

## ORIGINAL ARTICLE

## Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting

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## ABSTRACT

**Background** Asthma is a growing public health problem in developing countries. However, few studies have studied the role of urbanisation in this phenomenon. It was hypothesised that children living in a peri-urban setting in Peru have higher rates of asthma and allergy than rural counterparts.

**Methods** 1441 adolescents aged 13–15 years were enrolled from two settings: a peri-urban shanty town in Lima (n=725) and 23 rural villages in Tumbes (n=716). Participants filled in questionnaires on asthma and allergy symptoms, environmental exposures and sociodemographics, and underwent spirometry, and exhaled nitric oxide (eNO) and allergy skin testing. Indoor particulate matter (PM) concentrations were measured in 170 households.

**Results** Lima adolescents had higher rates of lifetime wheezing (22% vs 10%), current asthma symptoms (12% vs 3%) and physician-diagnosed asthma (13% vs 2%; all  $p < 0.001$ ). Current rhinitis (23% vs 12%), eczema (12% vs 0.4%), atopy (56% vs 38%), personal history of cigarette smoking (7.4% vs 1.3%) and mean indoor PM (31 vs 13  $\mu\text{g}/\text{m}^3$ ) were also higher in Lima (all  $p < 0.001$ ). The peri-urban environment of Lima was associated with a 2.6-fold greater odds (95% CI 1.3 to 5.3) of asthma in multivariable regression. Forced expiratory volumes were higher and FEV<sub>1</sub>/FVC (forced expiratory volume in 1 s/forced vital capacity) ratios were lower in Lima (all  $p < 0.001$ ). Higher eNO values in Lima ( $p < 0.001$ ) were attributable to higher rates of asthma and atopy.

**Conclusions** Peri-urban adolescents had more asthma, atopy and airways inflammation and were exposed to more indoor pollution. The findings provide evidence of the risks posed to lung health by peri-urban environments in developing countries.

## INTRODUCTION

Asthma is widely recognised for its high prevalence and public health importance in developed countries.<sup>1</sup> It is estimated to affect 300 million individuals worldwide,<sup>2</sup> and its burden in disability-adjusted life years lost is comparable with that of diabetes mellitus or cirrhosis.<sup>2</sup> Risk factors for asthma include allergic symptoms,<sup>3–5</sup> atopy<sup>3</sup> and elevated total serum immunoglobulin E (IgE).<sup>6</sup> Urbanisation has become recognised as an important contributor to childhood asthma.<sup>7–9</sup> Some purport that urbanisation leads to increased asthma due to higher levels of air pollution including particulate matter (PM),<sup>10</sup>

## Key messages

## What is the key question?

► We wanted to know whether the trend for increased urbanisation in developing countries could account in part for the increasing prevalence and morbidity of asthma.

## What is the bottom line?

► Our study showed that adolescents living in a peri-urban environment had increased levels of atopy, asthma and airway inflammation compared with their counterparts living in a rural environment.

## Why read on?

► The peri-urban environment of Lima conveyed a nearly threefold increased risk of current asthma. The higher levels of indoor air pollution may contribute to these findings.

while others have pointed to changes in diet.<sup>11 12</sup> Others hypothesise that exposure to fewer parasitic infections or a greater number of viral infections early in life while the immune system is developing may play a role in asthma risk.<sup>9</sup> As many major urban centres in the developing world are undergoing rapid growth accompanied by increases in outdoor air pollution, the incidence and burden of asthma are also likely to increase.

The effect of urbanisation on asthma risk is well known; however, few studies have been conducted in low- and middle-income countries. Moreover, unique exposures in developing countries such as to biomass fuels, peri-urban sprawl and inadequate water and sanitation warrant further consideration. Three African studies point to an urban environment as an important risk factor in developing countries.<sup>13–15</sup> Urban asthma prevalence ranged from 4% to 23% in these studies, and the increase in odds from rural to urban environments ranged between 1.5 and 4. These rates of asthma are in agreement with the region's results in the International Study of Asthma and Allergies in Childhood (ISAAC).<sup>1</sup> Peru is reported to have one of the highest prevalences of asthma worldwide.<sup>1</sup> ISAAC reported that 48% of adolescent children had ever wheezed and 26% had experienced wheezing within the previous year. A study in a Lima shanty town

reported that 21% of children ever had asthma-related symptoms, and 23% showed a decrease in forced expiratory volume in 1 s (FEV<sub>1</sub>) postexercise.<sup>16</sup> However, these studies were conducted in urban areas of Lima, where one-third of the population lives. There remains limited information on asthma in other regions of Peru or on risk factors driving this high burden of disease in Lima. We hypothesised that children living in a peri-urban setting would have a higher risk of asthma symptoms, allergy and airways inflammation than their rural counterparts.

## METHODS

We provide an abbreviated description of our data collection methods. Additional detail is provided in an online supplement.

### Study setting

We conducted our study in two coastal regions of Peru. Pampas de San Juan de Miraflores is a peri-urban shanty town in Lima with high population density centred on a heavily trafficked avenue. Tumbes is located in northern Peru near the Ecuador border and has little traffic and migration. We conducted our study in a cluster of 23 rural villages outside Tumbes city.

### Study subjects

In Lima, we invited an age- and sex-stratified sample of adolescents 13–15 years of age to participate. In Tumbes, we invited all 13- to 15-year-old adolescents in the above 23 villages. Inclusion and exclusion criteria are detailed in the online supplement.

### Study design

We carried out home visits to enrol participants, administer the survey and perform physical testing. During the first visit, we asked about asthma and allergy symptoms using a validated questionnaire,<sup>17</sup> asthma medications use, biomass fuel exposures and sociodemographics.

We conducted physical testing during a second visit. After measuring height and weight, we conducted spirometry presalbutamol and postsalbutamol according to standard guidelines.<sup>18</sup> We measured exhaled nitric oxide (eNO) levels in parts per billion (ppb) and applied allergy skin tests for cockroach, dust mite mix, cat hair, dog epithelium, mouse epithelium and mixed moulds. We measured approximate PM<sub>2.5</sub> concentrations (µg/m<sup>3</sup>) for 48 h using a portable nephelometer in a random subset of 100 households in Lima and 70 in Tumbes. We obtained outdoor PM data in Lima from DIGESA (<http://www.digesa.sld.pe>).

This study was approved by the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health in Baltimore, USA, and AB PRISMA in Lima, Peru.

### Definitions

We defined current asthma symptoms as wheezing or asthma medication use in the past year; atopy as a positive test to one or more skin test allergens; and reversibility as a ≥12% increase in FEV<sub>1</sub> from presalbutamol to postsalbutamol.<sup>18</sup> We graded asthma severity as per National Asthma Education Prevention Program guidelines.<sup>19</sup>

### Biostatistical methods

We used standard statistical methods for the calculation of ORs and  $\chi^2$  tests. We used logistic regression analysis to model the effect of multiple variables on the risk of asthma. We conducted analyses in R (<http://www.r-project.org>) and STATA 10. These methods are discussed in detail in the online supplement.

## RESULTS

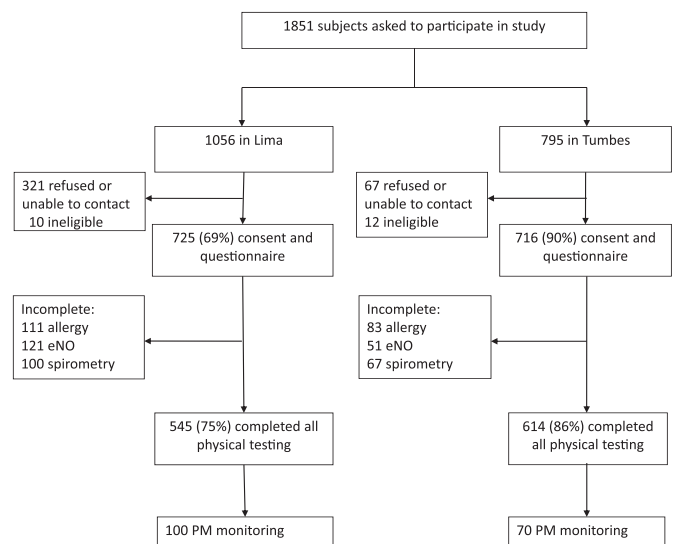
### Baseline characteristics

Of 1851 adolescents identified from census data, we enrolled 1441 (78%) during the first visit (figure 1). Seven hundred and twenty-five adolescents in Lima and 716 in Tumbes responded to our survey. Of those enrolled, 545 (75%) in Lima and 614 (86%) in Tumbes completed all aspects of physical testing. A total of 625 (86%) participants in Lima and 649 (91%) in Tumbes completed spirometry. There were no important differences in the distributions of sex or age by site (table 1). Body mass index (BMI) was greater in Lima than in Tumbes. Girls were taller in Tumbes than in Lima. Household incomes were lower in Tumbes than in Lima, as almost threefold more households reported total earnings of <US\$175 per month. Fewer households in Tumbes had private sanitation facilities (27% vs 92%,  $p<0.001$ ).

Six hundred and ninety-eight (96%) of the Lima adolescent participants had lived in Lima since birth, and >99% had lived in the study community for ≥5 years. A total of 661 (92%) of the Tumbes adolescent participants had lived in Tumbes since birth, and >99% have lived in the study community for ≥5 years. Immigration, however, was common among parents of Lima adolescents. Of the Lima participants, 556 (77%) had at least one parent that had emigrated from the highlands. In contrast, 564 (79%) of the Tumbes participants had both parents who were born in Tumbes. A greater proportion of peri-urban participants reported spending at least 11 h a day at home than did their rural counterparts (70% vs 60%;  $p<0.001$ ).

### Asthma symptoms

All indicators of asthma symptoms were 2–3 times greater in Lima (table 2). The onset of asthma symptoms occurred at an earlier age in Lima. There were no differences in lifetime or current asthma symptoms or age of onset between boys and girls at either site (all  $p \geq 0.12$ ). The most common precipitants of asthma symptoms were upper respiratory infections and exercise. There were no differences in asthma severity between sites (table 3). Approximately 50% of those with asthma were mild intermittent (table 3). A greater proportion of participants in Tumbes with asthma symptoms required emergency visits to hospitals or health centres, and fewer used inhaled



**Figure 1** Flow diagram of recruitment, questionnaires and procedures in Lima and Tumbes, Peru; 2009–2010. eNO, exhaled nitric oxide; PM, particulate matter.

**Table 1** Comparison of personal characteristics, sociodemographics and exposures of adolescents aged 13–15 in urban Lima and rural Tumbes; Peru 2009–2010

	Lima	Tumbes	p Value
No. of participants	725	716	
No. of males (%)	355 (49%)	387 (54%)	0.06
Mean age in years (SD)	14.9 (0.9)	14.9 (0.9)	1.00
Born in site	696 (96%)	659 (92%)	0.002
Both parents born in site	84 (11.6%)	564 (78.8%)	<0.001
≥1 parent from highlands	556 (76.7%)	20 (2.8%)	<0.001
≥1 parent from rainforest	17 (2.3%)	3 (0.4%)	<0.001
Income <175 US\$/month	181 (25%)	451 (63%)	<0.001
Electricity 24 h/day	722 (100%)	612 (85%)	<0.001
Water 24 h/day	668 (92%)	40 (6%)	<0.001
Concrete as predominant floor material	272 (37.5%)	398 (55.9%)	<0.001
Propane gas as main fuel for cooking	705 (97.2%)	609 (85.1%)	<0.001
Regular use of wood-burning stoves	72 (8.6%)	301 (42.0%)	<0.001
Mean number of people per house (SD)	5.7 (1.9)	5.1 (1.6)	<0.001
Households with ≥6 residents (%)	355 (49%)	212 (30%)	<0.001
Mean no. of rooms per house (SD)	4.9 (1.8)	4.9 (1.2)	1.00
Time spent inside house			<0.001
0–6 h per day	20 (2.8%)	14 (2.0%)	
7–10 h per day	198 (27.3%)	271 (37.8%)	
11–15 h per day	507 (69.9%)	428 (59.8%)	
≥15 h per day	0 (0%)	3 (0.4%)	
Sanitation facilities in home			<0.001
Private	668 (92.1%)	197 (27.2%)	
Latrine	0 (0.0%)	170 (23.7%)	
Blind hole	32 (4.4%)	212 (27.8%)	
Open field	0 (0.0%)	113 (15.8%)	
Household owns car	95 (13.1%)	70 (9.7%)	0.06
Household owns land line telephone	446 (61.5%)	74 (10.3%)	<0.001
Household owns cellular telephone	628 (86.6%)	658 (91.9%)	0.002
Mean paternal education in years (SD)	9.8 (3.1)	8.5 (4.2)	<0.001
Mean maternal education in years (SD)	8.2 (3.7)	8.2 (4.1)	<0.001
Height (cm)*	(n=651)	(n=661)	
Boys, mean (SD, Z-score)	162.0 (7.4); z=1.0	163.1 (8.3); z=0.9	0.07
Girls, mean (SD, Z-score)	152.8 (5.5); z=1.5	155.1 (5.7); z=1.0	<0.001
Weight (kg)	(n=651)	(n=661)	
Boys, mean (SD)	56.5 (11.2)	53.5 (10.2)	<0.001
Girls, mean (SD)	52.1 (9.4)	51.1 (8.1)	0.15
Body mass index*	(n=651)	(n=661)	
Boys, mean (SD, percentile)	21.4 (3.3);65th	20.0 (2.8);50th	0.001
Girls, mean (SD, percentile)	22.3 (3.5);75th	21.2 (3.1);60th	<0.001
Haematocrit	(n=552)	(n=579)	
Boys, mean (SD)	44.9 (3.1)	42.6 (2.8)	<0.001
Girls, mean (SD)	41.0 (2.9)	39.2 (2.4)	<0.001

\*Z-scores and percentiles as per 2007 WHO reference.

corticosteroids or long-acting  $\beta$ -agonists for asthma control compared with those in Lima.

Adolescents with current asthma symptoms were equally likely to have a lifetime history of rhinitis across sites (table 3). Among those with asthma, the rate of atopy was greater in Lima than in Tumbes (77% vs 56%, respectively); however, this increase only trended towards significance ( $p=0.09$ ). Adolescents in Lima without current asthma symptoms had a greater prevalence of lifetime rhinitis or atopy than adolescents in Tumbes. Overall, there was a higher prevalence of eczema and a greater number of positive allergen skin tests in Lima than in Tumbes, regardless of asthma symptoms. Rhinitis in the past 12 months, eczema in the past 12 months, atopy and being overweight (BMI >25) were all predictors of current asthma symptoms in Lima in both the unadjusted and multivariable analyses (table 4). In Tumbes, where we had fewer participants with

current asthma symptoms ( $n=22$ ), we identified rhinitis in the past 12 months as the only significant predictor of current asthma symptoms. When we pooled data from both sites, rhinitis in the past 12 months, atopy and being overweight remained important predictors of current asthma symptoms (table 4). The peri-urban environment of Lima was associated with a 2.6-fold greater odds (OR 2.6, 95% CI 1.3 to 5.3) of current asthma after controlling for atopy, allergy symptoms, environmental exposures, household size, sanitation and socio-demographics. We did not find interactions between urbanisation status and: atopy ( $p=0.38$ ), rhinitis ( $p=0.14$ ) or being overweight ( $p=0.67$ ).

#### Allergic symptoms

Self-reported symptoms of allergic rhinitis were almost twice as prevalent among participants in Lima as among those in Tumbes

**Table 2** Differences in asthma, allergic symptoms and atopy between Lima and Tumbes; Peru 2009–2010

	Lima (n = 725)	Tumbes (n = 716)	p Value
<b>Asthma</b>			
Lifetime wheezing	157 (21.7%)	68 (9.5%)	<0.001
Lifetime exercise-induced wheezing	58 (8%)	16 (2.2%)	<0.001
Lifetime night-time, non-productive cough	62 (8.6%)	30 (4.2%)	<0.001
Lifetime physician diagnosis of asthma	94 (13%)	16 (2.2%)	<0.001
Age at onset of symptoms, years	7.1 (4.6)	8.4 (4.1)	0.05
<b>Current asthma</b>			
Wheezing in the past 12 months	84 (11.6%)	22 (3.1%)	<0.001
Use of medications for asthma control in the past 12 months	73 (10.1%)	20 (2.8%)	<0.001
37 (5.1%)	11 (1.5%)	<0.001	
<b>Rhinitis</b>			
Lifetime rhinitis symptoms	189 (26.1%)	98 (13.7%)	<0.001
Rhinitis symptoms in the past 12 months	166 (22.9%)	86 (12.0%)	<0.001
Physician diagnosis of rhinitis	25 (3.4%)	9 (1.3%)	0.01
Parental rhinitis	150 (20.7%)	28 (3.9%)	<0.001
<b>Eczema</b>			
Lifetime eczema symptoms	113 (15.6%)	7 (1.0%)	<0.001
Eczema symptoms in the past 12 months	90 (12.4%)	3 (0.4%)	<0.001
Physician diagnosis of eczema	44 (6.1%)	10 (1.4%)	<0.001
Parental eczema	112 (15.4%)	19 (2.7%)	<0.001

(table 2). A physician diagnosis of rhinitis was exceptionally rare at either site despite a high proportion of symptom reporting among study participants. Parental rhinitis was fivefold higher in Lima, and in both sites it was a risk factor for rhinitis among offspring (OR 3.0, 95% CI 2.2 to 4.2). Eczema was more prevalent in Lima than in Tumbes (table 2). As with rhinitis, a physician diagnosis of eczema was low despite high symptom rates. Atopy was significantly higher in Lima than in Tumbes (56% vs 38%,  $p < 0.001$ ). The odds of atopy were not increased by having at least six residents in the household, a measure we used as a surrogate for sibling number in either Tumbes (OR 1.3, 95% CI 0.9 to 1.9) or Lima (OR 1.0, 95% CI 0.8 to 1.4).

### Spirometry and postbronchodilator reversibility

Six hundred and twenty-five (86%) participants in Lima and 649 (91%) in Tumbes completed spirometry according to standard quality criteria. FEVs were significantly greater in Lima than in Tumbes (table 5). These differences remained even after controlling for age and height within each sex group (all  $p < 0.001$ ). FEV<sub>1</sub>/forced vital capacity (FVC) values were also lower in Lima than in Tumbes (eFigure 1 (see online)). Reversibility was higher in Lima, but it did not achieve statistical significance (table 5).

### Airways inflammation

Mean eNO levels were significantly higher in Lima than in Tumbes (21.9 vs 17.6 ppb;  $p < 0.001$ ). Current asthma symptoms, rhinitis in the past 12 months and atopy increased mean eNO levels at both sites (all  $p < 0.001$ ). eNO measurements conducted in the spring were also higher than measurements conducted in the autumn at both sites ( $p \leq 0.05$ ). Otherwise, there was considerable heterogeneity in the effect of multiple predictors on eNO across sites (eTable 1 (see online)). After adjusting for asthma and atopy in multivariable regression, we found that there was no difference in eNO by site ( $p = 0.47$ ). In multivariable regression, there was a multiplicative interaction

**Table 3** Asthma severity, burden and relationship with atopy among those with current asthma in Lima and Tumbes; Peru 2009–2010

Asthma	Lima (n = 84)	Tumbes (n = 22)	p Value
<b>Severity</b>			
Mild intermittent	44 (52.4%)	12 (54.5%)	0.44
Mild persistent	18 (21.4%)	4 (18.2%)	
Moderate persistent	18 (21.4%)	3 (13.6%)	
Severe persistent	4 (4.8%)	3 (13.6%)	
Any emergency visits in the past 12 months	24 (28.6%)	10 (45.5%)	0.21
<b>Rescue medication use</b>			
Never	34 (40.5%)	10 (45.5%)	0.86
<1 use per week	49 (58.3%)	12 (54.5%)	
1–3 uses per week	6 (7.1%)	5 (22.3%)	
>3 uses per week	14 (16.7%)	3 (13.6%)	
Any medication use in the past 12 months	29 (31.1%)	11 (50.0%)	0.28
Short-acting bronchodilator	28 (33.3%)	10 (45.5%)	0.42
Long-acting bronchodilator	0 (0%)	0 (0%)	1
Inhaled corticosteroid	3 (3.6%)	0 (0%)	1
Oral corticosteroid	21 (25.0%)	2 (9.1%)	0.15
<b>Allergy and asthma</b>			
Overall skin test positivity	(n=614) 342 (55.7%)	(n=630) 242 (38.4%)	<0.001
<b>Allergy in asthmatics</b>			
Lifetime rhinitis symptoms	(n=84) 45 (53.6%)	(n=22) 13 (59.1%)	0.83
Lifetime eczema symptoms	22 (26.2%)	1 (4.5%)	0.04
<b>Skin test positivity</b>			
≥ 1	(n=74) 57 (77.0%)	(n=20) 11 (55.9%)	0.09
≥ 2	46 (62.2%)	7 (35.0%)	0.06
≥ 3	30 (40.5%)	4 (20.0%)	0.12
<b>Allergy in non-asthmatics</b>			
Lifetime rhinitis symptoms	(n=641) 151 (23.2%)	(n=694) 88 (12.7%)	<0.001
Lifetime eczema symptoms	107 (16.4%)	15 (2.2%)	<0.001
<b>Skin test positivity</b>			
≥ 1	(n=540) 285 (52.8%)	(n=610) 231 (37.9%)	<0.001
≥ 2	188 (34.8%)	119 (19.5%)	<0.001
≥ 3	111 (21.1%)	41 (6.7%)	<0.001

between the current asthma symptoms and atopy on eNO levels (table 6;  $p = 0.04$  for Lima and  $p < 0.001$  for Tumbes).

### Household exposures

The primary source of cooking fuel was propane gas at both sites (table 1). A greater proportion of households used wood-burning stoves for cooking on a daily or semi-daily basis in Tumbes than in Lima (42% vs 8.6%;  $p < 0.001$ ). While propane gas stoves were used exclusively indoors, wood-burning stoves were generally used outside of the house (data not shown). Tumbes adolescents had higher rates of secondhand smoking exposure versus Lima adolescents (20.3% vs 12.8%, respectively;  $p < 0.001$ ). A greater proportion of adolescents reported ever smoking in Lima than in Tumbes (7.4% vs 2.2%, respectively;  $p < 0.001$ ).

Median concentrations of indoor PM in Lima were ~2.4-fold higher than those in Tumbes (31  $\mu\text{g}/\text{m}^3$  vs 13  $\mu\text{g}/\text{m}^3$ ;  $p < 0.001$ ; figure 2). We speculate that indoor pollution levels probably reflect outdoor pollution levels at both sites for two reasons. First, most houses regularly left open doors (73% in Lima and 97% in Tumbes) or windows (75% in Lima and 94% in Tumbes) during the daytime year-round, and on average there were two



**Table 4** Multivariable analysis on the odds of current asthma symptoms stratified by study site; Peru, 2009–2010

Exposure	Lima (n=725)				Tumbes (n=716)				Mantel–Haenszel OR (95% CI)	Pooled multivariable OR (95% CI)
	% Asthma in unexposed	% Asthma in exposed	Unadjusted OR (95% CI)	Multivariable OR (95% CI)	% Asthma in unexposed	% Asthma in exposed	Unadjusted OR (95% CI)	Multivariable OR (95% CI)		
Rhinitis in past 12 months	7.3%	25.9%	4.4 (2.7 to 7.3)	3.7 (2.2 to 6.5)	1.4%	15.1%	12.1 (5.0 to 30.7)	11.4 (3.9 to 33.1)	5.3 (3.5 to 8.1)	4.8 (3.0 to 7.6)
Eczema in past 12 months	10.1%	21.1%	2.4 (1.3 to 4.3)	2.1 (1.1 to 4.1)	3.1%	0.0%				
Atopy	6.3%	16.7%	3.0 (1.7 to 5.6)	2.5 (1.4 to 4.5)	2.3%	4.5%	2.0 (0.7 to 5.6)	1.8 (0.7 to 4.8)	2.7 (1.7 to 4.4)	2.2 (1.3 to 3.7)
BMI (kg/m <sup>2</sup> ) >25	10.4%	21.7%	2.4 (1.3 to 4.2)	2.5 (1.4 to 4.5)	2.8%	7.0%	2.6 (0.6 to 8.5)	1.3 (0.3 to 5.5)	2.4 (1.5 to 3.9)	2.2 (1.3 to 3.8)
Income <US\$175/month	10.9%	13.6%	1.3 (0.7 to 2.2)	1.4 (0.7 to 2.5)	4.9%	2.0%	0.4 (0.1 to 1.0)	0.3 (0.1 to 0.9)	0.9 (0.6 to 1.5)	0.9 (0.5 to 1.6)
Concrete floor	11.9%	11.0%	0.9 (0.5 to 1.5)	0.7 (0.4 to 1.2)	2.2%	3.8%	1.7 (0.7 to 5.1)	1.6 (0.6 to 4.4)	1.1 (0.7 to 1.6)	0.8 (0.5 to 1.3)
6+ people/house	10.8%	12.4%	1.2 (0.7 to 1.9)	1.1 (0.6 to 1.9)	2.5%	4.2%	1.7 (0.6 to 4.3)	1.2 (0.4 to 3.5)	1.3 (0.8 to 1.9)	1.1 (0.7 to 1.8)
Maternal primary schooling	19.0%	10.0%	0.7 (0.4 to 1.3)	0.9 (0.5 to 1.7)	1.4%	3.7%	2.7 (0.8 to 14.3)	2.2 (0.6 to 8.5)	0.9 (0.6 to 1.5)	1.1 (0.6 to 1.9)
Wood stove	11.3%	14.5%	1.3 (0.6 to 2.9)	1.7 (0.7 to 4.0)	3.1%	3.1%	1.0 (0.4 to 2.4)	2.3 (0.7 to 7.1)	1.1 (0.6 to 2.0)	1.6 (0.8 to 3.1)
Personal smoke	12.0%	15.6%	1.3 (0.5 to 3.2)	1.3 (0.5 to 3.5)	3.6%	0.0%				
Secondhand smoke	12.1%	9.2%	0.7 (0.3–1.5)	0.7 (0.3 to 1.4)	3.8%	0.6%				
Private sanitation	8.8%	11.8%	1.4 (0.5 to 4.6)	1.9 (0.6 to 6.2)	2.5%	4.5%	1.8 (0.7 to 4.7)	0.6 (0.2 to 1.9)	1.6 (0.8 to 3.1)	1.3 (0.6 to 2.8)
1+ parent from highlands	11.8%	11.5%	1.0 (0.6 to 1.7)	0.9 (0.5 to 1.8)	3.6%	0.0%				
Peri-urban environment										2.6 (1.3 to 5.2)

All variables included in each of the multivariable models are listed under the exposure column. BMI, body mass index.

windows and 1.4 doors left open at all times. Secondly, average 24 h outdoor PM<sub>2.5</sub> concentrations in Lima were similar to indoor levels at 38 µg/m<sup>3</sup> for 2009. Outdoor PM<sub>2.5</sub> concentrations were not available in Tumbes.

## DISCUSSION

Adolescents living in peri-urban Lima were at a much higher risk of having asthma and allergy symptoms than their rural counterparts in Tumbes. Specifically, asthma symptoms were

2–3 times greater in Lima alongside a twofold increase in allergic symptoms, a 50% increase in atopy and a 15-fold increase in eczema. Adolescents in Lima also had a lower FEV<sub>1</sub>/FVC than did those in Tumbes. While postbronchodilator reversibility was also more common in Lima, this increase did not achieve statistical significance. Higher rates of asthma symptoms and atopy in Lima were associated with greater airways inflammation. Adolescents in Lima were exposed to higher levels of indoor air pollution, were more likely to smoke, had a greater mean BMI and were more likely to live in households with adequate sanitation facilities than adolescents in Tumbes. Thus, urbanisation is linked to several factors that may help explain why we would expect to see more asthma and atopy in Lima than in Tumbes.

It is well recognised that urbanisation is an important risk factor for asthma in both developed and developing countries.<sup>9 13–15</sup> Most of the in-depth studies on urbanisation and asthma in developing countries have been conducted in Africa.<sup>21</sup>

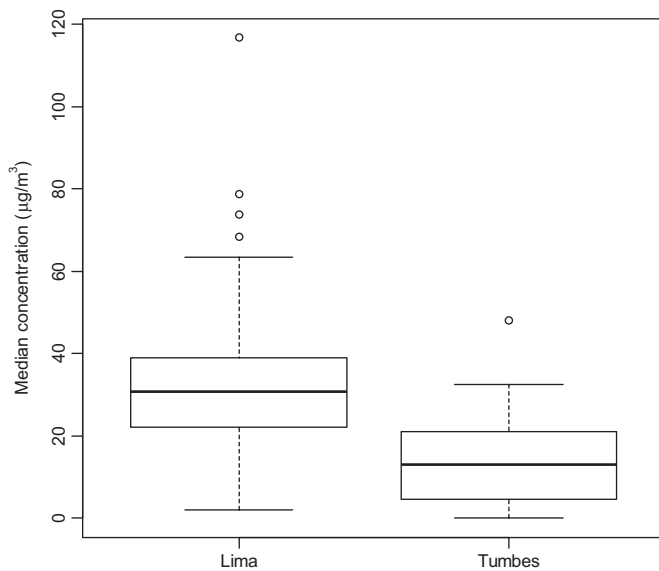
**Table 5** Comparison of forced expiratory volumes before and after bronchodilators in Lima and Tumbes; Peru, 2009–2010

	Lima (n=625)	Tumbes (n=649)	p Value
Sample size			
Boys	311	348	
Girls	314	301	
Mean pre-FVC in litres (SD)			
Boys	4.36 (0.7)	3.82 (0.7)	<0.001
% Predicted (SD)*	110% (13%)	94.2% (11%)	<0.001
Girls	3.46 (0.5)	3.08 (0.4)	<0.001
% Predicted (SD)*	109% (13%)	93.7% (12%)	<0.001
Mean pre-FEV <sub>1</sub> in litres (SD)			
Boys	3.83 (0.6)	3.44 (0.6)	<0.001
% Predicted (SD)*	111% (13%)	97% (12%)	<0.001
Girls	3.08 (0.4)	2.82 (0.4)	<0.001
% Predicted (SD)*	109% (12%)	97% (111%)	<0.001
Mean pre-FEV <sub>1</sub> /FVC % (SD)			
Boys	88% (6%)	90% (6%)	<0.001
Girls	89% (6%)	92% (6%)	<0.001
Reversibility, n (%)			
Boys	24 (3.8%)	15 (2.3%)	0.16
Girls	11 (3.5%)	9 (2.6%)	0.63
Girls	13 (4.1%)	6 (2.0%)	0.14

\*All the percentage predicted values are based on models from Hankinson *et al.*<sup>20</sup> for Mexican-Americans. FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

**Table 6** Exhaled nitric oxide levels stratified by current asthma symptoms and atopy in Lima and Tumbes; Peru, 2009–2010

	Mean	SD	N
Overall (n=1199)	19.5	22.2	1199
Asthma, atopy	52.6	52.3	64
Asthma, no atopy	25.5	29.9	25
No asthma, atopy	22.6	21.9	492
No asthma, no atopy	13.8	12.0	618
Tumbes (n=625)	17.6	19.0	625
Asthma, atopy	33.0	19.9	11
Asthma, no atopy	48.3	40.5	9
No asthma, atopy	22.9	23.7	229
No asthma, no atopy	13.1	13.1	376
Lima (n=574)	21.7	25.2	574
Asthma, atopy	56.7	56.0	53
Asthma, no atopy	12.7	8.1	16
No asthma, atopy	22.3	20.2	263
No asthma, no atopy	14.4	10.2	242



**Figure 2** Boxplots of median particulate matter concentrations (approximate  $PM_{2.5}$ ) in Lima and Tumbes; Peru 2009–2010.

A recent study conducted in Ghana found that urban poor adolescents had similar rates of exercise-induced bronchoconstriction to their rural counterparts, whereas wealthy urban adolescents had much higher rates.<sup>22</sup> In our study, unlike the study in Ghana, urban poor adolescents had a two- to three-fold greater risk of asthma symptoms. Meanwhile, there is limited published information on how urbanisation affects asthma symptoms or quantitative asthma phenotypes in Latin America and what unique exposures may drive differences in the prevalence of asthma across varying degrees of urbanisation. One study performed in Costa Rica found that sensitisation to *Ascaris lumbricoides* was associated with reductions in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC, increased airway responsiveness and a greater number of asthma hospitalisations.<sup>23</sup> Other studies have shown that the prevalence of asthma symptoms increases among Peruvian children living in areas of high traffic density,<sup>24</sup> and that higher levels of air pollutants were associated with higher rates of emergency room asthma visits in Mexico City.<sup>25</sup> In addition, the contributions of biomass fuels and indoor air pollution to asthma risk have not been carefully characterised in urban versus rural studies. In our study, we collected detailed information on biomass fuels and quantitative measurements of indoor PM. In Tumbes, nearly half of the households cooked with firewood on a daily or semi-daily basis. However, we did not observe a greater risk of asthma in adolescents who lived in households that used wood-burning stoves frequently. This may be because most wood-burning stoves in Tumbes were exclusively located outdoors. Since indoor PM concentrations were on average twice as great in Lima, outdoor biomass cooking did not appear to have a significant effect on indoor PM concentrations in Tumbes. As households in both sites had open connections to the environment year-round, we believe that these increased levels in Lima probably reflect high outdoor air pollution.

There are several risk factors that may help explain differences in asthma between our sites, such as obesity, diet and exposure to infections early in childhood. An increased BMI may be a consequence of a more sedentary lifestyle or changes in diet. In our study, overweight was a risk factor for asthma, which supports the conclusions of a recent systematic review.<sup>26</sup> Diet has also been implicated in the development of asthma.<sup>27</sup> Increased urbanisation can have a direct effect on changes in

diet; however, we did not collect diet information. It is also possible that differences in rates of infections between Lima and Tumbes may help explain differences in asthma. Participants in Tumbes were more likely to have less access to adequate sanitation facilities that may increase their risk of infection; however, we did not have information on past history or current history of infections, nor did we test for parasitic infections. A greater sibship size is thought to be protective against asthma. We did not collect data on sibship size; however, there was no relationship between household size and either asthma or atopy. We also did not assess for airways hyper-responsiveness. Airways hyper-responsiveness is a marker of asthma, and previous studies in developing countries have shown >20% rates of exercise-induced bronchoconstriction in urban areas.<sup>13 16</sup>

We were surprised to find that adolescents in Lima had 10–15% larger FEV<sub>1</sub>s than did those from Tumbes, accompanied by significantly larger percentage predicted values for FEV<sub>1</sub> and FVC. We initially speculated that this difference may have been related to parental origins as they could not be explained by differences in the distributions of age, height or sex. While >95% of adolescents from our Lima site were born in Lima, over three-quarters had at least one parent that had emigrated from high-altitude rural areas. It has been previously reported that lung volumes are elevated in both native highlanders and non-native individuals living in the highlands.<sup>28–30</sup> One possible explanation is that these children had a genetic predisposition to having greater lung volumes; however, this hypothesis needs further investigation. Despite these lung function differences, we did not see additional risk of asthma conveyed by having one or both parents from the highlands among Lima adolescents.

The peri-urban environment of Lima was associated with a 2.6-fold greater odds of current asthma after controlling for atopy, allergy symptoms, environmental exposures, household size, sanitation and sociodemographics. On the other hand, the risk of atopy only increased by 50%. This suggests that the higher prevalence of asthma in the peri-urban setting cannot be explained by the increase in atopy alone; there may be several contributing factors. For example, traffic in peri-urban Lima is poorly regulated and may be associated with an increased risk of both childhood asthma<sup>24 31</sup> and atopy.<sup>31</sup> Heavy traffic volumes also contribute to poor air quality. Our study found that indoor air pollution was also higher in Lima; however, we only collected indoor air pollution levels in a subset of households at both study sites and the relationship between environment and asthma and how it interacts with other risk factors such as genetic predisposition needs to be further explored. A higher rate of smoking alongside a higher prevalence of allergic rhinitis in peri-urban Lima may further predispose children to asthma symptoms.<sup>32</sup> A higher rate of smoking may also contribute to decreased effectiveness of inhaled corticosteroid therapy in asthmatics.<sup>33</sup>

While it has become clear that eNO may be less useful in the diagnosis of asthma,<sup>34</sup> it may be helpful in identifying participants with co-morbid asthma and atopy. In our study, eNO levels in Lima were higher because there was more asthma and atopy in this population. This corroborates recent findings,<sup>35</sup> meanwhile suggesting that atopic asthma may be more severe than non-atopic asthma or that it may even be a related but distinct process altogether.

In summary, we found that the peri-urban environment is a risk factor for asthma and atopy. As urban centres in developing countries continue to grow, governments can implement policies to curb the effects of rapid urbanisation and urban health exposures. In doing so, they will not only improve quality

of life for their urban inhabitants, but may also help curb the emerging asthma epidemic in many developing countries.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health in Baltimore, USA, and AB PRISMA in Lima, Peru.

**Contributors** All authors were involved in the study design and writing of the manuscript. CLR directly contributed to the study design, supervision of field activities in both Tumbes and Lima, and is responsible for data management and analysis, and writing of this manuscript. LMB contributed equally to the study design, administration of field work, and data management and analysis, and also contributed to the writing of the manuscript. RHG is the main investigator at the Lima site and provided technical support during the conduct of the study. KR, JMC and AG were the on-site study physicians who performed most physical testing and were extensively involved in administering field work. LC is the field work supervisor at the Lima site, and provided census data and technical support. GG is the physician supervisor for research activities at the Tumbes site, and provided census data and technical support. NNH and RAW contributed to the study design and provided technical support for the study. KCB contributed to the study design and provided logistical support for the study. PNB contributed to study design of the environmental measurements, and provided both technical support and equipment for our study. WC had ultimate oversight over the study design and administration, and was equally responsible for the analysis and writing of the manuscript.

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## **METHODS**

### **Study setting**

We conducted our study in two coastal regions of Peru: Lima and Tumbes. Pampas de San Juan de Miraflores is a peri-urban shanty town with high-population density centered on a heavily-trafficked avenue. Pampas currently has 57,000 inhabitants, many of whom are highland immigrants (1,2). Average ambient temperatures in Lima range from 17°C to 30°C. Relative humidity ranges from 55% to 80%. Mean annual precipitation is 50 mm per year. The Tumbes site is located along the Tumbes River near the Peru-Ecuador border and has low traffic and low migration. We conducted our study in 23 rural villages situated 3 to 35 kilometers from Tumbes city. Average ambient temperature in Tumbes ranges from 25°C to 33°C, relative humidity ranges between 55% and 80%, and precipitation can reach 2200 mm per year.

### **Study subjects**

Our target population was adolescents 13 to 15 years of age. We identified participants from censuses available in both communities. In Lima, we invited an age and sex random stratified sample of subjects from the census to participate in our study. In Tumbes, we invited all 13 to 15 year old adolescents in the first 23 villages along the Tumbes River to participate.

Adolescents were eligible to participate if they were capable of understanding or performing procedures, if their parents or guardians were capable of providing written informed consent and they were capable of providing assent; if they had no ocular, abdominal, or thoracic surgery in the last three months; and if they were not hospitalized for cardiac reasons in the last three months. Children were ineligible to participate if they had a chronic respiratory condition other than asthma such as cystic fibrosis or chronic lung disease of prematurity, if they were



pregnant, or if they had pulmonary tuberculosis or were currently receiving treatment for pulmonary tuberculosis. We recruited only one adolescent per household.

### **Study design**

We conducted a cross-sectional study of the prevalence of asthma in two regions of Peru between January 2009 and February 2010. We carried out home visitations to enroll participants, administer the survey, and perform physical testing. During the first visit, we asked about asthma and allergy symptoms using the previously validated Spanish ISAAC questionnaire in Peru (3). We also asked about use of asthma medications, asthma severity, biomass fuel exposures and sociodemographics.

We conducted all other tests during a second visit. We measured height with a locally-made stadiometer and weight with a digital scale (Seca, Hamburg, Germany). We conducted spirometry pre- and post-bronchodilator in accordance with joint guidelines from the European Respiratory Society and the American Thoracic Society (4). We used portable, handheld spirometers (SpiroPro, Jaeger/CareFusion, San Diego, USA). We allowed for a maximum of eight forced expiratory maneuvers to achieve three maneuvers that met acceptability and reproducibility criteria (4). We then administered four doses of inhaled salbutamol (100 $\mu$ g each) and repeated spirometry 15 minutes later. All maneuvers were performed seated upright and with a nose clip. Participants who did not meet quality criteria were revisited up to two more times on a different day and asked to repeat spirometry. We asked participants to withhold any short-acting bronchodilators within 8 hours and long-acting bronchodilators for 24-48 hours of testing unless clinically necessary; however, we did not have instances where this occurred. We

revisited participants who reported having a respiratory infection in the last two weeks on a later date.

We measured eNO levels in parts per billion (ppb) using the NIOX MINO portable eNO monitor (Aerocrine, New Providence, USA). We applied allergy skin prick tests for cockroach, dust mite mix, cat hair, dog epithelium, mouse epithelium, and mixed molds (ALK-Abello, Round Rock, USA) using the Multi-Test II allergen applicator (Lincoln Diagnostics, Decatur, USA). After 20 minutes, we recorded induration and erythema dimensions, presence of pruritis and pseudopodia. We interpreted results with an algorithm designed according to the manufacturer's recommendations. Briefly, an allergy skin test was considered positive if the sum of the vertical and horizontal dimensions of the induration was  $\geq 3$  mm than the negative control and if the sum of the vertical and horizontal dimensions of erythema was  $\geq 5$  mm larger than the negative control.

We measured 48-hour PM concentrations ( $\mu\text{g}/\text{m}^3$ ) on weekdays with a portable nephelometer (pDR-1000, Thermo Scientific, Franklin, MA, USA) operated in the passive mode, i.e., without an air-sampling pump. This device incorporates a pulsed, high output, near-infrared light emitting diode source (880 nm). The intensity of the light scattered over the forward angle by particles passing through the sensing chamber is linearly proportional to airborne PM concentration. The pDR-1000 detects particles of  $0.3 \mu\text{m}$  ( $\text{PM}_{0.3}$ ) to  $\text{PM}_2$  in size more efficiently than  $\text{PM}_2$  to  $\text{PM}_{10}$  (5–7); however, there is a high level of agreement between PM determined by the pDR-1000 and gravimetric measurements of  $\text{PM}_{2.5}$  (5, 7). Therefore, PM measured with the pDR-1000 is a good approximation for  $\text{PM}_{2.5}$ . We placed the pDR-1000 approximately 1.0 to 1.5 meters above the floor in the living room or main room in the house where adolescents spent most of their time. We measured relative humidity (RH) and temperature using the HOBO Data

Logger (Onset Corp., Bourne, USA) and PM measurements were adjusted by RH as previously described (8). In Lima, we randomly selected 100 participating households from 11 geographic zones based on 300-meter intervals from the main avenue. In Tumbes, we randomly selected 70 participating households from all 23 villages. Outdoor PM data in Lima were provided by DIGESA ([www.digesa.sld.pe](http://www.digesa.sld.pe)).

This study was approved by the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, USA, and A.B. PRISMA in Lima, Peru.

## **Definitions**

We defined participants as having current asthma symptoms if they reported wheezing in the past 12 months or if they used asthma medications in the past 12 months. We defined atopy as a positive test to one or more skin test allergens. We defined reversibility as a  $\geq 12\%$  increase in FEV<sub>1</sub> from pre- to post-salbutamol (4). We defined asthma severity as per National Asthma Education Prevention Program guidelines (9).

## **Biostatistical methods**

We used Chi-square tests or Fisher exact tests to compare differences in proportions in dichotomous or categorical outcomes between sites. We compared values of lung function between sites using linear regression adjusting for height and age in sex-stratified models. We used standard techniques to calculate unadjusted odds ratios for each risk factor to assess the odds of asthma stratified by site and used the Mantel-Haenszel procedure to estimate an overall summary odds ratio. We used logistic regression stratified by study site to assess the odds of current asthma symptoms as a function of multiple variables. We conducted a pooled

multivariable logistic regression to determine the contribution of peri-urban environment on the odds of asthma after controlling for all other exposures. We used a generalized linear model with a log-normal distribution stratified by site to determine factors that affected eNO. We compared the distribution of indoor PM concentrations using a Wilcoxon signed-rank test. We conducted our analyses in R ([www.r-project.org](http://www.r-project.org)) and STATA (StataCorp, College Station, USA).

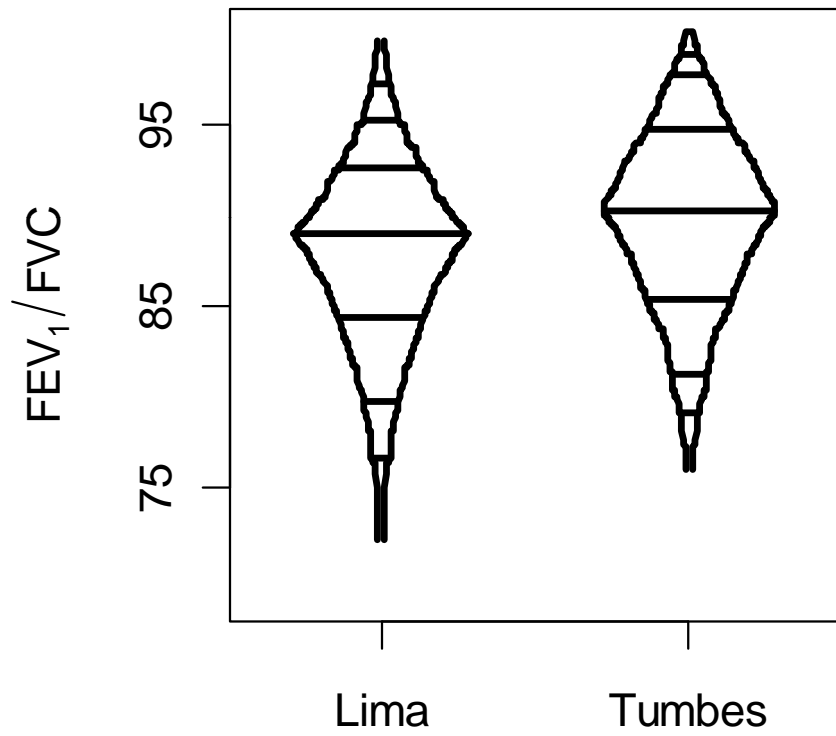
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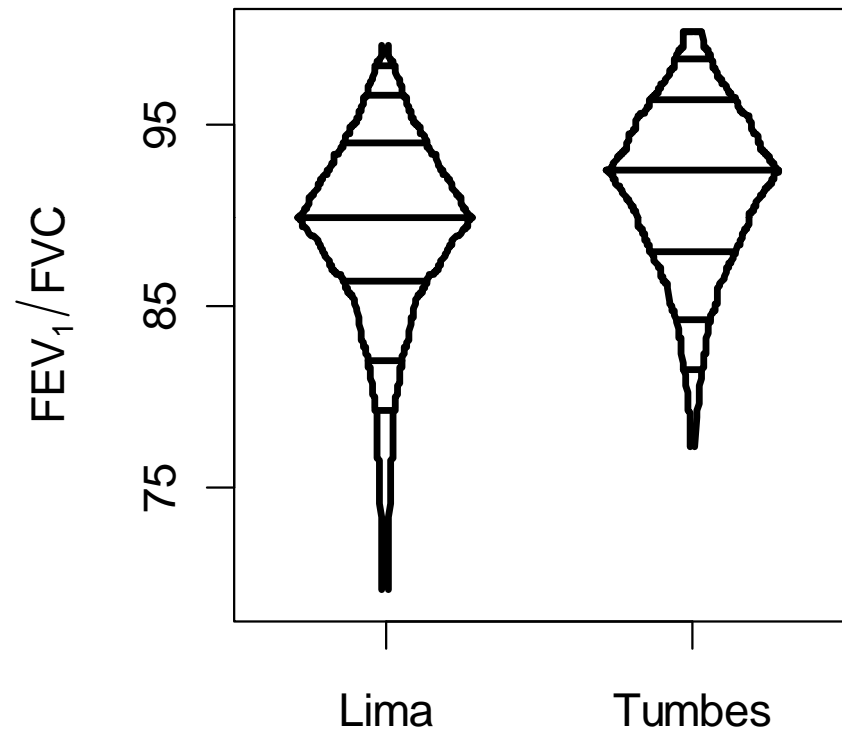


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### Boys



### Girls



**eFigure 1.**

**eTable 1. Multivariable analysis of exhaled nitric oxide (eNO) levels stratified by study site; Peru, 2009-2010.**

Exposure	Lima (n=604)		Tumbes (n=656)		Heterogeneity (p-value)
	Difference in mean log eNO	p-value	Difference in mean log eNO	p-value	
Current asthma symptoms	0.78	<0.001	0.49	<0.001	0.04
Rhinitis in past 12 months	0.45	<0.001	0.54	<0.001	0.82
Atopy	0.67	<0.001	0.45	<0.001	0.06
Eczema in past 12 months	-0.35	<0.01	-1.4	0.52	0.66
Age	0.17 per year	<0.001	-0.003 per year	0.94	0.03
Private sanitation facility	0.40	0.10	-0.32	<0.01	<0.01
Woodstove use	-0.65	<0.01	0.13	0.19	<0.01
Concrete floor	0.21	<0.01	-0.05	0.56	0.04
Mother had primary schooling	0.04	0.66	0.31	<0.01	1.0
BMI	0.01 per kg/m <sup>2</sup>	0.46	0.03 per kg/m <sup>2</sup>	0.03	0.34
Female sex	-0.18	0.07	-0.13	0.19	0.23
Height	0.04 per 10 cm	0.46	0.07 per 10 cm	0.25	0.11
Second hand smoke	-0.04	0.73	0.11	0.27	0.15
Personal smoking	0.27	0.02	-0.65	0.12	0.13
Measured in spring	0.12	0.41	0.09	0.41	0.43
Measured in summer	0.33	0.02	0.26	0.02	0.94
Measured in winter	0.11	0.47	-0.38	0.80	0.99
Income <175USD per month	-0.04	0.68	-0.12	0.19	0.18
1+ parent from highlands	0.15	0.12	0.10	0.62	0.78