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Have the prevalence of eczema symptoms increased in the Mexican pediatric population? Prevalence and associated factors according to Global Asthma Network Phase I

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ABSTRACT

Background: In children, atopic dermatitis or eczema is the most common inflammatory disease of the skin. According to the International Study of Asthma and Allergies in Childhood (ISAAC) Phase IIIB in Mexico, 5.8% of children and 4.9% of adolescents had eczema symptoms. In 2012, Global Asthma Network (GAN) was established to update the prevalence of eczema and estimate potential factors contributing to its development.

Objective: To estimate the prevalence and associated factors for atopic eczema symptoms and diagnosis in children and adolescents according to GAN Phase I and compare the results with ISAAC Phase IIIB in Mexico.

Methods: A cross-sectional, multicenter survey was conducted in 15 Mexican centers during the period of 2015–2017 using the GAN Phase I questionnaires in children (6–7-year-olds) and adolescents (13–14-year-olds). The prevalences obtained from the GAN Phase I study, were compared with ISAAC Phase IIIB results; a Spearman's correlation analysis was conducted between temperature, relative humidity, and altitude and eczema symptoms, and a logistic regression was performed to predict current eczema symptoms by age group.

Results: A total of 35 777 children and 41 399 adolescents were included. Since ISAAC Phase IIIB, the prevalence of itchy rash in the past 12 months significantly increased in the children's group [6.6% (95% CI 5.7–7.4) vs 7.8 (95% CI 7.5–8.1), p = 0.000] and adolescents' group [5.8% (95% CI 5.0–6.7) vs 6.7% (95% CI 6.5–7.0), p = 0.000].
In the adolescents' group, the prevalence of nocturnal awakenings caused by rash symptoms on more than one night per week had a negative correlation between altitude (Spearman's Rho = −0.558, p value = 0.031), and a positive correlation with the average annual temperature (Spearman's Rho = 0.604, p value = 0.017) and annual relative humidity (Spearman's Rho = 0.742,

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p value = 0.002). The most significant associations in children were the presence of sneezing or runny or blocked nose in the past 12 months [(OR 3.13, 95% CI 2.60–3.77), p = 0.000], the use of paracetamol in the first year of life ([OR 1.52, 95% CI 1.15–2.01), p = 0.003] and the use of antibiotics in the first year of life [(OR 1.30, 95% CI 1.08–1.55) p = 0.004]. Moreover, altitude at 100–1000 m above sea level was associated with current eczema symptoms in adolescents (p = 0.001).

Conclusions: There has been a significant increase in eczema symptoms in both age groups since ISAAC Phase IIIB study. Additionally, eczema symptoms were associated with temperature, relative humidity, asthma, hay fever symptoms, the use of paracetamol and antibiotics.

Keywords: Eczema, Prevalence, Associated factors, GAN, Pediatric

Atopic dermatitis (AD), or atopic eczema, is the most common inflammatory disease of the skin.[1] As a skin inflammatory disorder, "atopic eczema" or "atopic dermatitis" is commonly described by intense itching, erythematous patches, blisters, scabs, and in late stages, lichenification or thickening of the skin associated with a personal or family history of another allergic disorder.[2,3] According to estimates, this condition affects 20% of the worldwide pediatric population, although the prevalence varies widely among countries.[2] In the first 2 years of life, over 41% of children develop this disease with periods of exacerbation;[4,5] and is considered an early manifestation of the atopic march, which describes IgE-mediated symptoms of allergic rhinitis and asthma during childhood.[6] According to the IgE blood level, AD patients can be classified into 2 categories: intrinsic (normal and non-allergic IgE) and extrinsic (high levels of IgE associated with greater disease severity).[7]

Furthermore, atopic eczema symptoms can be influenced by genetic,[8] immunological, and environmental factors,[9] suggesting that there are several subgroups of atopic eczema and other allergic diseases that vary in their symptoms and course of development.[10,11]

Children and adults who suffer from eczema have significant challenges that affect their quality of life, regardless of the severity and location of their lesions.[12] It is estimated that over 40% of children with AD suffer from sleep disturbances for constant scratching, sore skin, or skin infections,[13,14] 25% suffer from depression or anxiety, and 31.6% from social problems,[15] representing an impactful global health care economic burden.[16]

There have been numerous efforts to determine the prevalence of atopic eczema around the world with the objective of monitoring changes in prevalence and severity of symptoms and understanding the possible causes of variability across countries. The International Study of Asthma and Allergies in Childhood (ISAAC) is one of the largest and most useful of these efforts.[17] The study began in 1991 and was a multinational study to determine the prevalence of atopic eczema and other allergic diseases. The study described the prevalence and severity of atopic eczema, asthma, and rhinitis in various regions, examined risk factors, and evaluated temporary trends in the prevalence of these conditions in three phases from 1992 to 2003.[18]

The ISAAC Phase I study with 256 410 children aged 6 to 7 and 458 623 adolescents aged 13 to 14 found a prevalence of atopic eczema symptoms of just over 7%.[2,17–19] At both ages, the highest prevalence was found in urban Africa, the Baltics, Australia, as well as Northern and Western Europe.[19] As part of ISAAC Phase I, Mexico participated with a center (Cuernavaca). The prevalence of eczema symptoms in children and adolescents was 4.9% and 4.4%, respectively.[17]

According to ISAAC Phase IIIB, there has been a significant change in the prevalence of atopic eczema, with an increase in low-income countries such as Africa and East Asia. There has also been a large variation in the prevalence of current symptoms of eczema among groups aged 6–7 years (from 0.9% to 22.5%) and 13–14 years (from 0.2%

to 24.6%).[2,20] Solé et al reported a prevalence of 10% of eczema symptoms among Latin American children (n = 93,851) and 8.3% among adolescents (n = 165,917). Mexico participated in this phase with 8 centers from 7 cities in the group for children (n = 23 391) and 10 centers from 8 cities in the group for adolescents (n = 29 723). There was a 5.8% (95% CI 5.0–6.7) prevalence of eczema symptoms among children and a 4.9% (95% CI 4.1–5.7) prevalence among adolescents and no associations observed between mean temperatures, altitudes, or air pollution levels in 35 Latin American countries and the current prevalence of eczema symptoms.[20]

Based on the valuable data regarding the variability of eczema symptoms among pediatric populations around the world and the contrast of factors associated with this disease, the Global Asthma Network (GAN) was established in 2012 in order to update the prevalence and associated factors of various allergic diseases, including atopic eczema.[21]

In accordance with the results of GAN Phase I, this study aimed to estimate the prevalence and associated factors of eczema symptoms and diagnoses in children and adolescents, as well as compare the results with the findings of ISAAC Phase IIIB in Mexico.

METHODS

Study design

A comparative cross-sectional study was carried out in school-age populations of 6–7-year-olds (children) and 13–14-year-olds (adolescents) in 15 centers of 14 cities in Mexico including Puerto Vallarta, Matamoros, Mexicali, Tijuana, Ciudad Victoria, Córdoba, Ciudad Juárez, Chihuahua City, Xalapa, San Luis Potosí, Aguascalientes, Michoacán, Mexico City north area, Toluca urban area, and Toluca rural area.

According to the methodology established by GAN, the sample unit was the entire population of children or adolescents within each school. Each center's public and private schools were randomly selected.[21] Children's questionnaires were completed by their parents, and adolescents' questionnaires were completed at school by themselves. Legal guardians of children and adolescents signed informed consent forms. In addition to the standardized written core questionnaires developed for ISAAC Phases I and III, GAN questionnaires also included a question regarding a doctor-confirmed diagnosis of eczema. In Mexico, the questionnaires were translated and back-translated into Spanish by 3 independent linguistic professionals according to the ISAAC English language questionnaire translation guidelines.[22] After the Spanish version of each questionnaire was completed, a pilot test was conducted in Mexico City with children and adolescents. Each of the centers involved in this study used the same version of the questionnaire according to the age group. Written questionnaires collected information regarding demographics such as age, date of birth, gender, school, and date of interview, as well as questions regarding eczema prevalence and severity, and associated factors such as paracetamol use and antibiotic use in the first year of life, physical activity, place of residence, food consumption, and daycare attendance. To ensure confidentiality, the questionnaires were coded using a unique number for each center, school, and participant. Additionally, fieldworkers took height and weight measurements in schools using a standardized approach. Details on the GAN methodology can be found at the Global Asthma Network Manual.[21]

Definitions

Regarding the symptoms and diagnosis of eczema, we considered the following 8 questions (Supplementary material 1). According to the ISAAC Phase IIIB study and GAN study, "current eczema symptoms" prevalence was estimated based on affirmative responses to the questions: "Have you (has this child) had this itchy rash at any time in the past 12 months?" and, "Has this itchy rash at any time affected any of the following places: the folds of the elbows; behind the knees; in front of the ankles; under the buttocks; or around the neck, ears, or eyes". "Severe eczema symptoms" prevalence was defined as current symptoms being the cause of awakening 1 or more times per week, with a positive answer to: "In the past 12 months, how often, on average, have you (has this child) been kept awake at night by this itchy rash? (one or more nights per week).[20,23]

Sample size

A sample size of 3000 was sought in each age group (with a minimum of 1000 deemed acceptable), which would have sufficient power (>90%) to detect 5% differences in eczema prevalence (at a significance level of 0.01) and allow for testing multiple hypotheses.[21] All Mexican centers reached the average level of participation (at least 80% for adolescents and 70% for children).[24]

Data collection and analysis

Data entry was carried out by the medical personnel at the study center for the electronic GAN database. To minimize the possibility of errors, 10% of questionnaires were double entered.[21] As part of the quality control process for Spanish and Portuguese-speaking centers in Spain, the GAN databases were checked and approved in 2019 by the Murcia data center.

In accordance with the years in which the field work was conducted at each center, climatic data such as precipitation, temperature, relative humidity, the percentage of urban populations, and the type of climate according to Köppen-Geiger climate classification was obtained from the national databases of the Instituto Nacional de Estadística y Geografía (https://www.inegi.org.mx/) and Comisión Nacional del Agua (https://smn.conagua.gob.mx/es/).

A descriptive data analysis was conducted using central tendency measurements (mean, standard deviation [SD], and 95% confidence intervals [95% CI]), in addition to percentages and frequencies corresponding to each of the questions described in the Supplementary Material 1 on eczema prevalence. The prevalences obtained from the GAN Phase I study (including 15 centers) were compared with the prevalences obtained from the ISAAC Phase IIIB study (including 8 centers for children and 10 centers for adolescents) by chi-square test with a statistically significant p-value <0.05 for both age groups. We performed a Spearman's correlation analysis between climatic variables and the prevalences of eczema symptoms by center, (previously described in Supplementary Material 2), with a statistically significant p-value <0.05. Furthermore, an association analysis was performed between the current and cumulative eczema prevalence by sex and variables related to asthma symptoms, hay fever symptoms, history of breastfeeding, contact with domestic animals (dog, cat), frequency of consumption of antibiotics and paracetamol, frequency of hours of television, hours of exercise, food consumption by category and body mass index. Chi-square tests was used to identify all variables that might be influencing the prevalence of current symptoms ($p < 0.05$). These factors were further analyzed using backward conditional logistic regression to develop models to predict current eczema symptoms by age group.

In order to organize the data, Microsoft Excel 2016 v16.0.6568.2036 (Microsoft Corporation) was used, along with IBM SPSS Statistics v25.0 (SPSS Inc., IBM) and Stata Statistical Software (Stata Corporation, LLC, College Station, TX, 2017) for statistical analysis.

RESULTS

A total of 35 777 children and 41 399 adolescents were included from 790 schools; 51.7% of the population were female. The mean weight and height of children were 24.60 ± 5.48 kg and 1.21 ± 0.06 m, respectively. Among adolescents, the mean weight and height were 54.28 ± 11.53 kg and 1.59 ± 0.81 m, respectively.

The national response rate of the delivered questionnaires was 88.55% for children and 91.19% for adolescents. A description of the climatic characteristics and percentage response by center can be found in Supplementary Material 2.

Comparison of the results of the ISAAC Phase IIIB and GAN Phase I study

Since ISAAC Phase IIIB, the national prevalence of itchy rash in the past 12 months significantly increased in the children's group [6.6% (95% CI 5.7–7.4) vs 7.8 (95% CI 7.5–8.1), p = 0.000] and adolescents' group [5.8% (95% CI 5.0–6.7) vs 6.7% (95% CI 6.5–7.0), p = 0.000]. The prevalence of eczema ever in the children's group also increased by 2.4% points [3.3% (95% CI 2.6–3.9) vs 5.7% (95% CI 5.5–6.0), p = 0.000] (see Table 1).

In both age groups, the prevalence of flexure rash decreased by 1.1–1.2 percentual points, and the prevalence of clearance of rash in the past 12 months decreased significantly [7.1% (95% CI 6.2–8.0) vs 5.9% (95% CI 5.6–6.1), p = 0.000] in the

Variable	Children 6-7 years old			Adolescents 13-14 years old		
	ISAAC Phase 3B (n = 23,391)	GAN Phase I (n = 35,777)	P value	ISAAC Phase 3B (n = 29,723)	GAN Phase I (n = 41,399)	P value
Itchy rash ever (%,95% CI)	9.5 (8.5–10.6)	9.4 (9.1–9.7)	0.425	8.3 (7.3–9.3)	8.8 (8.5–9.0)	0.300
Itchy rash in the past 12 months (%,95% CI)	6.6 (5.7–7.4)	7.8 (7.5–8.1)	0.000*	5.8 (5.0–6.7)	6.7 (6.5–7.0)	0.000*
Rash in flexures (%,95% CI)	7.1 (6.2–8.0)	5.9 (5.6–6.1)	0.000*	5.8 (5.0–6.7)	4.7 (4.5–4.9)	0.000*
First occurrence: <2 years old (%,95% CI)	3.3 (2.7–3.8)	2.9 (2.7–3.1)	0.056	NI	NI	NI
2–4 years old (%,95% CI)	2.6 (2.0–3.1)	2.5 (2.4–2.7)	0.878	NI	NI	NI
>4 years old (%, 95% CI)	3.5 (2.8–4.1)	2.7 (2.5–2.9)	0.000*	NI	NI	NI
Clearance of rash in the past 12 months (%,95% CI)	15.9 (15.1–16.7)	5.1 (4.9–5.4)	0.000*	12.2 (11.5–12.9)	5.9 (5.7–6.1)	0.000*
One or more nighttime awakenings due to itchy rash in the past 12 months (%,95% CI)	0.9 (0.6–1.3)	0.8 (0.7–0.8)	0.156	0.8 (0.5–1.2)	0.9 (0.8–1.0)	0.548
Eczema ever (%,95% CI)	3.3 (2.6–3.9)	5.7 (5.5–6.0)	0.000*	2.7 (2.1–3.3)	3.1 (2.9–3.2)	0.000*
Eczema confirmed by a doctor (%,95% CI)	NI	5.4 (5.2–5.7)	NI	NI	2.1 (2.0–2.2)	NI
Current symptoms of eczema (%,95% CI)	5.8 (5.0–6.7)	5.7 (4.9–5.4)	0.854	4.9 (4.1–5.7)	4.6 (4.4–4.8)	0.000*
Current symptoms of severe eczema (%,95% CI)	0.7 (0.4–1.0)	0.6 (0.6–0.7)	0.847	0.6 (0.4–0.9)	0.8 (0.7–0.8)	0.111

Table 1. Prevalence and severity of eczema symptoms in children and adolescents of Mexico according to ISAAC Phase IIIB (2002) and GAN Phase I (2015–2017). *NI, No information.*p < 0.05-Statistically significant difference*

children's group and in the adolescents' group [12.2% (95% CI 11.5–12.9) vs 5.9% (95% CI 5.7–6.1), p = 0.000]. The prevalence of current symptoms of eczema decreased in the adolescents' group [4.9% [95% CI 4.1–5.7) vs 4.6% (95% CI 4.4–4.8), p = 0.000], and the current prevalence of severe eczema symptoms ranged from 0.6 to 0.8 in both age groups, without a significant difference (Table 1).

In the 4 centers that participated in ISAAC Phase IIIB and GAN Phase I (Mexico City north area, Mexicali, Toluca urban area, and Ciudad Victoria), the prevalence of itchy rash in the past 12 months increased significantly, as did the prevalence of eczema symptoms in the first 2 years of life and eczema ever in at least 3 of the 4 centers in both age groups (p < 0.05). Please refer to Table 2.

Children in the north area of Mexico City reported a decrease in current eczema symptoms by 1.6% points and adolescents by 4.6% points. In adolescents, a significant decrease of over 3% points was also observed in the prevalence of itchy rash ever [11.3% (95% CI 10.3–12.3) vs 8.0% (95% CI 7.1–8.9), p = 0.000] and rash in flexures [10.1% (95% CI 9.1–11.0) vs 4.0% (95% CI 3.4–4.7), p = 0.000].

On the other hand, Ciudad Victoria reported the highest increase in current eczema symptoms in children and adolescents (3.8% points, p = 0.000 and 1.4% points, p = 0.030, respectively) and in symptoms of severe eczema in children (0.8% points, p = 0.001). However, both groups reported the lowest prevalence of eczema medical diagnoses (3.4% in children and 1.3% in adolescents).

According to Mexicali, in adolescents, nighttime awakenings due to rash in the past 12 months increased by 0.4% points (p = 0.026), as did current symptoms of severe eczema by 0.5% points (p = 0.002). In the children group, the prevalence of eczema ever increased significantly by 7.8% points (p = 0.000) and reported the highest prevalence of eczema medical diagnoses [11.1% (95% CI 9.7–12.5)].

The Toluca urban area reported a significant increase of at least 2% points in the prevalence of itchy rash ever [7.8% (95% CI 6.9–8.7) vs 9.9% (95% CI 8.8–11.0), p = 0.004]), itchy rash in the last 12 months [5.9% (95% CI 5.1–6.7) vs 8.9% (95% CI 7.8–10.0), p = 0.000]), and eczema ever among children [3.4% (95% CI 2.8–4.0) vs 7.7% (95% CI 7.8–10.0), p = 0.000]).

GAN Phase I study results

There was a wide variety of the current prevalence of eczema between centers. According to the children group, Córdoba, Ciudad Victoria, and Ciudad Juárez had the highest prevalence (more than 6%). Among adolescents, Mexico City, Mexicali, Chihuahua, and Puerto Vallarta had the highest current prevalence of eczema (>7%), while Michoacán had the lowest prevalence in both age groups (<3.5%). (Supplementary materials 3a and 3b) The prevalence of eczema confirmed by a doctor ranged from 2.1% (95% CI 2.0–2.2) to 5.4% (95% CI 5.2–5.7) in adolescents and children, respectively (see Table 1). Additionally, over fifty percent of the children and adolescents with current eczema symptoms were also diagnosed as having asthma or hay fever by a doctor.

In the adolescents' group, the prevalence of nocturnal awakenings caused by rash symptoms on more than one night per week had a negative correlation between altitude (Spearman's Rho = −0.558, p value = 0.031), and a positive correlation with the average annual temperature (Spearman's Rho = 0.604, p value = 0.017) and annual relative humidity (Spearman's Rho = 0.742, p value = 0.002) (Figs. 1–3). Children did not show any statistically significant correlations.

Tables 3 and 4 present factors associated with current symptoms of eczema in children and adolescents by sex, respectively. The most significant associations in children were the presence of sneezing or runny or blocked nose in the past 12 months [males (OR 3.13, 95% CI 2.60–3.77), p = 0.000] vs [females (OR 2.92, 95% CI 2.42–3.52), p = 0.000], the use of paracetamol during the pregnancy of the child more than once a month [males (OR 2.02, 95% CI 1.38–2.93), p = 0.000] vs [females (OR 1.50, 95% CI 1.01–2.21), p = 0.040], the use of paracetamol in the first year of life [males (OR 1.10, 95% CI 0.84–1.45), p = 0.471] vs [females (OR 1.52, 95% CI 1.15–2.01), p = 0.003] and the use of antibiotics in the first year of life [males

Variable	Center	Children 6-7 years old			Adolescents 13-14 years old		
		ISAAC Phase 3B (n = 11,611)	GAN Phase I (n = 9672)	P value	ISAAC Phase 3B (n = 13,022)	GAN Phase I (n = 10,972)	P value
Itchy rash ever (%,95% CI)	Mexico City north area	12.4 (11.2–13.5)	11.5 (10.2–12.7)	0.301	11.3 (10.3–12.3)	8.0 (7.1–8.9)	0.000*
	Toluca urban area	7.8 (6.9–8.7)	9.9 (8.8–11.0)	0.004*	7.4 (6.4–8.3)	8.5 (7.4–9.6)	0.122
	Mexicali	12.5 (11.2–13.8)	11.4 (10.0–12.8)	0.254	5.4 (4.6–6.2)	7.9 (6.8–9.0)	0.000*
	Ciudad Victoria	4.6 (3.8–5.4)	10.2 (9.0–11.4)	0.000*	8.9 (7.9–9.9)	11.6 (10.4–12.9)	0.001*
Itchy rash in the past 12 months (%,95% CI)	Mexico City north area	9.5 (8.5–10.5)	9.9 (8.7–11.0)	0.633	8.9 (8.0–9.8)	6.4 (5.5–7.2)	0.001*
	Toluca urban area	5.9 (5.1–6.7)	8.9 (7.8–10.0)	0.000*	4.1 (3.4–4.8)	6.9 (6.0–7.9)	0.000*
	Mexicali	6.2 (5.3–7.1)	9.6 (8.4–10.9)	0.000*	3.3 (2.6–3.9)	5.8 (4.9–6.8)	0.000*
	Ciudad Victoria	3.3 (2.6–4.0)	8.0 (6.9–9.1)	0.000*	5.8 (5.0–6.6)	9.6 (8.5–10.8)	0.000*
Rash in flexures (%,95% CI)	Mexico City north area	10.9 (9.8.-12.0)	7.8 (6.7–8.8)	0.000*	10.1 (9.1–11.0)	4.0 (3.4–4.7)	0.000*
	Toluca urban area	5.4 (4.6–6.2)	6.3 (5.4–7.2)	0.142	3.6 (2.9–3.7)	4.9 (4.1–5.8)	0.013
	Mexicali	7.6 (6.6–8.6)	7.8 (6.6–9.0)	0.799	3.7 (3.0–4.4)	4.1 (3.3–4.9)	0.409
	Ciudad Victoria	3.2 (2.5–3.9)	6.1 (5.2–7.1)	0.000*	7.0 (6.1–7.9)	6.5 (5.5–7.5)	0.441
First occurrence: <2 years old (%,95% CI)	Mexico City north area	14.4 (13.2–15.6)	4.1 (3.4–4.9)	0.000*	NI	NI	NI
	Toluca urban area	1.2 (0.8–1.6)	3.2 (2.5–3.9)	0.000*	NI	NI	NI

(continued)

Variable	Center	Children 6-7 years old			Adolescents 13-14 years old		
		ISAAC Phase 3B (n = 11,611)	GAN Phase I (n = 9672)	P value	ISAAC Phase 3B (n = 13,022)	GAN Phase I (n = 10,972)	P value
	Mexicali	1.7 (1.2–2.2)	3.9 (3.1–4.8)	0.000*	NI	NI	NI
	Ciudad Victoria	0.9 (0.5–1.2)	1.7 (1.2–2.2)	0.009*	NI	NI	NI
2–4 years old (%,95% CI)	Mexico City north area	3.6 (2.9–4.2)	3.4 (2.7–4.1)	0.670	NI	NI	NI
	Toluca urban area	2.1 (1.6–2.6)	2.9 (2.3–3.6)	0.037*	NI	NI	NI
	Mexicali	2.5 (1.9–3.1)	3.6 (2.8–4.4)	0.029*	NI	NI	NI
	Ciudad Victoria	1.7 (1.2–2.2)	2.1 (1.6–2.7)	0.256	NI	NI	NI
>4 years old (%,95% CI)	Mexico City north area	5.1 (4.3–5.8)	3.3 (2.6–4.0)	0.001*	NI	NI	NI
	Toluca urban area	2.4 (1.9–2.9)	3.8 (3.0–4.5)	0.002*	NI	NI	NI
	Mexicali	3.7 (3.0–4.4)	3.2 (2.3–3.9)	0.269	NI	NI	NI
	Ciudad Victoria	2.3 (1.7–2.9)	4.1 (3.3–4.9)	0.000*	NI	NI	NI
One or more nighttime awakenings due to itchy rash in the past 12 months (%,95% CI)	Mexico City north area	1.0 (0.7–1.3)	0.8 (0.5–1.2)	0.522	1.0 (0.7–1.3)	0.8 (0.5–1.1)	0.365
	Toluca urban area	0.4 (0.2–0.6)	0.5 (0.2–0.8)	0.513	0.9 (0.6–1.2)	0.6 (0.3–0.9)	0.151
	Mexicali	1.1 (0.7–1.5)	0.8 (0.4–1.3)	0.414	0.3 (0.1–0.5)	0.7 (0.4–1.1)	0.026*
	Ciudad Victoria	0.5 (0.2–0.8)	1.4 (0.9–1.9)	0.001*	1.5 (1.1–1.9)	1.3 (0.9–1.7)	0.511

Eczema ever (%,95% CI)	Mexico City north area	4.1 (3.4–4.8)	11.4 (10.2–12.7)	0.000*	2.3 (1.8–2.8)	5.7 (4.9–6.5)	0.000*
	Toluca urban area	3.4 (2.8–4.0)	7.7 (6.7–8.7)	0.000*	4.1 (3.4–4.8)	4.9 (4.0–5.7)	0.146
	Mexicali	3.6 (2.9–4.3)	11.4 (10.0–12.8)	0.000*	1.3 (0.9–1.7)	2.2 (1.6–2.8)	0.010*
	Ciudad Victoria	2.0 (1.5–2.5)	3.7 (3.0–4.5)	0.000*	0.8 (0.5–1.1)	1.9 (1.4–2.4)	0.000*
Current symptoms of eczema (%,95% CI)	Mexico City north area	8.7 (7.7–9.7)	7.1 (6.1–8.1)	0.024*	8.5 (7.6–9.4)	3.9 (3.2–4.5)	0.000*
	Toluca urban area	5.4 (4.6–6.2)	6.0 (5.1–6.9)	0.319	3.1 (2.5–3.7)	4.5 (3.7–5.3)	0.004*
	Mexicali	5.4 (4.5–6.3)	7.2 (6.1–8.3)	0.013*	2.8 (2.2–3.4)	4.0 (3.2–4.8)	0.016*
	Ciudad Victoria	2.3 (1.7–2.9)	6.1 (5.1–7.0)	0.000*	5.1 (4.4–5.9)	6.5 (5.5–7.5)	0.030*
Current symptoms of severe eczema (%,95% CI)	Mexico City north area	0.7 (0.4–1.0)	0.6 (0.3–0.9)	0.816	0.9 (0.6–1.2)	0.7 (0.4–0.9)	0.233
	Toluca urban area	0.3 (0.1–0.5)	0.4 (0.2–0.7)	0.527	0.5 (0.2–0.7)	0.5 (0.2–0.7)	0.811
	Mexicali	0.8 (0.4–1.1)	0.6 (0.3–1.0)	0.689	0.1 (0.0–0.2)	0.6 (0.3–0.9)	0.002*
	Ciudad Victoria	0.3 (0.1–0.5)	1.1 (0.7–1.5)	0.001*	1.1 (0.7–1.5)	1.1 (0.7–1.5)	0.916
Eczema confirmed by a doctor (%,95% CI)	Mexico City north area	NI	11.0 (9.8–12.2)	NI	NI	4.7 (4.0–5.4)	NI
	Toluca urban area	NI	7.3 (6.4–8.3)	NI	NI	3.9 (3.2–4.6)	NI

(continued)

Variable	Center	Children 6–7 years old			Adolescents 13–14 years old		
		ISAAC Phase 3B (n = 11,611)	GAN Phase I (n = 9672)	P value	ISAAC Phase 3B (n = 13,022)	GAN Phase I (n = 10,972)	P value
	Mexicali	NI	11.1 (9.7–12.5)	NI	NI	1.4 (0.9–1.8)	NI
	Ciudad Victoria	NI	3.4 (2.7–4.2)	NI	NI	1.3 (0.9–1.7)	NI

Table 2. (Continued) Prevalence and severity of eczema symptoms in children and adolescents of Mexico according to ISAAC Phase IIIB (2002) and GAN Phase I (2015–2017) in four centers. *NI, No information; *p < 0.05-Statistically significant difference*

(OR 1.19, 95% CI 0.98–1.45), p = 0.066] vs [females (OR 1.30, 95% CI 1.08–1.55) p = 0.004]. For the adolescents' group, the most significant associated factors were wheezing or whistling in the past 12 months [males (OR 2.45, 95% CI 1.97–3.03), p = 0.000] vs [females (OR 2.03, 95% CI 1.77–2.35) p = 0.000], sneezing or a runny or blocked nose without a cold or a flu in the past 12 months [males (OR 2.93, 95% CI 2.44–3.52), p = 0.000] vs [females (OR 3.01, 95% CI 2.64–3.42), p = 0.000], hay fever ever [males (OR 2.14, 95% CI 1.67–2.75), p = 0.000] vs [females (OR 1.84, 95% CI 1.55–2.18), p = 0.000] and the use of paracetamol at least once a month [males (OR 1.68, 95% CI 1.29–2.20), p = 0.000] vs (females [OR 1.71, 95% CI 1.39–2.10), p = 0.000].

Among the children, living in centers located between 1500 and 2000 m above sea level was reported by both sexes as a protective factor for current eczema symptoms (males = OR 0.74, 95% CI 0.56–0.96, p < 0.028 ; females = OR 0.65, 95% CI 0.50–0.84, p < 0.001). In the adolescent group, living in centers with an altitude of 100–1000 m above sea level was reported as an associated factor for current eczema symptoms in both sexes (males = OR 1.50, 95% CI 1.14–1.96, p < 0.003 ; females = OR 1.34, 95% CI 1.12–1.61, p < 0.001).

DISCUSSION

According to the GAN Phase I methodology, this study represents one of the most comprehensive attempts to estimate the prevalence of atopic dermatitis symptoms in children and adolescents in Mexico. ISAAC Phase IIIB and GAN prevalence data were examined over time to determine patterns of change over more than a decade (2002–2017) and found that prevalence and severity of eczema vary by age group, center, and can be correlated with climatic characteristics. Additionally, in both age groups, GAN Phase I results indicated a national increase in eczema ever prevalence (from 0.4 to 2.4% points) and itchy rash in the past 12 months prevalence (from 0.9 to 1.2% points) compared to the ISAAC Study Phase IIIB. Nevertheless, it was determined that among the 4 centers involved in both phases, eczema prevalence increased by at least 1.5% points among children in the 4 centers and 1 percentage

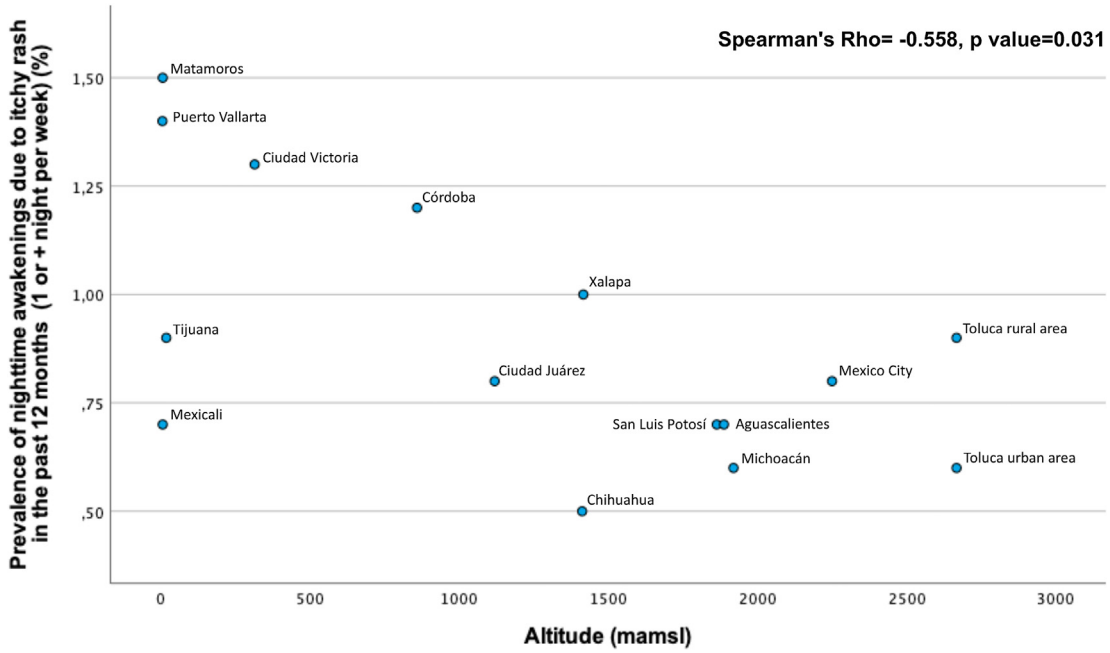

Fig. 1 Spearman's correlation between the prevalence of nighttime awakening due to itchy rash in the past 12 months and the altitude of the fifteen GAN Phase I centers in 13–14-year-old.

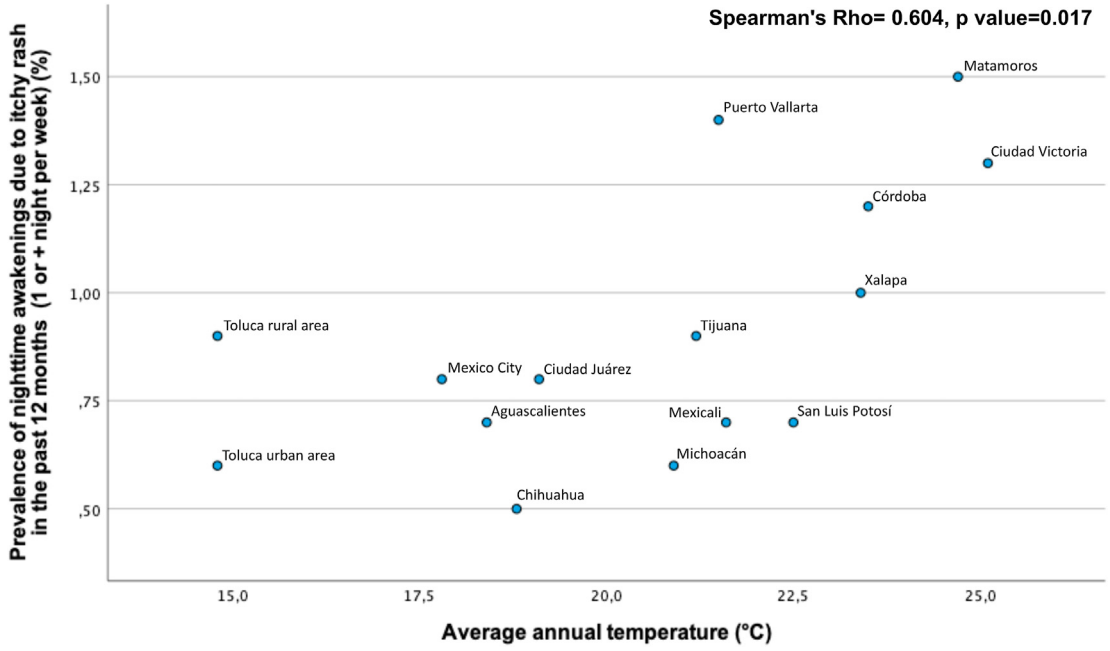

Fig. 2 Spearman's correlation between the prevalence of nighttime awakening due to itchy rash in the past 12 months and the average annual temperature of the fifteen GAN Phase I centers in 13–14-year-old.

point among adolescents in Mexico City and Ciudad Victoria centers.

We found a substantial burden of current eczema symptoms in Ciudad Victoria and Mexicali: 6 to 7 out of 100 children and 4 to 6 adolescents had eczema symptoms in their flexures areas or on their face within the last 12 months, and 1 out of 100 had nocturnal awakenings as a result. An estimated 46%–80% of children with AD suffer from sleep disturbances, manifesting as difficulty falling asleep, frequent awakenings during the night, and excessive sleepiness during

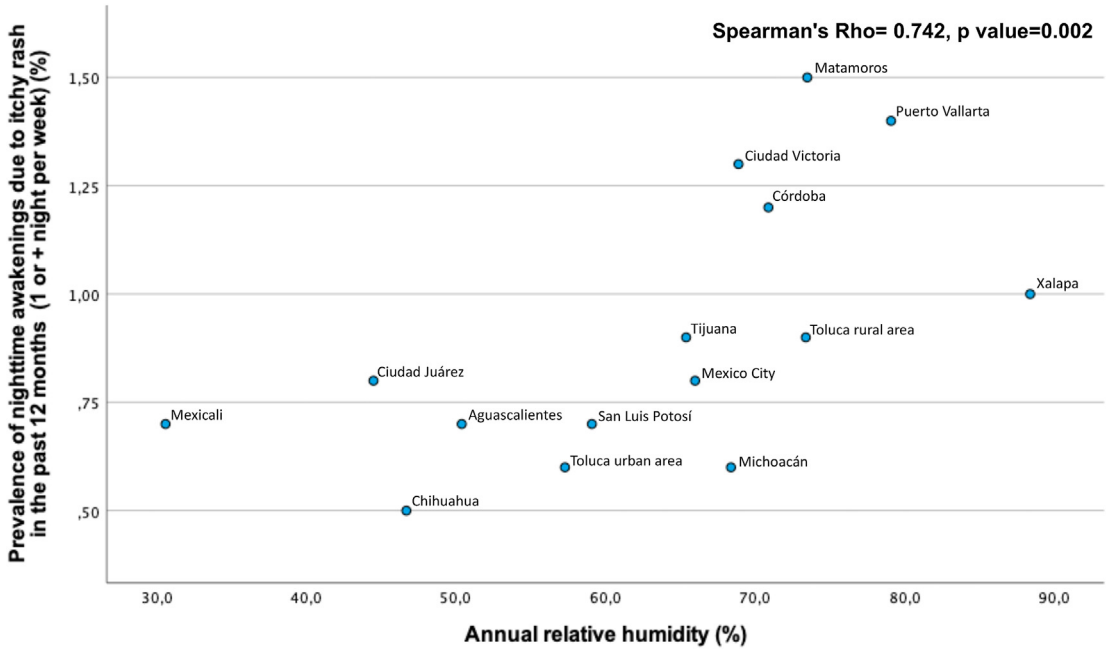

Fig. 3 Spearman's correlation between the prevalence of nighttime awakening due to itchy rash in the past 12 months and the annual relative humidity of the fifteen GAN Phase I centers in 13–14-year-old.

Variables according to GAN study Phase I	Males 6–7		Females 6–7	
	OR (95% CI)	p	OR (95% CI)	p
Wheezing or whistling in the chest in the **past 12 months**	1.91 (1.54–2.39)	0.000	1.61 (1.27–2.03)	0.000
Asthma ever	1.07 (0.82–1.40)	0.591	1.19 (0.88–1.60)	0.239
Sneezing or a runny or blocked nose without a cold or a flu In the **past 12 months**	3.13 (2.60–3.77)	0.000	2.92 (2.42–3.52)	0.000
Hay fever ever	1.70 (1.37–2.11)	0.000	1.39 (1.10–1.76)	0.005
Frequency of maternal **paracetamol consumption** during pregnancy:				
Once compared to never	1.41 (1.18–1.69)	0.000	1.24 (1.04–1.48)	0.014
Once a month compared to never	1.56 (1.18–2.08)	0.002	1.21 (0.91–1.61)	0.186
More than once a month compared to never	2.02 (1.38–2.93)	0.000	1.50 (1.01–2.21)	0.040
More frequent compared to never	2.05 (0.66–6.35)	0.211	1.80 (0.52–6.25)	0.351
Regular maternal contact (at least once a week) with **farm animals during pregnancy**	1.73 (1.31–2.29)	0.000	1.48 (1.11–1.96)	0.006

(continued)

Variables according to GAN study Phase I	Males 6-7		Females 6-7	
	OR (95% CI)	p	OR (95% CI)	p
Premature birth	1.01 (0.80–1.27)	0.905	1.03 (0.81–1.30)	0.805
Breastfeeding duration:				
6–12 months compared to less than 6 months	0.97 (0.80–1.16)	0.744	0.94 (0.78–1.12)	0.508
More than 12 months compared to less than 6 months	1.14 (0.92–1.41)	0.209	0.96 (0.77–1.18)	0.716
Antibiotics during the first year of life	1.19 (0.98–1.45)	0.066	1.30 (1.08–1.55)	0.004
Paracetamol for fever during the first year of life	1.10 (0.84–1.45)	0.471	1.52 (1.15–2.01)	0.003
Contact with a **dog** during the **first year of life**	1.29 (1.08–1.54)	0.005	1.28 (1.07–1.52)	0.006
Contact with a **cat** during the **first year of life**	1.15 (0.86–1.54)	0.320	1.24 (0.95–1.63)	0.109
Frequency of paracetamol use for fever in the past 12 months:				
At least once a year compared to never	1.19 (0.87–1.64)	0.262	1.02 (0.76–1.38)	0.865
At least once a month compared to never	1.30 (0.92–1.84)	0.130	1.31 (0.95–1.82)	0.097
Contact with a **dog** during the past 12 months	0.86 (0.72–1.02)	0.091	0.89 (0.75–1.05)	0.179
Contact with a **cat** during the past 12 months	1.05 (0.82–1.34)	0.670	0.96 (0.76–1.21)	0.766
Altitude (mamsl) comparison <100 mts				
100–1000 m	1.01 (0.77–1.33)	0.912	0.87 (0.67–1.15)	0.348
>1000–1500 m	0.93 (0.72–1.20)	0.618	0.75 (0.58–0.96)	0.022
>1500–2000 m	0.74 (0.56–0.96)	0.028	0.65 (0.50–0.84)	0.001
>2000–2500 m	1.36 (0.97–1.19)	0.074	0.95 (0.68–1.33)	0.792
>2500 m	1.26 (0.96–1.65)	0.095	1.17 (0.91–1.50)	0.212

Table 3. (Continued) Associated factors for current eczema symptoms identified in the logistic regression in the 6–7-year age group according to the Global Asthma Network (GAN) study in Mexico 2015–2017

Variables according to GAN study Phase I	Males 13-14		Females 13-14	
	OR (95% CI)	p	OR (95% CI)	p
Wheezing or whistling in the chest in the **past 12 months**	2.45 (1.97–3.03)	0.000	2.03 (1.77–2.35)	0.000
Asthma ever	1.21 (0.95–1.55)	0.122	1.04 (0.86–1.24)	0.665
Sneezing or a runny or blocked nose without a cold or a flu In the **past 12 months**	2.93 (2.44–3.52)	0.000	3.01 (2.64–3.42)	0.000
H**ay fever ever**	2.14 (1.67–2.75)	0.000	1.84 (1.55–2.18)	0.000
Frequency of paracetamol use for fever in the past 12 months:				
At least once a year	1.23 (0.97–1.58)	0.087	1.27 (1.04–1.55)	0.019
At least once a month	1.68 (1.29–2.20)	0.000	1.71 (1.39–2.10)	0.000
Contact with a **dog** during the past 12 months	0.99 (0.81–1.22)	0.960	1.23 (1.06–1.42)	0.006
Contact with a **cat** during the past 12 months	1.18 (0.97–1.43)	0.089	1.13 (0.99–1.29)	0.064
Altitude (mamsl) comparison <100 mts				
100–1000 m	1.50 (1.14–1.96)	0.003	1.34 (1.12–1.61)	0.001
>1000–1500 m	1.13 (0.86–1.48)	0.378	1.05 (0.88–1.26)	0.566
>1500–2000 m	0.90 (0.68–1.20)	0.495	0.94 (0.78–1.13)	0.553
>2000–2500 m	0.88 (0.58–1.33)	0.566	1.09 (0.85–1.39)	0.488
>2500 m	1.67 (1.28–2.19)	0.000	0.91 (0.72–1.13)	0.404

Table 4. Associated factors for current eczema symptoms identified in the logistic regression in the 13–14 year age group according to the Global Asthma Network (GAN) survey in Mexico 2015–2017

the day.[25,26] Sleep disturbance is the second most common cause of impairment of quality of life among children with AD, after itch.[27] An interesting finding in adolescents was the moderate positive correlation between nocturnal awakenings caused by eczema symptoms and the annual temperature of the centers at the time of recruitment, along with a high positive correlation with relative humidity. Even though relative humidity is influenced by temperature and air condition, it has been observed that high humidity could encourage the growth and reproduction of allergens such as mold,[28] and high temperatures are associated with poorly controlled eczema.[29] Sargen et al found that for every 5 °F increase in temperature, the odds (OR = 0.85, 95% CI 0.82–0.89, p < 0.001) for patients who describe their disease as poorly controlled increased by 15%. In addition, the association between temperature and disease control (OR = 0.90, 95% CI: 0.87–0.93, p = 0.001) was statistically significant after adjusting for potential confounders such as race, ethnicity, sex, annual household income, and use of topical medications (topical steroids, topical tacrolimus, topical pimecrolimus). With

respect to humidity, this study initially reported a 10% increase in the odds of poorly controlled diseases (OR = 0.90, 95% CI 0.81–1.00, p = 0.04) for every 10% increase in humidity. Nevertheless, the statistical significance of this association was lost in the multivariate analysis (OR = 0.93, 95% CI 0.84–1.02, p = 0.14).[29] In contrast, in the centers of Spain, Suárez-Varela et al reported a positive correlation between the prevalence of eczema symptoms and humidity and a negative correlation between annual temperature and eczema symptoms in children between 6 and 7 years of age.[30] Numerous studies have shown that eczema incidence increases in low temperatures and low humidity as a consequence of dehydration,[31] increased production of IL-α1[32] and mast cell granulation.[33] However, one explanation for our findings may be that high relative humidity and elevated temperatures may reduce evaporative heat loss during sweating and irritate the skin when central heating is increased, which may result in increased itching due to neuropeptide-induced vasodilation.[34–37] The external humidity was taken into account in this study and not the indoor humidity or the possibility of heating or air conditioning.

For altitude, it was found that higher altitudes were associated with a lower prevalence of nocturnal awakenings at least once a week in adolescents, while lower altitudes were associated with an increased risk of eczema symptoms in centers below 1000 m. Furthermore, altitudes of 1500 to 2000 m were observed to protect against eczema symptoms in a group of schoolchildren. This is consistent with a systematic review that included 15 observational studies involving 40,148 patients with atopic dermatitis on therapy at high altitude centers (>1000 m). In this study, 96% of patients (n = 39,006) reported decreased disease activity during treatment, 64% reported improved symptoms in the last 12 months following treatment (n = 2670),[38] and 82% (n = 1178) reduced or stopped the use of local corticosteroid during treatment and at the 12-month follow-up (72% of the n = 3008).[39] Also, urinary eosinophilic protein X (EPX)[40] decreased and was significantly correlated with SCORAD.[41] However, the authors reported a very low quality of the information due to heterogeneity between the studies and the lack of description in some outcomes.[42]

There have been high rates of eczema reported in pediatric populations near the equator, but altitude has not been associated with eczema in ISAAC studies.[43,44] However, other studies that have used questionnaires other than the ISAAC methodology, including the Prevalence and Risk Factors of Allergies in Turkey (PARFAIT), have assessed the prevalence and risk factors of asthma, hay fever, and eczema among children, as well as the geographical variables and weather conditions associated with them. Several factors were associated with atopic dermatitis prevalence in this study, including altitude <1000 m, annual temperature >15 °C, relative humidity >70%, and atmospheric pressure >1000 mbars.[45] Considering the heterogeneity of the associations between altitude, temperature, and relative humidity, it is necessary to conduct multicenter studies in order to determine how these factors relate to eczema symptoms.

It was found that the use of paracetamol and antibiotics was also associated with the presence of eczema symptoms in children and the frequency of paracetamol use among adolescents. It has been reported that in Latin American children, paracetamol use in the first year of life was associated with the presence of eczema with an OR of 1.49 (1.26–1.76)[46] and in Polish adolescents, paracetamol use at least once per month was associated with eczema with an OR of 1.5 (1.11–2.01), p < 0.05.[47] Even though the use of paracetamol and antibiotics in children are usually associated with respiratory infections, there are also other reasons for its use, such as otitis media, vaccination fever, infections in other organs, etc. Paracetamol, at recommended therapeutic doses, may deplete glutathione and glutathione-dependent enzymes, and reduce the body's ability to withstand oxidative stress.[48] As a result, reactive oxygen species in response to allergic, viral, or other non-allergic stimuli, may lead to enhanced inflammation and the development or worsening of pre-existing asthma, rhinoconjunctivitis, or eczema, depending on the organ system affected.[49–51] In addition, long-term use of broad-spectrum antibiotics has been shown to cause dysbiosis of the intestinal tract, which

negatively impacts extraintestinal organs such as the lungs, the brain, and the skin, leading to chronic AD progression and asthma.[52,53] However, it is important to take into account the potential confounding effects of familial and genetic factors in this association.[54]

Studies have found that having parents with a history of allergic disease and/or having a diagnosis of allergic disease are risk factors for developing another disease involving an allergic component in the future.[55] In the ISAAC Phase III study, 0.8–1.2% of children and adolescents had asthma, rhinitis, and eczema symptoms, with significant associations between the three conditions.[17,55] As a result of our study, wheezing, nasal symptoms in the past 12 months, and hay fever are the most significant risk factors for eczema. Despite a similar association between asthma symptoms and hay fever with eczema among children of both sexes, wheezing in the past year and hay fever were more prevalent among adolescent males. According to research, asthma, allergic rhinitis, and atopic eczema are more common among children of both sexes during their school years;[56,57] however, males are more sensitive to grass pollen, mites, and tree pollens[58] resulting in a greater likelihood of developing allergic disorders by the age of 14. Women, however, are more likely to develop eczema symptoms during their reproductive years (between 15 and 49 years old), when they are most likely to become sensitized to environmental allergens.[59]

Finally, according to our study, more than 50% of children and adolescents with current eczema symptoms were also diagnosed as having asthma or hay fever by a doctor. Although eczema symptoms have increased since the ISAAC study in Mexico, less than 5.5% of patients in both groups received a diagnosis from a doctor. There are similar results in the literature, as only 6% of 17.1% of American patients with eczematous symptoms were diagnosed with atopic dermatitis[60] and 93% of Puerto Rican children with symptoms of atopic dermatitis and sensitization to at least one allergen were not diagnosed with this disease.[61] This suggests significant underdiagnosis and undertreatment of the condition in low-income settings, possibly related to limited access to healthcare specialists.

Limitations

As an observational study, this multicenter cross-sectional study has certain limitations, such as memory bias. Furthermore, this study did not include representative centers from southern Mexico due to a lack of information, preventing analysis by region (Pacific, Northeast, Bajío, Central, and Southeast).

While the GAN study has demonstrated an adequate method for estimating the prevalence of allergic disease symptoms, we did not obtain biological samples to determine genetic differences or levels of IgE or confirm the presence of atopic eczema lesions.

CONCLUSION

This is Mexico's most extensive epidemiological study to estimate eczema symptoms in children and adolescents. There has been an increase in eczema symptoms in both age groups since the ISAAC Phase IIIB study and a low prevalence of diagnosis of eczema. Several interesting and potentially associated factors were also described, including temperature, relative humidity, asthma and hay fever symptoms, paracetamol use, and antibiotic use, so further investigation is required.

Abbreviations

GAN, Global Asthma Network; ISAAC, International Study of Asthma and Allergies in Childhood; OR, Odds ratio; 95% CI, 95% Confidence interval

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Authors' contributions

NREM: Made substantial contributions to conception and drafting the manuscript.
DRNBE: Made substantial contributions to conception, design, acquisition of data and drafting the manuscript.
RNN: Made substantial contributions to design, acquisition of data and drafting the manuscript.
BA: Made substantial contributions to the analysis, interpretation of data and drafting the manuscript.
MPV: Made substantial contributions to design and acquisition of data.
GAR: Made substantial contributions to design and acquisition of data.
EP: Made substantial contributions to the analysis and drafting the manuscript.
RGBDC: As centre coordinator, made substantial contributions on the acquisition of data.

EDAJ: As centre coordinator, made substantial contributions on the acquisition of data.
LZF: As centre coordinator, made substantial contributions on the acquisition of data.
GML: As centre coordinator, made substantial contributions on the acquisition of data.
OLGG: As centre coordinator, made substantial contributions on the acquisition of data.
HMLO: As centre coordinator, made substantial contributions on the acquisition of data.
LSJS: As centre coordinator, made substantial contributions on the acquisition of data.
SHJA: As centre coordinator, made substantial contributions on the acquisition of data.
JPMA: As centre coordinator, made substantial contributions on the acquisition of data.
SCMG: As centre coordinator, made substantial contributions on the acquisition of data.
RPN: As centre coordinator, made substantial contributions on the acquisition of data.
AMMDJ: As centre coordinator, made substantial contributions on the acquisition of data.
DRNBE: Involved in revising it critically for important intellectual content.
SROJ: Involved in revising it critically for important intellectual content.

Ethics approval and consent to participate
The authors declare that all procedures were carried out in accordance with the ethical standards of the institutional committee on human investigation, the World Medical Association, and the Helsinki Declaration.
The authors obtained informed consent from the parents or guardians of participants in the present study. The corresponding author accepts responsibility for this manuscript.
The present study was approved by the Ethics, Research, and Biosafety committees of the Hospital Infantil de México Federico Gómez (HIMFG, protocol HIM/2016/065) in accordance with the guidelines of the institution.

Consent for publication
All authors consent this article for publication.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest
The authors declare that they have no conflict of interest in relation to the methods or materials employed in this study.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100710.

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