



Altitude above 1500 m is a major determinant of asthma incidence. An ecological study

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ABSTRACT

Background: Previous studies suggest an inverse correlation between asthma and altitude. In the present work, we performed an in-depth analysis of asthma incidence in the 758 Mexican counties covered by the largest medical institution in the country (~37.5 million insured subjects), and evaluated its relationships with altitude and other factors.

Methods: Asthma incidence in each county was calculated from new cases diagnosed by family physicians. Other variables in the same counties, including selected diseases, geographical variables, and socioeconomic factors, were also obtained and their association with asthma was evaluated through bivariate and multivariate analyses. **Results:** Median asthma incidence was $296.2 \times 100,000$ insured subjects, but tended to be higher in those counties located on or near the coast. When asthma incidence was plotted against altitude, a two-stage pattern was evident: asthma rates were relatively stable in counties located below an altitude of ~1500 m, while these rates progressively decreased as altitude increased beyond this level ($r_s = -0.51$, $p < .001$). Multivariate analysis showed that, once each variable was adjusted by the potential influence of the others, asthma incidence was inversely correlated with altitude (standardized β coefficient, -0.577), helminthiasis (-0.173), pulmonary tuberculosis (-0.130), and latitude (-0.126), and was positively correlated with acute respiratory tract infection (0.382), pneumonia (0.289), type 2 diabetes (0.138), population (0.108), and pharyngotonsillitis (0.088), all with a $p \leq .001$.

Conclusion: Our study showed that altitude higher than ~1500 m comprises a major factor in determining asthma incidence, with the risk of new-onset asthma decreasing as altitude increases. Other less influential conditions were also identified.

1. Introduction

The pathogenesis of asthma has proven to be a very complex phenomenon involving a large array of conditions that appear to increase or decrease the risk for developing the disease. Traditionally, these conditions have been classified as genetic and environmental, the latter including exposure to allergens, tobacco smoke, endotoxins, industrial chemicals, air pollutants, viruses, bacteria, etc. [1]. In the mid 1990s, it was described that among the 32 Mexican states, the frequency of medical services provided to patients with asthma progressively declined as geographical altitude increased [2,3]. More recently, this

negative correlation has also been corroborated in this country for asthma incidence [4]. The inverse relationship between asthma and altitude is in agreement with the fact that asthma control and lung function greatly improve when patients with asthma move to a place or a sanatorium located at a relatively high altitude (> 1500 m) [5–7]. Thus, altitude above sea level appears to be an additional factor that deeply impacts on the development of asthma.

The Mexican Institute of Social Security (IMSS) is the largest medical institution in Mexico and it provides medical care to more than one half of the country's population. In 2012, this institute had about 56 million insured subjects in its ordinary insurance regimen, including

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workers and their parents, husbands or wives, and sons or daughters under 17 years of age. In that year, IMSS medical facilities comprised 1499 primary-level medical-care units, 273 secondary-level units, and 36 tertiary-level units, mainly located in counties with highest population densities. A strict regulation exists for the referral of patients to a secondary- or tertiary-level unit; thus, for any new disease the patients' first contact with the health system always corresponds to their family physicians in primary-level units. At the IMSS, this workforce includes more than 16,000 family physicians, who are specialists who spent a full 3-year residency for training in the diagnosis and treatment of the most frequent diseases occurring in the insured population. Moreover, family physicians are compelled to adhere to the institutional clinical practice guidelines, which in turn are in compliance with international guidelines. Each medical unit gathers information on every instance of medical care given to their insured population, including individual data on diseases diagnosed for the first time in a specific patient, i.e., newly diagnosed cases, and sends this information to the corresponding central units. Data coding according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) is carried out by technicians specialized in statistics and specifically trained for this task. Because new cases of a disease are registered only once by family physicians, when the number of new cases are adjusted by the insured population, the resulting data can be considered a surrogate of the incidence rate. In this institutional data base, it was impossible to evaluate prevalence because the same patient can have had several subsequent visits due to the same disease, which would lead to overestimation of prevalence.

The aims of the present work were the following: 1) to show a global scope of the geographical distribution of asthma incidence in all counties covered by the IMSS; 2) to evaluate the correlation between asthma incidence and altitude, and 3) to search for ecological associations between asthma incidence and other factors.

2. Methods

2.1. Study design

Nationwide data concerning first-time medical consultations provided by IMSS family physicians to patients of all ages was obtained and grouped by county. In order to improve data accuracy, a 6-year period (from 2007 to 2012) was analyzed. Data from each county were adjusted by dividing the number of new cases of each disease during that period by the cumulative number of insured subjects during the same period, expressing the result as rate $\times 100,000$ insured subjects. All data were age-adjusted by employing the standard population recommended by the World Health Organization [8]. Because only newly diagnosed cases were analyzed, in the present report data were considered as incidence rate. In addition to asthma (ICD-10 codes J45 and J46), other diseases that might have some biological or epidemiological bases for suspecting their involvement in asthma inception were also analyzed. In this context, we included some infectious or parasitic diseases in order to test their relationship with asthma according to the hygiene hypothesis [9]. These diseases take into account acute respiratory tract infections (J00 to J06, J20 and J21, except J02 and J03), acute pharyngitis/tonsillitis (J02 and J03), pneumonias (J12 to J18, except J18.2), pulmonary tuberculosis (A15 to A16), and helminthiasis including ascariasis, taeniasis, filariasis, trichuriasis, enterobiasis, and others (B65 to B83). Diabetes mellitus (E11 to E14), a disease that has been linked with obesity and asthma [10], was also analyzed.

Information on geographical variables (the counties' altitudes and latitudes) was obtained from the publicly available database of the National Institute of Statistics and Geography (INEGI) website (www.inegi.org.mx). Data concerning counties' temperatures was obtained from the National Water Commission (CONAGUA). Finally, data regarding socioeconomic variables (counties' population and marginality index) was obtained from the National Population Council (CONAPO)

website (www.gob.mx/conapo). The marginality index is a composite indicator that evaluates the following nine variables: percentage of subjects ≥ 15 years of age with 1) illiteracy or 2) less than full primary education; percentage of occupants of houses without 3) drainage or an exclusive toilet, 4) electricity, or 5) indoor water; percentage of occupants of houses with 6) earth floor or 7) some degree of overcrowding; 8) percentage of population living in communities with fewer than 5000 inhabitants, and 9) percentage of working population earning less than two minimal daily wages. In 2010, the marginalization index ranged from -2.3 (lowest level of marginalization) to 4.4 (highest level of marginalization).

2.2. Data analysis

Bivariate associations between asthma and other conditions were evaluated by means of the Spearman correlation coefficient and regression analysis. Because the relationship between altitude and asthma clearly revealed that a changepoint divided two different linear trends, a piecewise regression analysis, also known as segmented regression, was performed by using specialized software (Joinpoint Regression Program, v4.1.1, National Cancer Institute, USA). Finally, multiple linear regression was carried out to identify variables that predict asthma incidence. Individual values from some variables were log-transformed prior to their entry into the regression analysis to obtain better linearity. In some diseases, it was unclear whether zero values corresponded to real zero values or to missing data. Thus, among the 758 counties, all zero values in pulmonary tuberculosis (178 values), pharyngotonsillitis (63 values), and pneumonia (28 values) were treated as missing data, and the incidence for these counties was inferred through the average of up to 50 multiple-imputations performed with the *mi* command of Stata v13 (StataCorp, College Station, TX, USA). Statistical significance was set at two-tailed $p < .05$.

3. Results

First-time consultations provided by family physicians in each county were evaluated nationwide. Although the IMSS ordinary regimen only covered 758 (30.9%) of the nation's 2456 counties, a total of 78.4% of Mexican population reside in those counties. Persons included in the present study were those who were registered with a family physician, amounting to an average of 37.5 million subjects ($\sim 35\%$ of total Mexican population). The age distribution of the study population can be found in [Supplemental Fig. 1](#).

Asthma incidence rates ($\times 100,000$ insured subjects) across all studied counties ranged from 16.2 to 4030.8, with a median value of 296.2, and with the majority of counties having relatively low incidence rates ([Fig. 1](#)). Geographical distribution demonstrated that asthma incidence rates tended to be higher in counties located on or near the coast, although some counties in the northern region of Mexico also had high asthma rates ([Fig. 2](#), and [Supplemental Fig. 2](#)). When asthma incidence was correlated with the county's altitude above sea level, a two-stage pattern was evident ([Fig. 3](#)). Thus, asthma incidence was maintained relatively constant up to an altitude of ~ 1500 m altitude, with a progressive decline thereafter. The piecewise regression analysis ([Table 1](#)) showed that the joinpoint, i.e., the point at which a statistically significant change in the trend occurred, was located at an altitude of 1539 m. Although the Spearman correlation between asthma incidence and altitude for counties below the cut-off point of 1539 m altitude was statistically significant ($r_s = -0.18$, $p = .002$), this association was much more evident for the 304 (40.1%) counties located above an altitude of 1539 m ($r_s = -0.51$, $p < .001$).

As can be observed in [Table 2](#), the county-based (ecological) evaluation utilizing *bivariate analysis* revealed a statistically significant correlation between asthma and the majority of communicable diseases, especially acute respiratory tract infections ($r_s = 0.52$), pneumonia ($r_s = 0.52$), and diabetes ($r_s = 0.43$). Pulmonary tuberculosis,

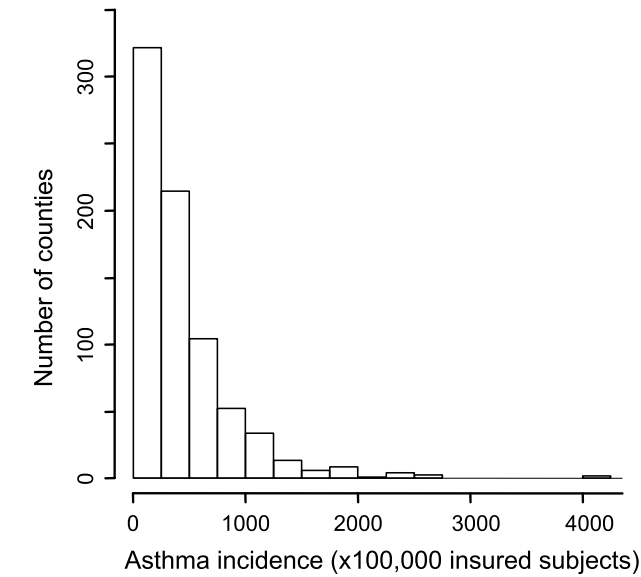


Fig. 1. Histogram showing the number of Mexican counties according to their asthma incidence rates ($\times 100,000$ insured subjects).

helminthiasis, and pharyngitis/tonsillitis also had a positive correlation with asthma. The bivariate analysis also demonstrated that the geographical or weather factor with the strongest (inverse) correlation with asthma was altitude ($r_s = -0.53$), followed by mean maximal temperature ($r_s = 0.50$). The relationship between asthma incidence and sociodemographic variables disclosed an inverse correlation of asthma with total population in the county ($r_s = -0.30$) and a positive correlation with marginalization ($r_s = 0.26$).

A somewhat different scenario emerged when *multivariate analysis* was employed to assess the direction and strength of the association of asthma with other variables. As compared with the bivariate analysis, once each variable was adjusted for the potential influence of the

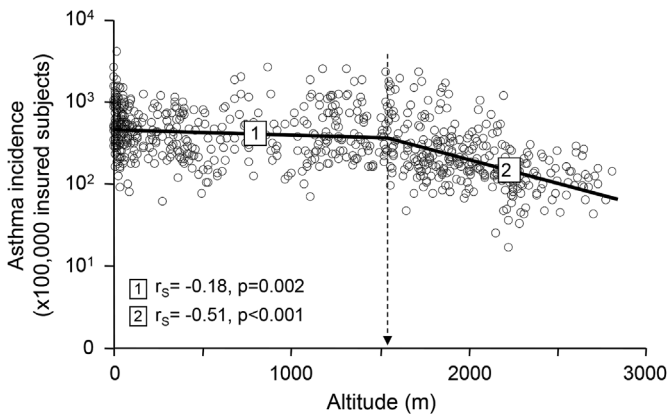


Fig. 3. Correlation of asthma incidence with altitude in 758 Mexican counties. Note the changepoint of the asthma/altitude regression line at 1539 m in altitude (broken arrow).

Table 1
Parameters estimated by piecewise regression analysis relating altitude (x-axis) and log-transformed asthma incidence (y-axis).

Parameter	Parameter estimate	Standard error	z	p
<i>Initial regression</i>				
Intercept	2.648	0.020	134.206	< .0001
Slope	-0.000057	0.000028	-2.065	.039
<i>Final regression</i>				
Intercept	3.440	0.116	29.683	< .0001
Slope	-0.000572	0.000056	-10.141	< .0001

The joinpoint (i.e., the best-fitting point where a change in the trend occurred) was calculated by the piecewise regression to occur at 1539 m altitude.

remaining variables in the final multiple linear regression model, some conditions (pulmonary tuberculosis, helminthiasis, and population) switched the direction of their association with asthma (Table 2). Likewise, in this multivariate analysis, other conditions (mean maximal

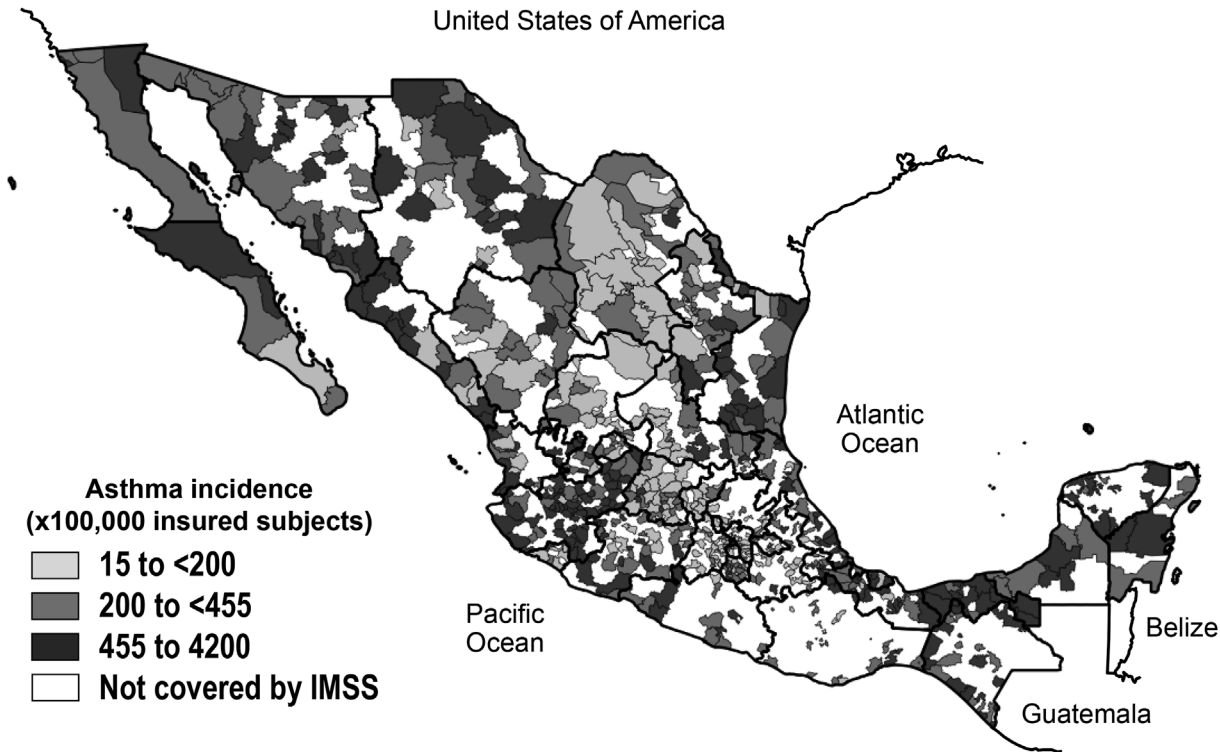


Fig. 2. Geographical distribution of asthma incidence rates in 758 Mexican counties covered by the Instituto Mexicano del Seguro Social (IMSS).

Table 2

Bivariate and multivariate analysis for prediction of log-transformed asthma incidence.

Asthma ^a vs	Bivariate analysis		Multivariate linear regression			
	Spearman Rho	p	β-coefficient (× 1000)	Standard error (× 1000)	Standardized β-coefficient	p
Comorbidities						
ARTI	0.523	< .001	0.0136	0.0012	0.382	< .001
Pneumonia ^a	0.517	< .001	280.382	28.993	0.289	< .001
Diabetes ^a	0.434	< .001	205.934	45.100	0.138	< .001
Pulmonary tuberculosis ^a	0.333	< .001	−115.497	27.554	−0.130	< .001
Helminthiasis ^a	0.289	< .001	−118.967	24.660	−0.173	< .001
Pharyngotonsillitis ^a	0.262	< .001	57.060	16.548	0.088	.001
Geographical or weather factors						
Altitude	−0.534	< .001	−0.240	0.0137	−0.577	< .001
Mean maximum temperature	0.498	< .001	---	---	---	---
Latitude	0.028	.447	−12.779	3.192	−0.126	< .001
Socioeconomic factors						
Population ^a	−0.298	< .001	71.021	19.430	0.108	< .001
Marginalization index	0.257	< .001	---	---	---	---

^a For the multivariate linear regression, individual values were log-transformed for better linearity. ARTI = acute respiratory tract infections. — = not included in the final model.

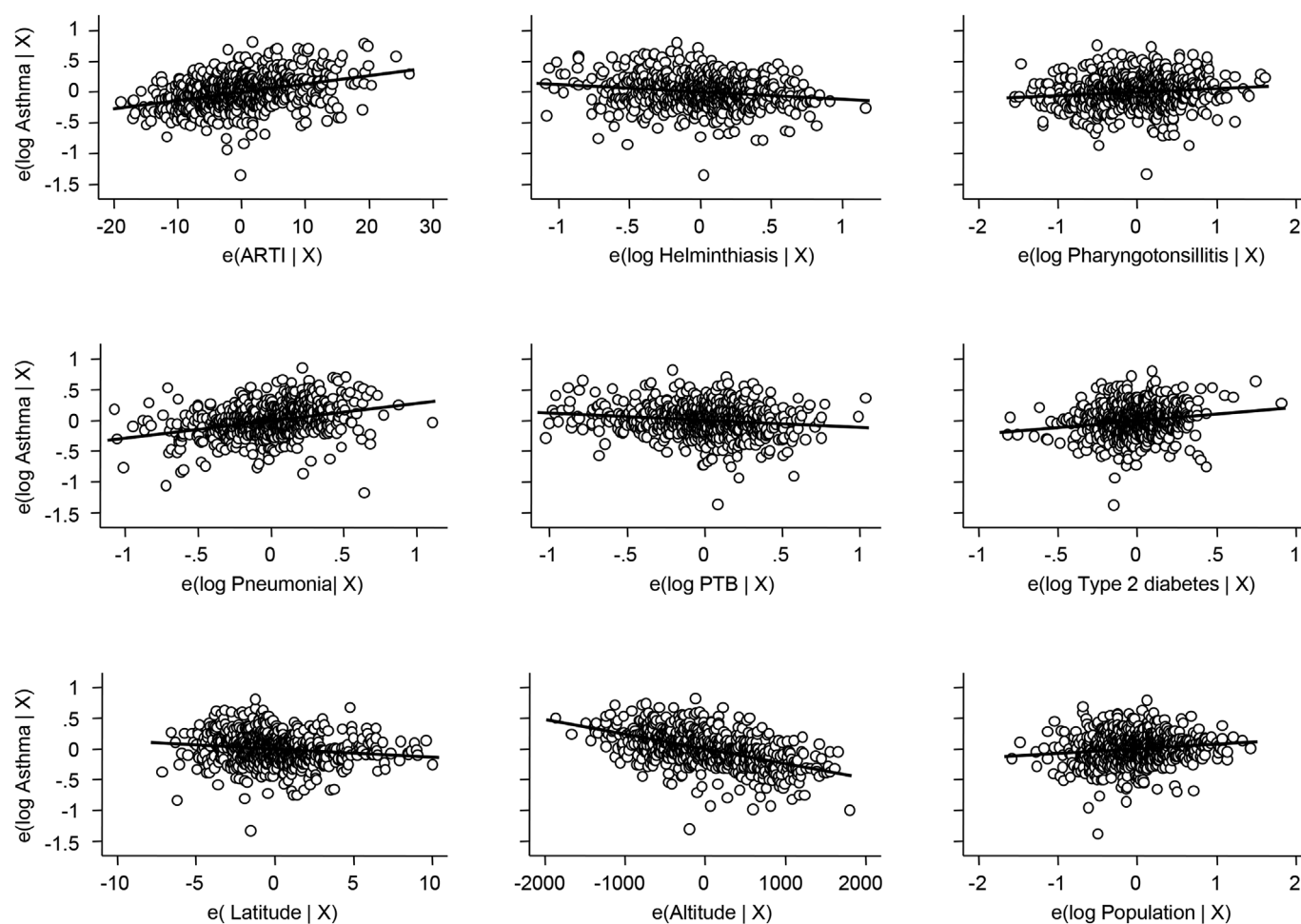


Fig. 4. Partial-correlation plots (avplots) of selected conditions and asthma incidence rates in 758 Mexican counties. These plots derive from the multiple linear regression model and represent the association of each variable with asthma incidence once the potential influence of the remaining variables has been adjusted. ARTI = acute respiratory tract infections, PTB = pulmonary tuberculosis.

temperature and marginalization) lost the statistical significance initially observed in the bivariate correlation, while others (latitude) achieved new statistical significance. The best way to illustrate the relationship between two variables after removing (adjusting for) the effects of all other variables included in the final regression model is through partial-regression plots, also known as added-variable plots

(avplots) [11]. Thus, the complete set of avplots derived from the final regression model can be observed in Fig. 4.

4. Discussion

In our study, the nationwide asthma-incidence median value was

$296.2 \times 100,000$ insured subjects (i.e., $\sim 0.30\%$), a figure that is consistent with the official incidence reported for all health institutions in Mexico (0.28% in 2012) [12]. However, we found a large variability of asthma incidence among Mexican counties. In 1998, the International Study of Asthma and Allergies in Childhood (ISAAC) survey applied in more than 150 locations worldwide confirmed for the first time that a great variability in asthma prevalence exists, with ~ 19 -fold differences among locations with respect to the question: “Have you ever had asthma?” [13]. Moreover, these large differences were even noted in different regions of the same country. To date, identification of factors explaining such a large variation has been elusive. Ecological analyses of the ISAAC Phase One study revealed that the prevalence of asthma-related symptoms entertained a weak, positive correlation with the Gross National Product per capita, trans fatty acids consumption, paracetamol sales, and women smoking [14]. Asthma symptoms also exhibited a weak, inverse association with the supply of food of plant origin, pollen counts, immunization rates, tuberculosis notifications, air pollution, and men smoking [14].

In 1999, Vargas et al. [2] described a strong inverse relationship between medical services due to asthma (including first-time and subsequent consultations, emergency room visits, and/or hospital admissions) and the weighted altitude in the 32 Mexican states ($r = -0.73$, $p < .001$). Thus, this study identified altitude as a potential factor that is closely associated with the development and severity of asthma. In the present study, we conducted a more in-depth analysis of the geographical distribution of asthma incidence in Mexico. To our surprise, the inverse correlation between asthma incidence and altitude was highly evident only in counties located above the ~ 1500 -m altitude. Although the previously mentioned ISAAC study did not find a statistically significant association between altitude and wheeze prevalence [14], on performing a secondary analysis of its published data [13], it can be demonstrated that the prevalence of ever asthma indeed had a weak but statistically significant inverse correlation with altitude ($r_s = -0.18$, $p = .03$), which is consistent with our results. Unfortunately, in the Phase One ISAAC study, fewer than 5% of cities were located at an altitude higher than 1500 m; thus, it is impossible to evaluate whether the same sharp drop beyond this altitude was also present as in our study. An investigation by Zanolin et al. [15] in nine Italian cities demonstrated that the prevalence of asthma markers in young adults was associated with annual mean temperature and was inversely associated with latitude, distance from the sea, and temperature range. It is well known that ambient temperature is strongly related to altitude and, in this regard, the authors' results are also in agreement with our findings. These authors speculated that the increased prevalence of asthma markers in cities with higher ambient temperature may be due to higher ozone exposure or to changes in exposure to pollens, molds, or allergens. In our study, we consider that air pollution by ozone may not be responsible for asthma-incidence changes, mainly because the majority of Mexican counties do not have cities sufficiently large to consider they produce high pollution levels. The relevance of changes in potential indoor and outdoor allergens is uncertain. Although some studies have found lower concentration of allergens at high altitudes [16,17], others discovered that house dust mite allergens continue to be present at high altitude (2800 m) [18], and that they did not decline with increasing altitude (400–2600 m) [19].

The inverse association of asthma and altitude is also in agreement with a number of clinical studies that have identified a beneficial effect of a temporary stay (from some weeks to months) at a relatively high altitude, i.e., > 1500 m, on asthma markers [20]. This beneficial effect has been documented for asthma control, spirometry, airway hyperresponsiveness, eosinophil/leukocyte count, eosinophilic cationic protein levels, and exhaled nitric oxide concentration [5–7]. The mechanism responsible for this effect has long been attributed to lesser allergen exposure at high altitudes [21] but, as stated previously, this issue remains controversial.

Although altitude was the most influential factor for asthma incidence, in the bivariate analysis, mean monthly temperature was also closely related to asthma. Because ambient temperature greatly depends on altitude ($r_s = -0.87$, data not shown), much of its potential influence on asthma incidence could be explained through its relationship with altitude. Therefore, temperature was discarded from the final multivariate regression model.

Regarding latitude, there have been conflicting reports, with some studies finding a positive relationship with asthma [22,23] and others, a negative association [24]. Our study revealed that, once adjusted for the remaining variables, latitude reached a statistically significant *inverse* association with asthma incidence.

We found that acute respiratory tract infections and pneumonias correlated positively with asthma incidence. Although the hygiene hypothesis claimed that infectious agents or their products may protect individuals from the development of allergies, including asthma, there have been contrasting results from studies addressing this issue. For acute respiratory tract infections, epidemiological evidence indicates that, contrary to the hygiene-hypothesis postulate, these infections appear to increase the risk for developing asthma, although this is particularly true only with respect to infections due to viruses, such as respiratory syncytial virus or rhinovirus [25,26], or atypical microorganisms such as *Mycoplasma* [27]. Our results support this latter concept, inasmuch as the majority of acute respiratory tract infections and acute pharyngitis/tonsillitis are produced by viral agents [28–30]. On the other hand, although acute respiratory tract infections might predispose to asthma inception, it must be borne in mind that the reverse relationship (i.e., that asthma increases the risk for infectious complications) is also biologically plausible. In this respect, it has been found that patients with asthma develop lower airway tract infections more often than control subjects [31], and that host responses to viral infections (e.g., antimicrobial peptides and antiviral interferons) are weaker in asthmatic airway secretions and/or peripheral blood mononuclear cells than in healthy subjects [32,33]. Perhaps the same complex, two-way causal relationship observed between asthma and respiratory tract infections could be applied for the association between asthma and pneumonias. In this regard, early colonization of 1-month-old infants' hypopharynx with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxella catarrhalis* (which are major pathogens of community-acquired pneumonias [34,35]) is associated with a higher risk for developing asthma at 5 years of age [36] and, in turn, patients with asthma are at an increased risk of invasive pneumococcal disease, including pneumonia [37].

When data are only analyzed through bivariate correlations, it is expected that two variables that are *inversely* correlated with a third one would exhibit a trend toward a *positive* correlation between them. In this context, because of the strong *inverse* association of asthma with altitude, it is possible that any other variable also exhibiting an *inverse* correlation with altitude would have a tendency for a *positive* correlation with asthma. This was probably the case of helminthiasis and pulmonary tuberculosis, the two infectious diseases with highest *inverse* correlation with altitude ($r_s = -0.43$, and $r_s = -0.58$, respectively, data not shown). Once the influence of altitude (and probably of other, less influential variables) was adjusted in the multivariate analysis, the true relationship between asthma and helminthiasis or pulmonary tuberculosis resulted to be in *inverse* fashion, which is in agreement with the postulate of the hygiene hypothesis and with other ecological studies [38–40]. Epidemiological evidences showed an *inverse* association between parasite infection and incidence of asthma, but probably not all helminths protect against asthma [41]. Thus, while *Ascaris* infection appears to increase the risk of asthma, other parasites, such as *Trichuris*, *Schistosoma*, and *Enterobius*, appear to protect from this disease [41,42].

Type 2 diabetes has been recognized as a worldwide epidemic and its growing pattern resembles the concurrent epidemic increase of asthma prevalence [43,44]. The origin of the type 2 diabetes epidemic

has been largely attributed to changes in human habits, especially sedentary lifestyle and dissemination of high-calorie, Western-type food, in addition to genetic susceptibility [45]. However, diabetes and asthma share the possibility that the ever-increasing number of chemicals introduced by the manufacturing industry in recent decades might be fueling the development of both diseases. This is the case, for example, of bisphenol A (BPA) and phthalates, two plasticizers commonly used in the production of polycarbonate containers, epoxy resins, and/or polyvinyl chloride products and often found in food packages, from where they can migrate into the food inside. These two compounds can be detected in many consumer products commonly used on a daily basis, such as body lotions, shampoos, soaps, creams, etc. [46]. Nearly the entire USA population has detectable urinary levels of BPA and phthalates [47,48], indicating that exposure to these chemicals is ubiquitous. BPA and phthalates can act as endocrine disruptors capable of causing a number of noxious effects, and both chemicals have been linked with the development of diabetes [49,50] and asthma [51,52]. Other widely used toxicants, such as pesticides, appear to be equally related to the development of both diabetes [53] and asthma [54]. Thus, in addition to the potential influence of obesity on asthma incidence, the finding of a positive correlation between asthma and diabetes could reflect the coincident effects of chemicals or other causal factors affecting, in the same manner, the development of diabetes and asthma.

Limitations of our study included those inherent in ecological studies, i.e., associations are only at population level and it might not be correct to extrapolate the results to individuals; associations might not reflect a cause-effect relationship; there may be confounding variables (for example, ethnicity, obesity, tobacco habit, dietary intake, indoor or outdoor allergens) that were not analyzed, etc. On the other hand, it is known that in ~59% of children who wheeze before the age of 3 years, respiratory symptoms may eventually disappear as they grow up, and these children may be misdiagnosed as patients with asthma [55]. In our study, this misclassification would lead to some degree of asthma overdiagnosis in this age group. However, we corroborated that the strong inverse relationship between asthma inception and altitude above ~1500 m does not only occur in young children, but also in all age groups (Supplemental Fig. 3), and therefore our major conclusions still stand. On the other hand, although we agree that in some patients, other diseases (chronic obstructive pulmonary disease, bronchitis, chronic rhinosinusitis, etc.) could have been misdiagnosed as asthma, it would be expected that this diagnostic bias would be similar for all counties, so associations with other variables would remain essentially the same. Finally, we only included diseases with a reasonable chance of being related with asthma, but other diseases with not-yet-reported relationships with asthma were not assessed. Thus, the present work must be considered a hypothesis-generating study that establishes the bases for further research. One strength of our study was that data on asthma and other diseases were obtained from diagnoses made by family physicians, which undoubtedly are more reliable than symptoms-based data reported by patients or relatives.

In summary, our study showed that altitude higher than 1500 m is a major factor that determines asthma incidence, with progressively lower asthma rates as the altitude increases. This finding may imply that living at a relatively high altitude lowers the risk of new-onset asthma. Other conditions were also inversely (helminthiasis, pulmonary tuberculosis, and latitude) or positively (acute respiratory tract infections, pneumonia, type 2 diabetes, population, and pharyngitis/tonsillitis) associated with asthma incidence. The mechanisms and implications of these associations deserve further investigation.

Conflicts of interest

None.

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Trial registration

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2017.12.010>.

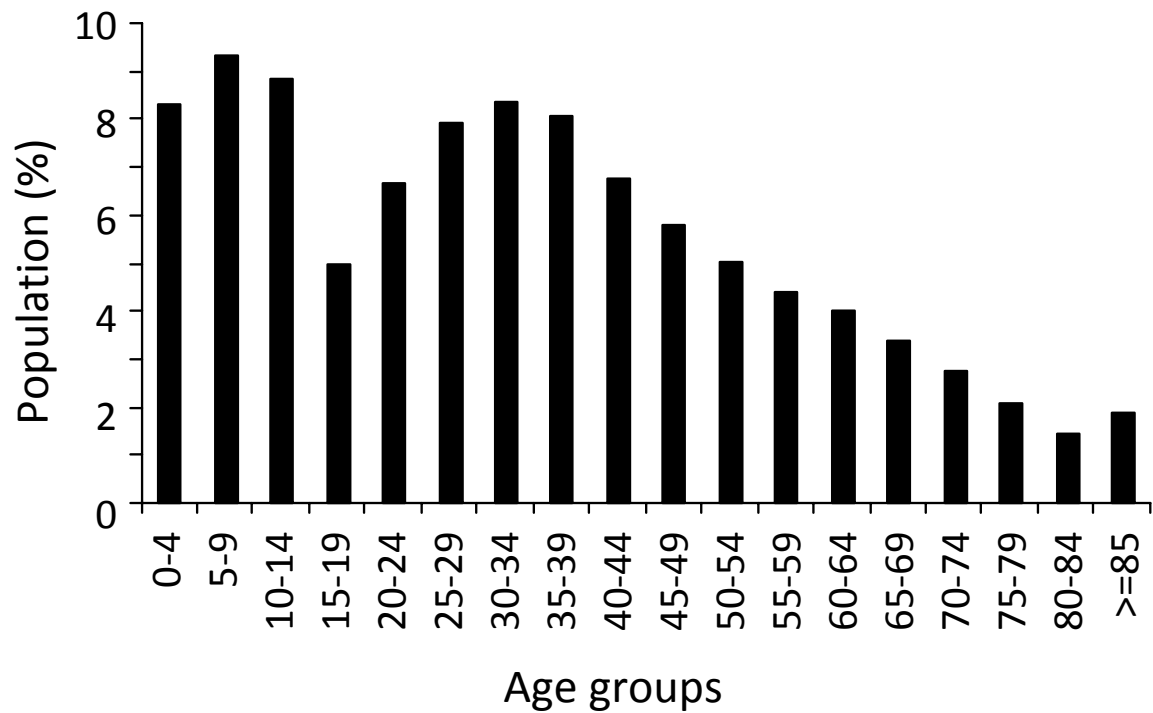
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Supplemental data

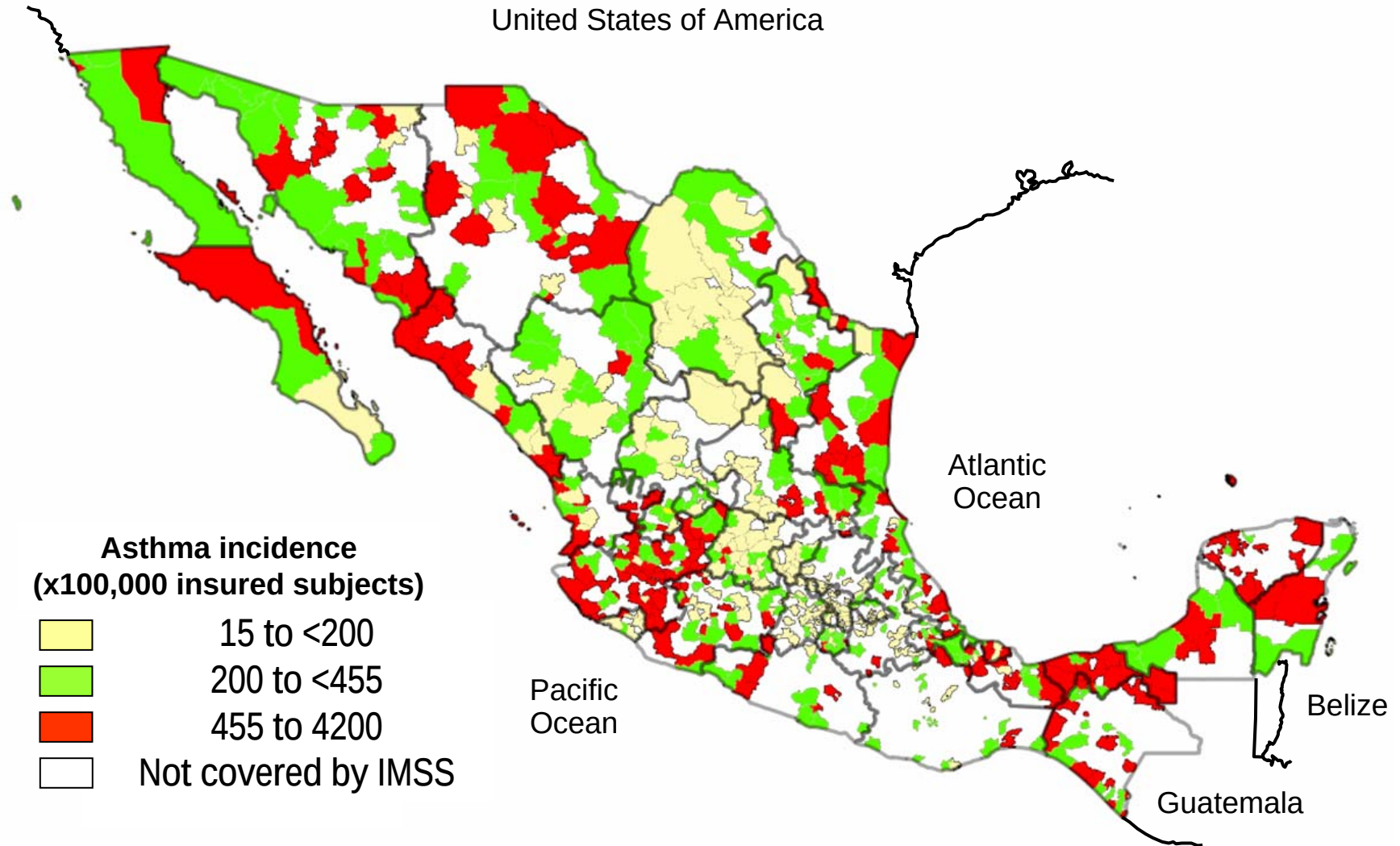
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Supplemental Fig. 1. Age distribution of the population included in the study (~37.5 million subjects).

Supplemental data

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Supplemental Fig. 2. Geographical distribution of asthma incidence rates in 758 Mexican counties covered by the Instituto Mexicano del Seguro Social (IMSS).

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