Atopic Sensitization and the International Variation of Asthma Symptom Prevalence in Children

Gudrun Weinmayr[1], Stephan K. Weiland[1†], Bengt Björkstén[2], Bert Brunekreef[3], Gisela Büchele[1], William O. C. Cookson[4], Luis Garcia-Marcos[5], Maia Gotua[6], Christina Gratziou[7], Marianne van Hage[8], Erika von Mutius[9], Mall-Anne Riikjärv[10], Peter Rzehak[1], Renato T. Stein[11], David P. Strachan[12], John Tsanakas[13], Kristin Wickens[14], Gary W. Wong[15], and the ISAAC Phase Two Study Group*

[1]Institute of Epidemiology, Ulm University, Ulm, Germany; [2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Institute for Risk Assessment Sciences, University of Utrecht, and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; [5]University of Murcia, Murcia, Spain; [6]Center of Allergy and Immunology, Tbilisi, Georgia; [7]Medical School, Athens University, Evgenidio Hospital, Athens, Greece; [8]Clinical Immunology and Allergy Unit, Department of Medicine, Karolinska Institutet and University Hospital, Stockholm, Sweden; [9]Dr. von Haunersches University Children's Hospital, Ludwig-Maximilians-University, Munich, Germany; [10]Tallinn Children's Hospital, Tallinn, Estonia; [11]Pontificia Universidade Catolica do Rio Grande do Sul, Porto Alegre, RS, Brazil; [12]St. George's, University of London, London, United Kingdom; [13]Paediatric Respiratory Unit, Hippokration Hospital, Thessaloniki, Greece; [14]Wellington Asthma Research Group, Wellington School of Medicine and Health Sciences, Wellington, New Zealand; and [15]Department of Paediatrics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, NT, Hong Kong, SAR China

Rationale: **Atopic sensitization has long been known to be related to asthma in children, but its role in determining asthma prevalence remains to be elucidated further.**

Objectives: **To investigate the role of atopic sensitization in the large international variation in the prevalence of childhood asthma.**

Methods: **Cross-sectional studies of random samples of 8- to 12-year-old children (n = 1,000 per center) were performed according to the standardized methodology of Phase Two of the International Study of Asthma and Allergy in Childhood (ISAAC). Thirty study centers in 22 countries worldwide participated and reflect a wide range of living conditions, from rural Africa to urban Europe. Data were collected by parental questionnaires (n = 54,439), skin prick tests (n = 31,759), and measurements of allergen-specific IgE levels in serum (n = 8,951). Economic development was assessed by gross national income per capita (GNI).**

Measurements and Main Results: **The prevalence of current wheeze (i.e., during the past year) ranged from 0.8% in Pichincha (Ecuador) to 25.6% in Uruguaiana (Brazil). The fraction of current wheeze attributable to atopic sensitization ranged from 0% in Ankara (Turkey) to 93.8% in Guangzhou (China). There were no correlations between prevalence rates of current wheeze and atopic sensitization, and only weak correlations of both with GNI. However, the fractions and prevalence rates of wheeze attributable to skin test reactivity correlated strongly with GNI (Spearman rank-order coefficient $\rho = 0.50$, $P = 0.006$, and $\rho = 0.74$, $P < 0.0001$, respectively). In addition, the strength of the association between current wheeze and skin test reactivity, assessed by odds ratios, increased with GNI ($\rho = 0.47$, $P = 0.01$).**

Conclusions: **The link between atopic sensitization and asthma symptoms in children differs strongly between populations and increases with economic development.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The prevalence of asthma symptoms has been shown to vary more than 15-fold among countries worldwide. The international variation in the prevalence of atopic sensitization in children and its relevance for the variation in asthma symptoms is unknown.

What This Study Adds to the Field

Prevalence rates of asthma symptoms and atopic sensitisation in children vary widely among 22 countries worldwide. The link between atopic sensitization and asthma symptoms differs strongly among populations and increases with economic development.

Keywords: wheeze; ISAAC Phase Two; IgE; population attributable risk; gross national income per capita

Atopic sensitization has long been known to be related to childhood asthma (1, 2). However, Pearce and colleagues, in a systematic review, concluded that its role may have been overemphasized (3). The available evidence at the time suggested that usually only less than half of the asthma cases were attributable to atopic sensitization. In addition, studies showing a strong relation between asthma and atopy come mainly from affluent Western countries. Results from studies in less affluent countries provide a more heterogeneous picture (4–7). Thus, it may be that the link between asthma and atopic sensitization differs between countries. The European Community Respiratory Health Survey, involving approximately 13,500 adults, aged 20 to 44 years, in 36 study centers in 16 countries, recently showed that the overall attributable fraction (AF) of asthma symptoms caused by atopy in adults was 30% (8). Between centers, the AF varied widely, ranging from 4 to 61%.

Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC I) found that the prevalence of symptoms of asthma, allergic rhinitis and atopic eczema in

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* ISAAC study group members are listed before the REFERENCES.

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Correspondence and requests for reprints should be addressed to Dr. Gudrun Weinmayr, Ph.D., Institute of Epidemiology, Ulm University, Helmholtzstrasse 22, D-89075 Ulm, Germany. E-mail: gudrun.weinmayr@uni-ulm.de

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children aged 6 to 7 years and in those aged 13 to 14 years, assessed by standardized questionnaires, differed more than 20-fold between the 155 study centers around the world (9, 10). Phase Two of ISAAC (ISAAC II) aims to identify determinants of these differences by studying informative populations. The participating study centers reflect the full range in asthma prevalence observed in ISAAC I and include additional study centers with particular living conditions (e.g., rural areas in Ghana and Ecuador). The current article is the first report of ISAAC II findings relating to asthma and atopy. It investigates the role of atopic sensitization in the international variation in prevalence rates of asthma symptoms, with a focus on a potential interaction with economic development in the study areas. Some results of this study have been previously reported in the form of abstracts (11–13).

METHODS

Study Populations and Field Work

The study methods of ISAAC II have been described in detail elsewhere (14), and additional information is given in the online supplement. Briefly, random samples of schools (≥10) from defined geographical areas were chosen and children (n ≥ 1,000 per center) attending classes with a majority of 9- to 11-year-olds were invited to participate. Standardized parental questionnaires on asthma symptoms were used (15). In four countries, the questions were posed by trained interviewers because illiteracy was a problem.

The ISAAC II methodology allowed objective measurements to be performed either in the full sample (option A) or in random subsamples (option B) of children (14). Most centers invited all children to participate in the skin prick testing, whereas blood samples were collected mostly in stratified random subsamples of children with and without reports of wheeze in the past year (~100 in each stratum). All centers obtained approval by local ethics committees and made major efforts to ensure comparable data quality (14).

Skin Test Reactivity

The skin prick tests were performed according to a detailed protocol (14). Extracts of six common aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, *Alternaria tenuis*, mixed tree pollen, and mixed grass pollen) produced by ALK (Horsholm, Denmark) were used. The centers were encouraged to add allergens of local relevance. Additional allergens were tested in 18 centers and included the following: olive pollen, *Parietaria officinalis*, cockroach, dog, mixed molds, horse, mixed weeds (16), *Cladosporium*, bird epithelium, and Turkish tree mix (16). A positive skin reaction was defined as a wheal size of 3 mm or greater, after subtraction of the negative control.

Serum IgE

Allergen-specific IgE antibodies to a mix of common inhalant allergens (*D. pteronyssinus*, *D. farinae*, birch, timothy, mugwort, cat, dog, horse, *Cladosporium*, olive pollen, and *Parietaria*) were measured by Phadiatop (Phadia AB, Uppsala, Sweden). For almost all centers (except two German centers), the measurements were done in one central laboratory (14). Elevated levels were defined as those 0.35 allergen-specific kilounits per liter (kU_A/L) or higher.

Gross National Income

To assess economic conditions, we used gross national income per capita (GNI) converted into U.S. dollars using the World Bank Atlas method (17).

Statistical Analyses

Prevalence rates were calculated. If centers had studied stratified subsamples, prevalence rates and odds ratios (ORs) were calculated applying appropriate sampling weights (18, 19). Ecological correlations were assessed using Spearman rank order coefficients (ρ). Population attributable fractions (PAFs) were calculated using the formula: $PAF = P_{ec} \times (OR - 1)/OR$, where P_{ec} is the prevalence of exposure among the cases (e.g., atopic sensitization among children with wheeze). Population attributable prevalences (PAPs) were obtained by multiplying the PAF with the prevalence of disease. Combined estimates across several study centers were calculated using random effects meta-analysis models (20).

Two strata were defined for the initial analyses relating to GNI: (*1*) centers classified by the World Bank as "high income countries" (i.e., GNI per capita per year ≥ $9,200); (*2*) the remaining centers were combined in a group called "nonaffluent countries." For the correlation analyses, GNI was used as a continuous variable. The analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC) and SUDAAN (version 9.0; RTI International, Research Triangle Park, NC).

RESULTS

A total of 54,439 children, ages 8 to 12 years old, had completed parental questionnaires, 31,759 underwent skin prick tests, and 8,951 participated in the measurement of IgE antibodies. Participation rates ranged from 36 to 100% for the questionnaire, from 24 to 99% for skin prick tests, and from 12.5 to 76% for IgE measurements (Table 1).

Prevalence Rates of Asthma Symptoms and Atopic Sensitization

The prevalence rates of asthma-related symptoms varied widely between study centers (Table 2). Current wheeze (i.e., wheeze during the last year) ranged from 0.8% in Pichincha Province, rural Ecuador, to 25.6% in Uruguaiana, Brazil. Similar variation was observed in the prevalence of severe asthma symptoms. The prevalence of skin prick test reactivity was lowest in Kintampo, rural Ghana (1.7%), and highest in Hong Kong, China (45.3%). Elevated levels of allergen-specific IgE were least common in Tallinn, Estonia (16.7%), and most common in Almeria, Spain (48.5%). The prevalence of atopic wheeze (defined as current wheeze plus skin prick test reactivity) and nonatopic wheeze also varied widely between centers. Atopic wheeze was least prevalent in Pichincha, Ecuador (0.2%), and most prevalent in Hawkes Bay, New Zealand (13.4%). The prevalence of nonatopic wheeze was lowest in Guangzhou, China (0.4%), and highest in Uruguaiana, Brazil (20.9%).

Association between Asthma Symptoms and Atopic Sensitization

The association between current wheeze and skin prick test reactivity was statistically significant in all centers in affluent countries, except for Reykjavik, Iceland, where the association did not reach formal statistical significance (Figure 1). The combined odds ratio (OR) for the affluent countries was 4.0 (95% confidence interval [CI], 3.5–4.6). The observed associations were substantially weaker in nonaffluent countries (combined OR, 2.2; 95% CI, 1.5–3.3). Guangzhou, China, was not included in the calculation of this estimate because the OR for this area was an extreme outlier (OR, 58.9) due to the virtual absence of nonatopic wheeze in the sample (Table 2). There was no significant evidence for heterogeneity among centers in affluent countries estimated from random effects meta-analysis ($P = 0.21$). There was a suggestion of heterogeneity among centers in nonaffluent countries only when the OR of Guangzhou was included in the meta-analysis ($P = 0.052$). A similar pattern emerged for elevated allergen-specific IgE levels where estimates for the combined OR were 3.5 (95% CI, 2.9–4.2) for centers in affluent countries and 1.9 (95% CI, 1.0–3.9) for centers in nonaffluent countries. Again, there was no apparent heterogeneity ($P = 0.26$ for affluent and $P = 0.43$ for nonaffluent countries).

TABLE 1. DATA ON FIELD WORK AND PARTICIPATION BY STUDY CENTER

			Questionnaire	Skin Prick Test	Allergen-specific IgE	
Country	Study Period Questionnaire	Characteristic of Study Area	n* (%)†	n* (%)†	n* (%)†	GNI (*US$*)
Albania						
Tirana	Feb–April 1999	Urban	1,052 (94.9)	929 (84.0)	113‡ (52.8)	970
Brazil						
Uruguaiana	March 2003–March 2004	Urban	1,971 (96.3)	1,192§ (96.2)	—	3,900
China						
Beijing	Oct 1997–Feb 1998	Urban	4,214 (92.5)	1,044§ (90.8)	—	780
Guangzhou	Oct 1997–Feb 1998	Urban	3,510 (93.3)	1,078§ (36.1)	—	780
Hong Kong	Oct 1997–Feb 1998	Urban	3,011 (96.7)	1,324§ (63.8)	—	25,580
Ecuador						
Pichincha	May 2001–Jan 2002	Rural	894 (100.0)	894 (99.9)	—	1,370
Estonia						
Tallinn	Dec 1996–Feb 1997	Urban	971 (83.9)	642 (55.5)	161‡ (39.7)	3,540
France						
Créteil	June–Dec 1996	Urban	1,400 (66.1)	‖	—	24,640
Georgia						
Tbilisi	March 2001–June 2002¶	Urban	1,012 (87.7)	173‡ (75.9)	173‡ (75.9)	680
Germany						
Dresden	Sept 1995–June 1996	Urban	3,023 (82.8)	2,259 (61.6)	2,084 (56.8)	25,740
Munich	Sept 1995–Dec 1996	Urban	3,301 (87.5)	2,317 (60.6)	1,737 (45.4)	25,740
Ghana						
Kintampo	Feb 2000–July 2000	Rural	1,354 (ND)	1,322 (ND)	—	380
Greece						
Athens	Oct 2000–Feb 2001	Urban	985 (85.3)	985 (85.3)	190‡ (75.5)	11,700
Thessaloniki	Sept–Nov 2001	Urban	1,018 (63.0)	1,018 (63.0)	207‡ (54.6)	11,700
Iceland						
Reykjavik	May 2000¶	Urban	937 (46.6)	633 (38.0)	—	29,920
India						
Mumbai	2000–2001	Urban	1,658 (ND)	1,556 (ND)	133‡ (ND)	450
Italy						
Rome	Oct 2000–April 2001	Urban	1,354 (83.5)	1,307 (62.3)	93‡ (24.0)	20,170
Latvia						
Riga	May–Nov 1999¶	Urban	908 (87.4)	295 (30.8)	—	2,570
The Netherlands	April 1997–July 1998	Urban	3,541 (64.7)	1,286§ (43.3)	1,989‡ (37.4)	25,270
New Zealand						
Hawkes Bay	Feb–June 2000	Urban/rural	1,320 (84.3)	1,288 (82.2)	—	13,480
Norway						
Tromsø	March–June 2000¶	Urban/rural	3,669 (81.3)	722§ (60.2)	155‡ (64.2)	35,660
Spain						
Almeria	March 2000–June 2001	Urban	1,126 (49.9)	1,075 (47.7)	209‡ (40.3)	14,790
Cartagena	March 2000–March 2001	Urban	1,429 (54.6)	1,030 (39.6)	188‡ (26.8)	14,790
Madrid	Feb 2001–April 2002	Urban	981 (35.8)	653 (23.9)	341 (12.5)	14,790
Valencia	Dec 2000–Dec 2001	Urban	1,362 (40.4)	1,023 (30.5)	539 (16.1)	14,790
Sweden						
Linköping	Jan–April 1997	Urban	907 (81.7)	857 (77.0)	172‡ (50.4)	28,540
Östersund	Jan–April 1997	Urban/rural	1,195 (86.0)	991 (71.4)	268‡ (63.0)	28,540
Turkey						
Ankara	Oct 1999–April 2000	Urban	2,976 (87.6)	2,747 (81.0)	—	2,800
United Kingdom						
West Sussex	Oct 1998–July 1999	Urban/rural	1,056 (78.6)	898 (66.7)	199‡ (68.9)	24,070
West Bank						
Ramallah	Sept 2000	Urban/rural	2,304 (85.4)	221‡ (65.0)	—	1,750
Total			54,439	31,759	8,951	

Definition of abbreviations: GNI = gross national income per capita; ND = no data.
Em dash (—) = not performed.
* Number of children ages 8–12 years old.
† Participation rate refers to those who were invited (either full or subsamples).
‡ Stratified subsample.
§ Random subsample.
‖ The core standard allergens were not licensed in France (where allergens from Stallergènes were tested in 1,451 children).
¶ Average period between questionnaire and skin prick testing > 180 days: Tbilisi (197 d), Tromso (218 d), Reykjavik (354 d), and Riga (385 d).

Population Attributable Risks

Table 3 shows that the highest fractions of current wheeze that were attributable to skin prick test reactivity (PAFs) were observed in Guangzhou (93.8%), Hong Kong (59.6%), and the Netherlands (58.6%). The very high PAF in Guangzhou was again due to the low number of nonatopic children with wheeze in this center. The lowest PAFs were found in Ankara, Turkey (0%, OR < 1), and Mumbai, India (2%). Overall, the combined PAFs were substantially higher in affluent countries (40.7%) than in nonaffluent countries (20.3%). A similar pattern was observed for IgE antibodies with a combined PAF of 45.6% for the centers in affluent countries and of 18.3% for the centers in nonaffluent countries. The combined estimate for the PAP based on skin prick test reactivity was 4.1% for centers in affluent

TABLE 2. PREVALENCE OF ASTHMA-RELATED SYMPTOMS, SKIN PRICK TEST REACTIVITY, AND ELEVATED (≥ 0.35 allergen-specific kilounits per liter [kU_A/L]) SERUM ALLERGEN-SPECIFIC IgE LEVELS

		12-mo Prevalence							
Country	Center	Wheeze	≥ 4 Asthma Attacks	Severe Wheeze Limiting Speech	Asthma Ever	Positive Skin Prick Tests*	Allergen-specific IgE (≥ 0.35 kU_A/L)	Atopic† Wheeze Past Year	Nonatopic‡ Wheeze Past Year
Albania	Tirana	4.4 (3.1 to 5.6)	0.5 (0.1 to 0.9)	0.5 (0.1 to 0.9)	2.7 (1.7 to 3.7)	15.0§ (12.7 to 17.3)	19.5 (11.6 to 27.4)	1.2 (0.5 to 1.9)	3.1 (2.0 to 4.2)
Brazil	Uruguaiana	25.6 (23.7 to 27.5)	6.5 (5.4 to 7.6)	5.9 (4.8 to 6.9)	12.7 (11.2 to 14.1)	13.3 (11.3 to 15.2)	—	5.4 (4.1 to 6.7)	20.9 (18.6 to 23.2)
China	Beijing	3.7 (3.2 to 4.3)	0.8 (0.5 to 1.1)	0.5 (0.2 to 0.7)	6.4 (5.7 to 7.2)	23.9§ (21.3 to 26.4)	—	1.6 (0.9 to 2.4)	1.7 (0.9 to 2.5)
	Guangzhou	3.2 (2.6 to 3.8)	0.5 (0.3 to 0.7)	0.2 (0.1 to 0.4)	4.4 (3.7 to 5.0)	32.0§ (29.2 to 34.8)	—	7.8 (6.2 to 9.4)	0.4 (0.0 to 0.7)
	Hong Kong	5.5 (4.7 to 6.3)	1.3 (0.9 to 1.7)	0.5 (0.2 to 0.7)	7.9 (6.9 to 8.8)	45.3§ (42.6 to 48.0)	—	6.9 (5.6 to 8.3)	2.1 (1.3 to 2.9)
Ecuador	Pichincha	0.8 (0.2 to 1.4)	0.2 (−0.1 to 0.5)	0.2 (−0.1 to 0.5)	—	19.7§ (17.1 to 22.3)	—	0.2 (−0.1 to 0.5)	0.6 (0.1 to 1.1)
Estonia	Tallinn	8.4 (6.7 to 10.2)	1.5 (0.7 to 2.2)	1.1 (0.5 to 1.8)	2.5 (1.5 to 3.5)	14.6§ (11.9 to 17.4)	16.7 (10.7 to 22.7)	2.2 (1.1 to 3.4)	6.4 (4.5 to 8.3)
France	Creteil	7.6 (6.2 to 9.0)	1.8 (1.1 to 2.4)	0.9 (0.4 to 1.5)	9.2 (7.6 to 10.7)	—	—	—	—
Georgia	Tbilisi	9.2 (7.4 to 11.1)	1.7 (0.9 to 2.6)	1.1 (0.5 to 1.8)	3.2 (2.1 to 4.3)	33.0§ (25.1 to 40.9)	30.6 (22.9 to 38.4)	3.5 (2.3 to 4.7)	5.7 (4.5 to 7.0)
Germany	Dresden	7.9 (6.9 to 8.8)	1.6 (1.2 to 2.1)	1.9 (1.4 to 2.4)	3.6 (3.0 to 4.3)	25.7 (23.9 to 27.5)	37.0 (35.0 to 39.1)	4.5 (3.6 to 5.3)	3.2 (2.5 to 4.0)
	Munich	8.3 (7.3 to 9.2)	2.1 (1.6 to 2.6)	2.5 (2.0 to 3.1)	4.8 (4.0 to 5.5)	22.3 (20.6 to 24.0)	37.4 (35.1 to 39.7)	4.3 (3.5 to 5.2)	4.1 (3.3 to 4.9)
Ghana	Kintampo	6.4 (5.1 to 7.7)	2.5 (1.7 to 3.4)	2.4 (1.6 to 3.3)	15.8 (13.9 to 17.8)	1.7 (1.0 to 2.4)	—	0.3 (0.0 to 0.6)	6.2 (4.9 to 7.5)
Greece	Athens	5.6 (4.2 to 7.1)	1.0 (0.4 to 1.7)	0.6 (0.1 to 1.1)	7.5 (5.9 to 9.2)	14.4§ (12.2 to 16.6)	33.6 (26.3 to 40.9)	1.6 (0.8 to 2.4)	4.0 (2.8 to 5.2)
	Thessaloniki	8.4 (6.7 to 10.1)	0.7 (0.2 to 1.2)	1.6 (0.8 to 2.3)	11.6 (9.6 to 13.5)	26.8§ (24.1 to 29.5)	32.3 (25.1 to 39.5)	3.6 (2.4 to 4.7)	4.8 (3.5 to 6.2)
Iceland	Reykjavik	9.2‖	3.5‖	1.7‖	22.9‖	23.5 (20.2 to 26.9)	—	3.1‖	6.4‖
India	Mumbai	6.1 (4.9 to 7.3)	0.8 (0.4 to 1.2)	1.6 (1.0 to 2.2)	4.8 (3.8 to 5.8)	6.4 (5.2 to 7.6)	39.7 (30.2 to 49.2)	0.5 (0.2 to 0.9)	5.8 (4.6 to 7.0)
Italy	Rome	7.9 (6.5 to 9.4)	1.5 (0.9 to 2.2)	1.2 (0.6 to 1.8)	14.3 (12.5 to 16.2)	28.9§ (26.5 to 31.4)	43.1 (31.3 to 54.9)	5.2 (4.0 to 6.4)	2.5 (1.6 to 3.4)
Latvia	Riga	6.9 (5.3 to 8.6)	1.0 (0.4 to 1.7)	0.7 (0.1 to 1.2)	3.2 (2.1 to 4.4)	19.3 (14.8 to 23.9)	—	6.4 (3.6 to 9.3)	3.7 (1.6 to 5.9)
The Netherlands	The Netherlands	8.7 (7.8 to 9.6)	2.7 (2.1 to 3.2)	1.6 (1.2 to 2.0)	7.8 (6.9 to 8.7)	30.9§ (28.4 to 33.5)	30.1 (28.0 to 32.1)	6.5 (5.1 to 7.8)	2.8 (1.9 to 3.7)
New Zealand	Hawkes Bay	21.9 (19.7 to 24.1)	6.8 (5.5 to 8.2)	4.6 (3.5 to 5.8)	35.6 (33.0 to 38.2)	34.5 (31.9 to 37.2)	—	13.4 (11.6 to 15.3)	8.8 (7.2 to 10.3)
Norway	Tromsø	14.0 (12.9 to −15.2)	6.3 (5.5 to 7.1)	1.8 (1.3 to 2.2)	10.3 (9.3 to 11.3)	32.7 (29.3 to 36.1)	36.5 (27.0 to 45.9)	9.1 (7.0 to 11.3)	5.0 (3.4 to 6.7)
Spain	Almeria	15.5‖	3.5‖	2.8‖	14.6‖	43.0 (40.0 to 45.9)	48.5 (40.5 to 56.4)	10.3‖	4.6‖
	Cartagena	11.9‖	2.1‖	1.6‖	10.9‖	23.8§ (21.2 to 26.4)	40.4 (31.8 to 48.9)	6.0‖	5.5‖
	Madrid	11.6‖	3.6‖	2.8‖	11.4‖	34.5§ (30.8 to 38.1)	40.1 (34.7 to 45.5)	7.6‖	6.7‖
	Valencia	9.1‖	1.7‖	1.0‖	9.8‖	14.3§ (12.1 to 16.4)	32.9 (28.9 to 36.9)	3.3‖	5.7‖
Sweden	Linköping	7.9 (6.2 to 9.7)	2.3 (1.3 to 3.3)	1.0 (0.3 to 1.6)	9.6 (7.7 to 11.5)	19.8§ (17.2 to 22.5)	30.7 (22.7 to 38.6)	3.7 (2.4 to 5.0)	3.8 (2.5 to 5.2)
	Östersund	10.2 (8.5 to 12.0)	4.4 (3.2 to 5.5)	1.5 (0.8 to 2.2)	10.9 (9.1 to 12.7)	26.5§ (23.8 to 29.3)	36.7 (30.1 to 43.3)	6.2 (4.7 to 7.7)	4.0 (2.7 to 5.2)
Turkey	Ankara	10.9 (9.8 to 12.0)	2.0 (1.5 to 2.6)	2.2 (1.6 to 2.7)	—	24.6§ (23.0 to 26.2)	—	2.6 (2.0 to 3.2)	8.6 (7.6 to 9.7)
United Kingdom	West Sussex	16.2 (13.9 to 18.4)	6.5 (5.0 to 8.0)	2.4 (1.5 to 3.3)	20.3 (17.9 to 22.8)	17.5 (15.0 to 20.0)	41.8 (34.7 to 49.0)	6.5 (4.9 to 8.2)	10.0 (8.0 to 12.0)
West Bank	Ramallah	8.8 (7.6 to 9.9)	1.5 (1.0 to 2.0)	2.0 (1.4 to 2.6)	9.4 (8.2 to 10.6)	10.3§ (6.2 to 14.4)	—	1.9 (0.8 to 3.0)	7.0 (5.9 to 8.2)

Prevalence values are in % with 95% confidence intervals in parentheses. Em dashes (—) = not performed/question not asked.

* Wheal size of ≥3 mm to at least one of the tested aeroallergens.

† Defined as wheeze with skin prick test reactivity (≥3 mm).

‡ Defined as wheeze without skin prick test reactivity (≥3 mm).

§ Local allergens were tested in addition to standard set of six common allergens.

‖ The reported frequencies should not be interpreted as prevalence estimates because participation was <60% (*see* METHODS).

countries and 1.2% for centers in nonaffluent countries. Again, the results were very similar for allergen-specific IgE (i.e., 4.6 and 1.1%, respectively).

Correlations at the Center Level

The prevalence of current wheeze was not correlated with the prevalence of skin prick test reactivity or elevated allergen-specific IgE (Figure 2). Prevalence rates of current wheeze ($\rho = 0.39$, $P = 0.05$) and skin test reactivity ($\rho = 0.37$, $P = 0.05$) were only weakly correlated with GNI (Figure 2). The prevalence of atopic wheeze (i.e., current wheeze in combination with a positive skin prick test) was strongly associated with GNI ($\rho = 0.60$, $P = 0.002$); rates of nonatopic wheeze were not ($\rho = -0.02$, $P = 0.92$; not shown in Figure 2). The PAFs, based on skin prick test reactivity and elevated IgE antibody levels, were both significantly correlated with GNI (Figure 3). The correlations between PAPs and GNI were even stronger ($\rho = 0.74$, $P \leq 0.0001$ for skin test reactivity, and $\rho = 0.74$, $P = 0.003$, for IgE antibodies). Finally, the strength of the association between skin prick test reactivity and current wheeze (assessed by OR) also increased significantly with GNI. There was a suggestion for a similar correlation with IgE, but this correlation did not reach statistical significance.

DISCUSSION

ISAAC II is the first large international study on children that can rely on methodologically comparable prevalence rates of skin prick test reactivity and elevated allergen-specific IgE levels in addition to questionnaire-based reports of asthma symptoms. We observed large variations in the prevalence of asthma symptoms and of atopic sensitization among populations. An intriguing finding is that the link between atopic sensitization and asthma symptoms increased with economic development.

Our findings confirm the wide international variation in the prevalence and severity of asthma symptoms in children observed during ISAAC I (9, 10). Study centers that had ranked high (e.g., New Zealand, United Kingdom) or low (e.g., Albania, India) showed similar rankings in ISAAC II. The high prevalence of wheeze in the Brazilian center corroborates previous ISAAC observations of high asthma rates in urban centers in Latin America (9, 21). The ISAAC II data show that this high prevalence is mostly due to nonatopic wheeze, supporting similar findings from other areas in South America (22, 23).

The large variation in prevalence rates of current wheeze could not be explained by prevalence rates of skin test reactivity or elevated allergen-specific IgE levels as shown by the lack of correlation (Figures 2a and 2b). The prevalence of wheeze during the last year, however, increased with GNI, confirming previous analyses of the ISAAC I data (24). We also observed a significant correlation between the prevalence of skin test reactivity in children and GNI, a finding that has not been reported previously. The correlation between GNI and the prevalence of elevated allergen-specific IgE levels did not reach statistical significance, possibly due to the smaller number of centers. When restricting the skin test reactivity analysis to centers with data on IgE, there was also no correlation ($\rho = 0.29$, $P = 0.25$). The determinants of the large international variation in the prevalence of asthma symptoms and atopic sensitization are likely to be numerous and complex (25–27). A wide range of

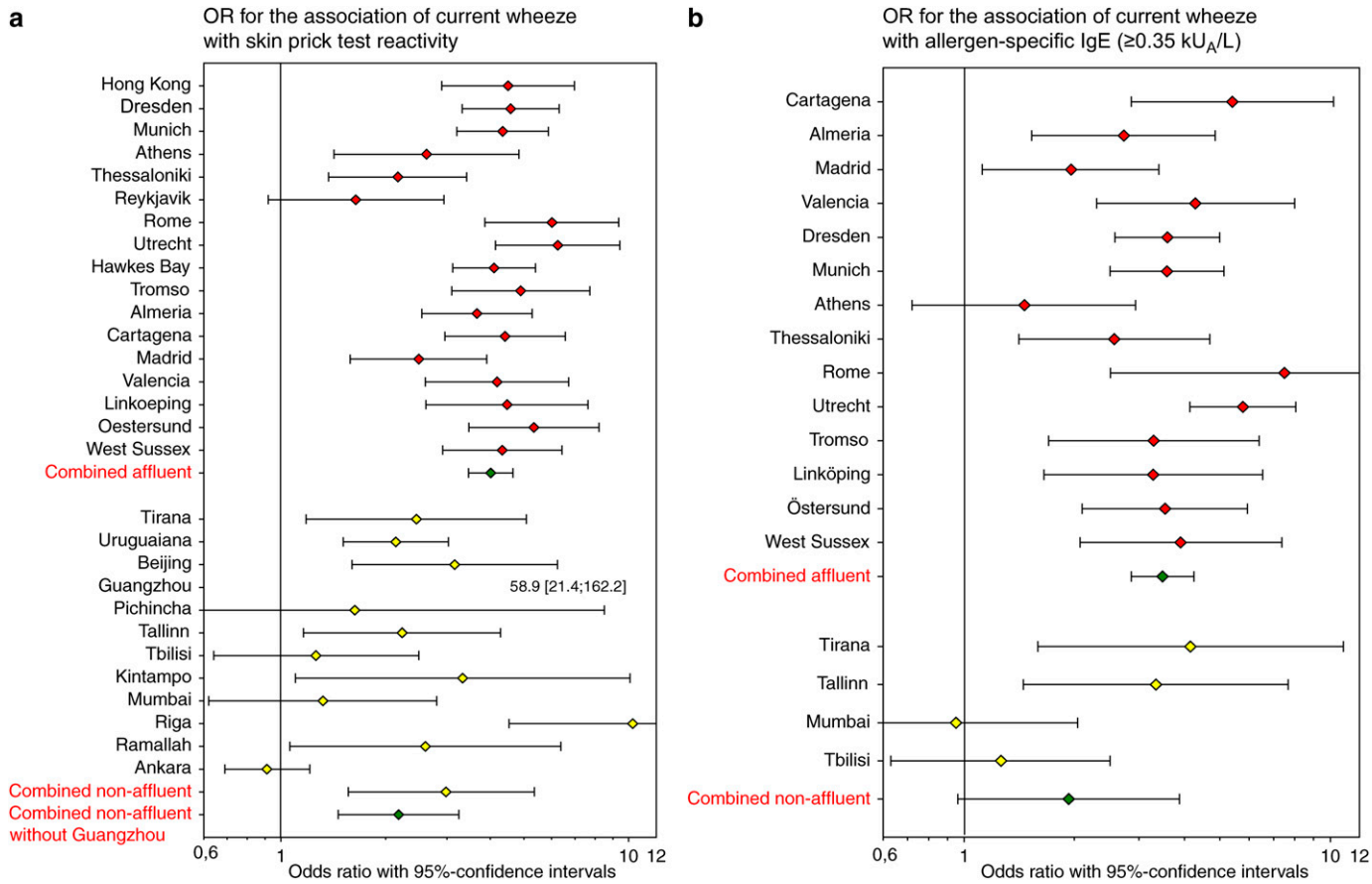

Figure 1. Odds ratios (OR) with confidence intervals for the association of current wheeze with skin prick test reactivity (*a*) and elevated (≥0.35 allergen-specific kilounits per liter [kU$_A$/L]) allergen-specific IgE (*b*) by study center. Centers are listed in alphabetical order (country, center name).

different factors, including nutrition, microbial and allergen exposure, housing conditions, exposure to pollutants, and so forth, may have played a role (28). Finally, it should to be kept in mind that we report an ecological correlation. A center-level correlation with GNI does not imply a similar relation at the individual level with personal wealth.

There was a wide variation in the prevalence of atopic sensitization across study centers. The variation was more pronounced for skin test reactivity than for elevated IgE antibodies, which could be partly due to the smaller number of centers with IgE data. Several study centers had tested additional allergens of local relevance, thereby enhancing the validity of findings on skin test reactivity. Inclusion of these additional allergens in the analyses, however, had only small effects on the parameters under investigation and mostly affected prevalence estimates (e.g., among centers that used additional allergens, the range of prevalence rates increased from 7.1 to 42.8% [using the six standard allergens] to 10.3 to 45.3%). For the same centers, the combined ORs for the association between wheezing and skin prick test reactivity changed from OR = 3.95 to OR = 4.06 in affluent countries and from OR = 2.62 to OR = 2.82 in nonaffluent countries after inclusion of the additional allergens. The correlation between GNI and ORs for the association between current wheeze and skin test reactivity became enhanced when additional allergens were included: $\rho = 0.68$, $P = 0.003$ without, and $\rho = 0.77$, $P = 0.0003$ with additional allergens. The ISAAC II findings are in line with previous reports of lower prevalence rates of skin test reactivity in less affluent countries (3, 4, 7, 22, 29–32). Our data also show large variations in the PAFs and attributable prevalence rates, particularly between centers in affluent and nonaffluent countries. The size of the observed PAFs corroborates and extends the findings by Pearce and colleagues for children (PAFs from 25 to 63%) (3) and by Sunyer and coworkers for adults (PAFs from 4 to 61%) (8).

We observed a strong correlation of the link between wheeze and atopic sensitization (measured by OR, PAF, and PAP) and GNI of the respective countries. Before discussion of potential interpretations, methodologic aspects need to be addressed. First, participation rates were low in some centers (e.g., <60% for questionnaires and <40% for skin prick or IgE measurements), raising concern about selective participation. In general, allergic symptoms (rhinoconjunctivitis and eczema) and parental allergies were slightly more often reported among participants with measurements of skin test reactivity or serum IgE than among children with completed questionnaires. For skin prick tests, statistically significant differences were only seen in one center (Tbilisi). For IgE measurements, significant differences (i.e., higher rates among those with IgE data) were observed for hay fever symptoms in Cartagena and Tbilisi, and for parental allergies in West Sussex and Tbilisi. However, although potential selection of children may have had some effect on prevalence estimates, it is less likely to introduce systematic bias for the assessment of associations within study centers (e.g., calculation of OR). When centers with low participation were excluded (i.e., <60% for questionnaires and <40% for skin prick or IgE measurements), most associations became substantially stronger (for skin prick test: PAF,

TABLE 3. ESTIMATED ATTRIBUTABLE FRACTIONS (%) AND ATTRIBUTABLE PREVALENCES (%) OF CURRENT WHEEZE IN RELATION TO SKIN PRICK TEST REACTIVITY (≥3 mm) AND ALLERGEN-SPECIFIC IgE (≥0.35 kU_A/L).

	Skin Prick Test Reactivity		Allergen-specific IgE	
Country	Fraction (%)	Prevalence (%)	Fraction (%)	Prevalence (%)
China				
Hong Kong	59.6*	3.3*	—	—
Germany				
Dresden	45.2	3.6	47.2	3.7
Munich	39.4	3.3	47.2	3.9
Greece				
Athens	18.0*	1.0*	13.2	0.7
Thessaloniki	22.8*	1.9*	32.4	2.7
Iceland				
Reykjavik	12.8	1.2	—	—
Italy				
Rome	56.2*	4.4*	72.2	5.7
The Netherlands	58.6*	5.1*	55.8	4.9
New Zealand				
Hawkes Bay	45.8	10.0	—	—
Norway				
Tromsø	51.4	7.2	42.6	6.0
Spain				
Almeria	50.4	7.7	43.6	6.8
Cartagena	40.4*	4.8*	61.2	7.3
Madrid	32.0*	3.7*	26.8	3.1
Valencia	27.8*	2.5*	49.4	4.5
Sweden				
Linköping	38.2*	3.0*	39.4	3.1
Östersund	49.6*	5.1*	46.0	4.7
United Kingdom				
West Sussex	30.4	4.9	51.4	8.3
Combined affluent	40.7	4.1	45.6	4.6
Albania				
Tirana	17.2*	0.8*	36.4	1.6
Brazil				
Uruguaiana	10.8	2.8	—	—
China				
Beijing	33.2*	1.2*	—	—
Guangzhou	93.8*	3.0*	—	—
Ecuador				
Pichincha	11.0*	0.1*	—	—
Estonia				
Tallinn	14.2*	1.2*	25.8	2.2
Georgia				
Tbilisi	7.8*	0.8*	7.2	0.7
Ghana				
Kintampo	3.2	0.2	—	—
India				
Mumbai	2.0	0.1	0	0
Latvia				
Riga	57.2	4.0	—	—
Turkey				
Ankara	0*	0*	—	—
West Bank				
Ramallah	12.8*	1.1*	—	—
Combined nonaffluent	20.3	1.2	18.3	1.1

— = not performed.

* Additional allergens of local relevance were tested (*see* METHODS).

$\rho = 0.81$, $P < 0.0001$; PAP, $\rho = 0.82$, $P < 0.0001$; OR, $\rho = 0.76$, $P < 0.0001$; and for allergen-specific IgE: PAF, $\rho = 0.79$, $P < 0.0001$; PAP, $\rho = 0.83$, $P = 0.0008$; OR, $\rho = 0.33$, $P = 0.29$). Exclusion of Tbilisi from our analyses had very little effect on the observed pattern of our findings. Furthermore, it could be speculated that the observed relations are due to differences in phenotype. Similar relations, however, were seen for reports of asthma-ever and frequent wheezing attacks during the past year (data not shown). In addition, when current wheeze was classified depending on whether it occurred in combination with symptoms of allergic rhinoconjunctivitis (i.e., therefore more likely to be related to atopic sensitization) or not, the relationship with GNI was enhanced for wheeze with rhinoconjunctivitis symptoms (e.g., correlation based on the OR: $\rho = 0.58$, $P = 0.002$ for prick test reactivity, and $\rho = 0.67$, $P = 0.002$ for allergen-specific IgE) and not present for wheeze without symptoms of allergic rhinitis (data not shown). Finally, GNI at the country level is not a precise measure of economic development in the study areas and the prevalence estimates from the study centers are not representative of the country as a whole. Thus, some misclassification cannot be ruled out. However, economic conditions and prevalence rates of asthma symptoms differ much more between countries than between regions within countries (9, 10). In addition, to explain the observed relations, misclassification would have to be differential—that is, dependent on the association between asthma symptoms and sensitization, which appears to be unlikely.

A possible explanation for an increasing link between asthma and atopic sensitization with economic development could be that factors that protect children with atopic sensitization against the development of manifest disease get attenuated or lost in more affluent settings. Differences in the association of wheeze with atopy between populations have been found before, with weaker associations seen mainly in rural or semirural nonaffluent locations (4, 6, 33). In these cases, it is difficult to tease apart the effects of rural/urban versus affluent/nonaffluent, because rural is generally equivalent to less affluent. However, a lack of association was also observed in a deprived but urban environment in Lima, Peru (22). Others reported attenuated associations of circulating IgE antibodies with positive skin prick tests and allergic disease in former socialist countries (34, 35). In our data, ORs for the relation of wheeze with skin prick test reactivity tended to increase with the prevalence of skin test reactivity ($\rho = 0.31$, $P = 0.10$), not with the prevalence of elevated allergen-specific IgE ($\rho = 0.07$, $P = 0.79$), possibly indicating that the relevant factors may affect both the development of skin test reactivity and its link with clinical asthma symptoms.

Few studies have specifically investigated the factors that may influence the relation between allergen-specific IgE, skin prick test reactivity, and manifest atopic disease, and most of those relate to helminth infections (36, 37). There is evidence that increased production of IL-10 concomitant with helminth infections down-regulates allergic inflammatory responses (37). However, a cluster-randomized trial of geohelminth treatment in an endemic area showed no increase in atopic sensitization 1 year after the start of treatment (38). Other conditions that may modify the relation between atopic sensitization and asthma symptoms include overweight and obesity (39). A study in urban and rural South Africa observed that increasing body mass index was associated with a greater strength of association between allergen-specific IgE and the corresponding skin test (40).

It has also been hypothesized that commensal bacteria acquired very early in life play an important role in the induction of tolerance (41). Less or an altered microbial exposure (e.g., an altered gut flora) could therefore weaken normal immune regulatory function and tolerance. Differences in the gut flora have been reported between children with and without allergic disease (41) and between countries with different prevalence rates of allergic disease (41) (e.g., between Estonia and Sweden) (41, 42). Within affluent countries, special

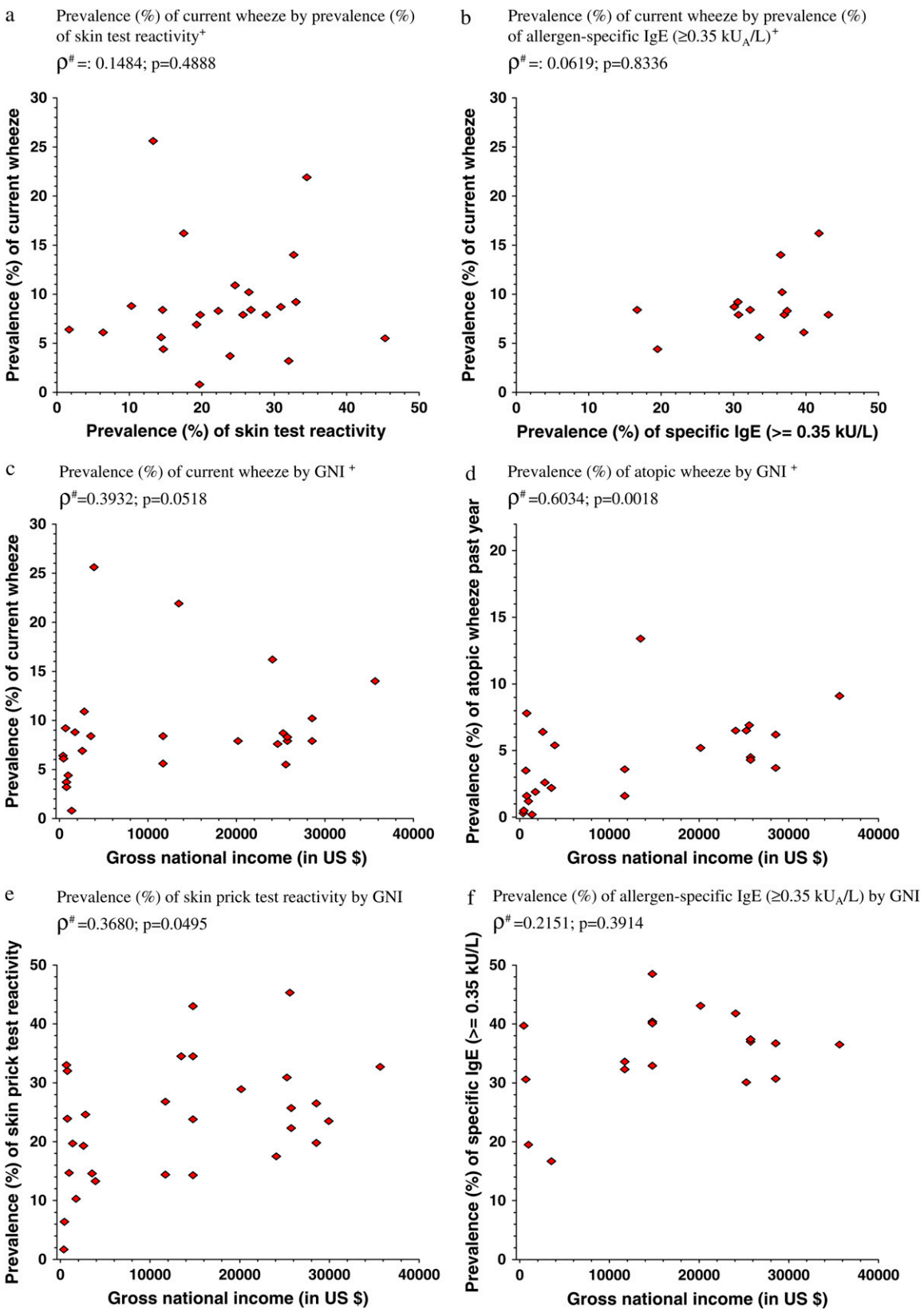

Figure 2. (*a–f*) Correlations at center level of prevalence rates of current wheeze, skin prick test reactivity, elevated allergen-specific IgE (⩾0.35 kU_A/L), and gross national income per capita (GNI). #Spearman rank order correlation coefficient; +participation > 60% for the written questionnaires.

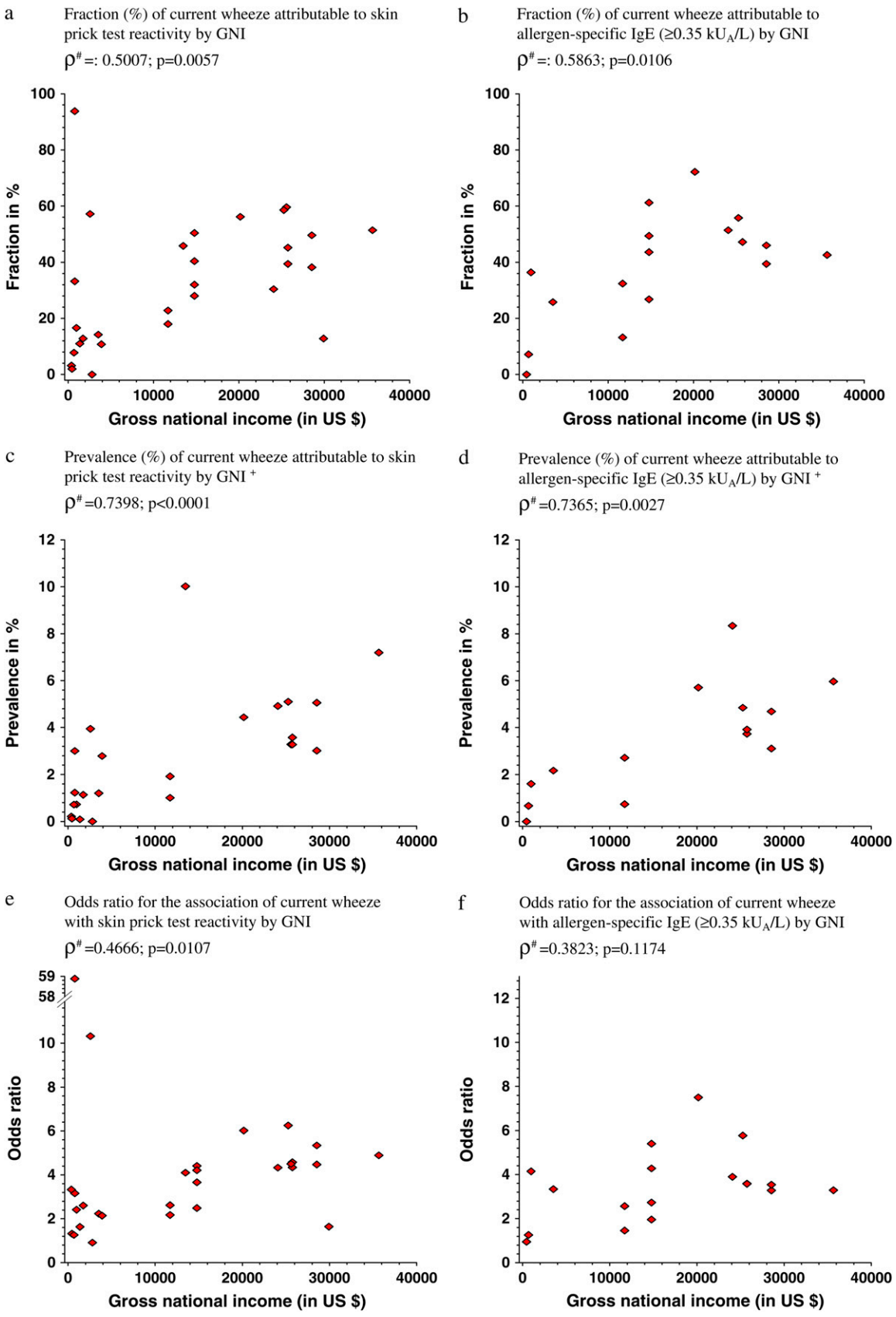

Figure 3. Attributable fractions (%), attributable prevalences (%), and odds ratios for the relation of current wheeze with skin prick test reactivity (*a, c, e*) and allergen-specific IgE (≥0.35 kU$_A$/L) (*b, d, f*) by gross national income per capita (GNI). #Spearman rank order correlation coefficient; +participation > 60% for the written questionnaires.

subgroups of children—for example, those living on farms or having an anthroposophic lifestyle—have been found to be at lower risk for asthma and allergies (43–45). The degree of urbanization is one factor that increases with higher GNI. In our study, using national data provided by the Food and Agriculture Organization of the United Nations (http://faostat.fao.org), urbanization was in fact correlated with the prevalence of wheeze attributable to skin test reactivity. However, after adjustment for economic development, only GNI remained significant in the model (*see also* the online supplement).

Our findings show that, at age 8 to 12 years, nonatopic wheeze represents a frequent form of wheeze. In many countries, it comprised the majority of cases, particularly in centers in nonaffluent countries. Studies from affluent settings described a phenotype of asthma that is linked to respiratory infections in early life and outgrown during later childhood (46, 47). The relatively high prevalence of nonatopic wheeze in some of our study centers may be related to increased susceptibility and/or high exposure to infections. The age at which the wheezing episodes are outgrown may also differ among countries, particularly between affluent and nonaffluent settings. The substantial proportion of nonatopic wheeze in many populations warrants further investigation of the determining factors. Several studies have shown that the patterns of risk factors for atopic versus nonatopic wheeze may differ (44, 48–50).

In conclusion, our study shows that prevalence rates of asthma symptoms and of atopic sensitization vary widely in 8- to 12-year-old children living under very different conditions worldwide. The fractions and prevalences of wheeze that were attributable to atopic sensitization, as well as the strength of the associations between wheeze and atopic sensitization, increased with economic development.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

The ISAAC Phase Two Study Group consists of the following members:

ISAAC Phase Two Steering Group: B. Björkstén (Stockholm, Sweden), B. Brunekreef (Utrecht, The Netherlands), W. Cookson (Oxford, UK), E. von Mutius (Munich, Germany), D. Strachan (London, UK), S. K. Weiland, ISAAC Phase Two Coordinator (Ulm, Germany).

ISAAC Phase Two Coordinating and Data Centre (Institute of Epidemiology, Ulm University, Germany): G. Büchele, C. Dentler, A. Kleiner, P. Rzehak, G. Weinmayr, S. K. Weiland (Director).

Principal Investigators and Scientific Team: *Tirana, Albania*: A. Priftanji, A. Shkurti, J. Simenati, E. Grabocka, K. Shyti, S. Agolli, A. Gurakuqi; *Uruguaiana, Brazil*: R. T. Stein, M. Urrutia de Pereira, M. H. Jones, P. M. Pitrez; *Pichincha Province, Ecuador*: P. J. Cooper, M. Chico; *Beijing, China*: Y. Z. Chen; *Guangzhou, China*: N. S. Zhong; *Hong Kong, China*: C. Lai (National Coordinator), G. Wong; *Tallinn, Estonia*: M.-A. Riikjärv, T. Annus; *Créteil, France*: I. Annesi-Maesano; *Tblisi, Georgia*: M. Gotua, M. Rukhadze, T. Abramidze, I. Kvachadze, L. Karsanidze, M. Kiladze, N. Dolidze; *Dresden, Germany*: W. Leupold, U. Keil, E. von Mutius, S. Weiland; *Munich, Germany*: E. von Mutius, U. Keil, S. Weiland; *Kintampo, Ghana*: P. Arthur (deceased), E. Addo-Yobo; *Athens, Greece*: C. Gratziou (National Coordinator), C. Priftis, A. Papadopoulou, C. Katsardis; *Thessaloniki, Greece*: J. Tsanakas, E. Hatziagorou, F. Kirvassilis; *Reykjavik, Iceland*: M. Clausen; *Mumbai, India*: J. R. Shah, R. S. Mathur, R. P. Khubchandani, S. Mantri; *Rome, Italy*: F. Forastiere, R. Di Domenicantonio, M. De Sario, S. Sammarro, R. Pistelli, M. G. Serra, G. Corbo, C. A. Perucci; *Riga, Latvia*: V. Svabe, D. Sebre, G. Casno, I. Novikova, L. Bagrade; *Utrecht, The Netherlands*: B. Brunekreef, D. Schram, G. Doekes, P. H. N. Jansen-van Vliet, N. A. H. Janssen, F. J. H. Aarts, G. de Meer; *Hawkes Bay, New Zealand*: J. Crane, K. Wickens, D. Barry; *Tromsø, Norway*: W. Nystad, R. Bolle, E. Lund; *Almeria, Spain*: J. Batlles Garrido, T. Rubi Ruiz, A. Bonillo Perales, Y.Gonzalez Jiménez, J. Aguirre Rodriguez, J. Momblan de Cabo, A. Losilla Maldonado, M. Daza Torres; *Cartagena, Spain*: L. García-Marcos (National Coordinator), A. Martinez Torres, J. J. Guillén Pérez, A. Piñana López, S. Castejon Robles; *Madrid, Spain*: G. García Hernandez, A. Martinez Gimeno, A. L. Moro Rodríguez, C. Luna Paredes, I. Gonzalez Gil; *Valencia, Spain*: M. M. Morales Suarez-Varela, A. Llopis González, A. Escribano Montaner, M. Tallon Guerola; *Linköping, Sweden*: L. Bråbäck (National Coordinator), M. Kjellman, L. Nilsson, X.-M. Mai; *Östersund, Sweden*: L. Bråbäck, A. Sandin; *Ankara, Turkey*: Y. Saraçlar, S. Kuyucu, A. Tuncer, C. Saçkesen, V. Sumbuloğlu, P. Geyik, C. Kocabaş; *West Sussex, UK*: D. P. Strachan, B. Kaur; *Ramallah, West Bank*: N. El-Sharif, B. Nemery, F. Barghuthy, S. Abu Huij, M. Qlebo.

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ISAAC Steering Committee: N. Aït-Khaled (Paris, France), H. R. Anderson (London, UK), I. Asher (Auckland, NZ), R. Beasley (Wellington, NZ), B. Björkstén (Stockholm, Sweden), B. Brunekreef (Utrecht, The Netherlands), W. Cookson (Oxford, UK), J. Crane (Wellington, NZ), P. Ellwood (Auckland, NZ), S. Foliaki (Wellington, NZ), U. Keil (Münster, Germany), C. Lai (Hong Kong), J. Mallol (Santiago, Chile), E. Mitchell (Auckland, NZ), S. Montefort (Malta), E. von Mutius (Munich, Germany), J. Odhiambo (Nairobi, Kenya), N. Pearce (Wellington, NZ), C. Robertson (Parkville, Australia), J. Shah (Mumbai, India), A. Stewart (Auckland, NZ), D. P. Strachan (London, UK), S. K. Weiland (Ulm, Germany), H. Williams (Nottingham, UK).

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