The role of atopic sensitization in flexural eczema: Findings from the International Study of Asthma and Allergies in Childhood Phase Two

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Background: The association between allergic sensitization and eczema has been debated for years.
Objective: We sought to determine and compare the strength of the association between allergen skin sensitization and eczema in both developing and industrialized countries.
Methods: Twenty-eight thousand five hundred ninety-one randomly selected 8- to 12-year-old schoolchildren in 20 countries were physically examined for flexural eczema and received skin prick testing to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat hair, *Alternaria tenuis*, mixed tree and grass pollen, and allergens of local relevance.
Results: The age- and sex-adjusted odds ratios (ORs) for a positive association between flexural eczema and atopy ranged between 0.74 (95% CI, 0.31-1.81) and 4.53 (95% CI, 1.72-11.93), with a significantly stronger association in affluent compared with nonaffluent countries (combined age- and sex-adjusted $OR_{affluent} = 2.69$ [95% CI, 2.31-3.13] and $OR_{nonaffluent} = 1.17$ [95% CI, 0.81-1.70]). The combined population attributable fraction for atopy in flexural eczema was 27.9% for affluent and 1.2% for nonaffluent-country centers. Correlating gross national per-capita income with either ORs or population attributable fractions for atopy in flexural eczema confirmed a highly significant positive association ($P = .006$ and $P < .001$, respectively).
Conclusions: The association between atopy and flexural eczema is weak and more variable than previously suggested, and the strength of this association is positively linked to gross national income.
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Key words: *Eczema, atopic dermatitis, atopy, epidemiology*

There is currently debate in the dermatologic literature as to whether childhood eczema is truly an atopic disease. Those who advocate eczema as being an atopic disease typically study hospital populations, where the disease tends to be more severe and more children are sensitized to common environmental allergens.[1] We recently conducted a systematic review of the literature and found that the proportion of allergic sensitization among patients with eczema varied considerably between hospital (47% to 75%) and community (7% to 78%) settings.[2] The association between atopy and eczema also appeared weaker in developing countries than in industrialized nations. Similar observations have been made for asthma and rhinoconjunctivitis.[3,4]

Part of the variations in the proportion of patients with atopic eczema in previous studies could be due to differences in study methodology and quality. The second phase of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two provides a unique opportunity to examine the association between atopy and eczema by using the same standardized methodology in a large population-based data set from 20 countries. To our knowledge, this is the largest study ever conducted involving physical examination for eczema.

We sought to determine what proportion of children with flexural eczema was atopic and what proportion of flexural eczema was attributable to atopy at the population level (population attributable fraction [PAF]). We also examined whether there was a difference in the risk of expressing flexural eczema in atopic subjects compared with in nonatopic control subjects and whether such an association was related to gross national per-capita income (GNI). Furthermore, we assessed the data for a linear trend in the association between flexural eczema and the number of positive skin prick test responses because such a dose-response relationship would support a causative role for allergic sensitization in flexural eczema. In this article we use the term *atopy* interchangeably with *allergic sensitization* and *skin prick test response positivity. Flexural eczema* refers to childhood eczema

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Abbreviations used
GNI: Gross national per-capita income
ISAAC: International Study of Asthma and Allergies in Childhood
OR: Odds ratio
PAF: Population attributable fraction

with flexural involvement on physical examination, as defined by the ISAAC Phase Two study protocol.[5]

METHODS

The rationale and methods of ISAAC Phase Two have been described elsewhere in detail.[6] In brief and with reference to this article, ISAAC Phase Two was conducted among 8- to 12-year-old schoolchildren to evaluate the prevalence and risk factors of allergic disease between populations. Study centers were required to randomly select at least 10 schools from a complete sampling frame of schools in defined geographic areas, and children ($n \geq 1000$ per center) attending classes with a majority of 9- to 11-year-olds were invited to participate. Clinical examinations and skin prick tests were performed either on all children or in random subsamples.[6] Thirty thousand two hundred five children were physically examined for flexural eczema in the following 5 body areas: (1) around the eyes, (2) the neck, (3) in front of the elbows, (4) behind the knees, and (5) in front of the ankles. Participants were categorized as having flexural eczema if they had a typical erythematous rash with surface change (eg, fine scaling, vesicles, oozing, crusting, or lichenification) in any of the above flexural areas.[5] All fieldworkers were first trained and then formally tested in the recognition of flexural eczema by using a manual and photographic images specifically developed for this purpose.[5] Thirty-one thousand seven hundred fifty-nine children underwent skin prick testing for 6 common aeroallergens, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat hair, *Alternaria tenuis*, mixed tree and grass pollen, and histamine (10 mg/mL), and normal saline control solutions (ALK-Abelló, Hørsholm, Denmark). Study centers were allowed to add allergens of local relevance. Additional allergens were tested in 18 centers and included cockroach, dog, horse, olive, *Parietaria officinalis*, mixed weeds, Turkish tree mix, mixed molds, and *Cladosporium* species. A drop of each allergen and both control solutions was placed onto the volar aspect of the left forearm, which was then pierced vertically with a 1-mm ALK-Abelló lancet. Reactions were recorded after 15 minutes and considered positive if the mean wheal diameter was at least 3 mm greater than that elicited by the saline control.[6] Atopy was defined as having at least 1 positive skin prick test response to any of the allergens tested. As part of ISAAC Phase Two, data were also collected through parental questionnaires on allergy symptoms identical to those used for children 6 to 7 years of age in ISAAC Phase One.[7] Children were classified as having had "flexural eczema in the past 12 months" if their parents answered yes to the last 2 of the 3 following questions: "Has your child ever had an itchy rash which was coming and going for at least six months?"; "Has your child had this itchy rash at any time in the last 12 months?"; and "Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?"

After local data entry, the data were sent to the ISAAC Phase Two Coordinating Centre in Ulm, Germany, for consistency checks and statistical analysis. Prevalence rates for atopy and flexural eczema were calculated, as well as odds ratios (ORs) for atopy (exposure) and flexural eczema on physical examination (outcome) with corresponding 95% CIs as a measure of the strength of the association between atopy and flexural eczema. If centers had studied stratified subsamples, prevalence rates and ORs were calculated by applying appropriate sampling weights.[8,9] Combined OR estimates across study centers were calculated by using random-effects meta-analysis models.[10] Ecologic correlations were assessed by using Spearman rank-order correlation coefficients (ρ). PAFs, as a percentage expression of how much flexural eczema can be explained by skin prick test response positivity at the population level, were calculated by using the following formula: $PAF = P_{ec} \times (OR-1)/OR$, where P_{ec} is the prevalence of atopy among children with flexural eczema. By using World Bank criteria, 2 strata were defined for the analyses relating to GNI. Centers in countries classified by the World Bank in 2001 as "high-income countries" (GNI per capita of at least US $9200) were combined as affluent-country centers, and the remaining centers were grouped together as nonaffluent-country centers.[11] For the correlation analysis, GNI was considered a continuous variable. The statistical analyses were performed in the ISAAC Phase Two Co-ordinating Centre in Ulm by using SAS (version 9.1; SAS Institute, Inc, Cary, NC) and SUDAAN (version 9.0; Research Triangle Institute, Research Triangle Park, NC) software. All study centers obtained local ethics committee approval.

RESULTS

The mean participation rate across study centers was 63% for skin prick testing and 62% for skin examination. Both measurements were available for 28,591 children.

Prevalences of atopy and flexural eczema

Point prevalences for flexural eczema from skin examination ranged between 0.4% (5/1325) in Kintampo, Ghana, and 14.2% (169/1193) in Östersund, Sweden (see Fig E1 in the Online Repository at www.jacionline.org), whereas atopy prevalences varied between 1.7% (22/1324) in Kintampo and 45.3% (600/1324) in Hong Kong, China (see Fig E2 in the Online Repository at www.jacionline.org).

Association between atopy and flexural eczema

Large variations in the proportion of atopic children with flexural eczema were observed across study centers (Table I and Fig 1). Although none of the children with flexural eczema in Ramallah, Palestine, and Kintampo had a positive skin prick test response, 73.9% did in Hong Kong.

The age- and sex-adjusted ORs of flexural eczema in atopic compared with nonatopic individuals were significantly higher in affluent countries than in nonaffluent nations, ranging between 0.74 (95% CI, 0.31-1.81) in Pichincha, Ecuador, and 4.53 (95% CI, 1.72-11.93) in Madrid, Spain. Thirteen of 17 affluent country study centers had statistically significant ORs for a positive association between flexural eczema and atopy. The combined age- and sex-adjusted OR for all affluent-country centers was 2.69 (95% CI, 2.31-3.13; Table I and Fig 2). In nonaffluent countries only the ORs for Tallinn, Estonia, and Mumbai, India, reached borderline statistical significance (adjusted ORs of 2.32 [95% CI, 1.01-5.34] and 3.65 [95% CI, 0.98-13.60], respectively), with the combined age- and sex-adjusted OR being 1.17 (95% CI, 0.81-1.70; Table I and Fig 2).

Association between atopy and flexural eczema at the population level

Varying ORs corresponded to varying PAFs (Table I). Although more than half of all flexural eczema cases could be explained by allergic sensitization in Madrid and Hong Kong, the majority of PAFs among affluent-country centers was between 10% and 30%, with a combined PAF of 27.8% (Table I and Fig 3). All nonaffluent countries had PAFs of less than 15%, and the combined PAF across study centers was 2.8%.

TABLE I. Association between atopy and flexural eczema: ORs, PAFs, and the relationship between the number of positive SPT responses and flexural eczema probability

Country, center	Study center characteristics	Children without flexural eczema		Children with flexural eczema		Age- and sex-adjusted OR (95% CI)	PAF (%)	Test for linear trend between FE probability and SPT positivity (*P* value)
		No.	Percentage with atopy	No.	Percentage with atopy			
Affluent								
China, Hong Kong†	Urban	1277	44.3	46	73.9	3.66* (1.88-7.12)	53.2	<.001*
Germany, Dresden	Urban	2128	24.6	131	44.3	2.65* (1.83-3.82)	26.2	<.001*
Germany, Munich	Urban	2225	21.6	92	40.2	2.55* (1.65-3.93)	23.8	<.001*
Greece, Athens†	Urban	972	14.3	13	23.1	1.79 (0.49-6.52)	10.2	.16
Greece, Thessaloniki†	Urban	1004	26.8	14	28.6	1.14 (0.34-3.77)	2.4	.27
Iceland, Reykjavik	Urban	577	22.2	56	37.5	2.41* (1.33-4.37)	19.6	.01*
Italy, Rome†	Urban	1285	28.6	22	45.5	2.43* (1.03-5.75)	23.6	.11
The Netherlands, Utrecht†	Urban	1000	28.9	63	54.0	3.13* (1.86-5.27)	35.2	<.001*
New Zealand, Hawkes Bay	Urban/rural	1182	32.4	106	58.5	3.00* (1.99-4.53)	38.6	<.001*
Norway, Tromso	Urban/rural	598	27.9	71	45.1	2.32* (1.39-3.88)	23.8	<.001*
Spain, Almeria	Urban	1041	42.9	20	60.0	2.04 (0.81-5.13)	29.8	.68
Spain, Cartagena†	Urban	1004	23.5	7	42.9	2.44 (0.64-9.32)	25.2	.24
Spain, Madrid†	Urban	613	33.1	19	68.4	4.53* (1.72-11.93)	52.8	.001*
Spain, Valencia†	Urban	951	13.7	37	27.0	2.32* (1.09-4.91)	15.4	.008*
Sweden, Linköping†	Urban	150	20.6	18	46.2	3.72* (1.19-11.64)	40.2	.005*
Sweden, Östersund†	Urban/rural	200	29.8	43	48.9	2.67* (1.13-6.30)	33.2	.005*
United Kingdom, West Sussex	Urban/rural	835	16.3	61	34.4	2.89* (1.65-5.08)	21.6	<.001*
Pooled adjusted OR						2.69* (2.31-3.13)	27.9‡	
Nonaffluent								
Albania, Tirana†	Urban	879	15.1	23	13.0	0.85 (0.25-2.91)	−2.4	.74
China, Beijing†	Urban	1034	23.9	10	20.0	0.77 (0.16-3.76)	−5.0	.72
China, Guangzhou†	Urban	1070	32.0	8	37.5	1.24 (0.31-5.01)	8.2	.22
Ecuador, Pichincha†	Rural	854	19.9	40	15.0	0.74 (0.31-1.81)	−6.2	.92
Estonia, Tallinn†	Urban	612	14.1	30	26.7	2.32* (1.01-5.34)	14.6	.02*
Georgia, Tbilisi†	Urban	148	33.9	25	26.8	0.75 (0.28-2.03)	−11.8	.63
Ghana, Kintampo	Rural	1317	1.7	5	0.0	—	—	—
India, Mumbai	Urban	1537	6.3	15	20.0	3.65 (0.98-13.60)	14.6	.05
Latvia, Riga	Urban	184	17.4	12	16.7	1.00 (0.25-4.10)	−0.8	.80
Palestine, Ramallah†	Urban/rural	215	10.6	6	0.0	—	—	—
Turkey, Ankara†	Urban	2669	24.4	37	24.3	1.06 (0.50-2.26)	0	.76
Pooled adjusted OR						1.17 (0.81-1.70)	1.2‡	

FE, Flexural eczema.
*Statistically significant at the 5% level.
†Local allergens were added to the 6 standard aeroallergens.
‡Mean PAF.

Association between GNI, atopy, and flexural eczema

Plotting GNI as a continuous variable against either ORs or PAFs for atopy in flexural eczema (Fig 4 and see Fig E3 in the Online Repository at www.jacionline.org) revealed a highly significant positive association (correlation coefficient [ρ] = 0.53 and $P = .006$ for the ORs and ρ = 0.74 and $P < .001$ for PAFs). To assess for climate as a possible confounder, we adjusted for latitude. The observed strong positive association of GNI with PAFs and ORs remained virtually unchanged and statistically highly significant (data not shown).

Is there a linear relationship between the number of positive skin prick test responses and flexural eczema probability?

There was a significant linear relationship between the number of positive skin prick test responses and the probability of having flexural eczema for a number of study centers, but this association was limited to centers in which the association between atopy and flexural eczema measured as an OR reached statistical significance (Table I). With the exception of Tallinn, Estonia, this was only the case in affluent countries.

Questionnaire-derived measure of flexural eczema in the past 12 months

Because we only examined children physically once and given the waning and waxing nature of eczema, we also performed the above analyses for the questionnaire-derived measure of flexural eczema in the past 12 months. This yielded very similar results. As for the association between atopy and flexural eczema in the past 12 months, the combined adjusted ORs were 2.03 (95% CI, 1.84-2.23) for affluent-country centers and 1.36 (95% CI, 1.07-1.74) for nonaffluent-country centers. The combined PAFs were

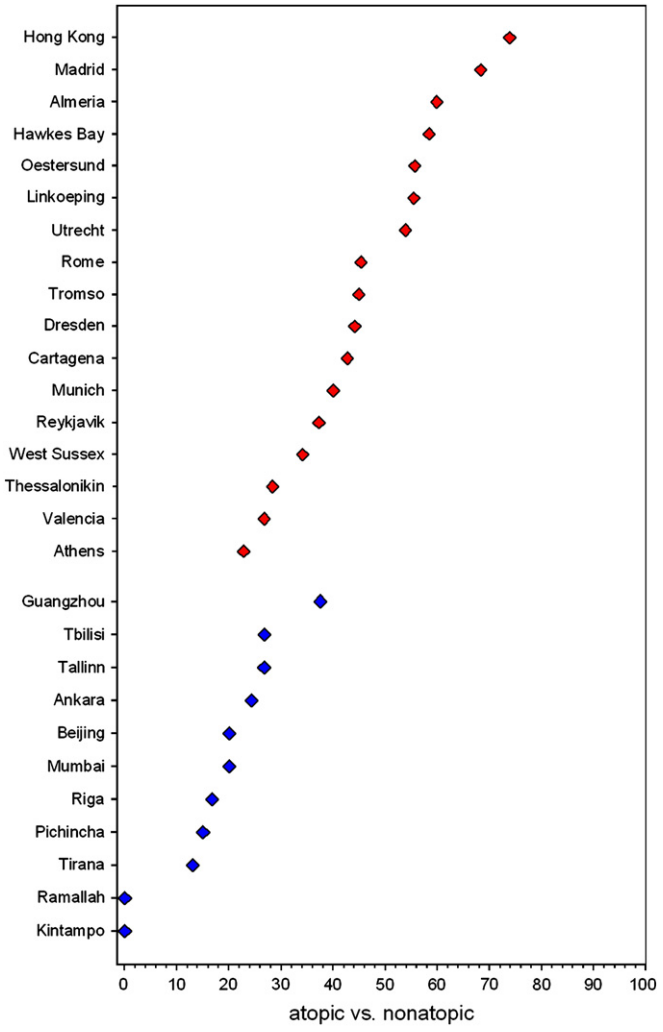

FIG 1. Proportion of atopy among children with flexural eczema for all study centers. Study centers are arranged in order of proportion of atopy separately for affluent *(red)* and nonaffluent *(blue)* countries.

17.8% for affluent-country centers and 4.1% for nonaffluent-country centers. The association between GNI as a continuous variable and ORs and PAFs remained positive but missed statistical significance for OR estimates ($\rho = 0.34$, $P = .07$). The association remained highly significant for PAFs and GNI ($\rho = 0.44$, $P = .02$).

Locally added allergens

Inclusion of locally added allergens did not change results significantly. For instance, among centers that used additional allergens, the atopy prevalence range increased only slightly, from 7.1% to 42.8% (based on 6 standard allergens) to 10.3% to 45.3%, after inclusion of additional allergens. Looking only at centers that tested additional allergens, the combined ORs for the association between flexural eczema and skin prick test reactivity changed from an OR of 2.66 to an OR of 2.68 in affluent countries and from an OR of 1.29 to an OR of 1.04 in nonaffluent countries. Equally, the correlation between GNI and ORs for the association between flexural eczema and skin test reactivity barely changed when additional allergens were included ($\rho = 0.52$ [$P = .007$] without and $\rho = 0.53$ [$P = .006$] with additional allergens).

DISCUSSION

Our study tested the strength of the association between atopy and flexural eczema. Although we found statistically significant associations between flexural eczema and skin prick test response positivity in almost all affluent countries, the association was weaker and statistically nonsignificant for most study centers in nonaffluent nations. It is the inconsistency of this association across pediatric populations that suggests that allergic sensitization is unlikely to be a main cause of disease in many settings. However, atopy should still be considered a potentially important risk factor in settings in which the association with flexural eczema was significant.

One possible explanation for the differences in the strength of the relation between atopy and eczema in affluent versus nonaffluent countries could be that there are at least 2 distinct forms of flexural eczema, an atopic and a nonatopic phenotype, and that the prevalence of these 2 phenotypes varies across the world. In fact, a distinction between atopic and nonatopic eczema has been made by a number of authors, and this has also been recognized in the new World Allergy Organization Nomenclature.[12-14] However, although this could explain the varying strength of the association between allergic sensitization and flexural eczema between countries, children with the atopic and nonatopic forms are phenotypically identical. Given the universal clinical picture of flexural eczema, it seems more plausible that the high prevalence of flexural eczema and the link with allergic sensitization in affluent countries is driven by the same environmental factors associated with affluence. In this case both flexural eczema and atopy would be statistically associated but not causally linked.

The strengths of the ISAAC Phase Two study include a standardized uniform methodology and quality control for ascertaining the physical signs of flexural eczema and for the determination of skin prick test response positivity in a very large sample from diverse geographic and ethnic backgrounds. At the same time, it is possible that nonflexural forms of eczema have different associations with atopy, but it was not possible to explore such associations in our study, which relied on a scientifically developed and stable phenotype of typical flexural eczema.[15] The main disadvantage of this study is its cross-sectional design, which limits our ability to explore the association between flexural eczema and sensitization over time. For instance, we are unable to say whether allergic sensitization occurred before or after the development of flexural eczema. However, other work has shown that eczema often starts before atopy can be demonstrated and that sensitization is not a good predictor of eczema later in life.[16,17]

Given the waning and waxing nature of the disease, it is possible that physical examination missed some children with flexural eczema. However, performing the same analysis for the questionnaire-derived outcome of flexural eczema in the past 12 months yielded very similar results and did not change the overall conclusions.

We showed in our previous systematic review on eczema and allergic sensitization that there appears to be a positive association between disease severity and the number of positive skin prick test responses, as well as specific serum IgE levels.[2] Although we did not assess for disease severity as part of ISAAC Phase Two, it is likely that the majority of children in this population-based study had mild-to-moderate rather than severe disease, and this would explain some of the weakness of

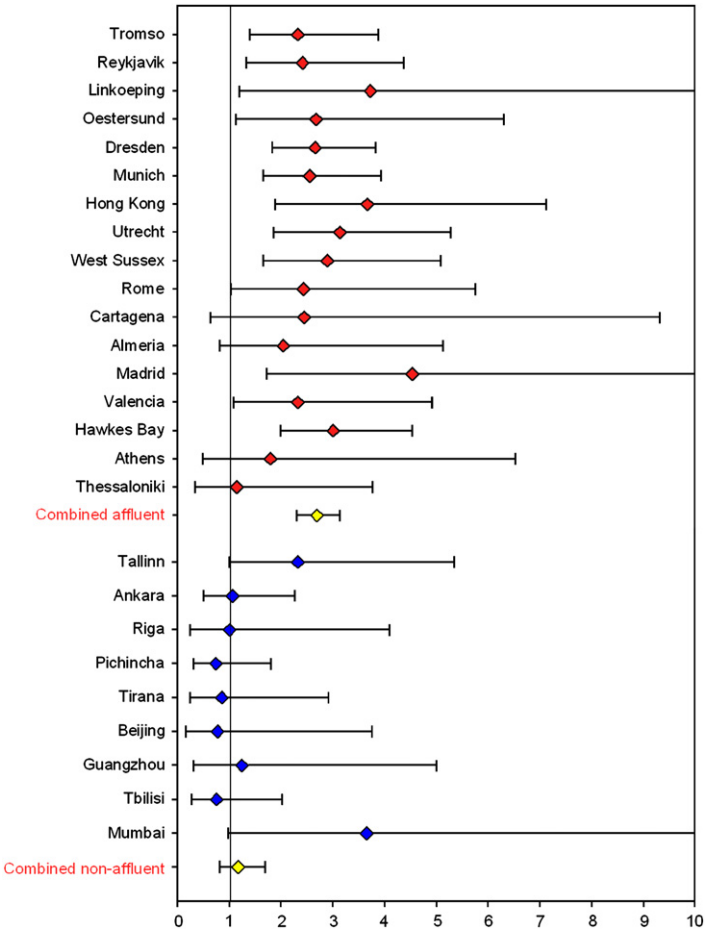

FIG 2. Forest plot of age- and sex-adjusted ORs for atopy (exposure) and flexural eczema (outcome) for each study center (*red*, affluent countries; *blue*, nonaffluent countries). Within each group, centers are arranged in order of GNI.

the association between skin prick test responses and flexural eczema. However, this is unlikely to explain the great variation in ORs and PAFs across study centers and countries.

A possible explanation for the association between disease severity and allergic sensitization is filaggrin deficiency resulting in impaired skin barrier function, which in turn leads to enhanced allergen penetration through the skin.[18-22] Although a recent study has suggested a link between filaggrin gene *(FLG)* mutations and asthma severity, we could find only 1 population-based study that has explored the role of filaggrin deficiency in children with eczema of varying severity.[23,24] Although this study found a statistically significant association between *FLG* mutations and eczema severity, *FLG* mutations could only explain 0.8% of the variations in disease severity (coefficient of determination $[R^2] = 0.8\%$). More data on the frequency of *FLG* deficiency in a variety of populations is needed to see whether some of the differences in the strength of the association between flexural eczema and allergic sensitization observed in our study could be explained by differences in the frequency of the *FLG* mutations between populations.

It is unlikely that the low proportion of atopy among children with flexural eczema in nonaffluent countries was because some of the 6 aeroallergens tested in all study centers might have been less common in low-income countries. Investigators were allowed to add allergens of local relevance, and inclusion of these additional allergens did not result in a significant change in the overall prevalence of skin test reactivity or the strength of the association between atopy, flexural eczema, and affluence.

We used World Bank criteria to make a broad distinction between affluent and nonaffluent countries. Such a distinction is, to a degree, arbitrary. In addition, using GNI as a measure of affluence is crude, and the per-capita income of individual study center populations might be substantially different from a country's GNI, especially because most of the ISAAC Phase Two data were collected in urban areas (Table I). It is likely, however, that the average per-capita income of city dwellers, especially in nonaffluent countries, is higher than the individual country's GNI. Therefore the use of the country's GNI has probably resulted in an underestimation of the already strong positive correlation among GNI, allergic sensitization, and flexural eczema.

Interestingly, in the only 2 rural ISAAC Phase Two centers (Kintampo, Ghana, and Pichincha, Ecuador) the relationship between sensitization and flexural eczema was not significant, with a lower proportion of atopy among participants with flexural eczema than among healthy children (Table I). A high prevalence of allergic sensitization and dissociation of atopy and allergic disease have been noted in developing country settings before, and it is possible that a nonspecific upregulation of IgE synthesis by

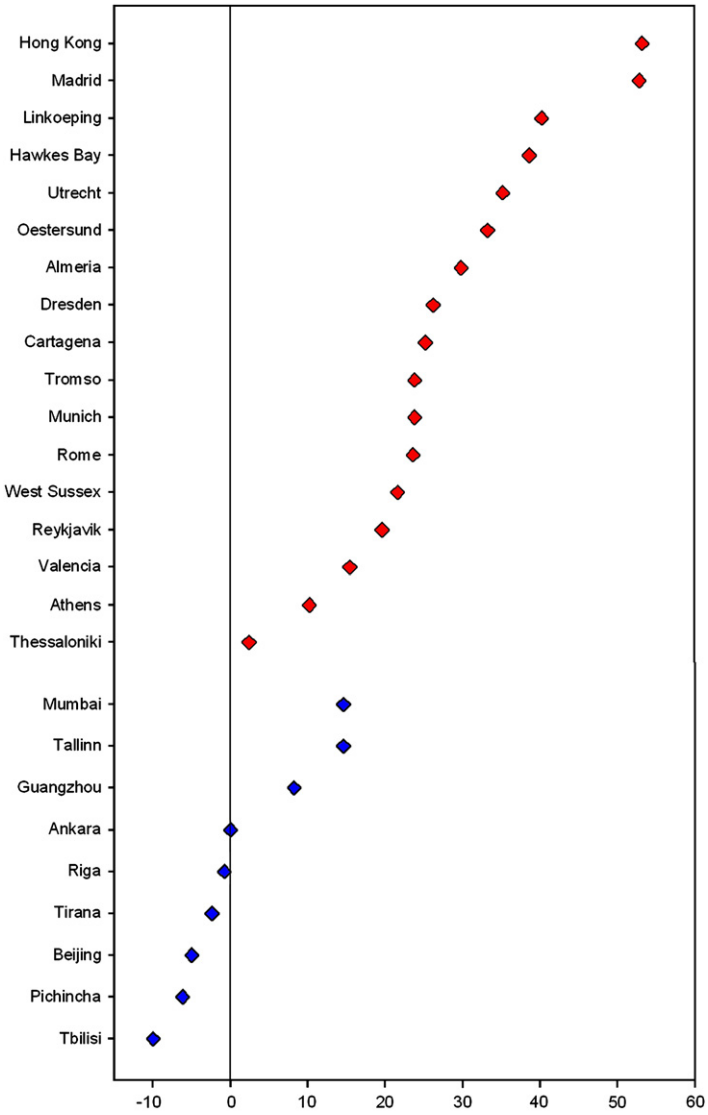

FIG 3. PAFs for all study centers (*red,* affluent countries; *blue,* nonaffluent countries). Study centers are arranged in order of magnitude of PAF.

parasitic infections increases skin sensitization while reducing clinical allergic disease.[25-30] However, the majority of studies on atopy-parasite links have shown the opposite: a downregulation of skin reactivity associated with endoparasitic infestation.[31] Similar, although less consistent, observations have been made with regard to eczema.[32-34]

One factor to explain the variation in flexural eczema and atopy prevalences across study centers, especially outside of tropical settings, might be microbial pressure differences between populations. For instance, evidence comes from studies comparing the gut microflora of children from Estonia and Sweden, suggesting that early physiologic gut colonization with enterococci and bifidobacteria is crucial in driving the immune system away from the T_H2 cell dominance found at birth into a T_H1 cell–dominated direction, protecting the individual from allergic predisposition and sensitization.[35] Young children with eczema are less likely to be colonized with lactobacilli in comparison with nonallergic children, and there is evidence from intervention studies that early bifidobacterial supplementation might help to prevent the development of eczema in individuals with a strong family history.[36,37] It has also been suggested that frequent prescribing of antibiotics and changes in diet can lead to changes in the composition of the gut microflora, and such lifestyle factors might contribute to the positive associations between GNI, allergic sensitization, and flexural eczema.[38] Furthermore, it is possible that affluence in this data set operates in part as a surrogate of climate, which in turn could alter the state of the skin and increase the risk of eczema.[39] However, the observed strong positive association of GNI with ORs and PAFs remained virtually unchanged and statistically highly significant after adjustment for latitude.

We conclude that the relation between flexural eczema and allergic sensitization varies widely between countries and that eczema and atopy might simply be associated because of shared causes. In this context it will be important to make a clear distinction between atopic and nonatopic eczema in future research (eg, when examining response to treatment or prognosis). Birth cohort studies in low-income countries could add particularly valuable information. Risk factors related to

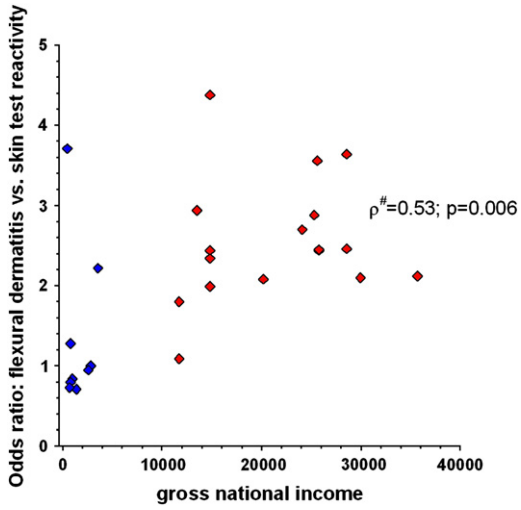

FIG 4. ORs for the association of atopy with flexural eczema plotted against GNI.

affluence must be sought to explain both the high prevalence of flexural eczema and the closer link with allergic sensitization in high-income countries.

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Clinical implications: The findings of this study suggest that allergen sensitization is primarily an epiphenomenon of disease activity rather than a uniform cause of flexural eczema.

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APPENDIX 1

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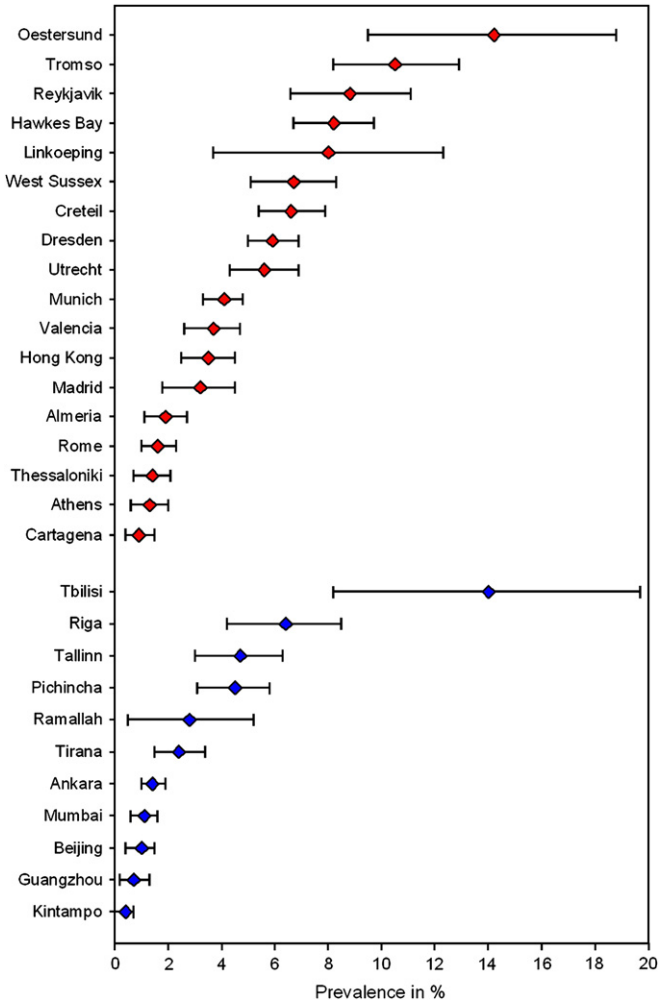

FIG E1. Flexural eczema prevalences with 95% CIs for all study centers. Study centers are arranged in order of flexural eczema prevalence, separately for affluent *(red)* and nonaffluent *(blue)* countries.

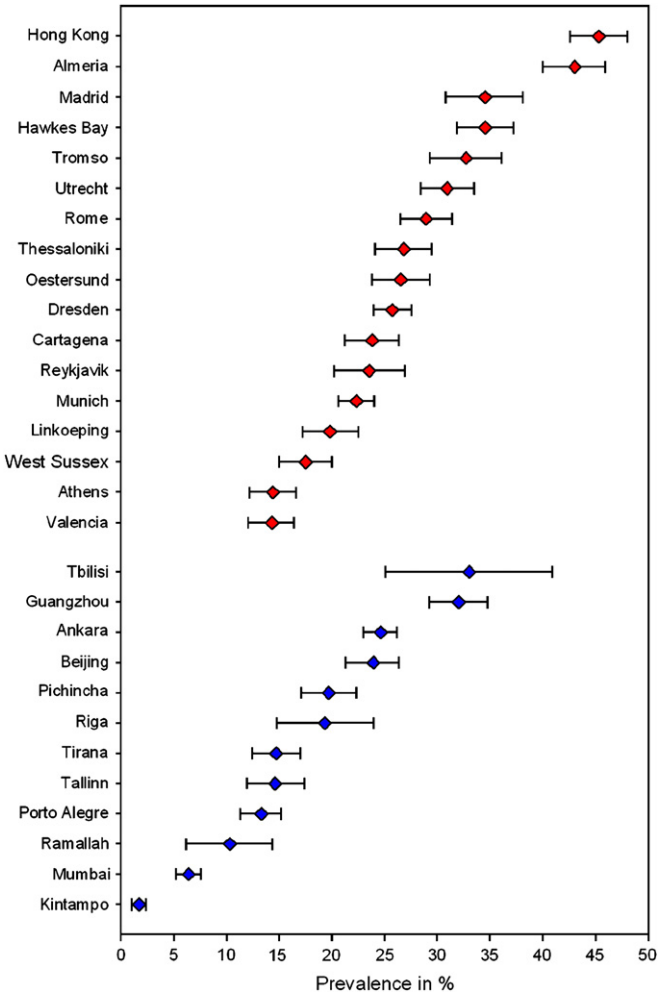

FIG E2. Atopy prevalences with 95% CIs for all study centers are arranged in order of atopy prevalence, separately for affluent *(red)* and nonaffluent *(blue)* countries.

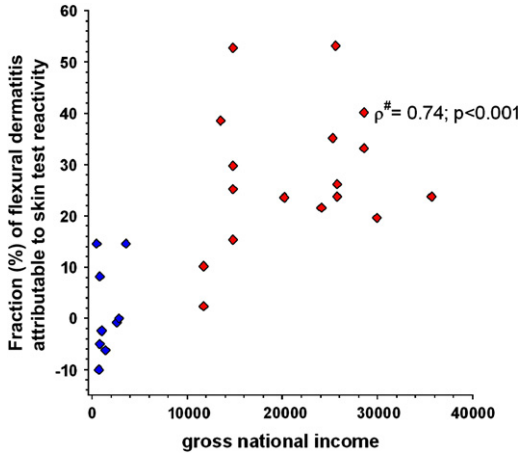

FIG E3. Fraction (%) of flexural eczema attributable to skin test reactivity (PAF) plotted against GNI.