,542	4.15	6.72
	Wulumuqi	3,884	8.32	18.95
Hong Kong	Hong Kong	3,321	13.91	26.80
Indonesia	Bali	2,569	26.00	5.10
	Bandung	2,826	11.92	5.87
	Semarang	2,435	10.27	4.31
Japan	Fukuoka	2,520	15.40	27.98
	Tochigi	4,466	3.56	26.76
Malaysia	Alor Setar	2,941	24.18	17.68
	Klang Valley	3,025	15.27	21.79
	Kota Bharu	2,989	27.57	6.96
Philippines	Metro Manila	3,658	6.83	3.66
South Korea	Provincial Korea	7,375	9.26	19.43
	Seoul	2,888	9.38	17.73
Taiwan	Taipei	6,378	8.97	32.08
	Taoyuan	3,190	14.83	27.18
Thailand	Bangkok	4,669	24.54	33.78
	Chantaburi	2,901	28.82	18.58
	Chiang Mai	3,538	15.72	31.85
	Chiangrai	1,809	12.38	15.15
	Khon Kaen	3,410	17.30	22.84
	Nakorn Pathom	6,975	16.72	12.40
Vietnam	Ho Chi Minh City	4,240	39.15	25.54
Eastern Mediterranean				
Egypt	Cairo	3,047	3.48	1.35
Iran	Birjand	2,829	12.12	8.62
	Rasht	3,004	0.37	25.60
	Tehran	3,119	10.52	12.95
	Zanjan	2,805	14.15	6.95
Jordan	Amman	2,447	15.53	4.54
Kuwait	Kuwait	2,882	19.99	6.14
Malta	Malta	4,136	16.20	26.04
Pakistan	Islamabad	4,069	13.03	21.82
	Karachi	2,999	11.64	10.87
Palestine	North Gaza	3,627	14.09	1.08
	Ramallah	3,929	10.79	1.99
Sultanate of Oman	Al-Khod	3,747	20.12	5.47
Syrian Arab Republic	Aleppo	3,063	4.70	6.33
	Lattakia	3,010	5.22	3.92
	Tartous	2,995	1.64	1.50
Indian subcontinent				
India	Bangalore	3,440	16.57	8.95
	Bikaner	3,059	22.20	19.75
	Chandigarh	3,122	14.64	6.47
	Davangere	2,945	0.58	9.95
	Jaipur	3,607	29.55	8.34
	Lucknow	3,000	28.77	11.80
	Ludhiana	3,108	24.00	18.89
	Chennai	2,181	7.79	1.65
	Mumbai	1,829	4.70	3.34
	Nagpur	4,150	5.20	4.46

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eTable 1 (*continued*)

Country	Center	No. of children	Intermittent rhinitis prevalence	Persistent rhinitis prevalence
	New Delhi	3,469	12.19	13.69
	Pimpri	3,128	1.79	0.74
Sri Lanka	Sri Lanka	3,717	17.73	6.91
Latin America				
Argentina	Córdoba	3,445	14.72	23.08
	Neuquén	3,172	18.13	19.83
	Rosario City	3,099	11.52	11.55
	Salta	3,000	15.90	21.73
Bolivia	Santa Cruz	3,257	31.29	11.30
Brazil	Aracaju	3,043	24.71	9.53
	Belo Horizonte	3,088	20.95	7.71
	Brasília	3,009	23.63	11.43
	Caruaru	3,026	18.21	9.25
	Curitiba	3,628	8.68	14.72
	Feira de Santana	1,732	28.29	13.28
	Itajaí	2,737	15.93	8.62
	Maceió	2,745	12.68	12.09
	Manaus Amazonas	3,009	15.29	6.68
	Nova Iguaçu	3,185	11.65	4.27
	Passo Fundo	2,949	18.51	12.55
	Porto Alegre	3,007	18.52	14.57
	Recife	2,865	0.28	31.13
	Rural Santa Maria	3,057	18.29	6.48
	Salvador	3,020	19.50	27.28
	Santa Maria	3,065	17.32	8.42
	Santo Andre	3,232	0.03	25.77
	São Paulo	3,161	13.67	11.80
	São Paulo West	3,181	17.73	14.05
	Vitória da Conquista	1,679	30.49	19.54
Chile	Calama	1,618	18.73	17.06
	Chiloe	3,000	18.40	16.40
	Punta Arenas	3,044	0.43	26.87
	South Santiago	3,026	18.31	18.54
	Valdivia	3,105	16.55	25.44
Colombia	Barranquilla	3,204	36.11	15.79
	Bogotá	3,830	23.94	15.56
	Cali	3,100	30.45	14.06
Costa Rica	Costa Rica	2,436	28.94	29.72
Cuba	La Habana	3,026	16.23	17.32
Ecuador	Guayaquil	3,082	20.12	13.95
	Quito	3,014	23.56	12.14
El Salvador	San Salvador	3,260	40.95	10.34
Honduras	San Pedro Sula	2,675	33.16	7.07
Mexico	Ciudad de México (1)	3,891	26.21	13.03
	Ciudad de México (3)	3,474	26.11	4.35
	Ciudad de México (4)	2,662	29.56	7.89
	Ciudad Victoria	3,122	19.25	13.45
	Cuernavaca	1,431	8.67	7.69
	Mérida	3,019	25.44	10.40
	Mexicali Valley	2,988	30.86	9.40
	Monterrey	3,006	18.76	10.91
	Toluca	3,021	5.96	3.08
	Villahermosa	3,109	25.96	13.70
Nicaragua	Managua	3,263	33.56	9.99
Panama	David-Panamá	3,183	21.05	14.58
Paraguay	Asunción	3,000	44.90	30.87
Peru	Lima	3,022	0.10	17.97
Uruguay	Montevideo	3,177	7.15	16.18
	Paysandú	1,738	7.71	10.87
Venezuela	Caracas	3,000	14.07	25.30
North America				
Barbados	Barbados	2,498	9.53	7.69
Canada	Vancouver	2,853	14.72	22.99
Trinidad and Tobago	St Augustine	3,512	11.10	22.61
	Tobago	1,464	11.89	19.54
USA	Sarasota	1,245	9.96	18.15
	Seattle	2,422	15.32	17.22
Northern and Eastern Europe				
Albania	Tiranë	2,983	12.67	3.96
Bulgaria	Sofia	1,926	12.51	8.88
Croatia	Rijeka	2,194	8.34	8.43
Estonia	Tallinn	3,603	12.13	12.96
Finland	Kuopio County	3,051	13.01	27.56
Former Yugoslav Republic of Macedonia	Skopje	3,026	8.66	14.71
Georgia	Kutaisi	2,650	7.17	6.94
Hungary	Svábhegy	4,219	3.48	12.97
	Szeged	2,889	3.98	9.69

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eTable 1 (*continued*)

Country	Center	No. of children	Intermittent rhinitis prevalence	Persistent rhinitis prevalence
Kyrgyzstan	Balykchi	1,382	2.10	13.39
	Bishkek	5,048	3.68	11.51
	Jalalabat	2,404	22.42	6.03
Latvia	Riga	1,283	8.81	9.74
Lithuania	Kaunas	2,723	8.01	9.33
	Panevezys	1,187	14.15	19.63
	Siauliai	3,516	12.71	12.37
Poland	Krakow	2,545	9.59	25.85
	Poznan	1,875	10.72	25.97
Romania	Cluj	3,019	15.07	21.00
Russia	Novosibirsk	3,769	16.95	15.47
Serbia and Montenegro	Belgrade	3,228	11.59	9.32
	Nis	1,207	18.64	13.67
	Novi Sad	1,171	7.94	6.58
	Podgorica	1,014	10.85	7.89
	Sombor	1,105	11.76	3.08
Sweden	Linköping	2,679	3.84	15.45
Ukraine	Kharkiv	2,428	2.59	6.26
	Rural Kharkiv	3,968	20.29	4.36
Oceania				
Australia	Melbourne	2,192	16.42	20.39
Cook Islands	Rarotonga	445	24.27	2.47
Fiji	Suva	3,093	31.52	10.67
Kingdom of Tonga	Nuku'alofa	2,671	0.04	17.48
New Zealand	Auckland	2,870	20.63	19.79
	Bay of Plenty	1,976	13.56	17.26
	Christchurch	3,116	11.07	17.36
	Nelson	2,305	10.07	19.70
	Wellington	3,050	16.95	28.72
Niue	Niue Island	79	22.78	18.99
Nouvelle Caledonie	Nouvelle Caledonie	7,247	24.49	11.77
Polynesie Francaise	Polynesie Francaise	4,289	20.73	10.89
Samoa	Apia	2,986	11.82	2.18
Tokelau	Tokelau	66	34.85	13.64
Western Europe				
Austria	Urfahr-Umgebung	1,439	7.44	11.88
Belgium	Antwerp	3,250	9.72	25.69
Channel Islands	Guernsey	1,248	12.74	18.91
	Jersey	773	11.64	16.30
Germany	Münster	4,132	10.91	19.46
Isle of Man	Isle of Man	1,716	16.84	21.45
Italy	Bari	1,287	18.34	18.57
	Colleferro-Tivoli	1,361	9.63	10.14
	Cosenza	925	6.49	8.76
	Emilia-Romagna	1,347	13.29	19.90
	Empoli	1,229	15.79	15.30
	Firenze	1,383	12.65	18.51
	Mantova	1,114	11.13	23.07
	Milano	1,410	10.85	22.34
	Palermo	1,221	11.96	18.18
	Roma	1,325	8.83	26.94
	Siena	1,082	11.74	24.77
	Torino	1,180	12.37	21.36
	Trento	1,311	4.35	11.82
The Netherlands	The Netherlands	6,896	8.45	18.16
Portugal	Coimbra	1,177	10.79	11.21
	Funchal	3,161	10.16	10.09
	Lisbon	3,024	12.10	15.31
	Portimao	1,109	0.09	20.02
	Porto	3,336	14.81	15.08
Republic of Ireland	Republic of Ireland	3,089	13.05	20.78
Spain	A Coruña	2,979	14.84	19.54
	Almeria	4,051	8.49	14.76
	Asturias	4,184	16.32	18.57
	Barcelona	3,066	9.65	12.26
	Bilbao	3,401	8.17	14.61
	Cartagena	3,998	14.76	15.68
	Castellón	4,024	11.16	19.38
	Madrid	2,652	12.14	14.86
	Pamplona	2,932	9.89	13.27
	San Sebastián	1,195	10.88	13.39
	Valencia	3,132	12.77	11.11
	Valladolid	2,944	15.18	15.29
United Kingdom	North Thames	2,356	16.38	20.12
	Scotland	4,662	12.91	22.31
	South Thames	2,432	15.79	17.56
	Surrey-Sussex	5,082	12.99	18.91
	Wales	2,501	13.39	21.63

eTable 2
Descriptive statistics for the centers with 6- to 7-year-olds

Country	Center	No. of children	Intermittent rhinitis prevalence	Persistent rhinitis prevalence
Africa				
Nigeria	Ibadan	2,396	16.65	0
South Africa	Polokwane	3,480	26.15	4.57
Asia-Pacific				
Hong Kong	Hong Kong	4,448	13.02	23.40
Indonesia	Bandung	2,503	12.74	2.36
Japan	Fukuoka	2,958	7.98	18.09
Malaysia	Alor Setar	3,786	10.17	3.86
	Klang Valley	3,044	9.59	4.86
	Kota Bharu	3,110	11.32	3.83
South Korea	Provincial Korea	4,258	6.95	16.67
	Seoul	1,760	7.05	18.58
Taiwan	Taipei	4,832	6.21	31.42
	Taoyuan	3,293	8.78	30.31
Thailand	Bangkok	4,209	19.51	22.62
	Chantaburi	3,321	18.85	14.39
	Chiang Mai	3,106	15.04	13.17
	Chiangrai	1,677	10.73	12.10
	Khon Kaen	2,658	11.96	18.81
	Nakorn Pathom	1,821	12.85	12.03
Vietnam	Ho Chi Minh City	3,879	19.49	15.49
Eastern Mediterranean				
Iran	Birjand	2,693	7.98	4.68
	Rasht	3,057	0.10	30.75
	Tehran	3,008	3.36	4.89
	Zanjan	2,777	17.21	8.64
Jordan	Amman	2,598	11.97	4.35
Malta	Malta	3,795	9.01	16.02
Pakistan	Islamabad	3,966	5.77	12.36
	Karachi	2,113	6.39	5.92
Palestine	North Gaza	3,575	11.78	2.66
	Ramallah	3,754	8.98	2.66
Sultanate of Oman	Al-Khod	4,130	10.94	3.95
Syrian Arab Republic	Lattakia	2,373	3.75	5.44
	Tartous	2,734	7.68	10.02
Indian subcontinent				
India	Davangere	3,043	0.82	7.59
	Jaipur	2,545	17.25	9.12
	Lucknow	3,000	15.07	7.57
	Ludhiana	3,225	9.64	7.26
	Mumbai	1,833	3.66	3.76
	Nagpur	4,294	3.89	3.31
	New Delhi	3,706	7.37	9.15
	Pimpri	3,838	4.22	3.31
Sri Lanka	Sri Lanka	3,345	10.40	7.41
Latin America				
Argentina	Neuquén	1,930	11.35	16.48
	Rosario City	2,952	6.30	9.79
Brazil	Aracaju	2,443	13.10	8.64
	Itajaí	1,511	11.05	9.79
	Maceió	1,990	11.96	10.10
	Manaus Amazonas	3,011	11.19	6.14
	Nova Iguaçu	3,249	14.40	10.19
	Salvador	1,069	11.51	26.47
	Santo Andre	2,167	0.14	29.72
	São Paulo	3,047	11.68	14.83
	São Paulo West	3,312	16.06	13.35
Chile	Punta Arenas	3,052	0.16	24.02
	South Santiago	3,075	7.97	18.05
	Valdivia	3,183	5.94	21.77
Colombia	Barranquilla	3,209	17.23	13.24
	Bogotá	3,256	15.14	14.28
	Cali	3,005	20.30	14.08
Costa Rica	Costa Rica	3,234	29.00	33.21
Cuba	La Habana	1,803	13.59	20.91
Ecuador	Quito	3,055	8.84	5.70
El Salvador	San Salvador	1,365	27.69	10.40
Honduras	San Pedro Sula	1,907	20.35	7.24
Mexico	Ciudad de México (1)	3,205	33.35	9.64
	Ciudad de México (3)	3,493	41.80	6.44
	Ciudad Victoria	2,603	11.64	9.80
	Cuernavaca	2,579	9.00	10.74
	Mérida	2,896	16.23	19.68
	Mexicali Valley	2,568	14.33	12.77
	Monterrey	3,030	10.40	10.59

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eTable 2 (*continued*)

Country	Center	No. of children	Intermittent rhinitis prevalence	Persistent rhinitis prevalence
	Toluca	3,235	10.39	7.54
	Villahermosa	2,678	20.43	13.18
Nicaragua	Managua	3,286	18.62	15.61
Panama	David-Panamá	2,942	20.90	14.41
Uruguay	Paysandú	1,512	6.75	11.11
Venezuela	Caracas	2,999	8.64	21.94
North America				
Barbados	Barbados	2,759	5.15	4.49
Canada	Saskatoon	1,255	3.43	21.35
Northern and Eastern Europe				
Albania	Tiranë	2,896	8.87	5.18
Bulgaria	Sofia	1,181	6.01	5.50
Croatia	Rijeka	1,633	3.74	12.80
Estonia	Tallinn	2,385	4.99	7.59
Georgia	Kutaisi	2,666	3.19	5.14
Hungary	Svábhegy	2,451	1.75	10.53
Kyrgyzstan	Bishkek	3,146	2.29	7.95
	Jalalabat	1,664	14.72	7.39
Lithuania	Kaunas	2,772	8.30	11.22
	Panevezys	1,176	7.65	13.69
	Siauliai	1,341	8.65	11.93
Poland	Krakow	2,497	4.45	25.11
	Poznan	1,999	3.75	22.41
Russia	Novosibirsk	2,730	9.78	11.10
Serbia and Montenegro	Belgrade	1,932	8.07	10.97
	Nis	1,002	3.29	9.58
	Novi Sad	1,044	6.51	6.99
	Sombor	1,029	3.98	5.93
Sweden	Linköping	2,089	1.58	10.29
Ukraine	Kharkiv	1,950	2.31	6.21
	Rural Kharkiv	3,000	15.57	4.87
Oceania				
Australia	Melbourne	2,968	5.63	18.09
New Zealand	Auckland	3,541	6.07	16.77
	Bay of Plenty	2,150	4.65	18.00
	Christchurch	3,315	3.59	19.16
	Nelson	1,867	3.00	15.05
Niue	Niue Island	47	12.77	6.38
Western Europe				
Austria	Kärnten	4,847	2.58	7.49
	Urfahr-Umgebung	2,029	2.61	9.46
Belgium	Antwerp	5,645	3.21	12.31
Germany	Münster	3,830	2.61	12.72
Greece	Thessaloniki	1,228	10.26	4.97
Isle of Man	Isle of Man	1,096	2.65	13.14
Italy	Bari	1,943	7.05	12.09
	Colleferro-Tivoli	1,143	2.97	12.51
	Emilia-Romagna	2,265	4.06	12.54
	Empoli	1,152	4.17	12.15
	Firenze	1,036	4.15	13.32
	Mantova	1,288	3.65	12.27
	Milano	2,249	4.36	13.34
	Roma	2,224	4.27	14.61
	Torino	2,361	4.62	12.88
	Trento	2,359	2.67	9.71
Portugal	Funchal	1,819	8.80	11.16
	Lisbon	2,477	8.48	15.46
	Portimao	1,069	0	21.33
	Porto	2,464	8.16	11.73
Spain	A Coruña	3,016	6.60	13.66
	Almeria	3,349	5.32	11.38
	Asturias	3,193	7.23	12.18
	Barcelona	3,002	2.73	5.26
	Bilbao	3,157	5.99	10.96
	Cartagena	2,948	5.90	9.77
	Castellón	3,915	3.32	10.19
	Madrid	2,347	10.01	11.55
	Pamplona	3,176	3.21	6.77
	Valencia	3,398	6.00	7.56

eTable 3
Between-country associations for intermittent and persistent rhinitis prevalence with environmental factors for the centers with 6- to 7-year-olds (132 centers in 57 countries)[a]

Country-level environmental factor	Average difference in country-level prevalence (95% CI) per 100 children per 1-U increase in country-level exposure	
	Intermittent rhinitis	Persistent rhinitis
Temperature		
Mean (10.6°C)	0.28 (−0.07 to 0.64)	0.09 (−0.30 to 0.47)
Maximum (5.3°C)	0.06 (−0.33 to 0.46)	−0.17 (−0.65 to 0.31)
Minimum (16.8°C)	0.22 (−0.03 to 0.47)	0.11 (−0.16 to 0.39)
SD (2.1°C)	−0.24 (−1.04 to 0.57)	−0.52 (−1.46 to 0.42)
Maximal difference (13.4°C)	−0.32 (−0.56 to −0.07)[b]	−0.09 (−0.37 to 0.18)
Precipitation		
Mean (67.7 mm)	0.03 (0 to 0.07)	0.02 (−0.02 to 0.06)
Maximum (201.2 mm)	0.02 (0 to 0.04)[b]	0.01 (−0.01 to 0.03)
Minimum (28.6 mm)	−0.04 (−0.10 to 0.02)	−0.01 (−0.08 to 0.07)
SD (64.6 mm)	0.09 (0.04 to 0.14)[c]	0.04 (−0.02 to 0.10)
Maximal difference (182.99 mm)	0.03 (0.01 to 0.05)[c]	0.02 (−0.01 to 0.04)
Vapor pressure		
Mean (11.1 hPa)	0.25 (−0.07 to 0.57)	0.18 (−0.19 to 0.54)
Maximum (9.8 hPa)	0.12 (−0.16 to 0.40)	0.04 (−0.30 to 0.38)
Minimum (10.6 hPa)	0.31 (0 to 0.62)	0.19 (−0.16 to 0.55)
SD (1.9 hPa)	0.02 (−1.05 to 1.09)	−0.37 (−1.68 to 0.94)
Maximal difference (5.4 hPa)	−0.30 (−0.61 to 0.01)	−0.11 (−0.50 to 0.28)
Vegetation[d]		
Mean (0.1)	3.90 (−10.82 to 18.62)	14.23 (−2.35 to 30.81)
Maximum (0.2)	4.84 (−8.09 to 17.78)	10.06 (−4.81 to 24.94)
Minimum (0.1)	0.81 (−14.67 to 16.29)	13.98 (−3.39 to 31.35)
SD (0.03)	3.62 (−39.50 to 46.74)	11.00 (−37.10 to 59.10)
Maximal difference (0.1)	4.90 (−9.54 to 19.33)	1.06 (−15.70 to 17.82)

Abbreviation: CI, confidence interval.
[a]All models adjusted for center mean exposure of interest, center and country mean population density, country gross national income per capita, and climate type.
[b]$P < .05$.
[c]$P < .01$.
[d]Vegetation data only available for 131 centers in 56 countries.

eTable 4
Within-country associations for intermittent and persistent rhinitis prevalence with environmental factors among countries with 2 or more centers per country for the centers With 6- to 7-year-olds (98 centers in 23 countries)[a]

Center-level environmental factor	Mean difference in center-level prevalence (95% CI) per 100 children per 1-U increase in center-level exposure	
	Intermittent rhinitis	Persistent rhinitis
Temperature		
Mean (10.9°C)	−0.37 (−0.85 to 0.10)	0.42 (−0.01 to 0.84)
Maximum (7.2°C)	−0.33 (−0.72 to 0.07)	0.32 (−0.02 to 0.67)
Minimum (13.4°C)	−0.32 (−0.77 to 0.13)	0.32 (−0.09 to 0.74)
SD (2.4°C)	−0.16 (−1.56 to 1.24)	0.48 (−0.77 to 1.72)
Maximal difference (12.7°C)	−0.02 (−0.48 to 0.43)	0.13 (−0.28 to 0.55)
Precipitation		
Mean (57.2 mm)	0.01 (−0.04 to 0.05)	0.01 (−0.03 to 0.05)
Maximum (177.7 mm)	0 (−0.02 to 0.02)	0 (−0.02 to 0.01)
Minimum (30.2 mm)	−0.01 (−0.08 to 0.06)	0 (−0.06 to 0.06)
SD (68.5 mm)	0 (−0.04 to 0.05)	−0.01 (−0.05 to 0.03)
Maximal difference (172.05 mm)	0 (−0.02 to 0.02)	0 (−0.02 to 0.01)
Vapor pressure		
Mean (9.0 hPa)	−0.38 (−0.79 to 0.03)	0.42 (0.05 to 0.79)[b]
Maximum (11.4 hPa)	−0.30 (−0.62 to 0.03)	0.32 (0.03 to 0.61)[b]
Minimum (7.9 hPa)	−0.25 (−0.71 to 0.20)	0.45 (0.04 to 0.86)[b]
SD (2.2 hPa)	−0.09 (−1.38 to 1.20)	0.63 (−0.50 to 1.77)
Maximal difference (5.7 hPa)	−0.17 (−0.66 to 0.31)	0.25 (−0.19 to 0.69)
Vegetation		
Mean (0.1)	−9.05 (−19.66 to 1.55)	8.37 (−1.04 to 17.77)
Maximum (0.2)	−7.58 (−17.01 to 1.85)	8.81 (0.53 to 17.09)[b]
Minimum (0.1)	−8.11 (−19.77 to 3.55)	6.90 (−3.52 to 17.31)
SD (0.05)	−30.47 (−74.18 to 13.25)	33.08 (−5.55 to 71.71)
Maximal difference (0.2)	−5.49 (−20.63 to 9.66)	11.09 (−2.22 to 24.40)

Abbreviation: CI, confidence interval.
[a]All models adjusted for the country mean exposure of interest, center and country mean population density, country gross national income per capita, and climate type.
[b]$P < .05$.

eTable 5

Between- and within-country associations between environmental factors and the prevalence of intermittent rhinitis and itchy eyes and persistent rhinitis and itchy eyes for the centers with 13- to 14-year-olds[a]

Environmental factor	Mean difference in country-level prevalence (95% CI) per 100 children per 1-U increase in country-level exposure[b]		Mean difference in center-level prevalence (95% CI) per 100 children per 1-U increase in center-level exposure[c]	
	Intermittent rhinitis and itchy eyes	Persistent rhinitis and itchy eyes	Intermittent rhinitis and itchy eyes	Persistent rhinitis and itchy eyes
Temperature				
Mean	0.36 (0.16 to 0.56)[d]	0.03 (−0.14 to 0.21)	0.23 (0.05 to 0.42)[e]	0.13 (−0.07 to 0.32)
Maximum	0.17 (−0.09 to 0.43)	−0.07 (−0.27 to 0.14)	0.21 (0.04 to 0.38)[e]	0.15 (−0.02 to 0.32)
Minimum	0.27 (0.13 to 0.41)[d]	0.03 (−0.10 to 0.16)	0.14 (−0.03 to 0.30)	0 (−0.18 to 0.17)
SD	−0.60 (−1.15 to −0.06)[e]	−0.21 (−0.67 to 0.25)	0.49 (−0.02 to 1.01)	0.61 (0.08 to 1.13)[e]
Maximal difference	−0.25 (−0.40 to −0.09)[d]	−0.04 (−0.18 to 0.10)	0.10 (−0.08 to 0.28)	0.18 (0 to 0.37)
Precipitation				
Mean	0.02 (0 to 0.04)[e]	0 (−0.01 to 0.02)	−0.02 (−0.04 to 0)[e]	−0.01 (−0.03 to 0.01)
Maximum	0.01 (0 to 0.02)[e]	0 (−0.01 to 0.01)	0 (−0.01 to 0)	−0.01 (−0.02 to 0)
Minimum	0 (−0.03 to 0.04)	0.01 (−0.02 to 0.04)	−0.03 (−0.06 to 0)[e]	−0.01 (−0.03 to 0.02)
SD	0.04 (0.01 to 0.07)[d]	0 (−0.03 to 0.03)	−0.01 (−0.03 to 0.02)	−0.02 (−0.04 to 0)
Maximal difference	0.02 (0 to 0.03)	0 (−0.01 to 0.01)	0 (−0.01 to 0.01)	−0.01 (−0.02 to 0)
Vapor pressure				
Mean	0.33 (0.14 to 0.53)[d]	0.11 (−0.07 to 0.28)	0.11 (−0.06 to 0.28)	0.10 (−0.07 to 0.28)
Maximum	0.24 (0.04 to 0.43)[e]	0.09 (−0.07 to 0.25)	0.11 (−0.02 to 0.24)	0.10 (−0.03 to 0.24)
Minimum	0.32 (0.13 to 0.51)[d]	0.10 (−0.07 to 0.28)	0.15 (−0.04 to 0.35)	0.13 (−0.06 to 0.33)
SD	0 (−0.80 to 0.80)	0.25 (−0.39 to 0.88)	0.62 (0.13 to 1.11)[e]	0.60 (0.09 to 1.10)[e]
Maximal difference	−0.19 (−0.44 to 0.05)	0.03 (−0.17 to 0.23)	0.14 (−0.05 to 0.32)	0.11 (−0.08 to 0.30)
Vegetation				
Mean	6.22 (−2.66 to 15.10)[f]	6.00 (−1.36 to 13.36)[f]	−0.74 (−5.17 to 3.70)	−2.56 (−7.03 to 1.91)
Maximum	3.18 (−4.70 to 11.05)[f]	4.22 (−2.37 to 10.81)[f]	−0.28 (−4.18 to 3.62)	−0.73 (−4.69 to 3.24)
Minimum	6.83 (−2.65 to 16.32)[f]	6.39 (−1.39 to 14.18)[f]	−1.39 (−6.33 to 3.56)	−4.33 (−9.30 to 0.63)
SD	−3.19 (−31.33 to 24.95)[f]	6.49 (−17.42 to 30.40)[f]	0.49 (−16.75 to 17.73)	3.59 (−14.00 to 21.18)
Maximal difference	−2.28 (−12.17 to 7.60)[f]	−0.19 (−8.52 to 8.14)[f]	1.26 (−4.57 to 7.09)	4.31 (−1.59 to 10.22)

Abbreviation: CI, confidence interval.

[a]All models adjusted for center mean exposure of interest (for between-country associations) or country mean exposure of interest (for within-country associations), as well as the center and country mean population density, country gross national income per capita, and climate type.

[b]On the basis of data from 222 centers in 94 countries.

[c]On the basis of data from 165 centers in 37 countries.

[d]$P < .01$.

[e]$P < .05$.

[f]Vegetation data only available for 215 centers in 87 countries.