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Effect of urbanization on the relation of total serum immunoglobulin E to asthma

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ABSTRACT

Background: It is unclear if the relationship of total serum immunoglobulin E (TsIgE) to asthma varies with degree of urbanization. We hypothesized that the relationship of TsIgE to asthma is more pronounced in an urban versus a rural environment.

Methods: We enrolled 1441 adolescents aged 13 to 15 years in a peri-urban shanty town in Lima (n=725) and 23 villages in rural Tumbes (n=716). We asked participants about asthma and allergy symptoms, environmental exposures, sociodemographics; and, performed spirometry, and exhaled nitric oxide (eNO) and allergy skin testing. We obtained blood for TsIgE in 1143 (79%) participants.

Results: Geometric means for TsIgE was higher in Lima versus Tumbes (262 vs 192 kU/L; $p<0.001$). The odds of asthma increased by factors of 1.6 (95%CI 1.3–2.0) versus 1.4 (95%CI 0.9–2.1), per log unit increase in TsIgE in Lima versus Tumbes, respectively. Atopy was an effect modifier of the relationship of TsIgE on asthma. Among atopics and non-atopics, the odds of asthma increased by a factor of 2.0 (95%CI 1.5–2.7) and 1.0 (95%CI 0.7–1.4) per log unit increase in TsIgE, respectively.

Conclusion: Total serum IgE was associated with atopic asthma but not with non-atopic asthma. Urbanization did not appear to be an effect modifier of this relationship.

INTRODUCTION

Asthma is a chronic lung disease that is associated with an inflammatory reaction of the airways, bronchial hyper-responsiveness and increased production of mucus, all which lead to reversible periods of airways obstruction. Over the last several decades, asthma has emerged as one of the most prevalent non-communicable diseases worldwide, particularly among children. It currently affects 300 million individuals around the world, is responsible for 255,000 deaths and results in 15 million disability-adjusted life-years lost each year (1). The worldwide burden of disease caused by asthma accounts for 1 percent of all disability life years lost, and is comparable to that of diabetes mellitus or cirrhosis (2, 3).

Atopic sensitization is a well-known risk factor for the development of asthma (4), and repeated exposure to high levels of allergens with previous sensitization can worsen asthma control (5, 6). The development of an allergic response is mediated by the production of immunoglobulin E (IgE) antibodies. Since the discovery of IgE (7), the relationship of total serum IgE with asthma (8-13) has been extensively studied to determine if it could be a useful adjunct in the diagnosis of asthma. However, due to considerable overlap in total serum IgE levels among atopic and non-atopic populations, the diagnostic utility of total serum IgE for asthma has been questioned. Moreover, sensitization to specific allergens may occur even in the setting of low total serum IgE levels. Interpretation of total IgE in developing countries is complicated even further with a high burden of parasitic infections.

While the relationship of total serum IgE to asthma is well described in developed countries, it is unclear if this relationship varies in different populations according to the types of allergens, levels of indoor and outdoor air pollution, the prevalence of atopy or parasitic infections (14) and other risk factors for asthma including obesity (15) and degree of urbanization. In this study, we

examined the relationship of total serum IgE to asthma, atopy, airway obstruction and airway inflammation in two regions of a developing country with disparate degrees of urbanization and a different profile of environmental exposures. We hypothesized that the relationship of total serum IgE to asthma may be more pronounced in an urban than a rural environment.

METHODS

Study Design

The study design is described in detail elsewhere (16-18). We conducted a cross-sectional study in 13 to 15 year-old adolescents in two regions in Peru. Lima, the highly urbanized capital of Peru, is located at sea level and has a population of 10 million. We conducted our study in Pampas de San Juan de Miraflores, a peri-urban shanty-town located 25 km south of central Lima. The second site was rural Tumbes, also at sea level, located in northern Peru. We asked about asthma and allergy symptoms, sociodemographics and environmental exposures, and obtained anthropometry, a blood sample, allergy skin test, exhaled nitric oxide (eNO) test, and spirometry before and after bronchodilators. The basis of questionnaire used in this study was a previously validated Spanish version of the ISAAC study (19). We conducted spirometry according to ATS/ERS guidelines (20) with the portable SpiroPro (Jaeger, Hoechberg, Germany). We used the handheld NIOXMINO (Aerocrine, Solna, Sweden) to measure eNO. We performed allergy tests with the Multi-Test II (Lincoln Diagnostics, Decatur, USA) using 10 common household allergens (17). **S**erum specimens were analyzed for total serum IgE using an US FDA cleared fluorescent enzyme immunoassay (ImmunoCAP250, Thermo Fisher Scientific, Kalamazoo, USA). We obtained approval from the Ethics Committees of A.B. PRISMA in Lima, Peru, and the Johns Hopkins University, Bloomberg School of Public Health, in Baltimore, MD.

Definitions

We defined asthma as wheeze in the last 12 months or use of asthma medications in the last 12 months. We defined atopy as a positive skin response to any of the allergen specificities as

previously described (17, 18). Briefly, an allergy skin test was considered positive if the sum of the vertical and horizontal dimensions of the induration was >3 mm than the negative control or if the sum of the vertical and horizontal dimensions of erythema was >5 mm larger than the negative control. We defined reversibility as a 12% increase in post- to pre-FEV_1.

Biostatistical methods

Our primary objective was to study the relationship of total serum IgE to asthma. We used multivariable logistic regression stratified by site and by atopic status and adjusted for age, gender, body mass index (> 25 kg/m^2), personal history of tobacco smoke, second-hand tobacco smoke and sociodemographics including maternal education (<6 years), monthly household income (< USD 175), household density (>6 people per household) and concrete floor. The distribution of total serum IgE was skewed left, with values that ranged from 2 to 9420 kU/L. Thus, we log transformed values of total IgE for statistical analyses. In exploratory analyses, we found that the relationship of log total IgE to the log odds of asthma was approximately linear. We also studied the relationship of total IgE to airways obstruction as measured by the ratio of forced expiratory volume at 1 second (FEV_1) to forced vital capacity (FVC). We conducted multivariable linear regression stratified by site and asthma status and adjusted for the same sociodemographic variables. Secondary objectives included analyses of the relationship of total IgE to both atopy and airways inflammation as measured by an eNO greater than 40 ppm. We used multivariable logistic regression adjusted by sociodemographics for these analyses. Finally, we used t-tests to compare the log transformed values of total IgE and chi-square tests for differences in proportions across strata. Analyses were restricted to the subgroup of 1143 participants for which we had a total serum IgE measurement. We used R (www.r-project.org)

for statistical analyses.

RESULTS

Baseline characteristics

Of 1441 individuals who agreed to participate in the study, we obtained blood samples for total serum IgE levels from 1143 (79%). There were no differences observed in the age (p=0.97), sex (p=0.70), prevalence of asthma (p=0.72) or atopy (p=0.24), pre-FEV_1/FVC (p=0.69), exhaled nitric oxide (p=0.35), body mass index (p=0.40), income (p=0.66) and maternal education (p=0.73) between participants with and without a blood sample for total serum IgE levels. Children living in the urban environment were less likely to live in households with a monthly income < 175 USD (25% vs. 63%, p<0.001), were more likely to live in households with uninterrupted water services (92% vs. 6%; p<0.001) or electricity (100% vs. 85%; p<0.001) , were more likely to have an indoor sewage connection (92% vs. 27%; p<0.001), and were less likely to live in households with regular use of biomass fuels (9% vs. 42%; p<0.001) or farm animals (72% vs. 23%; p<0.001) than those in the rural environment.

The average total serum IgE was 588 kU/L (SD=883) in Lima and 407 kU/L (SD=679) in Tumbes (p<0.001; t-test of log IgE); however, there was considerable overlap in the range of total IgEs between sites (Figure 1). Corresponding geometric means were 262 kU/L and 192 kU/L, respectively. The average age at the time of enrollment was comparable in both study groups, 14.8 years (SD=0.9) in Lima versus 14.9 years (SD=0.9) in Tumbes (p=0.44). In Lima, total IgE levels were higher in boys than in girls and higher in overweight participants (body mass index > 25 kg/m^2) than in those who were not overweight (Table 1). While these differences were not statistically significant in Tumbes, they trended in the same direction. We did not find significant differences in average total serum IgE levels across select socioeconomic

indicators such as maternal education, monthly income or household density in either site (Table 1).

Pets and farm animals were commonly found in households at both sites. There was a greater proportion of households with dogs (72% vs 57%; p<0.001), chickens (61% vs 21%; p<0.001), ducks (45% vs 9%; p<0.001) and turkeys (14% vs <1%; p<0.001) in Tumbes than in Lima. There was a similar proportion of households with cats (43% vs 45%; p=0.52) in Tumbes and Lima. There was a greater proportion of households with doves (16% vs 10%; p<0.01) and guinea pigs (12% vs 6%; p<0.001) in Lima than in Tumbes. Total serum IgE levels were not affected by the presence of pets or farm animals at either site (Table 1). Dogs (38% vs 13%; p<0.001) and cats (76% vs 32%; p<0.001) were more likely to be exclusively indoors in Lima than in Tumbes. The prevalence of atopic sensitization was significantly greater in Lima than in Tumbes for all tested allergens. While the rate of atopic sensitization was slightly greater for cockroach (57% vs 42%; p<0.001), mite (58% vs 35%; p<0.001) and cat (55% vs 32%; p<0.001), it was substantially greater for dog (52% vs 13%; p<0.001), mouse (52% vs 19%; p<0.001) and mold (53% vs 15%; p<0.001).

Relationship of total serum IgE to asthma, atopy and airways inflammation

Among the 1143 participants with a total serum IgE measurement, the prevalence of atopy as assessed by skin testing was 55% (292/527) in Lima and 37% (206/550) in Tumbes. The prevalences of atopic and non-atopic asthma in Lima were 17% (50/292) and 6% (13/235), respectively; in Tumbes, the corresponding prevalences of atopic and non-atopic asthma were 4% (8/206) and 3% (9/344), respectively.

Total serum IgE levels were higher in asthmatics than in non-asthmatics (Table 1). The prevalence of asthma across our sample increased with total serum IgE (Figure 2). This increase was more apparent in Lima than in Tumbes. In multivariable analyses, the odds of asthma increased by factors of 1.6 (95% CI 1.3 to 2.0) and 1.4 (95% CI 0.9 to 2.1) per log unit increase in total serum IgE in Lima and in Tumbes, respectively. In pooled analysis, the odds of asthma increased by a factor of 1.6 (95% CI 1.3 to 1.9) per log unit increase in total serum IgE. Further stratified analyses revealed that atopy was an effect modifier of the relationship of total IgE to asthma (Table 2). More specifically, total serum IgE was associated with asthma only among those who were atopic.

Total serum IgE levels were also higher in atopics than in non-atopics, and in participants with exhaled nitric oxide greater than 40 ppm versus those with lower values (Table 1). The prevalence of atopy across our sample increased with total serum IgE, and this increase was consistent across sites (Figure 3). In multivariable analyses, the odds of atopy increased by factors of 1.5 (95% CI 1.3 to 1.7) and 1.6 (95% CI 1.4 to 1.9) per log unit increase in total serum IgE in Lima and in Tumbes, respectively. Mean exhaled nitric oxide increased with total serum IgE, and this increase was consistent across sites (Figure 4). The odds of an exhaled nitric oxide greater than 40 ppm increased by factors of 4.0 (95% CI 2.7 to 5.8) and 2.5 (95% CI 1.9 to 3.4) per log unit increase in total serum IgE in Lima and in Tumbes, respectively. In pooled analysis, the odds of having an exhaled nitric oxide greater than 40 ppm increased by a factor of 3.0 (95% CI 2.4 to 3.8) per log unit increase in total serum IgE. When stratified by atopic status, the odds of having an exhaled nitric oxide greater than 40 ppm increased by a factor of 2.3 (95% CI 1.6 to 3.3) in non-atopics and 3.7 (95% CI 2.6 to 5.1) in atopics. This relationship remained significant even among those without asthma. Among non-asthmatics, the odds of having an exhaled nitric

oxide greater than 40 ppm increased by factors of 3.6 (95% CI 2.3 to 5.5) and 2.5 (95% CI 1.8 to 3.3) per log unit increase in total serum IgE in Lima and in Tumbes, respectively.

Relationship of total serum IgE to airway obstruction and airway reversibility

Pre- and post-FEV_1/FVC were inversely related to total serum IgE levels in Lima but not in Tumbes (Figure 5). In Lima, mean pre- and post-FEV_1/FVC decreased by 0.5% (95% CI -0.9% to -0.1%) and 0.3% (95% CI -0.7% to 0.0%) per log unit increase in total serum IgE, respectively. In a similar analysis in the subset of children without asthma, higher total serum IgE levels were also associated with lower pre- and post-FEV_1/FVC. Specifically, among non-asthmatics, mean pre- and post-FEV_1/FVC decreased by 0.5% (95% CI -0.9% to -0.1%) and 0.4% (95% CI -0.8% to -0.0) per log unit increase in total serum IgE, respectively. There were too few children with asthma and a total serum IgE (n=66) to adequately examine dose-response relationships between total serum IgE measurements and FEV_1/FVC. In Tumbes, the mean pre-FEV_1/FVC (p=0.65) and post-FEV_1/FVC (p=0.75) was not associated with total serum IgE levels.

Higher levels of total serum IgE were also associated with more bronchodilator reversibility. More specifically, in multivariable analysis, the odds of airway reversibility increased by factors of 1.4 (95% CI 1.0 to 2.1) and 1.4 (95% CI 0.9 to 2.1) per log unit increase in total IgE in Lima and in Tumbes, respectively. In pooled analysis, the odds of airway reversibility increased by a factor of 1.4 (9% CI 1.1 to 1.9) per log unit increase in total IgE.

DISCUSSION

Among our sample of Peruvian adolescents aged 13 to 15 years, total serum IgE levels were higher compared to children in the United States or Europe and directly related to the prevalence of atopic asthma but not to that of non-atopic asthma. The relationship of total serum IgE to atopic asthma was consistent across two regions with disparate degrees of urbanization. Airway inflammation, as measured by exhaled nitric oxide, and bronchodilator reversibility was also greater with higher levels of total serum IgE. The association between total serum IgE and exhaled nitric oxide remained significant in the subset of children without asthma. In addition, the degree of airways obstruction as measured by FEV_1/FVC was worse with increasing total serum IgE in Lima but not in Tumbes. This inverse association of total serum IgE and FEV_1/FVC remained significant in the subset of children without asthma living in the urban environment of Lima.

Our findings on the relationship of total IgE to asthma by atopic status were consistent with those of a recent survey conducted by the United States National Health and Nutrition Examination Study (NHANES) between 2005 and 2006 (12). Our data provide complementary information to the NHANES analysis in that we further examined the relationship of total IgE to quantitative measures of airways obstruction and airway inflammation. An important difference between our study and the NHANES study was that the geometric mean of total serum IgE of our study was approximately four times greater than that of children aged 12 to 15 years in the NHANES sample; however, the relationship of total IgE to atopic asthma persisted despite of these elevated levels. There are several reasons why total serum IgE may be higher in our Peruvian population than in the general population in the United States. One possibility for this increase is the higher prevalence of enteric infections, including protozoans (21, 22), and soil-

based helminths (14) in Peru than in the United States. However, the levels of total serum IgE in our sample of Peruvian adolescents were not as high as in other regions with high levels of parasitism (14). The geometric means between asthmatics and non-asthmatics in our study were similar in magnitude to those identified in a smaller, cross-sectional study of 198 children aged 10 to 13 years conducted in Costa Rica (23). As with the study in Costa Rica, we did not examine stool samples for ova and parasites in our study children. However, the prevalence of soil-based heminthic infections in children of similar age in our study areas is low (Online Supplement) and therefore unlikely to explain the higher levels of total serum IgE when compared with values of similarly aged children in the NHANES sample.

On the other hand, our findings were different from those of a large general population study of 2657 subjects in Tucson, United States (8), 1916 young adults in five areas of Spain (10) and 1219 consecutive pulmonary patients to a pulmonary practice in Frankfurt, Germany (11), in that we did not find a direct relationship between total serum IgE and non-atopic asthma. The Tucson study tested 18 allergens by prick test; however, this study did not include allergens for common household pets such as cat and dog, and household pests such as cockroach and mice. In contrast, our study and the NHANES study (12) tested for these common household allergens. It is possible that several asthmatics in the Tucson study were misclassified as non-atopic and this could explain why there was a linear relationship of total IgE to non-atopic asthma. In our study, geometric means for total IgE for atopic asthmatics were 754 kU/L in Lima and 472 kU/L in Tumbes, higher than those in the Tucson study. The geometric means for total IgE for non-atopic asthmatics were 137 kU/L in Lima and 251 kU/L in Tumbes, also higher than those in the Tucson study. The Spain study also tested fewer (i.e., five) allergen specificities than ours (i.e., 10) and the NHANES study, and as a result may have had a similar

degree of misclassification. The Frankfurt study, unlike our study and others (8, 10, 12), was not a population study but included a large range of 14 common allergens that did not include cockroach or mouse and eight food allergens. In this study, the odds of asthma increased by a factor of 5.1 (95% CI 2.6 to 10.1) when total serum IgE was greater than 150 kU/L. In contrast, in our study, there was no single cutoff for total serum IgE between 100 kU/L and 800 kU/L that was associated with non-atopic asthma. Possible explanations for an effect are that the Frankfurt study included a more select group of asthmatics that sought attention for respiratory complaints or follow-up, and their sample of non-atopic asthmatics was larger than ours. However, the Frankfurt study did not include normal healthy controls from the general population.

Our study also identified a greater chance of airway reversibility and greater levels of airways inflammation at higher levels of total serum IgE. This finding is consistent with previous studies that found a relationship between IgE and more labile airways (24, 25). These studies, however, used methacholine for bronchoprovocation. Hence our study provides complementary information on quantitative measures of airway effects in the setting of higher levels of total serum IgE. We also found a greater degree of airway obstruction as measured by FEV_1/FVC with higher levels of total serum IgE in Lima and not in Tumbes. This could be explained in part by the higher prevalence of asthma and atopy in Lima; however, in subset analyses, we observed that this relationship persisted among non-asthmatics in Lima. Our findings of an inverse relationship of total serum IgE to FEV_1/FVC are consistent with those of previous studies of asthmatics (26, 27).

Our study has some potential shortcomings. First, our study design was cross-sectional. Therefore, we were not able to characterize the effects of early life exposures (including respiratory infections or environmental exposures in early childhood) on our observed

relationships. Second, we did not conduct an evaluation of parasitic infections in our study children; however, previous population-based evaluations by our team on the burden of soil-based helminths in our study areas were found to be low (Online Supplement). Nonetheless, this low burden of parasitic infections, in light of elevated total serum IgE levels, needs to be further confirmed in future studies. Third, our study did not include an evaluation of diet habits or micronutrients, which may also have an effect on our observed relationships. However, our findings are largely consistent with a large, population-based study in the United States (12).

The relationship of total serum IgE to severity of airway obstruction is poorly understood. One possible explanation is that higher total serum IgE may reflect more severe asthma due to elevations in allergen-specific IgE levels. Another possibility is that elevated total serum IgE may also contribute indirectly to airway inflammation, which may help explain why we observed an inverse relationship of total serum IgE to FEV_1/FVC among non-asthmatics living in Lima. In the Normative Aging Study, a longitudinal study of 2,280 healthy adult volunteers in Boston without a history of asthma, skin test reactivity to four common aeroallergens was a significant predictor of decline in both FEV_1 and FEV_1/FVC (28). Persistent exposure in sensitized individuals may be associated with chronic bronchial inflammation, which may help explain the findings of a reduced lung function over time in the Normative Aging Study. In the longitudinal Tucson Epidemiological Study of Airways Obstructive Disease, total serum IgE was not associated with a FEV_1 decline in ever smokers without asthma (29). Studies have shown that allergen exposure affects cytokine and anti-inflammatory production. TNF-alpha, IL-6 and IL-8 are upregulated in airway epithelium after exposure to allergen (30). A recent study comparing inflammatory markers in atopic versus non-atopic patients with COPD found that IL-8 was upregulated in patients with mite allergies (31).

In summary, total serum IgE was associated with atopic asthma in a developing country setting despite high background levels of total serum IgE. Urbanization did not appear to be an effect modified of this relationship. Our study also confirms the lack of association between total serum IgE and non-atopic asthma. Despite the lack of association with non-atopic asthma, we found that total serum IgE was associated with markers of airway inflammation and lung function even among non-asthmatics living in an urban environment. Markers of airway obstruction such as response to bronchodilators, exhaled nitric oxide and FEV_1/FVC were also associated with total serum IgE.

REFERENCES

1. Braman SS. The global burden of asthma. Chest 2006;130;4-12.
2. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004;59:469–78.
3. Bousquet J, Bousquet PJ, Godard P, Daures JP. The public health implications of asthma. Bull World Health Organ 2005; 83: 548-54.
4. Pearce N, Pekkanen K, Beasley R. How much asthma is really attributable to atopy? Thorax 1999 54: 268-272.
5. Gruchalla RS, Pongracic J, Plaut M, Evans R 3rd, Visness CM, Walter M, Crain EF, Kattan M, Morgan WJ, Steinbach S, Stout J, Malindzak G, Smartt E, Mitchell H. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol 2005;115:478-85.
6. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997;336: 1356-63.
7. Bennich HH, Ishizaka HK, Johansson SG, Rowe DS, Stanworth DR, Terry WD. Immunoglobulin E: a new class of human immunoglobulin. Immunology 1968; 3:323-324.
8. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320:271-7.

9. Burrows B, Halonen M, Lebowitz MD, Knudson RJ, Barbee RA. The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. J Allergy Clin Immunol 1982;70:199-204.
10. Sunyer J, Anto JM, Soriano JB, Roca J. Total serum IgE is associated with asthma independently of specific IgE levels. Eur Respir J 1996; 9: 1880-1884.
11. Beeh KM, Ksoll M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. Eur Respir J 2000;16:609-14.
12. Gergen PJ, Arbes SJ Jr, Calatroni A, Mitchell HE, Zeldin DC. Total IgE levels and asthma prevalence in the US population: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2009;124:447-53.
13. Barron-Casella EA, Strunk RC, Hamilton RG, Casella JF, Debaun MR. Elevation of IgE in children with sickle cell disease is associated with doctor diagnosis of asthma and increased morbidity. J Allergy Clin Immunol. 2011;127:1440-6.
14. Houba V, Rowe DS. A comparison of African and European serum levels of immunoglobulin E. Bull World Health Organ 1973;49:539-45.
15. Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, Liu AH, Calatroni A, Zeldin DC. Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2009;123:1163-9.
16. Robinson CL, Baumann LM, Gilman RH, Romero K, Combe JM, Gomez A, Cabrera L, Gonzalvez G, Hansel NN, Wise RA, Breysse PN, Barnes K, Hernandez JE, Checkley W. Effects of varying degrees of urbanization on asthma, allergy and airways inflammation in a developing country setting. Thorax 2011;66:1051-7..

17. Baumann LM, Robinson CL, Combe JM, Gomez A, Romero R, Gilman RH, Cabrera L, Hansel NN, Wise RA, Breysse PN, Barnes K, Hernandez JE, Checkley W. Effects of distance from a heavily transited avenue on asthma and atopy in a peri-urban shanty-town in Lima, Peru. J Allergy Clin Immunol 2011,127:875-82.
18. Robinson CL, Baumann LM, Gilman RH, Romero R, Combe JM, Cabrera L, Hansel NN, Barnes K, Gonzalvez G, Wise RA, Breysse PN, Checkley W. The Peru Urban versus Rural Asthma (PURA) Study: Methods and baseline quality control data for a cross-sectional investigation into the prevalence, severity, genetics, immunology, and environmental factors affecting adolescent asthma in Peru. BMJ Open 22;2(1):e000421.
19. Mata Fernández C, Fernández-Benítez M, Pérez Miranda M, Guillén Grima F. Validation of the Spanish version of the Phase III ISAAC questionnaire on asthma. J Investig Allergol Clin Immunol 2005;15:201-10.
20. Miller MR, Hankinson JL, Brusasco V, Burgos F, Casaburi R, Coates A, et al. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
21. Jiménez JC, Fontaine J, Grzych JM, Dei-Cas E, Capron M. Systemic and mucosal responses to oral administration of excretory and secretory antigens from Giardia intestinalis. Clin Diagn Lab Immunol 2004;11:152-60.
22. Pérez O, Lastre M, Bandera F, Díaz M, Domenech I, Fagundo R, Torres D, Finlay C, Campa C, Sierra G. Evaluation of the immune response in symptomatic and asymptomatic human giardiasis. Arch Med Res 1994;25:171-7.
23. Celedon JC, Soto-Quiros ME, Hanson LA, Weiss ST. The relationship among markers of allergy, asthma, allergic rhinitis, and eczema in Costa Rica. Pediatr Allergy Immunol 2002: 13: 91–97.

24. Sunyer J, Antó JM, Sabrià J, Roca J, Morell F, Rodríguez-Roisin R, Rodrigo MJ. Relationship between serum IgE and airway responsiveness in adults with asthma. J Allergy Clin Immunol. 1995;95:699-706.
25. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991;325:1067-71.
26. Carroll WD, Lenney W, Child F, Strange RC, Jones PW, Whyte MK, Primhak RA, Fryer AA. Asthma severity and atopy: how clear is the relationship? Arch Dis Child 2006: 91: 405–9.
27. Haselkorn T, Szefler SJ, Simons FER, Zeiger RS, Mink DR, Chipps BE, Borish L, Wong DA, for the TENOR Study Group. Allergy, total serum immunoglobulin E, and airflow in children and adolescents in TENOR. Pediatr Allergy Immunol 2010: 21: 1157–1165.
28. Gottlieb DJ, Sparrow D, O'Connor GT, Weiss ST. Skin test reactivity to common aeroallergens and decline of lung function: The Normative Aging Study. Am J Respir Crit Care Med 1996;153:561-66.
29. Sherrill DL, Lebowitz MD, Halonen M, Barbee RA, Burrows B. Longitudinal evaluation of the association between pulmonary function and total serum IgE. Am J Respir Crit Care Med 1995;152:98-102.
30. Vroling AB, Duinsbergen D, Fokkens WF, van Drunen CM. Allergen induced gene expression of airway epithelial cells shows a possible role for TNF-α. Allergy 2007;62:1310–1319.
31. Tsai JJ, Liao EC, Hsu JY, Lee WJ, Lai YK. The differences of eosinophil- and neutrophil-related inflammation in elderly allergic and non-allergic chronic obstructive pulmonary

disease. J Asthma 2010;47:1040-4.

Table 1. Geometric mean and average total serum IgE levels across demographic variables, asthma status, atopic status, airways inflammation and socioeconomic variables, stratified by study site; Peru, 2009-2010.

	Total serum IgE (kU/L)					
	Lima (n=566)			Tumbes (n=577)		
Characteristic	**Geometric mean**	**Mean (SD)**	**p-value**	**Geometric mean**	**Mean (SD)**	**p-value**
Overall	262	588 (883)		192	407 (679)	
Demographics						
Sex						
Male	326	692 (962)		204	416 (725)	
Female	210	484 (784)	<0.001	178	397 (623)	0.20
BMI > 25 kg/m^2						
No	240	566 (921)		189	396 (652)	
Yes	432	712 (630)	<0.001	235	549 (951)	0.28
Asthma and atopy						
Asthma status						
No	238	546 (891)		188	397 (666)	
Yes	516	894 (760)	<0.001	338	743 (1006)	0.12
Atopy status						
No	182	440 (745)		147	355 (773)	
Yes	351	716 (992)	<0.001	294	479 (463)	<0.001
Asthma phenotype						
Atopic	761	1080 (794)		472	662 (438)	
Non-atopic	136	302 (290)	<0.01	251	816 (1358) [Median=119]	0.38
eNO > 40 ppm						
No	217	478 (764)		172	367 (666)	
Yes	1142	1404 (877)	<0.001	611	838 (709)	<0.001
Socioeconomic indicators						
Maternal education $\geq$ 6 years						
No	308	589 (680)		182	380 (507)	
Yes	249	590 (943)	0.11	194	419 (747)	0.60
Income < USD 175/month						

No	274	616 (946)		189	429 (672)	
Yes	229	509 (668)	0.17	193	394 (685)	0.85
6+people/house						
No	255	595 (925)		185	400 (731)	
Yes	268	581 (841)	0.68	212	428 (519)	0.26
Concrete floor						
No	255	537 (691)		216	485 (876)	
Yes	273	673 (1132)	0.59	175	347 (468)	0.05
Pets in household						
Dogs						
No	279	571 (834)		201	433 (629)	
Yes	249	601 (920)	0.32	188	397 (698)	0.56
Cats						
No	267	632 (978)		192	413 (730)	
Yes	255	535 (750)	0.69	191	399 (607)	0.98
Chicken						
No	250	552 (771)		175	345 (487)	
Yes	311	728 (1214)	0.12	203	446 (775)	0.16
Ducks						
No	257	581 (886)		191	385 (528)	
Yes	324	665 (848)	0.23	192	434 (828)	0.97
Turkeys						
No	262	590 (886)		190	413 (714)	
Yes	177	353 (244)	0.71	204	374 (413)	0.61
Dove						
No	257	564 (808)		190	412 (701)	
Yes	287	719 (1205)	0.50	204	370 (444)	0.65
Guinea pig						
No	261	582 (830)		191	411 (691)	
Yes	266	639 (1224)	0.91	196	352 (441)	0.90

Table 2. Multiple variable regression of predictors of asthma stratified by atopic status; Peru, 2009-2010.

	OR (95% CI)			
Variable	**Atopic asthma (n=461)**	**p-value**	**Non-atopic asthma (n=541)**	**p-value**
log total serum IgE (kU/L)	1.9 (1.4 to 2.6)	<0.001	1.0 (0.7 to 1.4)	0.91
BMI >25 kg/m^2	3.5 (1.7 to 7.1)	0.001	2.4 (0.8 to 7.3)	0.11
Maternal education≥6 years	1.4 (0.6 to 2.9)	0.43	0.9 (0.3 to 2.3)	0.79
6+people/house	1.8 (1.0 to 3.4)	0.07	0.9 (0.4 to 2.2)	0.83
Income < USD175/month	0.6 (0.3 to 1.3)	0.20	0.6 (0.2 to 1.3)	0.22
Concrete floor	0.6 (0.3 to 1.2)	0.13	0.8 (0.3 to 1.8)	0.59
Female gender	0.7 (0.4 to 1.2)	0.24	1.6 (0.6 to 3.6)	0.32
Age	1.0 (0.7 to 1.4)	0.99	0.9 (0.5 to 1.4)	0.59
Personal history of tobacco smoke	2.1 (0.7 to 6.4)	0.20	1.6 (0.2 to 13.9)	0.67
Second-hand tobacco smoke	0.5 (0.2 to 1.3)	0.18	0.5 (0.1 to 2.1)	0.32

Figure 1. Distribution of total serum IgE stratified by site; Peru, 2009-2010. X-axis is in log-scale.

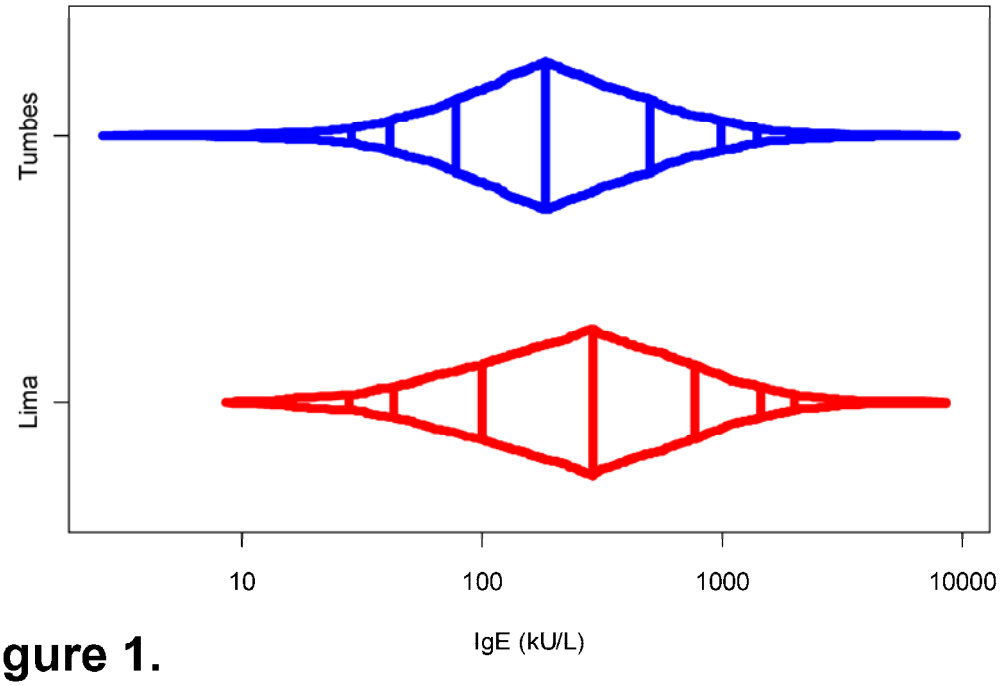

Figure 1.

Figure 2. Prevalence of asthma (%) by deciles of total serum IgE stratified by study site; Peru, 2009-2010.

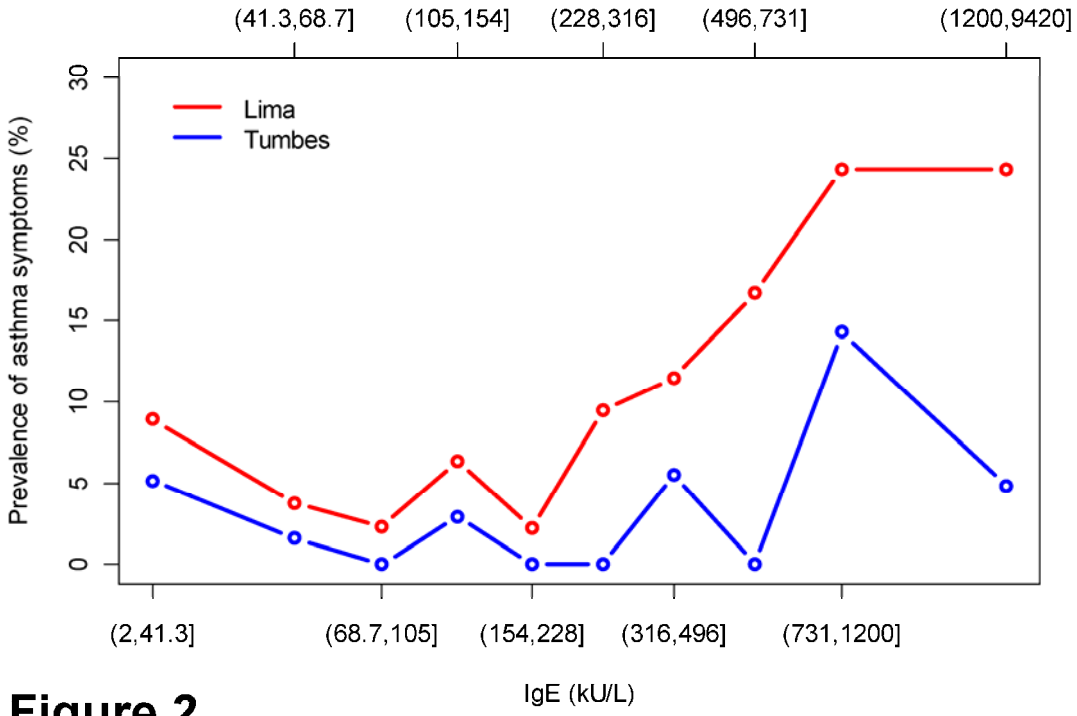

Figure 2.

Figure 3. Prevalence of atopy (%) by deciles of total serum IgE stratified by study site; Peru, 2009-2010.

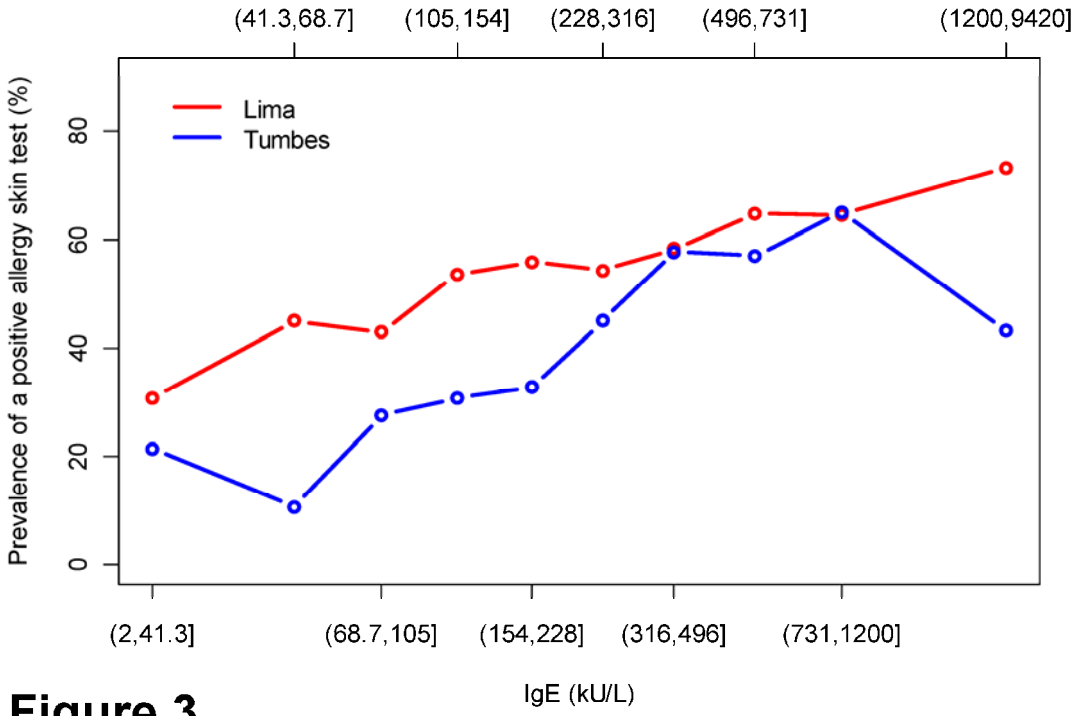

Figure 3.

Figure 4. Mean levels of exhaled nitric oxide (ppm) by deciles of total serum IgE stratified by study site; Peru, 2009-2010.

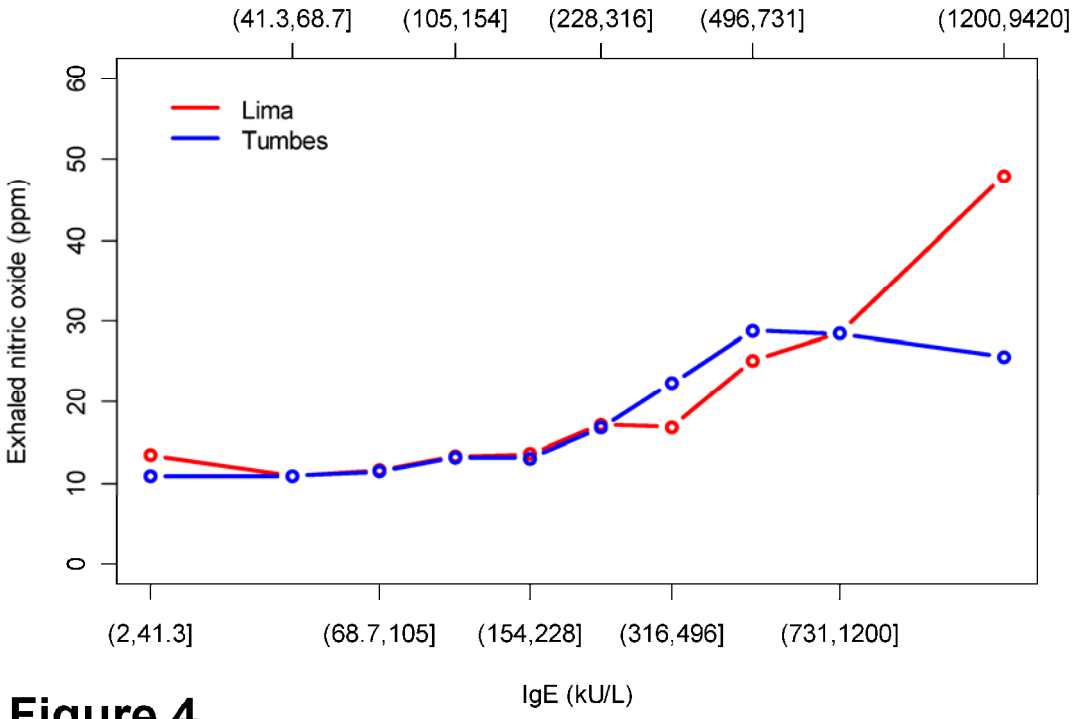

Figure 4.

Figure 5. Mean pre- and post- FEV_1/FVC by deciles of total serum IgE stratified by study site; Peru, 2009-2010.

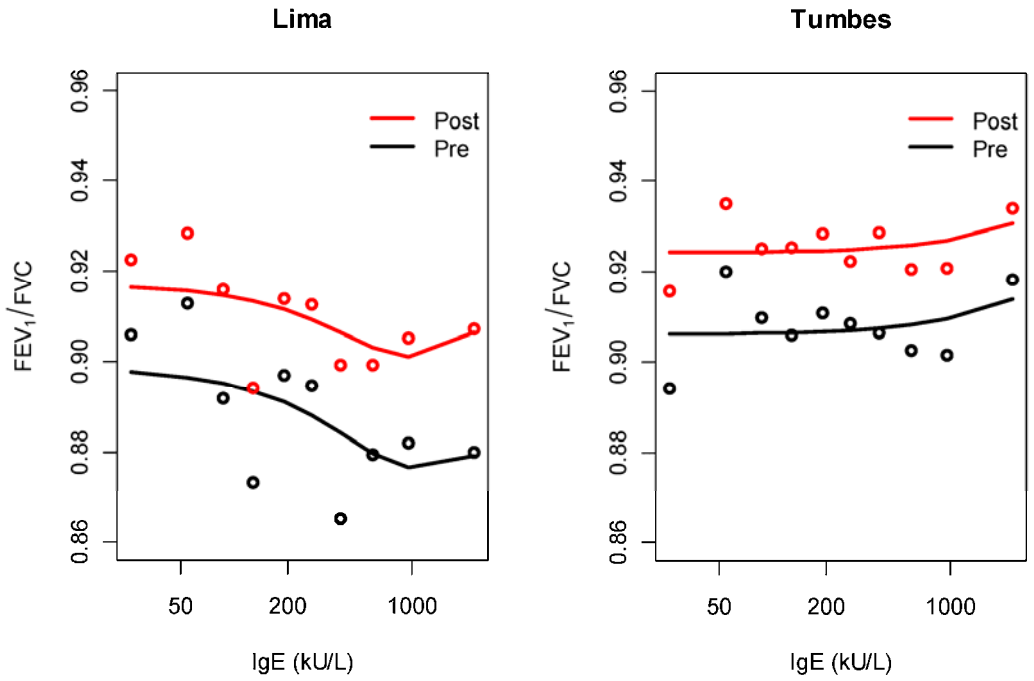

Figure 5.