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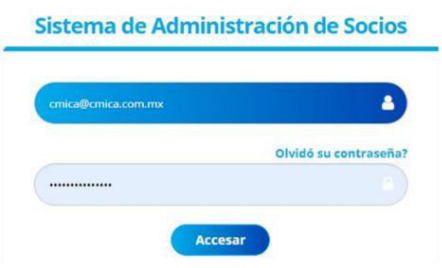

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–ACERCA DE LA PORTADA–

"Esta portada evoca la convergencia entre la expresión clínica de la urticaria crónica espontánea y mecanismos inmunogénicos que se asocian y participan en su coexistencia con la tiroiditis de Hashimoto. Los habones cutáneos remiten a la manifestación de la enfermedad, mientras que la glándula tiroides resaltada alude a la autoinmunidad tiroidea como comorbilidad asociada a la inmunopatología de la condición. La hélice de ADN y los elementos moleculares incorporados en la composición representan el enfoque genético del estudio, centrado en los polimorfismos del promotor de TNF-α (rs361525 y rs1800629) y en la variante rs2476601 de PTPN22, traduciendo en un lenguaje contemporáneo de la complejidad biológica de esta asociación clínica y destaca el valor de la investigación básica aplicada en enfermedades inmunomediadas."

Breve descripción de la portada: Carlos Octavio Arroyo Movilla. Inspirada en el artículo *Genetic variants of TNF-α and PTPN22 and their association with Hashimoto's thyroiditis in patients with chronic spontaneous urticaria from the Colombian Caribbean*. La imagen propone una síntesis visual de la interacción entre inflamación, susceptibilidad genética y autoinmunidad. En su elaboración se utilizó la herramienta tecnológica (algoritmo de IA): CHATGPT 5.4 pro y Gemini 2.5 Pro.

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Original article

Genetic variants of *TNF-α* and *PTPN22* and their association with Hashimoto's thyroiditis in patients with chronic spontaneous urticaria from the Colombian Caribbean

Variantes genéticas del TNF-α y PTPN22 y su relación con tiroiditis de Hashimoto en pacientes con urticaria crónica espontánea del Caribe Colombiano

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Abstract

OBJECTIVE: To evaluate the association of *TNF-α* promoter polymorphisms (rs361525, rs1800629) and the *PTPN22* rs2476601 variant with the coexistence of CSU and HT in an admixed Caribbean Colombian population.

METHODS: A retrospective case-control study was conducted in 86 patients with confirmed CSU (45 with CSU-alone and 41 with CSU+HT). Single-nucleotide polymorphism (SNP) genotyping was performed using TaqMan® assays. Hardy-Weinberg equilibrium (HWE), genotype, and allele frequencies were analyzed using chi-square tests and logistic regression models.

RESULTS: The *PTPN22* G allele showed a protective association in the CSU+HT group (OR: 0.02, 95% CI: 0.00–0.49; p = 0.015). While *TNF-α* SNPs conformed to HWE, *PTPN22* deviated in the CSU+HT group due to the complete absence of AG heterozygotes. No significant associations were found between *TNF-α* polymorphisms and HT, though the *TNF-α* rs361525 G allele exhibited a near-significant trend (p = 0.061). The GG genotype was predominant across all evaluated SNPs.

CONCLUSION: In this admixed Caribbean Colombian study, we observed a hypothesis-generating association between the *PTPN22* rs2476601 G allele and lower odds of concomitant HT in CSU patients. Larger, adequately powered studies incorporating rigorous ancestry adjustment are required to confirm this finding.

KEYWORDS: Caribbean colombian; Chronic spontaneous urticaria; TNF-α; PTPN22; Promoter polymorphisms; Hashimoto's thyroiditis; Allele.

Resumen

OBJETIVO: Evaluar la asociación de los polimorfismos del promotor del TNF-α (rs361525, rs1800629) y la variante PTPN22 rs2476601 con la coexistencia de urticaria crónica espontánea (UCE) y tiroiditis de Hashimoto (TH) en una población mixta caribeña colombiana.

MÉTODOS: Estudio retrospectivo de casos y controles, llevado a cabo en 86 pacientes con UCE confirmada (45 con UCE sola y 41 con UCE+TH). Se realizó la genotipificación de polimorfismos de un solo nucleótido (SNP) mediante ensayos TaqMan®. El equilibrio de Hardy-Weinberg (EHW), los genotipos y las frecuencias alélicas se analizaron mediante pruebas de chi-cuadrado y modelos de regresión logística.

RESULTADOS: El alelo G de PTPN22 mostró una asociación protectora en el grupo UCE+TH (OR: 0,02; IC del 95%: 0,00–0,49; p = 0,015). Si bien los SNP de TNF-α se ajustaron al equilibrio de Hardy-Weinberg (EHW), el PTPN22 presentó desviaciones en el grupo CSU+HT debido a la ausencia total de heterocigotos AG. No se encontró asociación significativa entre los polimorfismos de TNF-α y la HT, aunque el alelo G del TNF-α rs361525 mostró una tendencia casi significativa (p = 0.061). El genotipo GG fue predominante en todos los SNP evaluados.

CONCLUSIONES: En este estudio con población mixta caribeña colombiana se encontró una asociación que genera hipótesis entre el alelo G del PTPN22 rs2476601 y una menor probabilidad de HT concomitante en pacientes con CSU. Se requieren estudios más amplios y con suficiente potencia estadística, que incorporen un ajuste riguroso de la ascendencia, para confirmar este hallazgo.

PALABRAS CLAVE: Caribe colombiano; Urticaria espontánea crónica; TNF-α; PTPN22; Polimorfismos del promotor; Tiroiditis de hashimoto; Alelo.

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a persistent inflammatory skin disorder characterized by recurrent wheals and/or angioedema lasting for more than six weeks without an identifiable trigger. It predominantly affects middle-aged women and imposes a significant psychological, social, and economic burden on patients' quality of life.[1-3]

Beyond the skin, CSU is increasingly recognized as a systemic immune-mediated disease frequently associated with autoimmune comorbidities, most notably autoimmune thyroid disease (AITD), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).[4-7] Current evidence indicates that CSU is not a single homogeneous condition but a spectrum of endotypes driven by distinct immunopathogenic mechanisms. Two major subtypes have been proposed: the autoallergic (type I) variant, mediated by IgE autoantibodies, and the autoimmune (type IIb) variant, characterized by IgG autoantibodies directed against IgE or its high-affinity receptor FcεRI, strongly linked to AITD.[8-10]

Several studies and meta-analyses have confirmed a higher prevalence of AITD among patients with CSU compared to the general population.[6,11-15] Positivity for anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, as well as ultrasonographic evidence of thyroid autoimmunity, support shared immunological pathways underlying both conditions.[11,13,16,17] Furthermore, thyroid autoimmunity has been associated with more severe and treatment-refractory CSU phenotypes.[17,18]

Genetic susceptibility appears to play a critical role in shaping these phenotypes. Genome-wide and candidate gene association studies have identified multiple single nucleotide polymorphisms (SNPs) in immune-regulatory genes that may predispose individuals to both CSU and AITD.[19-22] Among these, tumor necrosis factor alpha (TNF-α) has emerged as a key pro-inflammatory cytokine involved in endothelial activation, mast cell degranulation, and leukocyte recruitment—processes fundamental to the chronic inflammatory response observed in CSU. Despite its established role in autoimmunity, evidence directly linking *TNF-α* promoter variants to the coexistence of CSU and AITD remains limited and often inconsistent across populations.[20,23-25]

The most widely studied *TNF-α* polymorphisms are −308 G/A (rs1800629) and −238 G/A (rs361525), both located in the promoter region and known to modulate transcriptional activity.[23,24,26-28] The −308A allele has been associated with enhanced *TNF-α* expression and increased susceptibility to inflammatory and autoimmune diseases, whereas the −238A variant has been linked to reduced transcriptional activity and possible protective effects.[19,21] Studies from European and Asian populations have reported conflicting results regarding the relationship between these SNPs and CSU susceptibility, suggesting that ethnic genetic heterogeneity and population admixture may influence their effects.[28-31]

In addition to *TNF-α*, protein tyrosine phosphatase non-receptor type 22 (PTPN22) is another relevant candidate in the immunogenetic network underlying autoimmunity and CSU. PTPN22 encodes the lymphoid tyrosine phosphatase (Lyp), a key negative regulator of T-cell receptor (TCR) signalling that helps maintain immune tolerance. Variants in this gene—particularly rs2476601 —have been associated with type 1 diabetes, RA, DLE, and occur most frequently in Northern European populations (e.g., Nordic countries and the United Kingdom).[32,33] In Latin American cohorts, this same variant has also been linked to lupus nephritis in children, suggesting population-specific differences in allele frequency and pathogenic impact.[34]

Within the context of CSU, other *PTPN22* polymorphisms, including rs2488457 C, rs1310182 T, and rs3811021 T, have been investigated for their potential contribution to autoimmune dysregulation and mast-cell signalling pathways, implying that *PTPN22* may influence the autoimmune endotype of the disease.[35-37] Given the lack of genetic data from Latin American populations, particularly those with high admixture such as the Colombian Caribbean, where African, Indigenous, and European ancestries converge, investigating *TNF-α* and *PTPN22* variants in this context may help clarify population-specific genetic influences on CSU associated with HT. Therefore, this study aimed to exploratorily evaluate the association between *TNF-α* and *PTPN22* with the coexistence of CSU and HT in a cohort from the Colombian Caribbean.

MATERIALS AND METHODS

Study population

A total of 86 patients diagnosed with chronic spontaneous urticaria (CSU) were retrospectively included from a specialized allergy clinic in Barranquilla, Colombian Caribbean. Of these, 45 had CSU without autoimmune comorbidities (CSU-alone) and 41 presented concomitant Hashimoto's thyroiditis (HT) (CSU + HT).

The diagnosis of CSU followed the EAACI/GA²LEN/EuroGuiDerm/APAAACI international guideline.[38] HT was confirmed based on the presence of at least two of the following: *1)* clinical or ultrasonographic features consistent with chronic lymphocytic thyroiditis (e.g., diffuse gland enlargement, heterogeneous or hypoechoic parenchyma), *2)* elevated anti-TPO (>35 IU/mL), and/or *3)* biochemical thyroid dysfunction (elevated TSH with or without low free T4).[39] Given the retrospective design and variability in documentation, not all diagnostic components were available for every patient. As a result, the CSU + HT group may include individuals with different combinations of serologic, imaging, and biochemical findings. This composite definition was intended to reflect real-world clinical practice.

Patients with inducible urticaria, urticarial vasculitis, active lymphoproliferative disorders, or malignancy were excluded. Demographic data, clinical features, comorbidities, serum total IgE, anti-TPO levels, and treatment regimens were extracted from medical records. All participants provided written informed consent prior to enrolment. The study was approved by the Ethics Committee of Universidad del Norte, Barranquilla, Colombia (Approval #00062, 15 October 2021), and conducted according to the Declaration of Helsinki and national research ethics regulations.

Genetic analysis

Genomic DNA was isolated from peripheral blood samples using a modified salting-out protocol. DNA concentration and purity were determined spectrophotometrically (NanoDrop 2000, Thermo Scientific, Waltham, MA, USA), with acceptable purity defined as A260/A280 between 1.7 and 2.0. DNA integrity was verified by electrophoresis on 0.8% agarose gels. These variants were selected based on their reported functional relevance in immune regulation and prior associations with autoimmune/inflammatory phenotypes. Three SNPs were analyzed: two *TNF-α* promoter variants—rs361525 (−238 G/A) and rs1800629 (−308 G/A)—and the *PTPN22* regulatory variant rs2476601.

Genotyping was performed using TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA) on an ABI Prism 7300 Real-Time PCR System. Allelic discrimination was performed using Applied Biosystems software. Only samples achieving the predefined call-rate threshold (≥90%) were included in the final analysis. Hardy–Weinberg equilibrium (HWE) was evaluated separately within each group using an exact test based on a Markov chain Monte Carlo approach. Given the retrospective nature of the study, additional laboratory quality-control procedures—such as duplicate genotyping or manual review of allelic discrimination cluster plots—were not prespecified; therefore, although standard quality metrics were applied, the possibility of technical artifacts cannot be entirely ruled out.

Statistical analysis

Continuous variables were assessed for normality using the Kolmogorov–Smirnov test and are presented as median (range). Categorical variables were expressed as frequencies and percentages. Allelic and genotypic frequencies for each SNP were compared between the CSU-alone and CSU + HT groups using Pearson's chi-square or Fisher's exact test, as appropriate. HWE was evaluated as described above. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression models for each SNP (*TNF-α* rs361525, *TNF-α* rs1800629, and *PTPN22* rs2476601), adjusting for potential confounders, including age and sex. Statistical significance was defined as $p < 0.05$. To account for multiple comparisons across the three SNPs evaluated, we applied a Bonferroni correction, establishing a significance threshold of $p < 0.0167$ (0.05/3). Additionally, a post hoc power calculation was performed to quantify the statistical strength of the observed associations. Analyses were conducted using R Studio (version 2025; R Foundation for Statistical Computing, Vienna, Austria).[40]

RESULTS

Sociodemographic and clinical characteristics

A total of 86 patients were analyzed: 45 with CSU-alone and 41 with CSU + HT. The median age was 64.6 years (range 25.2–73.6) in the CSU group and 50.6 years (range 22.7–90.4) in the CSU + HT group ($p = 0.5$). Women represented 83% of the cohort, with similar proportions between groups (80% vs. 85%; $p = 0.4$). No significant differences were observed in the prevalence of asthma, allergic rhinitis, or other atopic conditions between groups. However, anti-TPO positivity was markedly higher in the CSU + HT group (43 vs. 4.5%; $p < 0.001$). Clinical characteristics and treatments are summarized in **Table 1**.

Table 1. Clinical Characteristics of the Study subjects.

Variables	Overall	CSU-alone	CSU + HT	p
	n = 86	n = 45	n = 41	
Demographics				
Age, years	53 (22.7, 90.4)	64.6 (25.2, 73.6)	50.6 (22.7, 90.4)	0.5[2]
Sex				0.4[3]
Female	71 (83%)	36 (80%)	35 (85%)	
Male	15 (17%)	9 (20%)	6 (15%)	
Disease Characteristics				
Disease Duration, Months	27 (9, 238)	29 (12, 238)	19 (9, 106)	**0.04**[2]
Angioedema	59 (78%)	40 (89%)	19 (61%)	**0.005**[3]

...continuation table 1.

Variables	Overall	CSU-alone	CSU + HT	
	n = 86	n = 45	n = 41	p
Allergic rhinitis	21 (24%)	9 (20%)	12 (29%)	0.3[3]
Conjunctivitis	4 (4.7%)	3 (6.7%)	1 (2.4%)	0.6[4]
Asthma	4 (4.7%)	1 (2.2%)	3 (7.3%)	0.3[4]
Comorbidities				
Diabetes mellitus	2 (2.3%)	1 (2.2%)	1 (2.4%)	>0.9[4]
Hypertension	4 (4.7%)	2 (4.4%)	2 (4.9%)	>0.9[4]
Immunological Markers				
Positive Anti-TPO	17 (22%)	2 (4.5%)	15 (43%)	**<0.001**[3]
Total Serum IgE >100 IU/ml	17 (26%)	11 (30%)	6 (21%)	0.4[3]
Treatment				
H1 Blockers	8 (11%)	4 (9.1%)	4 (13%)	0.7[2]
H2 Blockers	63 (85%)	38 (86%)	25 (83%)	0.7[2]
H3 Blockers	17 (23%)	13 (30%)	4 (13%)	0.10[3]
Montelukast	61 (82%)	39 (89%)	22 (73%)	0.089[3]
Glucocorticoids	48 (65%)	29 (66%)	19 (63%)	0.8[3]
Hydroxychloroquine	26 (35%)	14 (32%)	12 (40%)	0.5[3]
Cyclosporine	9 (12%)	7 (16%)	2 (6.7%)	0.3[2]
Omalizumab	5 (6.8%)	3 (6.8%)	2 (6.7%)	>0.9[2]

CSU: Chronic Spontaneous Urticaria; HT: Hashimoto's thyroiditis; TPO: anti-thyroid peroxidase.

[1]Median (Min, Max); n (%).
[2]Wilcoxon rank sum test.
[3]Pearson's Chi-squared test.
[4]Fisher's exact test.

TNF-α and PTPN22 polymorphisms

Two SNPs in the *TNF-α* promoter, rs361525 (−238 G/A) and rs1800629 (−308 G/A), were successfully genotyped. In the CSU + HT group, 11 samples did not meet the ≥90% call-rate threshold and were excluded, leaving 30 successfully genotyped samples for the final analysis. Both polymorphisms conformed to HWE in both groups ($p > 0.05$). In contrast, *PTPN22* rs2476601 did not conform to HWE in the CSU + HT group; notably, no AG heterozygotes were observed in this subgroup.

No statistically significant associations were observed between *TNF-α* polymorphisms and the presence of HT ($p > 0.05$). An exploratory inverse association was observed for the G allele of *PTPN22* rs2476601 in the CSU + HT group (OR: 0.02, 95% CI: 0.00–0.49; $p = 0.015$). This association remained below the Bonferroni-corrected threshold ($p < 0.0167$). In both study groups, the GG genotype was predominant, while heterozygous and homozygous genotypes of minor alleles were rare. The G allele of *TNF-α* rs361525 showed a trend toward statistical significance in association with HT ($p = 0.061$). Overall, these findings suggest that the *TNF-α* promoter variants evaluated were not significantly associated with autoimmune comorbidity in CSU in this cohort; however, the observed signals for *PTPN22* rs2476601 and *TNF-α* rs361525 warrant confirmation in larger studies (**Table 2**).

DISCUSSION

We investigated the potential association between promoter polymorphisms of the *TNF-α* gene, rs361525 (−238 G/A) and rs1800629 (−308 G/A), as well as the regulatory variant *PTPN22* rs2476601, and the coexistence of CSU with HT in a genetically admixed Caribbean Colombian population.

Although no statistically significant associations were identified for the *TNF-α* polymorphisms, a near-significant trend for the G allele of rs361525 suggests a potential modulatory role in thyroid autoimmunity among CSU patients. This finding supports the hypothesis that subtle variations in *TNF-α* transcriptional regulation may influence inflammatory pathways relevant to disease heterogeneity, given the cytokine's central role in endothelial activation, mast cell degranulation, and amplification of inflammatory responses.[28-30]

Table 2. Analysis of association between TNF and PTPN22 single nucleotide polymorphisms, Chronic Spontaneous Urticaria and Hashimoto's thyroiditis.

Genotype	CSU-alone	HWE	CSU + HT	HWE	p	OR 95% CI	p
	n = 45		n = 41†				
TNF-α (rs361525)		1		1	>0.9[2]		
AG	2 (4.4%)		1 (3.3%)				
GG	43 (96%)		29 (97%)			0.84 (0.09-7.54)	0.9
A	2 (2.2%)		1 (1,7%)			1.14 (0.13-10.0)	>0.9
G	88 (97.8%)		59 (98,3%)			0.04 (0.00-1.23)	0.061
TNF-α (rs1800629)		0.35		0.22	0.4[2]		
AA	1 (2.2%)		2 (6.7%)				
AG	7 (16%)		7 (23%)			0.85 (0.12-6.05)	0.9
GG	37 (82%)		21 (70%)			0.45 (0.07-2.86)	0.4
A	9 (10%)		11 (18.3%)			1.66 (0.54-5.10)	0.4
G	81 (90%)		49 (81.7%)			0.44 (0.05-3.82)	0.5

...continuation table 2.

Genotype	CSU-alone	HWE	CSU + HT	HWE	p	OR 95% CI	p
	n = 45		n = 41†				
PTPN22 (rs2476601)		1	0.079[2]	1			
AG	5 (11%)		0 (0%)				
GG	40 (89%)		30 (100%)			10.2 (0.52-198)	0.12
A	5 (5.6%)		0 (0%)			0.10 (0.00-1.88)	0.12
G	40 (94,4%)		30 (100%)			0.02 (0.00-0.49)	**0.015**

CSU: Chronic Spontaneous Urticaria; HT: Hashimoto's thyroiditis; HWE: exact test of Hardy–Weinberg equilibrium; OR: Estimated odds ratio from logistic regression adjusted for sex.

[1]n (%).

¥ Exact test of population differentiation by 100.000 steps of Markov chain and 1000 dememorization steps.
*P < 0.05.
†Genetic analysis was performed on n = 30. Eleven samples were excluded due to missing genotypes (failure to meet the ≥90% call-rate quality control threshold). Percentages are calculated based on successfully genotyped samples.

The relevance of *TNF-α* in CSU pathogenesis has been demonstrated in studies reporting elevated serum *TNF-α* levels correlated with disease activity.[29,30] Promoter polymorphisms −308 G/A and −238 G/A alter gene expression and have been linked to autoimmune diseases such as RA, SLE, and celiac disease.[19,21] However, findings across populations have been inconsistent: while an Iranian cohort showed that the G allele and GG genotype at both loci were more frequent in CSU patients[28] a Polish study found no significant association.[31] Such discrepancies likely reflect ethnic heterogeneity, sample size variation, and genetic admixture patterns, emphasizing the importance of analysing population-specific data.[31,41]

For this reason, a large-scale genome-wide meta-analysis in urticaria (including broader urticaria phenotypes beyond CSU) identified susceptibility variants implicating mast cell biology and type 2 immune pathways (including loci related to FCER1A and STAT6 signaling), highlighting the relevance of effector cell activation and immune signaling networks.[42] The study also reported robust associations at loci such as 1q44 (*GCSAML*) and 1q23.2 (*FCER1A*).[42] Furthermore, integrative analyses in that meta-analysis supported functional links between risk alleles and gene regulation in disease-relevant tissues, consistent with a contribution of mast cell–associated mechanisms to urticaria susceptibility.[42]

In addition, a GWAS focused specifically on CSU identified strong signals in the HLA region (including HLA-DQA1) and additional associations such as *ITPKB*, supporting a role for antigen presentation and adaptive immune regulation in CSU risk and heterogeneity.[43] A recent GWAS by Zhang et al[44] in a Chinese Han population identified five genome-wide significant loci for CSU, including a variant in the *PTPN22* gene (rs3789612). Notably, the *PTPN22* risk allele in that study was significantly associated with autoimmune-related CSU phenotypes, including positive anti-TPO and anti-FcεRIα autoantibodies.[43] This robust genome-wide evidence directly aligns with our candidate-gene observation, reinforcing the concept that *PTPN22* variants may contribute fundamentally to the autoimmune endotype of CSU across diverse ethnic populations.[44]

Within this framework, our candidate-gene findings involving *TNF-α* promoter variants and *PTPN22* rs2476601 should be considered complementary and hypothesis-generating rather than definitive. This is particularly relevant given differences in study design (candidate-gene approaches versus GWAS), phenotypic heterogeneity, and the potential impact of population-specific linkage disequilibrium patterns in admixed Latin American cohorts.

Regarding the *PTPN22* rs2476601 variant, this study found that the G allele showed an exploratory inverse association with CSU + HT comorbidity, which appears to contrast with findings from other international cohorts.[35,36] In international, particularly European, studies, the A allele has generally been associated with increased risk for various autoimmune diseases, including Hashimoto's thyroiditis, SLE, REis, and others.[35,36] This observation could be particularly relevant in the Latin American genetic context, where admixture among European, African, and Indigenous ancestries might influence allele frequency and the functional impact of immunoregulatory SNPs. For example, a study by Escamilla-Tilch et al[45] in a Mexican population with leprosy found an absence of the minor homozygous genotype, reported as TT on the forward strand, corresponding to the AA genotype in our reverse-strand nomenclature, and no association with

the *PTPN22* rs2476601 polymorphism. These findings are consistent with our own results, specifically, the complete absence of the AA genotype and a notably low frequency of both the AG genotype and the A allele, which were exclusively observed in the CSU group without thyroid involvement.[45]

These results suggest that, in Latin American populations, the risk possibly conferred by *PTPN22* (rs2476601) may differ from that observed in more genetically homogeneous populations. PTPN22 encodes the lymphoid tyrosine phosphatase, which functions as a key negative regulator of TCR signalling. Variations in this gene may influence autoreactive T-cell activation and potentially contribute to the loss of immune tolerance, a mechanism that could be relevant to both CSU and HT.[40,47] The combined findings for *TNF-α* and *PTPN22* may support the concept that autoimmune comorbidities in CSU could result from complex interactions between proinflammatory cytokines and adaptive signalling regulators, rather than from the isolated action of a single gene.[19,21,30,31,48]

However, clinical and genetic interpretations are constrained by several limitations. Clinically, the retrospective design lacked consistently available standardized instruments to assess CSU severity or treatment response (e.g., UAS7 reduction following omalizumab exposure), as well as validated markers to differentiate autoallergic from autoimmune endotypes (e.g., ASST/BAT or IgG anti-FcεRI/IgE).[38] Additionally, HT ascertainment relied on a composite definition, potentially introducing phenotypic heterogeneity. Genetically, because this study derives from an admixed population without ancestry-informative markers, residual confounding from population stratification cannot be excluded. Furthermore, the modest sample size (n = 86) and the very low minor allele frequency of *PTPN22* rs2476601 substantially limited statistical power, yielding an estimated post hoc power of ~55%, which reduces precision and increases the risk of inflated effect sizes.

CONCLUSIONS

Taken together, our findings provide exploratory evidence that *TNF-α* rs361525 and *PTPN22* rs2476601 could be involved in the immune pathways relevant to the coexistence of CSU and HT in this admixed population. Although the *PTPN22* rs2476601 association met the multiple-comparison threshold, these observations are strictly hypothesis-generating. They warrant confirmation in larger, adequately powered multiethnic cohorts utilizing standardized clinical severity assessments, robust genetic quality-control, and comprehensive ancestry adjustment strategies.

DECLARATIONS

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of Universidad del Norte, Barranquilla, Atlántico, Colombia (Approval No. 00062, October 15, 2021). The research was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Colombian regulations for medical research involving human participants. All participants provided written informed consent prior to inclusion in the study.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

E.E-B, A.D.V, and C.A-M conceptualized and designed the study. A.M-W and L.F performed clinical data collection. A.D.V, L.F, and C.A-M analyzed and interpreted the data. A.D.V, C.A-M, and L.F drafted the initial version of the manuscript. G.G-D.E and E.E-B critically reviewed and edited the manuscript. All authors read and approved the final version.

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Original article

Satisfaction assessment with subcutaneous immunotherapy by ESPIA questionnaire in a pediatric population with allergic phenotype asthma

Evaluación de la satisfacción con inmunoterapia por vía subcutánea mediante el cuestionario ESPIA en pacientes pediátricos con asma de fenotipo alérgico

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Abstract

OBJECTIVE: Assess satisfaction with subcutaneous immunotherapy in patients with asthma, by using the Satisfaction Scale for Patients Receiving Allergen Immunotherapy (ESPIA) questionnaire which was validated in Spanish language.

METHODS: A cross-sectional, observational, unicenter study was carried out in a National Allergy Reference Center in Mexico in patients older than 6 years of age, diagnosed with Allergic Asthma with positive allergy biomarkers (IgE, Skin Tests, Nasal Mucus Cytology, Eosinophils in Blood) with a mild or moderate severity classification with a Subcutaneous Immunotherapy scheme lasting a minimum of 12 months. The level of satisfaction was assessed during the treatment by the ESPIA questionnaire, and the level of control was measured by using the Asthma Control Test. The correlation between the characteristics of the population, the control of the disease, the severity of the disease and the satisfaction with the treatment was analyzed using the ANOVA test (categorical variables) or the Pearson and Spearman coefficients correlation (continuous variables).

RESULTS: A total of 147 patients (mean age 10.08 years, range 4-17 years, 82 men [56%]) were included in the study. Among them 122 (82.9%) suffered some type of comorbidity. The average Score of the ESPIA questionnaire to measure Satisfaction of treatment with Subcutaneous Immunotherapy was 87.12. No statistical differences were found in treatment satisfaction between men and women ($p>0.05$) and between polysensitized patients with more than 3 allergens and with less than 3 allergens. ($p>0.05$). There was a lower level of satisfaction with Immunotherapy measured with the ESPIA questionnaire in patients with comorbidity of Atopic Dermatitis. A correlation was demonstrated between levels of disease control and levels of satisfaction with treatment with Subcutaneous Immunotherapy measured with the ESPIA Questionnaire.

CONCLUSION: Subcutaneous allergen immunotherapy was associated with high treatment satisfaction in pediatric patients with allergic asthma. Treatment satisfaction showed a positive correlation with asthma control, supporting the clinical relevance of patient-reported outcomes in the evaluation of immunotherapy effectiveness.

KEYWORDS: Allergic asthma; ESPIA questionnaire; Quality of life; Satisfaction; Asthma control; Subcutaneous immunotherapy.

Resumen

OBJETIVO: Evaluar el grado de satisfacción de la inmunoterapia por vía subcutánea en pacientes pediátricos con asma, mediante el cuestionario ESPIA (Escala de Satisfacción para Pacientes que Reciben Inmunoterapia con Alérgenos), validado en español.

MÉTODOS: Estudio transversal, observacional y unicéntrico, llevado a cabo en un centro nacional de referencia de alergia en México, con pacientes mayores de 6 años, diagnosticados de asma alérgica con biomarcadores positivos (IgE, pruebas cutáneas, citología de moco nasal, eosinófilos en sangre) de gravedad leve o moderada, que recibieron un esquema de inmunoterapia por vía subcutánea con duración mínima de 12 meses. El grado de satisfacción se evaluó con el cuestionario ESPIA, y el control mediante la Prueba de Control del Asma. Se analizó la correlación entre las características de la población, el control de la enfermedad, la gravedad de la enfermedad y la satisfacción con el tratamiento mediante la prueba ANOVA (variables categóricas) o los coeficientes de correlación de Pearson y Spearman (variables continuas).

RESULTADOS: Se incluyeron 147 pacientes (edad media 10.08 años, rango 4-17 años, 82 hombres [56%]), de los que 122 (82.9%) tuvieron algún tipo de comorbilidad. La puntuación media del cuestionario ESPIA fue de 87.12. No se encontraron diferencias estadísticamente significativas en la satisfacción con el tratamiento entre hombres y mujeres ($p>0.05$) ni entre pacientes polisensibilizados con más o menos de 3 de 3 alérgenos ($p>0.05$).

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Se observó un menor grado de satisfacción con la inmunoterapia, con el cuestionario ESPIA, en pacientes con dermatitis atópica como comorbilidad. Se demostró una correlación entre el control de la enfermedad y la satisfacción con el tratamiento mediante inmunoterapia subcutánea, medida con el cuestionario ESPIA.

CONCLUSIÓN: La inmunoterapia subcutánea con alérgenos se asoció con alto grado de satisfacción en pacientes pediátricos con asma alérgica. La satisfacción con el tratamiento mostró una correlación positiva con el control del asma, lo que respalda la relevancia clínica de la eficacia de la inmunoterapia.

PALABRAS CLAVE: Asma alérgica; Cuestionario SPY; Calidad de vida; Satisfacción; Control del asma; Inmunoterapia subcutánea

INTRODUCTION

Asthma is defined by major international guidelines, including GINA, GEMA, and GUIMA, as a heterogeneous disease characterized by chronic airway inflammation. This condition is manifested by a history of respiratory symptoms such as wheezing, dyspnea, chest tightness, and cough, which vary over time and in intensity, along with variable or reversible expiratory airflow limitation.[1-3] The World Health Organization estimates that approximately 300 million individuals worldwide are affected by asthma, making it the most common chronic disease in the pediatric population.1-3 The global prevalence of asthma ranges from 1 to 18%. In Latin America, data from the International Study of Asthma and Allergies in Childhood (ISAAC) indicate a high prevalence of asthma symptoms, affecting approximately 17% of children aged 6-7 years and 15% of adolescents aged 13–14 years. In Mexico, ISAAC data have documented prevalence rates ranging from 5% to 14% across different urban areas.[4]

Asthma-related mortality continues to represent a significant global burden, with approximately 180,000 deaths reported annually. Mortality rates vary considerably across continents, age groups, and socioeconomic settings. In Mexico, data based on the International Classification of Diseases (ICD-10) recorded 1,296 asthma-related deaths in 2015. The economic burden of asthma also differs substantially by region, with estimated average annual costs per patient of approximately USD 1,900 in Europe and USD 3,100 in the United States.[5]

For research and clinical purposes, asthma has been classified into distinct phenotypes and endotypes. According to GINA, five major phenotypes are recognized: allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma associated with obesity. Among these, allergic asthma represents the most prevalent phenotype.[1-3]

The main aims of asthma management are to keep symptoms under control over time, prevent flare-ups, protect lung function, and lower the chances of illness and death caused by asthma. In this context, allergen immunotherapy (AIT) offers a one-of-a-kind long-term treatment option for people with IgE-mediated respiratory allergy. In addition to reducing symptoms and medication requirements, AIT is currently the only intervention shown to modify the natural course of allergic disease.

The immunological mechanisms underlying AIT involve allergen-specific desensitization characterized by reduced mast cell and basophil reactivity, mediated in part by increased expression of histamine type 2 receptors (H2R) on immune cells, along with a progressive decrease in allergen-specific IgE levels. This process is accompanied by immune deviation from Th2 and Th2A lymphocytes toward tolerogenic regulatory T and B cell populations, with increased production of IL-10, TGF-β, IgA, and IgG4. IgG4 antibodies exert blocking activity by inhibiting IgE-mediated inflammation through engagement of inhibitory Fcγ-RIIB (CD32) receptors on antigen-presenting and effector cells. The persistence of these mechanisms, together with the involvement of follicular regulatory T cells (Tfr) in secondary lymphoid organs, promotes long-term immune tolerance through allergen-specific T-cell anergy and clonal deletion.[6-8]

Current international guidelines from GUIMIT, EAACI, ACAAI, and DGAKI recommend allergen immunotherapy for children and adults who have mild to moderate allergic asthma and are clearly sensitive to important aeroallergens, especially house dust mites and pollens. In these groups, solid evidence shows that asthma control gets better, symptoms ease up, medication use decreases, and quality of life improves. There is moderate evidence that using it helps patients who are sensitive to cat, dog, or cockroach allergens, mostly by cutting down their symptoms and the need for medication.[9-11]

International asthma management guidelines (GINA, GEMA, GUIMA) recommend subcutaneous allergen immunotherapy (SCIT) in children older than six years and in adults with well-controlled allergic asthma receiving low- to medium-intensity pharmacologic treatment (therapeutic steps 2–4), provided that clinically relevant IgE-mediated sensitization to common aeroallergens has been demonstrated and standardized, well-characterized extracts are used. Allergen immunotherapy is recommended in adult patients with asthma and allergic rhinitis sensitized to house dust mites who have persistent asthma symptoms despite low- to medium-dose inhaled corticosteroids and a forced expiratory volume in one second (FEV_1) greater than 70% of predicted values (steps 3–4). Across all guidelines, additional benefits of AIT include sustained clinical efficacy after treatment discontinuation, reduced risk of asthma development in patients with allergic rhinitis or conjunctivitis, prevention of new allergen sensitizations in monosensitized individuals, and its unique role as a disease-modifying therapy.[1-3,9-11]

Even though allergen immunotherapy is widely used in clinics, there isn't much information about how satisfied patients feel about the treatment, especially among people in Latin America and Mexico. Treatment satisfaction is a clinically relevant outcome, as it may influence adherence, long-term persistence, and real-world effectiveness. Validated instruments such as the ESPIA questionnaire offer a structured and reliable approach to evaluating patient satisfaction with allergen immunotherapy in routine clinical practice.[17]

Based on the above, the objective of the study was: assess satisfaction with subcutaneous immunotherapy in patients with asthma, by using the Satisfaction Scale for Patients Receiving Allergen Immunotherapy (ESPIA) questionnaire which was validated in Spanish language.

METHODS

Study design and population

A single-center, observational, cross-sectional study was conducted at a National Referral Center for Allergy and Clinical Immunology in Mexico. Patients aged 6 years and older with a confirmed diagnosis of allergic asthma were consecutively recruited during routine follow-up visits.

Allergic asthma was defined by the presence of clinical symptoms consistent with asthma and objective evidence of IgE-mediated sensitization, demonstrated by at least one of the following biomarkers: elevated total or allergen-specific IgE levels, positive skin prick testing to clinically relevant aeroallergens, nasal mucus cytology with eosinophilia, and/or peripheral blood eosinophilia.

Eligible patients had mild or moderate asthma severity, according to international guidelines, and had been receiving subcutaneous allergen immunotherapy (SCIT) for a minimum of 12 consecutive months. Administration was parent-assisted in younger children.

Exclusion criteria included interruption of immunotherapy for more than 30 days, use of any alternative immunotherapy modality, treatment with systemic immunosuppressive agents, or inability to complete study questionnaires. Patients who discontinued immunotherapy before 12 months of treatment (dissatisfaction, adverse events, or other reasons) were excluded from the study.

Written informed consent was obtained from all participants or from parents/legal guardians when applicable. The study was approved by the Local Bioethics Committee of the Department of Clinical Immunology and Allergy and was conducted in accordance with the principles of the Declaration of Helsinki.

Treatment satisfaction assessment

Treatment satisfaction with allergen immunotherapy was assessed using the Satisfaction Scale for Patients Receiving Allergen Immunotherapy (ESPIA). This instrument consists of 16 items grouped into four domains: perceived efficacy, activities and environment, cost–benefit balance, and overall satisfaction. ESPIA questionnaires were completed by parents or caregivers in younger children, and jointly with patients in older children and adolescents.

The total ESPIA score was calculated by summing item responses, yielding an initial score range of 0–80, which was subsequently transformed to a standardized scale from 0 to 100. Lower scores indicate poorer satisfaction, whereas higher scores reflect greater treatment satisfaction.

Disease control assessment

Asthma control was evaluated using the Asthma Control Test (ACT). Patients aged ≥12 years completed the ACT questionnaire, and disease control was classified according to established cut-off values as well-controlled asthma, partially controlled asthma, or poorly controlled asthma.

Disease severity classification

Asthma severity was classified in accordance with recommendations from the Global Initiative for Asthma (GINA) and the Mexican Asthma Guidelines (GUIMA), based on the level of treatment required to achieve disease control:

- Mild asthma: adequate control with Step 1 or Step 2 therapy
- Moderate asthma: adequate control with Step 3 therapy
- Severe asthma: requirement of Step 4 or Step 5 therapy to maintain control

Statistical analysis

Statistical analysis was performed using SPSS software, version 24 (IBM Corp., Armonk, NY, USA). Associations between population characteristics, asthma control, asthma severity, and treatment satisfaction were analyzed using analysis of variance (ANOVA) for categorical variables, and Pearson or Spearman correlation coefficients for continuous variables, as appropriate.

A descriptive analysis of ESPIA questionnaire results was conducted. Overall satisfaction with subcutaneous allergen immunotherapy in bronchial asthma was expressed as a continuous variable on a 0–100 scale.

RESULTS

A total of 147 patients with allergic asthma receiving subcutaneous allergen immunotherapy (SCIT) were included in the analysis. The mean age of the study population was 10.08 years. Overall, 82% of patients presented at least one allergic comorbidity, with allergic rhinitis being the most frequent (38%). **Table 1**

The mean duration of SCIT at the time of evaluation was 2.2 years. At baseline, prior to initiation of immunotherapy, 82% of patients exhibited poorly controlled asthma. Following treatment with SCIT, only 2.7% of patients remained poorly controlled, while 92% achieved well-controlled asthma.

Mean treatment satisfaction, assessed using the ESPIA questionnaire, was 87.12 points (SD: 12.57), corresponding to a high level of satisfaction. A positive and direct correlation was observed between asthma control and treatment satisfaction scores. **Figure 1**

No statistically significant differences in ESPIA scores were observed between male and female patients ($P > .05$), nor between patients polysensitized to more than three allergens compared with those sensitized to three or fewer allergens ($P > .05$). Conversely, patients with atopic dermatitis as a comorbidity exhibited significantly lower satisfaction scores compared with those without this condition. **Figure 2**

Correlation between treatment satisfaction and asthma control

A strong and statistically significant positive correlation was observed between treatment satisfaction assessed by the ESPIA questionnaire and asthma control during follow-up

Table 1. Baseline characteristics of the study population (n = 147).

Variable	n (%)
Sex, n (%)	
Male	**82 (56%)**
Female	**65 (44%)**
Age	**10.08**
Presence of comorbidities, n (%)	**122 (82.9%)**
Allergic rhinitis	**57 (38.77%)**
Allergic conjunctivitis	**19 (12.9%)**
Allergic rhinoconjunctivitis	**32 (21.7%)**
Atopic dermatitis	**11 (7.4%)**
Pollen–Food Syndrome	**3 (2%)**
Duration of subcutaneous immunotherapy, mean (years)	**2.2**
Number of allergens in SCIT, n (%)	
≤3 allergens	**89 (60.55%)**
>3 allergens	**58 (39.45%)**
Total serum IgE, mean (IU/mL)	**585.14**
Blood eosinophils, mean (cells/µL)	**453.9**
ESPIA satisfaction score, mean (0-100)	**87.12**
• Asthma Control Test (ACT) score, mean	
At diagnosis	
During follow-up with SCIT	**13.42**
• Asthma control classification at diagnosis, n (%)	**22.10**
Poorly controlled asthma	
Partially controlled asthma	**121 (82.3%)**
Well-controlled asthma	**25 (17%)**
• Asthma control classification during SCIT, n (%)	**1 (0.6%)** **22.10**
Poorly controlled asthma	
Partially controlled asthma	**4 (2.7%)**
Well-controlled asthma	**22 (14.9%)** **121 (82.3%)**

ACT: Asthma Control Test; ESPIA: Satisfaction Scale for Patients Receiving Allergen Immunotherapy; SCIT: Subcutaneous Immunotherapy.

Asthma control was classified according to ACT score as follows: poorly controlled asthma (ACT ≤15), partially controlled asthma (ACT 16–19), and well-controlled asthma (ACT≥20).

The ESPIA questionnaire yields a total score ranging from 0 (lowest satisfaction) to 100 (highest satisfaction).

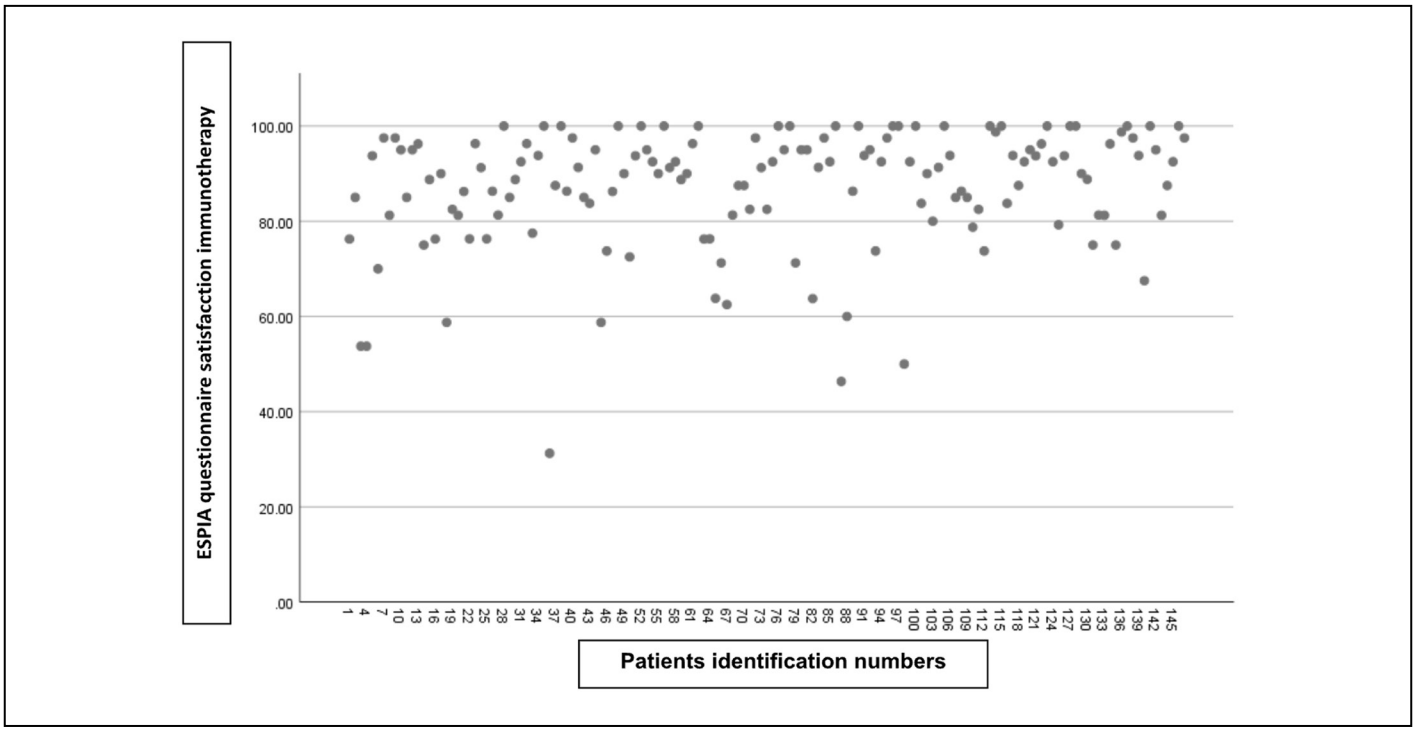

Figure 1. Individual distribution of patient satisfaction scores assessed by the ESPIA questionnaire.Each dot represents the total ESPIA score (0–100) for an individual patient receiving subcutaneous allergen immunotherapy. The x-axis corresponds to anonymized patient identification numbers, while the y-axis indicates the level of satisfaction with immunotherapy.

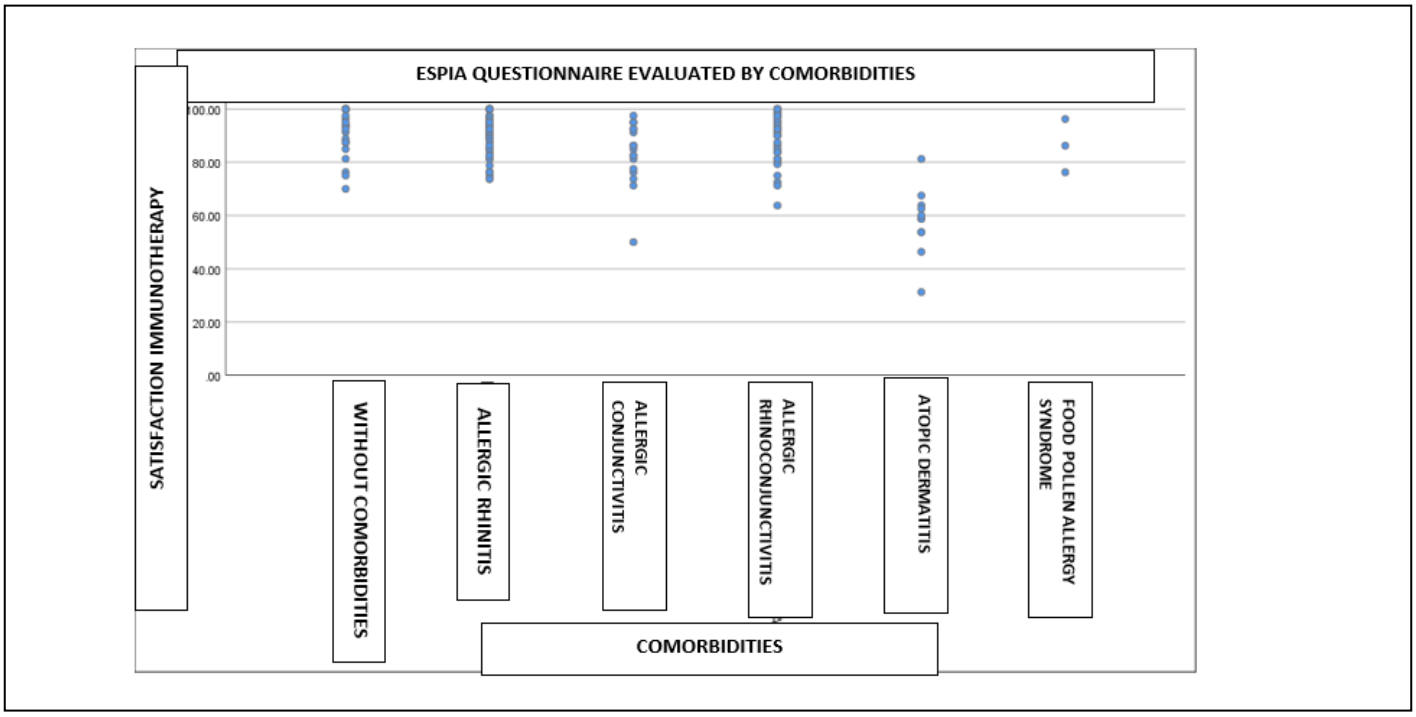

Figure 2. Patient satisfaction with subcutaneous allergen immunotherapy according to associated allergic comorbidities. ESPIA questionnaire scores (0–100) are shown stratified by the presence and type of allergic comorbidities, including no comorbidities, allergic rhinitis, allergic conjunctivitis, allergic rhinoconjunctivitis, atopic dermatitis, and oral allergy syndrome.

under subcutaneous immunotherapy. ESPIA scores correlated closely with follow-up ACT scores ($r = 0.91$, $p<0.001$; $n = 81$), indicating that higher perceived satisfaction was associated with better asthma control during SCIT. **Figures 3** and **4**

Correlation analysis revealed a moderate and statistically significant positive association between treatment satisfaction (ESPIA score) and asthma control during follow-up (ACT score) ($r = 0.499$, $p<0.001$). In contrast, no significant correlations were observed between ESPIA scores and total serum IgE levels ($r = 0.083$, $p = 0.317$) or peripheral blood eosinophil counts ($r = 0.047$, $p = 0.571$). **Table 2** and **3**

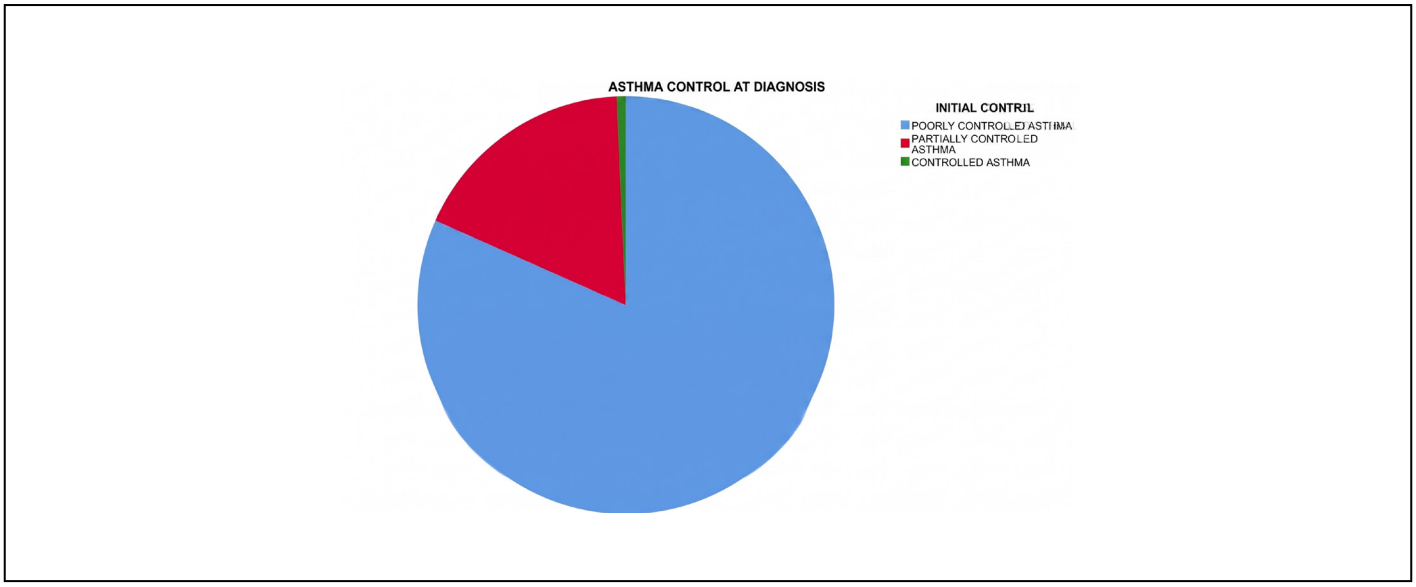

Figure 3. Baseline asthma control according to ACT score at diagnosis. Distribution of asthma control levels at the time of diagnosis based on the Asthma Control Test (ACT). Most patients presented with poorly controlled asthma, while a smaller proportion showed partially controlled asthma, and only a minimal percentage had well-controlled disease at baseline.

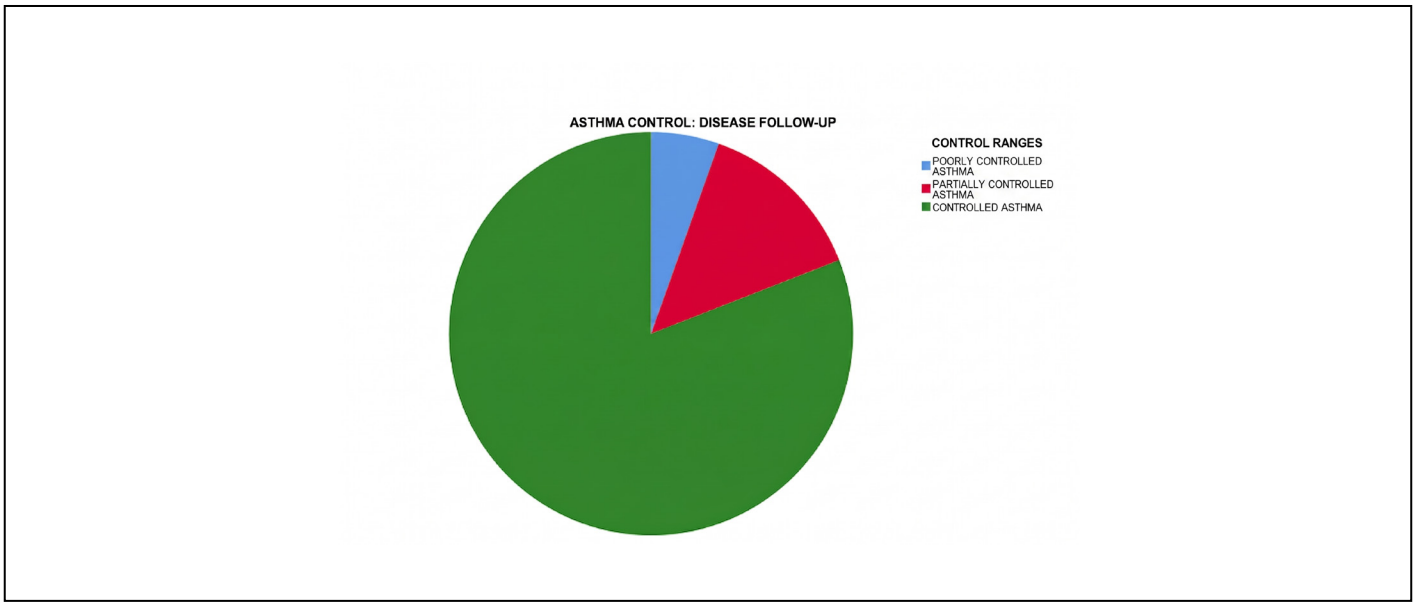

Figure 4. Asthma control according to ACT score during follow-up after subcutaneous immunotherapy. Distribution of asthma control levels during follow-up after subcutaneous immunotherapy, evaluated using the Asthma Control Test (ACT). A marked shift toward well-controlled asthma was observed, with a significant reduction in poorly controlled cases compared with baseline.

Table 2. Descriptive statistics of treatment satisfaction, immunological parameters, and asthma control during follow-up.

Variable	Mean	Median
ESPIA score (0–100)	87.12	91.25
Total IgE (IU/mL)	585.15	278.00
Blood eosinophils (cells/µL)	479.95	400.00
ACT follow-up score	22.56	23.00

Table 3. Correlation between treatment satisfaction (ESPIA score), asthma control, and immunological markers.

Comparison	r	p
ESPIA vs ACT (follow-up)	**0.499**	**< 0.001**
ESPIA vs Total IgE	0.083	0.317
ESPIA vs Blood eosinophils	0.047	0.571

DISCUSSION

Allergen-specific immunotherapy has historically been considered a controversial or adjunctive treatment for allergic asthma and is often positioned as an alternative therapy within international asthma management guidelines. Nevertheless, substantial evidence supports its clinical benefits. Abramson et al. demonstrated in a comprehensive meta-analysis that allergen immunotherapy significantly reduces asthma symptoms, medication use, and allergen-specific bronchial hyperresponsiveness across multiple randomized controlled trials.[12]

Further studies have reinforced these findings. Omnes et al. reported a favorable cost–benefit relationship of allergen immunotherapy in patients with allergic rhinitis and asthma secondary to pollen and house dust mite sensitization. Petersen et al. demonstrated significant improvements in quality of life among patients receiving SCIT for allergic rhinitis and/or allergic asthma.13 Long-term disease-modifying effects have also been documented; Möller et al. reported that SCIT administered for allergic rhinitis conferred a protective effect against the subsequent development of asthma, while Inal et al. observed a reduced incidence of new allergen sensitizations in pediatric patients undergoing immunotherapy.[14-15]

Despite these well-documented benefits and the relatively low risk of serious adverse events, the utilization of allergen immunotherapy remains remarkably low worldwide. Hankin and Law reported that only 2–9% of eligible allergic patients receive allergen immunotherapy, suggesting persistent gaps in awareness, access, and physician adoption of this disease-modifying treatment.[16]

Patient satisfaction represents a critical determinant of treatment adherence, and low satisfaction has consistently been associated with premature discontinuation of therapy. However, data evaluating satisfaction with allergen immunotherapy in patients with allergic asthma are scarce, and to our knowledge, no prior studies have addressed this outcome in the Mexican population.

In the present study, the presence of atopic dermatitis was associated with lower satisfaction scores with subcutaneous allergen immunotherapy (SCIT). Although this finding was not the primary objective of the study, it is clinically relevant and warrants consideration within the context of multisystem atopic disease. Moreover, expectations regarding allergen immunotherapy may differ in patients with concomitant atopic dermatitis. While SCIT is well established for allergic asthma and rhinitis, its effects on cutaneous manifestations are less consistent, potentially leading to unmet expectations and lower perceived benefit.

The present study demonstrates a high level of satisfaction with subcutaneous allergen immunotherapy among pediatric patients with allergic asthma, which correlates strongly with improved asthma control. These findings underscore the relevance of incorporating patient-reported outcomes, such as satisfaction, into the evaluation of immunotherapy effectiveness and support the broader implementation of SCIT in appropriately selected patients with allergic asthma.

Only patients who completed at least 12 months of subcutaneous immunotherapy were included, which may introduce survivorship bias and overestimate satisfaction levels by excluding early discontinuations. In addition, satisfaction was assessed at a single time point, limiting causal inferences regarding treatment adherence over time.

CONCLUSIONS

Subcutaneous allergen immunotherapy demonstrated high treatment satisfaction among pediatric patients with allergic asthma, as assessed by the ESPIA questionnaire. Treatment satisfaction showed a significant positive correlation with asthma control, supporting the close relationship between perceived therapeutic benefit and objective disease management. These findings reinforce the clinical value of subcutaneous allergen immunotherapy as a disease-modifying intervention in appropriately selected pediatric patients with allergic asthma and highlight the importance of incorporating patient-reported outcomes into routine clinical evaluation.

STATEMENTS

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Conflict of interest statement

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Ethical approval

This study was approved by the Institutional Review Board. Written informed consent was obtained from all participants, including consent for the use of photographs and personal data (**Appendix 1**).

Author contributions

Javier Hernández-Romero: contributed to patient recruitment, sample collection, and performance of diagnostic procedures. Contributed to study conception and design, patient recruitment, diagnostic testing, statistical analysis, and manuscript drafting. Andrea Aida Velasco-Medina contributed to diagnostic testing, data interpretation, and critical revision of the manuscript. Guillermo Velázquez-Sámano contributed to study supervision, data analysis, and critical review of the manuscript. Omar Delgado Martínez contributed to patient recruitment, sample collection.

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All figures and paintings are original.

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HOSPITAL GENERAL DE MEXICO "DR EDUARDO LICEAGA"
DIRECCION GENERAL ADJUNTA MÉDICA
LICENCIA SANITARIA No. 13 AM 09 015 0005
ALERGIA E INMUNOLOGIA CLINICA

Con el objeto de conocer su opinión respecto al uso de vacunas, le solicitamos de su colaboración para el llenado de la siguiente encuesta.

NOMBRE DEL PACIENTE:	EXPEDIENTE:
MEDICO TRATANTE:	CO:
FECHA DE INICIO DE INMUNOTERAPIA:	EDAD:
CON QUE FRECUENCIA SE ADMINISTRA LA VACUNA:	
ACEPTA QUE SE LE REALICE LA ENCUESTA:	

¿En que momento notó mejoria de sus molestias?	menos de 3 meses	3 a 6 meses	6 a 9 meses	9 a 12 meses	más de 12 meses

	SIEMPRE	MUCHAS VECES	LA MITAD DEL TIEMP	DE VEZ EN CUANDO	NUNCA
1. Desde que me vacuno para la alergia, tengo menos sintomas					
2. Mi vacuna funciona					
3. Gracias a la vacuna estoy menos pendiente de llevar encima otros farmacos (pastillas, inhaladores, etc.)					
4. Mi vacuna funciona más rápido de lo que esperaba.					
5. Gracias a la vacuna ya no evito cosas ni lugares que antes me causaban alergia					
6. Mi vacuna me ayuda a realizar mis actividades diarias.					
7. Desde que me vacuno puedo ir a cualquier sitio con mi familia o amigos.					
8. Gracias a la vacuna puedo trabajar o estudiar mejor.					
9. Desde que me vacuno disfruto más de las actividades al aire libre					
10. Desde que me vacuno no me encuentro en situaciones incomodas o comprometidas causadas por la alergia.					
11. Desde que me vacuno he ganado calidad de vida.					
12. El buen funcionamiento de la vacuna me compensa todas las gestiones que tengo hacer para conseguirla (visitas, recetas, permisos, etc)					
13. El buen funcionamiento de la vacuna compensa el esfuerzo economicoque me ocasiona.					
ocasionarme.					
15. En general, estoy satisfecho con mi vacuna para la alergia					
16. En general, recomendaría el tratamiento con vacuna a otras personas.					
Puntuación (Llenada por el encuestador)					

Ciudad de México a _____ de _____ de 201_____.

Gracias por su colaboración.

Appendix 1. Patient assessment questionnaire format.

RAM
Revista Alergia México

Original article

Effect of feeding regimen on the acquisition of immunological tolerance in mexican infants with IgE-mediated cow's milk protein allergy

Efecto del esquema de alimentación en la adquisición de tolerancia inmunológica en lactantes mexicanos con alergia a la proteína de leche de vaca mediada por IgE

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Abstract

OBJECTIVE: To compare the rate of tolerance acquisition in Mexican infants with IgE-mediated cow's milk protein allergy, fed according to three dietary regimens.

METHODS: A retrospective, observational cohort study was conducted on infants diagnosed with cow's milk protein allergy between 1 and 3 months of age, divided into three groups according to their feeding regimen: 1) exclusive breastfeeding with an elimination diet, 2) amino acid-based formula, and 3) hydrolyzed rice formula. Clinical characteristics, wheal size in skin prick tests against casein, alpha-lactalbumin, and beta-lactoglobulin, adherence to treatment, and coexisting allergic comorbidities were evaluated. Tolerance acquisition was determined by an open oral challenge test with whole milk after 12 months on an elimination diet. Comparative analyses and multivariate logistic regression were performed to identify associated factors.

RESULTS: 285 infants were selected and assigned to one of three study groups (n = 95 per group). 62.1% achieved clinical tolerance at the end of the follow-up period. The highest proportion was observed in the exclusive breastfeeding group (78.9%), followed by the amino acid-based formula group (68.4%) and the hydrolyzed rice formula group (65.3%), with no statistically significant differences between the regimens (p = 0.094). Adherence to the dietary treatment was significantly associated with the acquisition of tolerance in the multivariate model, while allergic comorbidities were associated with a lower probability of clinical cure.

CONCLUSIONS: The elimination diet is associated with the acquisition of tolerance in a considerable proportion of infants with IgE-mediated cow's milk protein allergy. Although no superiority was identified among the dietary regimens, the findings suggest that adherence to treatment plays a determining role in clinical outcomes and should be considered a central component in the management of the disease.

KEYWORDS: Infants; IgE-mediated cow's milk protein allergy; Allergy; Casein; Alpha-lactalbumin; Beta-lactoglobulin; Elimination diet; Exclusive breastfeeding.

Resumen

OBJETIVO: Comparar la tasa de adquisición de tolerancia en lactantes mexicanos con alergia a la proteína de leche de vaca mediada por IgE, alimentados con tres esquemas dietéticos.

MÉTODOS: Estudio observacional, retrospectivo, de tipo cohorte, efectuado en lactantes diagnosticados con alergia a la proteína de leche de vaca entre 1 y 3 meses de edad, distribuidos en tres grupos según el esquema de alimentación: *1)* lactancia materna exclusiva con dieta materna de eliminación, *2)* fórmula con aminoácidos y *3)* fórmula hidrolizada de arroz. Se evaluaron las características clínicas, tamaño del habón en las pruebas cutáneas frente a caseína, alfa-lactoalbúmina y beta-lactoglobulina, apego al tratamiento y coexistencia de comorbilidades alérgicas. La adquisición de tolerancia se determinó mediante la prueba de provocación oral abierta con leche entera después de 12 meses de dieta de eliminación. Se realizaron análisis comparativos y regresión logística multivariada para identificar los factores asociados.

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RESULTADOS: Se seleccionaron 285, asignados a uno de los tres grupos de estudio (n = 95 por grupo). El 62.1% tuvo tolerancia clínica al final del seguimiento. La mayor proporción se observó en el grupo de lactancia materna exclusiva (78.9%), seguido de fórmula con aminoácidos (68.4%) y fórmula hidrolizada de arroz (65.3 %), sin diferencias estadísticamente significativas entre los esquemas (p = 0.094). El apego al tratamiento dietético se asoció significativamente con la adquisición de tolerancia en el modelo multivariado, mientras que las comorbilidades alérgicas se relacionaron con menor probabilidad de curación clínica.

CONCLUSIONES: La dieta de eliminación se asocia con adquisición de tolerancia en una proporción considerable de lactantes con alergia a la proteína de leche de vaca mediada por IgE. Aunque no se identificó superioridad entre los esquemas dietéticos, los hallazgos sugieren que el apego al tratamiento desempeña un papel determinante en la evolución clínica y debe considerarse un componente central en el tratamiento de la enfermedad.

PALABRAS CLAVE: Lactantes; Alergia a las proteínas de la leche de vaca mediada por IgE; Alergia; Caseína; Alfa-lactoalbúmina; Beta-lactoglobulina; Dieta de eliminación; Lactancia materna exclusiva.

BACKGROUND

Cow's milk protein allergy (CMPA) is one of the most frequent allergic diseases in childhood. Its global prevalence is estimated to range between 2% and 7.5% in infants under one year of age, although these figures depend on the type of population, diagnostic method, and criteria used.[1,2,3,4] Of these cases, between 40% and 60% correspond to immunoglobulin E (IgE)-mediated forms, characterized by the rapid manifestation of symptoms after the consumption of milk proteins and a positive prick test.[5,6]

In Latin America, the prevalence of CMPA has been less documented, although various studies agree that it is within the same range as that reported globally. In countries such as Argentina, Brazil, and Chile, local research estimates an incidence between 2% and 5% in children under 1 year of age.[7] In Mexico, epidemiological evidence has increased in recent decades. A cross-sectional study in university students in Guadalajara found a prevalence of 1.4%, while in the María Inmaculada Clinic in Mexico City, 650 cases were documented between 2010 and 2015 in children under 9 years of age.[8] A recent analysis, published in *Acta Pediátrica Mexicana*, indicates that, despite greater diagnostic awareness, cases remain underestimated due to a lack of unified criteria and insufficient application of confirmatory tests such as the double-blind, placebo-controlled oral challenge.[9]

Although Mexico has national clinical guidelines and adheres to Latin American consensuses for CMPA treatment,[10] there is still little local evidence with robust comparative designs evaluating the immunological effect of different feeding regimens and standardized follow-up.[11,12,13] Most Mexican studies are simple observational studies or case reports that do not evaluate the evolution of sensitization or long-term tolerance rates.

The treatment of patients with CMPA, in both its IgE-mediated and non-IgE-mediated forms, is based on the total elimination of cow's milk proteins from the infant's diet.[14,15] The most common dietary strategies include breastfeeding with an elimination diet, amino acid-based formulas, and hydrolyzed rice formulas. Recent studies have shown that amino acid formulas enriched with synbiotics can accelerate immunological tolerance. Likewise, it has been found that breastfeeding with strict exclusion of dairy can be effective in symptom control.[16-19] In Mexico, rice formulas have been offered as a culturally accepted and clinically safe alternative.

Despite the recognition of these dietary strategies, there is little direct comparative evidence between them regarding the development of tolerance at 12 months of consumption. Factors such as adherence to the diet, cultural context, and clinical follow-up influence immunological evolution.

Cow's milk protein allergy usually appears during the first 12 months of life, coinciding with the introduction of infant formulas or complementary feeding. Symptoms of IgE-mediated CMPA include: urticaria, angioedema, vomiting, diarrhea, persistent crying, wheezing, or anaphylaxis.[20] The main proteins involved are caseins and those from the whey (beta-lactoglobulin and alpha-lactalbumin). Casein is considered the most allergenic and thermostable, persisting even after pasteurization.[21]

Several studies have shown that CMPA, especially in its IgE-mediated form, can precede the development of other allergic diseases: atopic dermatitis, asthma, rhinitis, or food allergies, a phenomenon known as the "atopic march." Clinical follow-up of patients must consider this type of complex immunological evolution.[22]

This study aims to compare the tolerance rate in Mexican infants diagnosed with IgE-mediated cow's milk protein allergy, fed according to different regimens. This seeks to provide useful local evidence to guide clinical decision-making in the treatment of this disease and optimize available therapeutic resources.

METHODS

Retrospective, observational, analytical, and comparative cohort study, conducted in infants seen at a private pediatric allergy practice between January 2017 and December 2024. Patients aged 1 to 3 months with clinical suspicion of IgE-mediated cow's milk protein allergy and diagnostic confirmation with a positive skin prick test to one or more milk allergens (casein, alpha-lactalbumin, and beta-lactoglobulin) were selected, using standardized extracts with a current sanitary registration in Mexico (IPI ASAC®). All patients had a minimum clinical follow-up of 12 months. Patients with primary or secondary immunodeficiencies, metabolic disorders, chronic gastrointestinal diseases, loss to follow-up before 12 months, or combined use of more than one feeding regimen during the observation period were excluded.

Patients were grouped according to the dietary treatment prescribed into three cohorts: 1) exclusive breastfeeding (EBF; maternal diet free of dairy and traces), 2) amino acid-based formula (AA), and 3) hydrolyzed rice formula (HR). Assignment to the feeding regimen was based on clinical indication and family possibilities, so it was not randomized.

During the monthly follow-up, the following were recorded: wheal size in the baseline prick test at 12 months, adherence to dietary treatment, coexistence of allergic comorbidities

(atopic dermatitis, rhinitis, infant wheezing, and conjunctivitis), and a family history of atopy in the first degree.

Adherence to treatment was classified as: good, fair, or poor through a retrospective review of clinical records, considering the dietary compliance reported by caregivers during follow-up consultations and the documentation of accidental exposures. This classification was performed independently of the oral challenge test result. No formal validated instrument was implemented for its measurement.

At the 12-month follow-up, an open oral food challenge test with whole milk was performed under the supervision of the pediatric allergist. The test was considered positive upon the appearance of clinical signs compatible with an immediate allergic reaction and negative in the absence of symptoms, interpreted as the acquisition of clinical tolerance.

A descriptive analysis was performed using frequencies, means, and standard deviations. Comparisons between groups were made using the χ^2 test for categorical variables and analysis of variance (ANOVA) for comparison of means. Comparisons between specific proteins using ANOVA were interpreted in an exploratory context, without formal correction for multiple comparisons. To identify factors associated with the acquisition of tolerance, a multivariate logistic regression model was constructed, expressing the results in odds ratios (OR) with 95% confidence intervals. The stability of the model was evaluated using the number of events per variable (>10), the Hosmer–Lemeshow test, and collinearity analysis. A p-value < 0.05 was considered statistically significant. IBM SPSS version 28 software and Python were used for statistical analysis.

RESULTS

We analyzed 285 records of Mexican infants diagnosed with IgE-mediated cow's milk protein allergy, distributed equally into three feeding regimens (n = 95 per group). Baseline characteristics are shown in **Table 1**. No significant differences were observed between the groups regarding age at diagnosis (p = 0.077), gender distribution (p = 0.684), or baseline wheal size for casein (p = 0.950). In contrast, significant differences were identified in baseline values for alpha-lactalbumin (p < 0.001) and beta-lactoglobulin (p = 0.003), as well as in allergic comorbidities (p = 0.041) and family history of atopy (p = 0.008).

Casein was the protein with the highest initial skin reactivity, with an average wheal size of 4.45 mm, higher than that observed for alpha-lactalbumin (4.04 mm) and beta-lactoglobulin (3.41 mm); ANOVA, p < 0.00001. By feeding regimen, the highest baseline reactivity for casein was observed in the exclusive breastfeeding group (4.79 mm), followed by the group that received amino acid-based formula (4.13 mm) and hydrolyzed rice formula (3.96 mm). After 12 months of dietary intervention, the wheal size for this protein decreased to approximately 1.1–1.4 mm in all groups, with the largest absolute reduction in group 1 (−3.39 mm; **Figure 1**). For alpha-lactalbumin, the amino acid formula group showed the highest baseline reactivity (4.58 mm) and also the largest reduction (−3.58 mm), reaching an average value of 1.00 mm at 12 months. In the exclusive breastfeeding group, the reduction was −3.17 mm, while in the hydrolyzed rice formula group, it was −2.34 mm. Regarding beta-lactoglobulin, the group that received amino acid formula showed the largest decrease, going from 3.64 mm to 1.58 mm (−2.06 mm), compared to −1.78 mm in group 1 and −0.98 mm in group 3 (detailed values for wheal size reduction by protein and feeding regimen are shown in **Table 2**).

Adherence to dietary treatment was classified as good in 57.9% of cases, fair in 22.1%, and poor in 20%. The group that received hydrolyzed rice formula reported the highest proportion of good adherence (76.8%), compared to 68.4% in the breastfeeding group and 65.3% in the amino acid formula group (**Figure 2**).

Table 1. Baseline characteristics of the study population according to feeding regimen.

Variable	EBF (n=95)	AA (n=95)	HR (n=95)	P
Age at diagnosis (days), mean ± SD	37.2 ± 18.4	39.6 ± 19.1	35.1 ± 17.8	0.077
Male (%)	52.6	55.8	50.5	0.684
Baseline casein (mm), mean ± SD	4.79 ± 2.0	4.13 ± 2.1	3.96 ± 1.9	0.950
Baseline alpha-lactalbumin (mm)	4.27 ± 1.8	4.58 ± 2.0	3.44 ± 1.7	<0.001
Baseline beta-lactoglobulin (mm)	2.78 ± 1.6	3.64 ± 1.9	1.99 ± 1.4	0.003
Allergic comorbidity (%)	57.9	66.3	48.4	0.041
Family history of atopy (%)	48.4	63.2	45.3	0.008

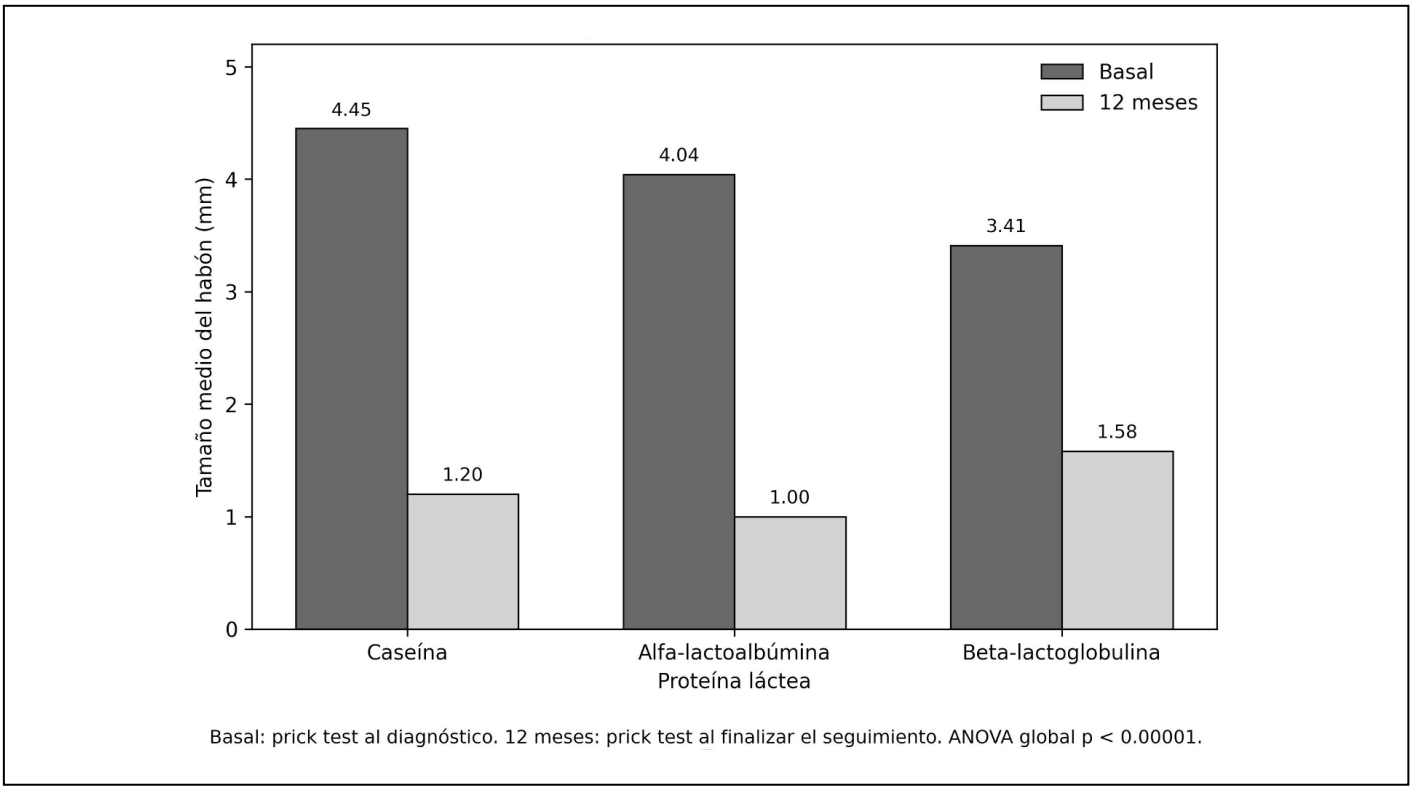

Figure 1. Evolution of the mean wheal size per protein at baseline and after 12 months of follow-up.

Table 2. Reduction in wheal size according to protein and feeding regimen.

Protein	Regimen	Baseline (mm)	12 months (mm)	Mean difference (mm)
Casein	EBF	4.79	1.40	-3.39
Casein	AA	4.13	1.30	-2.83
Casein	HR	3.96	1.20	-2.76
Alpha-lactalbumin	EBF	4.17	1.00	-3.17
Alpha-lactalbumin	AA	4.58	1.00	-3.58
Alpha-lactalbumin	HR	3.34	1.00	-2.34
Beta-lactoglobulin	EBF	3.56	1.78	-1.78
Beta-lactoglobulin	AA	3.64	1.58	-2.06
Beta-lactoglobulin	HR	2.56	1.58	-0.98

EBF: maternal diet free of dairy and traces; AA: amino acid-based formula; HR: hydrolyzed rice formula.

At the 12-month follow-up, 62.1% of infants developed clinical tolerance, defined by a negative oral food challenge. The proportion of tolerance was 78.9% in the exclusive breastfeeding group, 68.4% in the amino acid formula group, and 65.3% in the hydrolyzed rice formula group; however, these differences did not reach statistical significance ($\chi^2 = 4.8$; $p = 0.094$). **Figure 3**

The acquisition of tolerance showed a clear association with adherence to treatment. Tolerance rates were higher than 75% in patients with good adherence and lower than

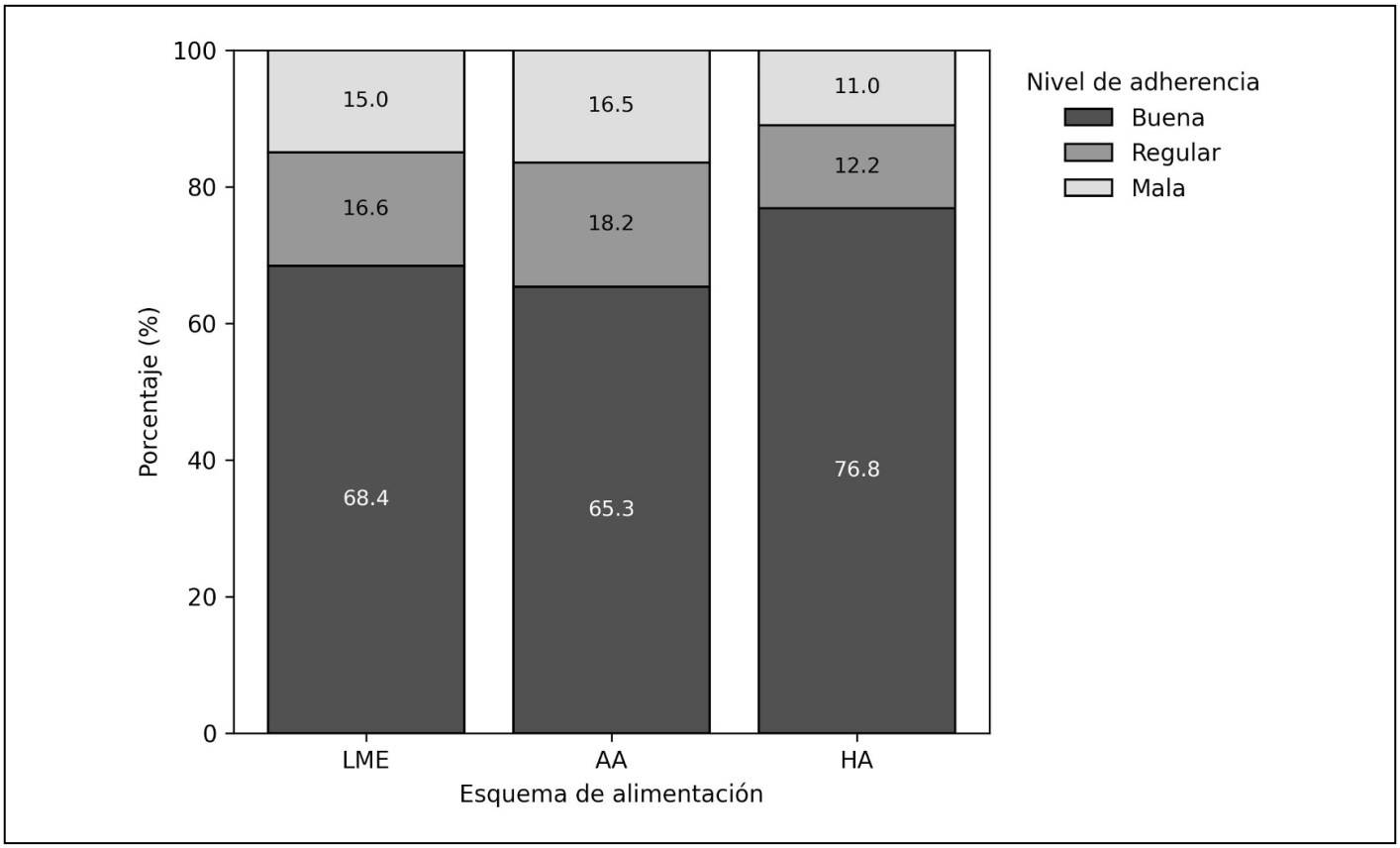

Figure 2. Adherence to treatment according to the feeding regimen.

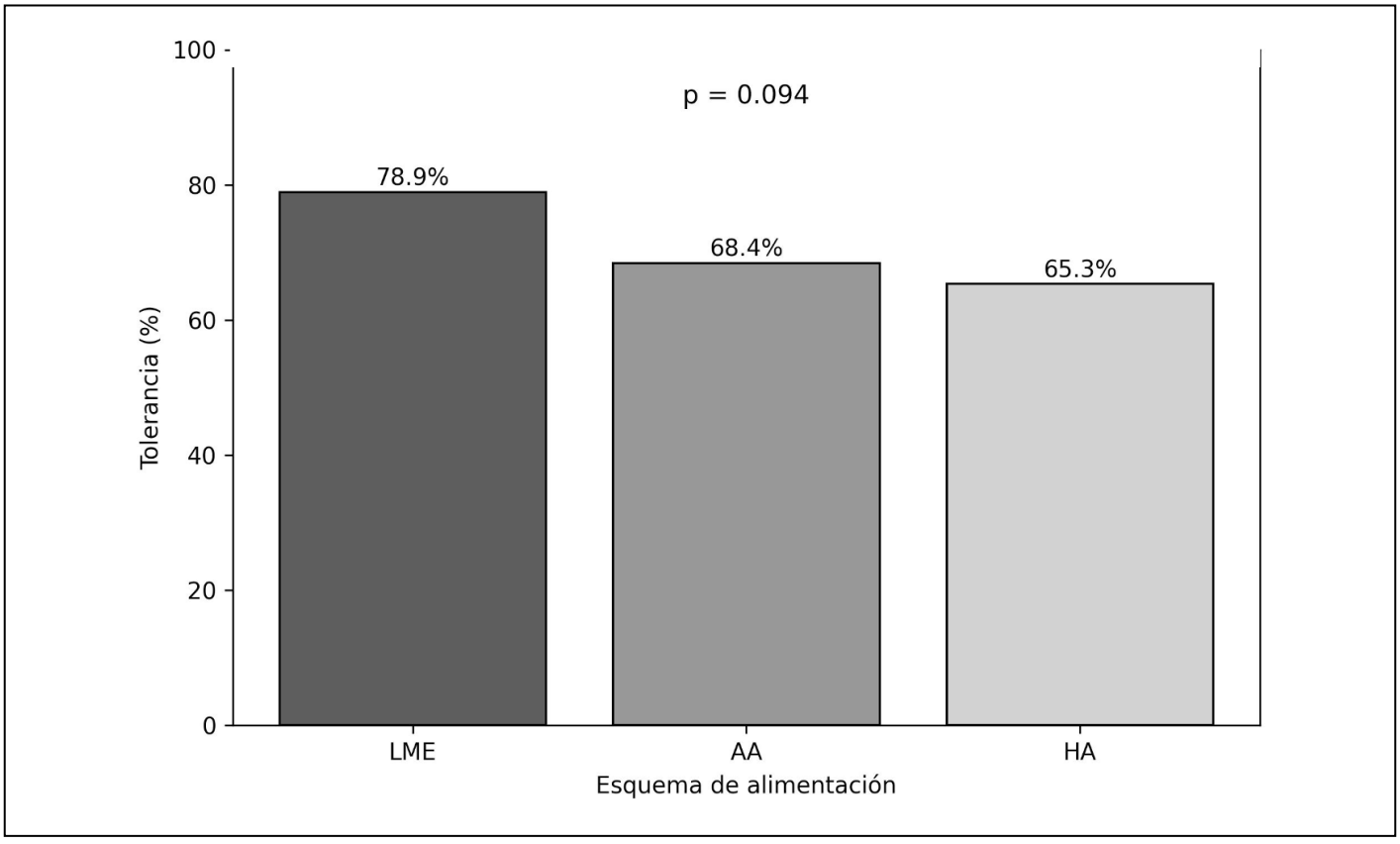

Figure 3. Clinical tolerance according to the feeding regimen.

25% in those who reported poor adherence, with statistical significance in all groups ($p < 0.001$ in groups 1 and 2; $p = 0.019$ in group 3).

Regarding allergic comorbidities, the most frequent were: atopic dermatitis (33.7%), wheezing (28.8%), allergic rhinitis (22.8%), and allergic conjunctivitis (11.9%), while 52.3% of patients had a family history of atopy. Allergic comorbidities were significantly associated with a lower probability of acquiring tolerance ($p < 0.001$), while family history of atopy showed no significant association with this outcome ($p = 0.617$).

In the multivariate logistic regression model adjusted for age, gender, allergic comorbidities, and family history of atopy, adherence to treatment remained the main factor associated with the acquisition of tolerance. Compared with poor adherence, good adherence showed an adjusted OR of 66.93 (95% CI 7.56–592.49; $p < 0.001$), while fair adherence reported an OR of 25.33 (95% CI 2.77–231.99; $p = 0.004$). No statistically significant differences were observed between feeding regimens after multivariate adjustment (amino acid formula vs. exclusive breastfeeding: OR 0.53, 95% CI 0.22–1.27; $p = 0.155$; hydrolyzed rice formula vs. exclusive breastfeeding: OR: 0.50, 95% CI 0.21–1.22; $p = 0.128$).

Allergic comorbidities were associated with a lower probability of acquiring tolerance (OR: 0.04, 95% CI 0.02–0.12; $p < 0.001$), while family history of atopy showed no significant association (OR: 1.66, 95% CI 0.83–3.33; $p = 0.154$). The model showed adequate fit (Hosmer–Lemeshow test $p = 0.83$) and statistical stability, without evidence of relevant collinearity. **Table 3**

DISCUSSION

This study analyzed the clinical evolution of Mexican infants with IgE-mediated cow's milk protein allergy (CMPA) undergoing an elimination diet for 12 months. The proportion of tolerance acquisition observed is within the range reported in the international literature for early cure of the disease during the first years of life.[23,24] However, since IgE-mediated CMPA shows a known rate of spontaneous recovery and the present study did not include a control group without dietary differentiation, it is not possible to determine precisely what proportion of the observed tolerance corresponds to the natural evolution of the disease.[25] Consequently, the findings should be interpreted as observational associations and not as evidence of a direct causal effect of the feeding regimen.

In the descriptive analysis, a higher proportion of tolerance was observed in the group receiving exclusive breastfeeding, followed by amino acid-based formula and hydrolyzed rice formula. However, these differences did not reach statistical significance. Although this result prevents establishing superiority among the evaluated feeding regimens, the consistency of the observed pattern suggests a possible clinical trend that can be explored in prospective studies with controlled designs.

The reduction in the size of the skin wheal for the dairy proteins evaluated after 12 months of an elimination diet suggests a decrease in immediate IgE-mediated reactivity during clinical follow-up. Nevertheless, the prick test exclusively evaluates the immediate skin response and does not allow for inferring more complex changes in immunological memory. Therefore, these findings should be interpreted primarily as evidence of a decrease in immediate clinical reactivity and not as a direct demonstration of systemic immunological modification.

The multivariate analysis identified adherence to dietary treatment as the factor most strongly associated with tolerance acquisition. This finding highlights the relevance of compliance in the treatment of patients with IgE-mediated cow's milk protein allergy. Although the magnitude of the odds ratio was high, the model showed statistical stability and an absence of relevant collinearity among the included variables. Nonetheless, the effect estimate should be interpreted with caution, because the retrospective nature of the study and the ordinal categorization of treatment adherence may amplify the effect size in this type of analysis.

Table 3. Multivariate logistic regression model for tolerance acquisition.

Variable	Adjusted OR	95% CI	p	Reference
Good adherence	66.93	7.56–592.49	<0.001	Poor adherence
Fair adherence	25.33	2.77–231.99	0.004	Poor adherence
AA regimen vs EBF	0.53	0.22–1.27	0.155	EBF
HR regimen vs EBF	0.50	0.21–1.22	0.128	EBF
Allergic comorbidities (yes vs no)	0.04	0.02–0.12	<0.001	Absence
Family history of atopy (yes vs no)	1.66	0.83–3.33	0.154	Absence

EBF: maternal diet free of dairy and traces; AA: amino acid-based formula; HR: hydrolyzed rice formula.

Allergic comorbidities were associated with a lower probability of tolerance acquisition. This finding may suggest a higher basal atopic burden in certain patients. However, the retrospective design prevented precise establishment of the temporality between the appearance of these comorbidities and the tolerance evaluation, as well as differentiation of their clinical severity. In this context, the observed association should be interpreted primarily as a possible prognostic marker of atopic susceptibility.

Limitations of the study include its retrospective design, the non-randomized assignment of feeding regimens, and the performance of open oral provocation tests. Although these tests were carried out under the supervision of pediatric allergists and following objective clinical criteria, observer bias cannot be completely ruled out, particularly in mild clinical manifestations. Likewise, the population analyzed comes from a private pediatric allergy clinic, which may limit the extrapolation of the results to other healthcare contexts with different access to specialized care.

Despite these limitations, the study systematically integrates clinical data, feeding regimens, and objective parameters of skin reactivity in a longitudinal cohort of Mexican infants with IgE-mediated cow's milk protein allergy. Taken together, these findings provide relevant observational evidence to contextualize the nutritional strategy for this disease in real clinical settings and contribute to generating hypotheses that should be evaluated in prospective studies with greater methodological robustness.

CONCLUSIONS

The elimination diet was associated with the acquisition of immunological tolerance in approximately two-thirds of infants with IgE-mediated cow's milk protein allergy (CMPA) at the 12-month follow-up. No statistically significant differences were identified between feeding regimens in the rate of tolerance, so the superiority of a specific regimen cannot be established.

The higher proportion observed in the group receiving exclusive breastfeeding should be interpreted as a descriptive finding. Adherence to dietary treatment was the main factor associated with the acquisition of tolerance after multivariate adjustment, while allergic comorbidities were related to a lower probability of clinical cure.

Casein was the allergen with the highest initial reactivity and showed significant reduction after dietary intervention in all groups. In contrast, a family history of atopy showed no association with the acquisition of tolerance.

Together, these findings provide relevant local clinical evidence for decision-making in the treatment of Mexican patients with IgE-mediated cow's milk protein allergy, and underscore the need for prospective studies that allow for the establishment of causal relationships with greater methodological robustness.

DECLARATIONS

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This study received no funding from any external source.

Ethical responsibilities

The procedures performed in this study adhere to the ethical principles governing human research in accordance with the General Health Law regarding research in Mexico. Likewise, they were conducted in accordance with institutional ethical standards and the 1964 Declaration of Helsinki and its subsequent amendments or comparable standards. As this is a retrospective observational study based on a review of clinical records, the study is considered to be of no risk to participants and did not require individual informed consent. Confidentiality and anonymity of the information were guaranteed at all times, protecting personal data in accordance with current regulations.

Authors' contributions

Hannia Bertha Matt Hernández: Conceptualization, study design, data collection, database creation, analysis and interpretation of results, writing of the original manuscript, and general project coordination. *Virginia María González Pérez*: Data collection, database creation and review, clinical supervision, methodological support, and critical review of the manuscript. *Víctor Soto Torres Septién*: Data collection, support in the creation and validation of the database, data analysis, scientific review of the manuscript, and approval of the final version.

All authors participated actively in the development of the study, critically reviewed the manuscript, and approved the final version for publication.

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Original article

Asthma mortality in Colombia: a three-decade analysis and the effect of the COVID-19 pandemic

Mortalidad por asma en Colombia: análisis de tres décadas y efecto de la pandemia por COVID-19

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Abstract

OBJECTIVES: To describe asthma mortality trends in Colombia from 1990 to 2021 and to assess the impact of the COVID-19 pandemic during the 2020-2021 period.

METHODS: A retrospective and observational study, carried out from the analysis of Global Burden of Disease 2021, was used to estimate age-standardized prevalence, mortality, and disability-adjusted life years (DALYs) for asthma in Colombia. Additionally, crude asthma mortality data for the period 2015–2023 were obtained from the National Department of Statistics of Colombia (DANE). Temporal trends were assessed using Joinpoint regression, and crude mortality rates before and during the COVID-19 pandemic were compared to estimate excess mortality.

RESULTS: A significant decline in asthma mortality was observed in Colombia between 1990 and 2021 (average annual percent change [AAPC]: −1.5%; 95%CI: −1.7 to −1.3), consistent with global trends. However, during 2020–2021, asthma-related mortality in Colombia increased from 0.43 to 0.63 per 100,000 population compared with the 2015–2019 period (RR = 1.49; 95% CI: 1.35–1.64), with a greater relative increase among individuals older than 65 years.

CONCLUSIONS: Despite sustained reductions in asthma mortality over three decades in Colombia, the COVID-19 pandemic was associated with a substantial increase in asthma-related deaths, highlighting the importance of maintaining continuity of care for chronic diseases during public health emergency.

KEYWORDS: Asthma; COVID-19 pandemic; Global burden of disease; Prevalence; Colombia; Chronic diseases; Public health; Emergency.

Resumen

OBJEVTIVE: Analizar las tendencias de mortalidad por asma en Colombia entre 1990 y 2021, y evaluar la repercusión de la pandemia por COVID-19 durante el período 2020-2021.

MÉTODOS: Estudio retrospectivo y observacional, llevado a cabo a partir del análisis datos del Global Burden of Disease 2021 para estimar la prevalencia, mortalidad y años de vida ajustados por discapacidad (DALYs), estandarizados por edad en Colombia. Adicionalmente, se analizaron los registros de mortalidad cruda por asma correspondientes al período 2015-2023 del Departamento Administrativo Nacional de Estadística (DANE). Las tendencias temporales se evaluaron mediante regresión Joinpoint y se compararon las tasas de mortalidad cruda antes y durante la pandemia para estimar la mortalidad en exceso.

RESULTADOS: Se observó una disminución significativa de la mortalidad por asma en Colombia entre 1990 y 2021 (AAPC: −1.5%; IC95%: −1.7 a −1.3), similar a la tendencia mundial. Sin embargo, durante 2020-2021 la mortalidad por asma se incrementó de 0.43 a 0.63 por cada 100,000 habitantes versus 2015-2019 (RR = 1.49; CI95%: 1.35-1.64), con un incremento relativo mayor en personas mayores de 65 años.

CONCLUSIONES: A pesar de la reducción sostenida de mortalidad por asma en Colombia durante tres décadas, la pandemia por COVID-19 se asoció con aumento significativo de las defunciones por esta causa, lo que resalta la necesidad de garantizar la continuidad de atención por enfermedades crónicas durante periodos de emergencia de salud pública.

PALABRAS CLAVE: Asma; Pandemia por COVID-19; Global burden of disease; Prevalencia; Colombia; Enfermedades crónicas; Salud pública; Emergencia.

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INTRODUCTION

Asthma is still a cause of morbidity and mortality worldwide, although epidemiological trends have changed in the last two decades.[1] In 2021, an estimated 260 million (95% UI 227–298) people were living with asthma globally.[2] At the same time, age-standardized asthma mortality has declined in many settings, likely reflecting improvements in diagnosis, access to care, and the implementation of asthma control strategies. According to the Global Burden of Disease (GBD) study, the global age-standardized asthma mortality rate decreased from 8.6 per 100,000 in 1990 to 5.96 per 100,000 in 2019.[1] However, these improvements have not occurred uniformly, and asthma mortality remains disproportionately concentrated in low- and middle-income countries, where underdiagnosis and inadequate treatment continue to be major challenges.[3]

In Latin America, asthma mortality shows marked heterogeneity across countries, with differences not only in asthma prevalence and mortality rates but also in the quality and reliability of death reporting systems. Consequently, published estimates sometimes yield conflicting results depending on the data source used.[4]

The COVID-19 pandemic was a period of notable impact on human health, causing a significant excess mortality worldwide[5,6] and may also have affected asthma mortality through multiple pathways, including disruptions in access to routine care, reduced emergency care utilization, and changes in health-service organization. However, the specific impact of the pandemic on asthma mortality at national and global levels has not been well characterized. Most previous studies on asthma and COVID-19 have focused on whether pre-existing asthma modifies the risk of SARS-CoV-2 infection or severe COVID-19 outcomes, rather than on whether the pandemic period altered mortality from asthma itself.[7,8]

The specific impact of COVID-19 on global or national rates of asthma mortality has not been previously assessed. In this study, we aimed to describe the trends in asthma burden in Colombia from 1990 to 2021 using age-standardized rates of prevalence, mortality and DALYs using Jointpoint regression and analyzed the impact of COVID-19 pandemic (2020–2021) on asthma mortality. Updating and analyzing national asthma mortality data is therefore crucial to understanding the current dynamics of the disease and identifying population-level factors that contribute to its persistence.

METHODS

Data source

Global burden of disease

Data about global burden of asthma (1990-2021) were extracted from the GBD 2021 dataset, using a publicly available resource tool (https://vizhub.healthdata.org/gbd-results/) managed by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington.[9] The GBD uses vital registration and surveillance data from the cause of death database, literature reviews, survey data, and some national claims data to model morbidity and mortality, obtain age-standardized values and make rates comparable among countries and regions. Disease Modelling Meta-Regression (DisMod-MR) 2.1 is employed to estimate disease incidence and prevalence. Death estimates are modeled via the Integrated Cause of Death Model (CODEm).[9] Age-standardized asthma prevalence, mortality and Disability-Adjusted Life Year (DALYs) for Colombia are used in this paper. These estimates, together with their uncertainty intervals, were used to assess long-term trends and to place Colombia in comparative perspective with other countries, regions, and the global context.

Crude mortality data

To describe excess mortality of asthma for both sexes, all ages, during COVID-19 pandemic (2020 - 2021) and the available information on post-pandemic years (2022-2023) in Colombia we extracted data on mortality of asthma using the ICD-10 codes J45-J46, during 2015-2023 from the *Vital Statistics* (variable: C_BAS1 from the *Non-fetal Deaths* database) managed and published by the National Department of Statistics in Colombia (DANE, *Departamento Administrativo Nacional de Estadisticas*).[10,11] The underlying cause of death is understood as the disease or injury that started the succession of morbid events that directly led to death. These data represent observed deaths recorded in the national registration system and were used to calculate crude mortality rates and to examine recent changes in asthma mortality at the country level, particularly during the pandemic period. Unlike GBD estimates, these data are not age-standardized and do not incorporate modelling-based uncertainty intervals.

Trend characterization using joint regression model

Rates of age-standardized -mortality (ASMR), -prevalence (ASPR) and -DALYs (ASDR) were inputs to construct Joinpoint regression models and characterize epidemiological trends of asthma. We used the "Methodology for Characterizing Trends" of the National Cancer Institute of the United States[12] that uses Joinpoint Regression Program Version 5.0.2. (Statistical Research and Application Branch, National Cancer Institute, Bethesda, Maryland, United States).[13] The Joinpoint software uses statistical criteria to determine a) the fewest number of segments necessary to characterize a trend, b) where the segments begin and end; and c) the annual percent change (APC) for each segment (a linear trend on a log scale implies a constant APC) and the average annual percentage change (AAPC).[14]

Analyses of crude mortality

Crude mortality rates (CMR) for asthma were calculated. Excess mortality due to asthma was estimated by calculating the percentage increase in asthma deaths between the pandemic and pre-pandemic periods:

$$\%\text{change} = \left(\frac{CMR_{2020-2021} - CMR_{2015-2019}}{CMR_{2015-2019}}\right) \times 100$$

CMR for asthma were stratified by age, sex and geographical units. For subgroup comparisons, chi-square tests were used to analyse categorical variables (sex). CMR for each department (the second administrative division of Colombia) were described.

To compare asthma mortality rates between the pre-pandemic (2015–2019) and pandemic (2020–2021) periods, we fitted a Poisson regression model using annual asthma death counts as the outcome, period as the main predictor, and the logarithm of the annual population as an offset. This approach allowed us to estimate a rate ratio (RR) comparing mortality rates between periods while accounting for differences in population size across years.

Data visualization and software

All statistical analyses were conducted using Python (version 3.9) and Joinpoint Regression Program (version 5.0.2). Figures, including mortality trends and regional comparisons, were generated using *matplotlib* and *seaborn*. Geographic disparities in asthma mortality were visualized using choropleth maps generated in Python (version 3.9) with the *geopandas* and *matplotlib* libraries. Statistical significance was set at $p < 0.05$, and 95% confidence intervals (CIs) were reported where applicable.

RESULTS

GBD statistics for asthma between 1990 and 2021

In 2021, there were 260.4 million (95% UI: 227.2–297.9) of people living with asthma worldwide. The global ASPR for asthma was 3,300.8 (2,879.6–3,775.2) per 100,000 people. Also, in 2021, there were 436,1 thousand (95% UI 357,7–555,6) deaths of all ages and both sexes by asthma worldwide. The global ASMR for asthma in 2021 was 5.53 (4.53–7.04) per 100,000 people. Epidemiological trends for asthma in Colombia were like to global statistics, observing decreasing ASPR and ASMR from 1990 to 2021 (**Table 1**). The ASMR of Colombia [0.48 per 100, 000 (0.40-0.57)] is ten times lower than the global rate. Notoriously, the total percentage change of the ASMR in Colombia was more pronounced than the mean ASMR Central Latin America region (**Figure 1** and **Table 1**). Colombia exhibited the lowest ASMR in this region in 2021 (**Supplementary Table 1, Figure 1B**), meanwhile Honduras showed the highest ASMR (2.86). The remaining countries ranked, in descending order, as Venezuela (1.32), Nicaragua (1.15), Panama (1.11), Mexico (0.93), and Costa Rica (0.92).

Table 1. Global Burden of Disease statistics for asthma in 2021.

	Number 95% UI (upper – lower)	ASR per 100,000 people 95% UI (upper – lower)	Percent change (2021/1990) 95% UI (upper – lower)
Global			
Prevalence	260,479,186.89 (297,967,236.94 to 227,209,547.47)	3,300.8 (2,879.6 to 3,775.2)	-38.72% (-39.17 to -38.66)
Mortality	436,192.95 (555,604.08 to 357,795.39)	5.53 (4.53 to 7.04)	-21.25% (-20.61 to -23.78)
Central Latin America			
Prevalence	7,429,524.99 (6,114,497.79 to 9,003,108.48)	2,936.55 (3,558.51 to 2,416.78)	-53.10% (-50.2 to -56.2)
Mortality	2,611.24 (2,320.02 to 2,923.27)	1.03 (0.92 to 1.16)	-68.30% (-64.43 to -71.83)
Colombia			
Prevalence	1,545,590.56 (1,894,948.87 to 1,251,859.25)	3,150.3 (2,551.6 to 3,862.4)	-48.47% (-48.57 to - 48.05)
Mortality	235.78 (278.35 to 196.10)	0.48 (0.40 to 0.57)	-77.61% (-80.36 to -74.90)

ASR: Age-standardized rate.

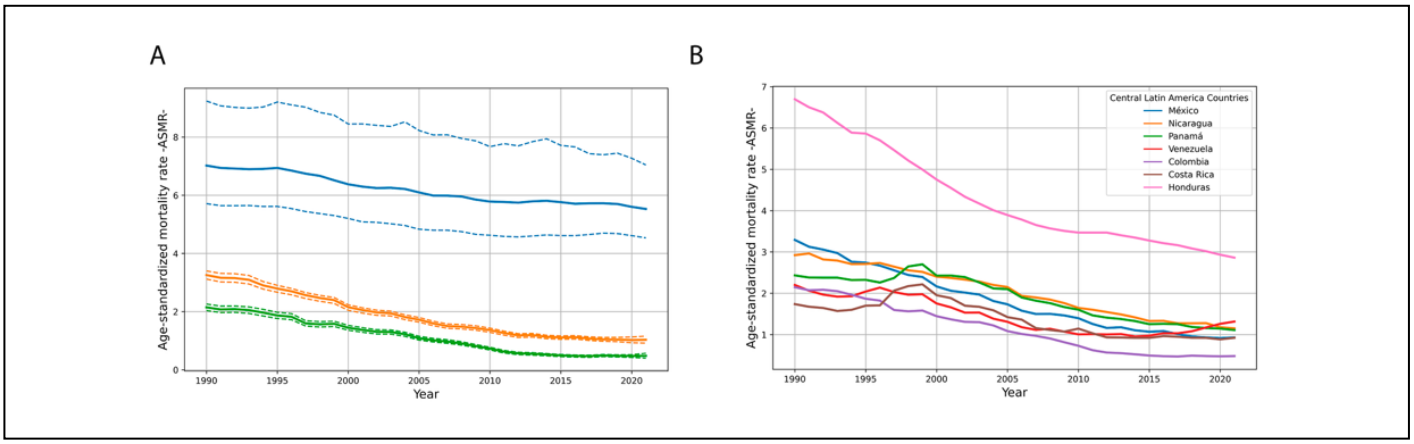

Figure 1. Comparison of age-standardized mortality rates (ASMR) in Colombia, Central Latin America and worldwide. (A) ASMR in Colombia, Central Latin America and the world. Dashed lines represent 95% UI values (B) ASMR for countries within the Central Latin America region. Rates are expressed per 100,000 population.

Joinpoint regression analysis results for Colombia and global statistics are shown in **Figure 2** and **Table 2**. Significant and negative AAPC were observed, both, in Colombia (-1.5% 95%UI: -1.7 to -1.3) and worldwide (-0.7%, 95%CI: -0.9 to -0.6). Global statistics of asthma prevalence showed a significant decrease from 1990 to 2004, and then, from 2014 to 2021. In Colombia, a sharper but later decline was observed from 1995 to 2004 and then, in the 2015 to 2021 period (**Figure 2A**). Mortality also declined worldwide and in Colombia, with different dynamics. Globally, the highest reduction in ASMR was observed from 1995-2007, then, it kept significantly decreasing at a lower rate until 2021. In Colombia, two Joinpoints were detected, a declining slope from 1990 to 2004, and, then the highest decreasing period starting from 2004 to 2014 (**Figure 2B**). DALYs statistics also diminished along the observation window (1990-2021) being the AAPC of age standardized DALYs rate higher in Colombia than worldwide (**Figure 2C**).

Asthma mortality during COVID-19 pandemic in Colombia

To analyze the impact of COVID-19 pandemics on mortality rates, we compared 2020-2021 death registers with the death counts within the five-year period before pandemics. To describe changes in mortality during the COVID-19 pandemic, we compared national death records from 2020–2021 with those from the five-year pre-pandemic period (2015–2019). During 2015–2019, a total of 1,151,461 deaths from all causes were registered in Colombia, compared with 663,942 deaths in 2020–2021. For asthma specifically, 1,013 deaths were recorded during 2015–2019 and 641 during 2020–2021. The pooled crude asthma mortality rate increased from 0.43 per 100,000 population in the pre-pandemic period to 0.63 per 100,000 during the pandemic period (46.51% of increase). In a Poisson regression model using annual asthma death counts with population as an offset, the mortality rate during 2020–2021 was significantly higher than during 2015–2019 (rate ratio [RR] = 1.49; 95%CI: 1.35–1.64). In the subsequent post-pandemic years, the crude asthma mortality rate remained elevated at 0.61 per 100,000 in both 2022 and 2023.

Chocó, Bolívar, and Norte de Santander were the departments with the greatest increase in asthma CMR during COVID-19 (**Supplementary Table 2, Figure 3**). Since Vichada and Guainía had scarce asthma death registers in the two analyzed periods, they were excluded from comparisons.

Analysis of CMR among age groups (**Figure 4**) showed that the APC for 2020-2021 was higher in persons >65 years of age than younger individuals (48.9 *vs.* 36.3%). **Table 3** shows all-cause and asthma mortality data for Colombia between 2015 to 2021 disaggregated by sex. CMR did not significantly differ between males and females.

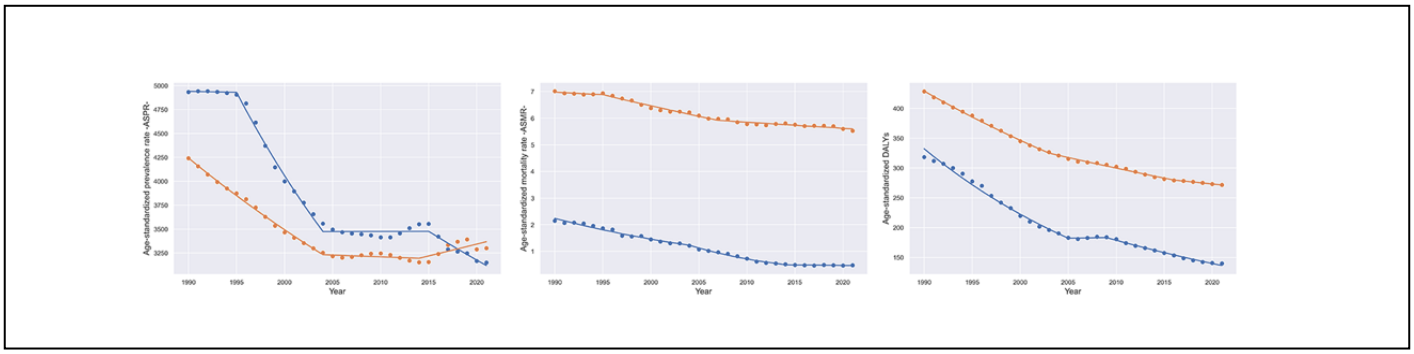

Figure 2. Trends of age-standardized asthma prevalence (A), mortality (B) and DALYs (C) rates, all ages, and both sexes, worldwide and in Colombia from 1990 to 2021. Modeled (lines) and observed values (dots) for worldwide and for Colombia are shown in orange and blue, respectively.

Table 2. Percentage change in age-standardized asthma prevalence, mortality and DALYs rates, all age and both sexes, worldwide and Colombia, 1990 and 2021.

Metric	Cohort	Period	APC (Lower CI - Upper CI)
Prevalence	Colombia – 3 Joinpoints (1995, 2004, 2015)	(1990 - 1995)	-0.04 (-0.79 - 0.72)
ASPR		(1995 - 2004)	-3.82* (-4.17 - -3.46)
		(2004 - 2015)	0.01 (-0.26 - 0.27)
		(2015 - 2021)	-1.79* (-2.35 - -1.23)
	Global - 2 Joinpoints (2004, 2014)	(1990 - 2004)	-1.93* (-2.08 - -1.77)
		(2004 - 2014)	-0.11 (-0.42 - 0.19)
		(2014 - 2021)	0.76* (0.31 - 1.21)
			AAPC (Lower CI - Upper CI)
	Colombia - 3 Joinpoints	(1990 - 2021)	-1.5* (-1.7 - -1.3)
	Global - 2 Joinpoints	(1990 - 2021)	-0.7* (-0.9 - -0.6)
			APC (Lower CI - Upper CI)
Mortality	Colombia - 2 Joinpoints (2004, 2014)	(1990 - 2004)	-4.18* (-4.69 - -3.56)
ASMR		(2004 - 2014)	-8.67* (-10.67 - -7.81)
		(2014 - 2021)	-0.8 (-2.53 - 1.8)
	Global - 2 Joinpoints (1996, 2007)	(1990 - 1995)	-0.27 (-0.8 - 0.68)
		(1995 - 2007)	-1.25* (-1.91 - -1.09)
		(2007 - 2021)	-0.40* (-0.54 - -0.22)
			AAPC (Lower CI - Upper CI)
	Colombia - 2 Joinpoints	(1990 - 2021)	-4.9* (-5.2 - -4.7)
	Global - 2 Joinpoints	(1990 - 2021)	-0.7* (-0.8 - -0.6)

...continuation table 2.

Metric	Cohort	Period	APC (Lower CI - Upper CI)
DALYs	Colombia - 2 Joinpoints (2005, 2009)	(1990 - 2005)	-3.93* (-4.15 - -3.75)
ASR		(2005 - 2009)	0.13 (-1.14 - 1.69)
		(2009 - 2021)	-2.43* (-2.78 - -2.21)
	Global - 2 Joinpoints (2003, 2016)	(1990 - 2003)	-2.11* (-2.2 - -2.05)
		(2003 - 2016)	-1.15* (-1.29 - -1.06)
		(2016 - 2021)	-0.59 (-0.88 - 0.04)
			AAPC (Lower CI - Upper CI)
	Colombia - 2 Joinpoints	(1990 - 2021)	-2.83* (-2.92 - -2.76)
	Global - 2 Joinpoints	(1990 - 2021)	-1.46* (-1.5 - -1.44)

CI: confidence interval.

*Indicates that the APC or AAPC is significantly different from zero at the alpha = 0.05 level.

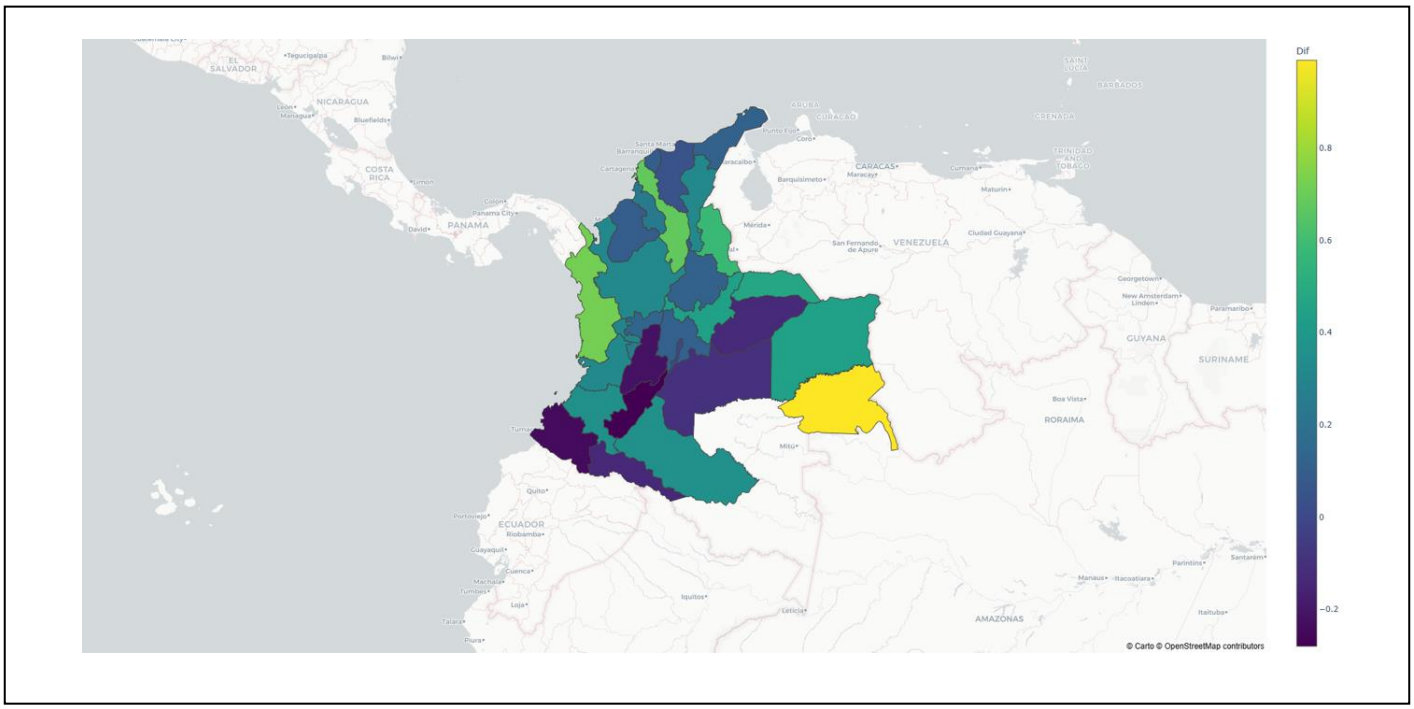

Figure 3. Differences in crude asthma mortality rates by departments in Colombia before and during the pandemic in Colombia 2015-2021.

Place of death

Most frequent asthma death locations in Colombia are hospitals and home (**Supplementary Figure 1**). Although during the last three decades, there have been a trend of reduction for deaths at home (-1.1% per year, ´<0.0001), and, conversely, a relative increase of hospital deaths (1.3% per year, p = <0.0001), during pandemics the dynamics of death locations showed a different pattern (**Supplementary Figure 2**);

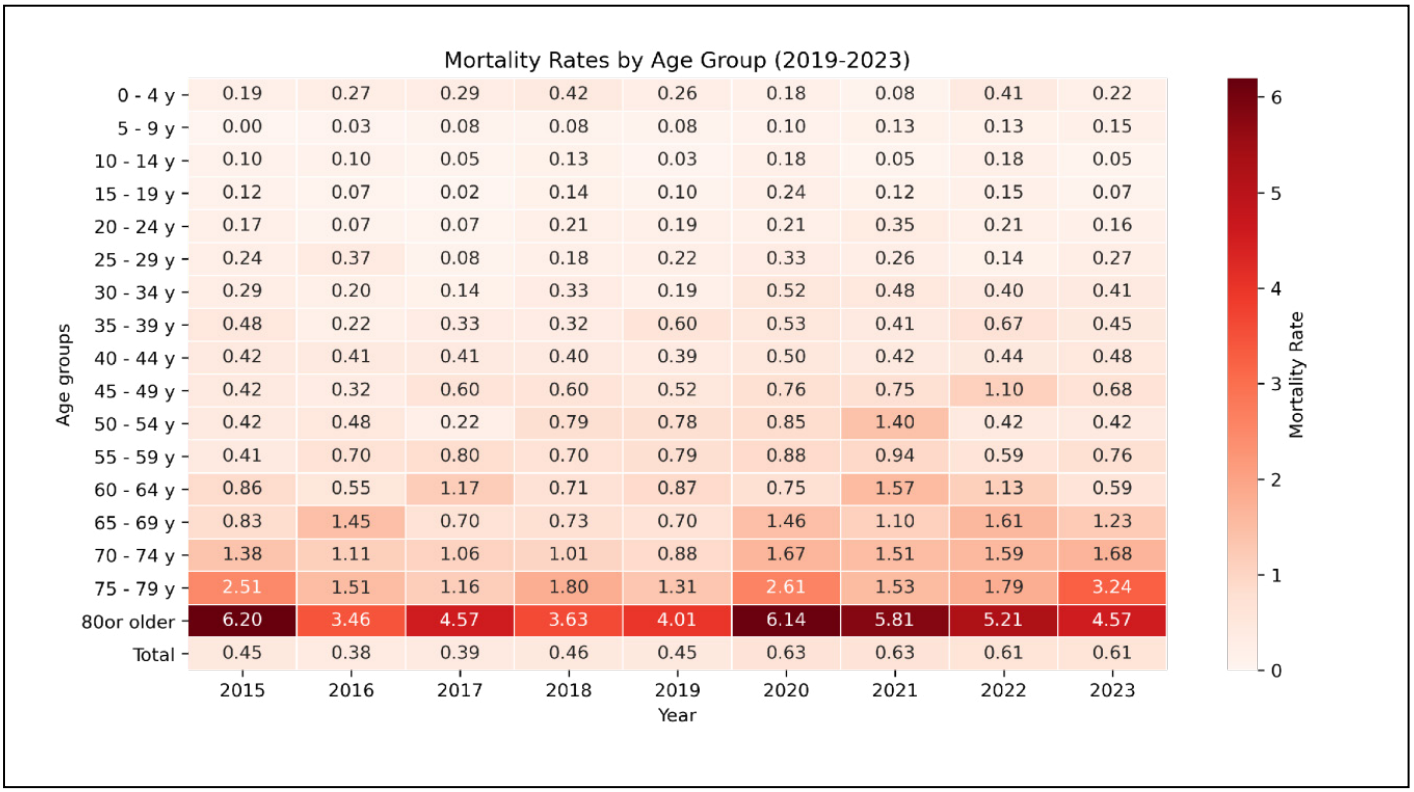

Figure 4. Crude asthma mortality rates by age groups in Colombia from 2015 to 2023.

Table 3. General mortality and mortality by asthma in Colombia 2015 - 2021.

Sex	2015	2016	2017	2018	2019	2020	2021
Total deaths by all causes							
Males	121,395	123,806	125,450	130,776	134,573	171,481	205,427
Females	98,037	99,242	102,119	106,075	109,689	129,288	157,596
NA	40	30	55	81	93	84	66
Total	219,472	223,078	227,624	236,932	244,355	300,853	363,089
CMR*	4.7	4.8	4.8	4.9	4.9	6.0	7.1
Death events due to asthma (ICD-10: J45 - J46)							
Males	84	76	78	106	95	152	156
Females	124	104	107	114	125	166	167
Total	208	180	185	220	220	318	323

...continuation table 3.

Sex	2015	2016	2017	2018	2019	2020	2021
CMR by asthma							
Males	0.37	0.33	0.34	0.45	0.39	0.62	0.63
Females	0.52	0.43	0.44	0.46	0.49	0.64	0.64
Total	0.45	0.38	0.39	0.46	0.45	0.63	0.63

NA: data not available, CMR*= Crude mortality rate per 100,000 people

63.8% of events were registered in hospitals for 2015-2019, but a significant reduction was observed for 2020-2021 (55.5%). An increase again to 60.4% was observed during 2022–2023. Deaths at home also increased in 2020-2021 with respect to 2015–2019.

DISCUSSION

This updated national assessment shows that asthma mortality in Colombia declined over the last three decades (1990–2021), consistent with regional and global patterns.[1] However, analyzes based on crude national mortality data indicate a substantial increase in asthma deaths during the COVID-19 period (2020–2021) compared with 2015–2019, without clear differences by sex. The excess burden was not evenly distributed across the country, with the highest increases concentrated in a small number of departments, and with a larger relative increase among individuals above 65 years.

Mortality from asthma in Colombia has decreased in the last three decades (1990–2021), finalizing the observation period as the country with lowest ASMR in the central America region. Previous studies for Colombia found that mortality decreased from 1974 to 1994, but it was still high at the end of this observation with a CMR of 1.6 per 100.000 inhabitants.[15] Both, the ASMR modeled by GBD for 2021 [0.46 80.40 – 0.57)] and the CMR obtained from National Colombian statistics (0.63), coincide in a decrease trend of asthma mortality in the country.

Among the factors that may have contributed to this decline in asthma mortality are improvements in access to healthcare, broader availability of inhaled corticosteroids.[16,17] and advances in asthma management.[16] Other countries that have faced important reductions of mortality are Brazil, due to inclusion of free inhaled corticosteroids for severe asthma patients.[17] The expansion of health insurance coverage after the implementation of Law 100 of 1993 may have facilitated access to essential services and chronic disease treatment, providing a plausible context for the observed decline.[18] However, our study did not directly assess these determinants, and these explanations should therefore be interpreted with caution. However, our study was not designed to directly evaluate the contribution of these health-system or therapeutic changes, and these interpretations should therefore be considered as plausible contextual explanations rather than causal inference.

The GBD analyses allow for international comparisons with a certain degree of certainty, but they include a wide margin of error in the modeling. This possibly reduces the ability to observe differences between years that are not as pronounced as the trends observed over the past 30 years and may have obscured the impact of COVID-19. For this reason, we decided to analyse raw mortality data at the country level, finding that during this period, more deaths from asthma were recorded than in previous years. Additionally, we confirmed in the records that COVID-19 was not listed as the second cause of death. There is controversy regarding the relationship between COVID-19 and asthma, but in general, the focus has been on determining whether asthma is a risk factor for developing more severe symptoms of this disease caused by SARS-CoV-2.[19]

A key methodological consideration is that the national mortality database and the GBD estimates are not directly comparable in absolute terms, as they reflect different epidemiological constructs. National mortality records provide observed deaths and crude mortality rates, which are appropriate for describing recent country-level changes, including those occurring during the COVID-19 period. By contrast, GBD estimates are model-based and yield age-standardized mortality rates with uncertainty intervals, allowing more robust comparisons over time and across settings by reducing the influence of differences in population age structure. Moreover, the GBD framework enabled us to place Colombia's asthma mortality profile in relation to the Latin American region and to global patterns. For these reasons, both data sources were interpreted as complementary rather than interchangeable.

Our findings are compatible with the hypothesis that disruptions in access to routine asthma care and acute exacerbation management during lockdowns and health-system strain contributed to increased mortality among people with asthma.[20] Although pediatric respiratory infections and asthma exacerbations may have decreased in some contexts during lockdowns,[21] reduced mobility and constrained services could have delayed urgent care for severe attacks in adults. The shift in place of death observed during the pandemic—with a higher proportion of deaths

occurring at home and fewer in hospital—also supports the possibility of reduced or delayed access to facility-based care. However, as access to healthcare and use of health resources were not formally measured and compared in this study, our interpretations and explanations remain hypothetical. In the Latin American region, the direction and magnitude of pandemic-period changes in asthma mortality have not been consistently observed across data sources; for example, Brazilian analyses have reported increases or decreases of mortality depending on the data source used.[4,22,23]

Notably, crude asthma mortality remained elevated in 2022–2023, suggesting that the impact of the pandemic may have extended beyond its acute phase. Several non-mutually exclusive explanations may account for this pattern. Persistent disruptions in routine asthma care, changes in healthcare utilization, and delayed presentation or treatment of severe exacerbations may have continued to affect outcomes after the most critical pandemic period. In addition, post-COVID respiratory sequelae could have contributed to a higher burden of respiratory symptoms and more difficult asthma control among survivors.[24] Previous studies have reported that dyspnea is a frequent long-term symptom after COVID-19,[25] including among patients with chronic respiratory diseases such as asthma and COPD,[26] and that individuals with asthma may be at increased risk of long-COVID manifestations compared with those without asthma.[27] Evidence from both international and Colombian populations also supports the persistence of respiratory symptoms after SARS-CoV-2 infection, with dyspnea being among the most commonly reported.[28]

Among sociodemographic factors of importance in mortality is sex. In our analysis, we did not observe significant sex differences in mortality during the pandemic, but in pre-pandemic years, women tend to have higher mortality rates. Other countries such as Brazil[22] and United States[29] have reported a higher mortality in women. About the geographical distribution, not all departments in the country showed the same increase in mortality, and the top three departments with the highest increase in deaths are in different regions and have varying levels of socioeconomical development, making it difficult to hypothesize which factors explain such differences. There are also weaknesses in the analyses when comparing crude mortality rates between departments, in addition to the fact that asthma-related deaths are relatively infrequent and likely suffer from significant underreporting in some areas of Colombia such as those Departments in the Amazon region.[30] Nevertheless, the descriptive nature of these analyses only allows us to suggest that asthma mortality trends were not homogeneous in Colombia during the pandemic.

This study has several limitations. First, GBD estimates are modelled and therefore depend on the quality and completeness of underlying data sources;[31] uncertainty may be substantial, particularly for short time windows and for outcomes that are relatively infrequent. This may partly explain why the pandemic-related increase was not apparent in the modelled indicators. Second, comparisons of crude mortality between departments are vulnerable to variation in death certification quality, underreporting, and small numbers, especially in sparsely populated or resource-limited regions (e.g., parts of the Amazon).[30] Third, cause-of-death misclassification is possible; while we verified that COVID-19 was not recorded as a secondary cause on asthma death certificates, indirect effects of SARS-CoV-2 infection or coexisting chronic respiratory conditions cannot be fully excluded, particularly in older adults, where diagnostic overlap with other chronic obstructive diseases, including asthma–COPD overlap (ACO), may affect cause-of-death certification. Fourth, our ecological analyses cannot establish causality for the observed increase during 2020–2021, and unmeasured factors (e.g., changes in air pollution, healthcare utilization, medication adherence, or health-service reorganization) could have contributed. Finally, the comparison between pre- and pandemic periods was based on a short annual series. Therefore, these findings should be interpreted as descriptive evidence, rather than as a formal causal estimate of the effect of COVID-19.

CONCLUSIONS

This study has analyzed different sources of information to estimate the burden of asthma in Colombia during the last three decades. Such evidence is essential to design effective public health interventions, allocate resources appropriately, and tailor strategies to reduce disparities in access, diagnosis, and treatment. By strengthening local epidemiological knowledge, this study aims to support the formulation of data-driven policies that improve asthma management, enhance patients' quality of life, and ultimately reduce the burden of asthma morbidity and mortality in Colombia.

STATEMENTS

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical responsibilities

This study was based exclusively on the secondary analysis of official national databases that are publicly available or accessed through institutional authorization and contain anonymized, de-identified information. No direct contact with human participants occurred, and no identifiable

personal data were accessed. In accordance with applicable regulations and institutional policies, this type of analysis does not constitute human subjects research requiring review and approval by an ethics committee/Institutional Review Board; therefore, formal ethics approval was not required.

Author contributions

NA conceptualized the study and led the design of the analytical approach. JZ and NA conducted the data analysis and drafted the initial manuscript. LC critically revised the manuscript, contributed to the writing of the discussion, and supported the design of specific analyses. All authors reviewed and approved the final version of the manuscript.

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Permissions

All figures and paintings are original.

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SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table 1. Age-standardized mortality rates of countries located in Central America.

Year	Colombia	Costa Rica	Honduras	México	Nicaragua	Panamá	Venezuela
1990	2,146497	1,737685	6,694687	3,291133	2,922955	2,433253	2,201177
1991	2,072922	1,674246	6,500794	3,12573	2,963327	2,380895	2,061385
1992	2,084735	1,644277	6,373786	3,056592	2,8191	2,377198	1,967539
1993	2,0505	1,571608	6,122953	2,972076	2,790831	2,377361	1,918713
1994	1,964143	1,599404	5,886949	2,763339	2,707081	2,320051	1,927534
1995	1,866991	1,700744	5,864613	2,741836	2,709649	2,324746	2,042499
1996	1,822868	1,707397	5,700769	2,669485	2,732206	2,259902	2,136452
1997	1,594951	2,064133	5,462507	2,555696	2,643596	2,370446	2,029049
1998	1,563687	2,173201	5,212242	2,442619	2,555679	2,648824	1,965073
1999	1,582425	2,21554	4,993802	2,393777	2,517148	2,700087	1,975788
2000	1,445281	1,953203	4,750593	2,164811	2,401254	2,427505	1,752641
2001	1,37002	1,883852	4,550402	2,061415	2,371485	2,429248	1,660879
2002	1,308098	1,699534	4,333939	2,016322	2,330554	2,390482	1,530812
2003	1,301198	1,672606	4,171614	1,969097	2,28323	2,263165	1,53432
2004	1,222083	1,588045	4,009815	1,812436	2,201437	2,117424	1,385235
2005	1,08465	1,422865	3,892711	1,73203	2,15029	2,101038	1,309391
2006	1,015602	1,362389	3,783027	1,578624	1,937869	1,898237	1,179729
2007	0,968786	1,157309	3,651944	1,498378	1,898038	1,820126	1,114124
2008	0,905686	1,111759	3,568888	1,50142	1,846868	1,760807	1,14125
2009	0,815817	1,072353	3,509159	1,463768	1,762223	1,666913	1,070636
2010	0,729584	1,14439	3,468365	1,396164	1,646056	1,602408	1,005794
2011	0,622452	1,031161	3,467026	1,25743	1,601839	1,465619	1,011647

...continuation supplementary table 1.

Year	Colombia	Costa Rica	Honduras	México	Nicaragua	Panamá	Venezuela
2012	0,565709	0,933474	3,468135	1,161248	1,54575	1,41028	1,004167
2013	0,550824	0,929215	3,403798	1,177638	1,488003	1,377193	1,013494
2014	0,523506	0,920986	3,346537	1,103869	1,416248	1,326893	0,954446
2015	0,49366	0,921513	3,275512	1,068975	1,328155	1,252775	0,974706
2016	0,477745	0,963772	3,211842	1,086062	1,331876	1,260779	1,03311
2017	0,470013	0,948418	3,163554	1,01094	1,273701	1,252523	1,030527
2018	0,491266	0,922582	3,083688	0,957687	1,274216	1,185141	1,080736
2019	0,480878	0,921143	3,016601	0,929695	1,277661	1,159245	1,17273
2020	0,474565	0,885062	2,933429	0,915039	1,178979	1,145648	1,260767
2021	0,480596	0,922621	2,861969	0,929125	1,15157	1,110112	1,31588

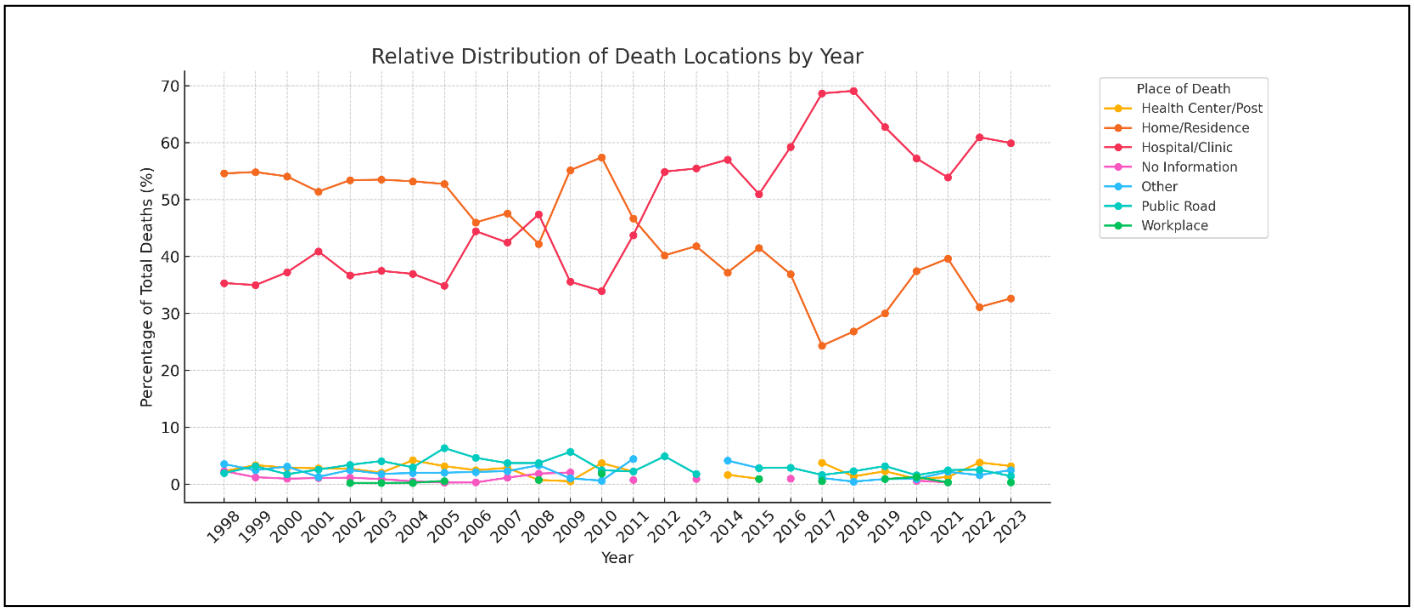
Source**:** these data were extracted from the GBD Results tool. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2023 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2024. Available from https://vizhub.healthdata.org/gbd-results/. They are publicly available for researchers only for academic purposes. Rates are expressed as 100,000 inhabitants.

Supplementary Table 2. Mortality by asthma by states, in all age and both sexes in Colombia before and after the pandemic in Colombia 2015-2021.

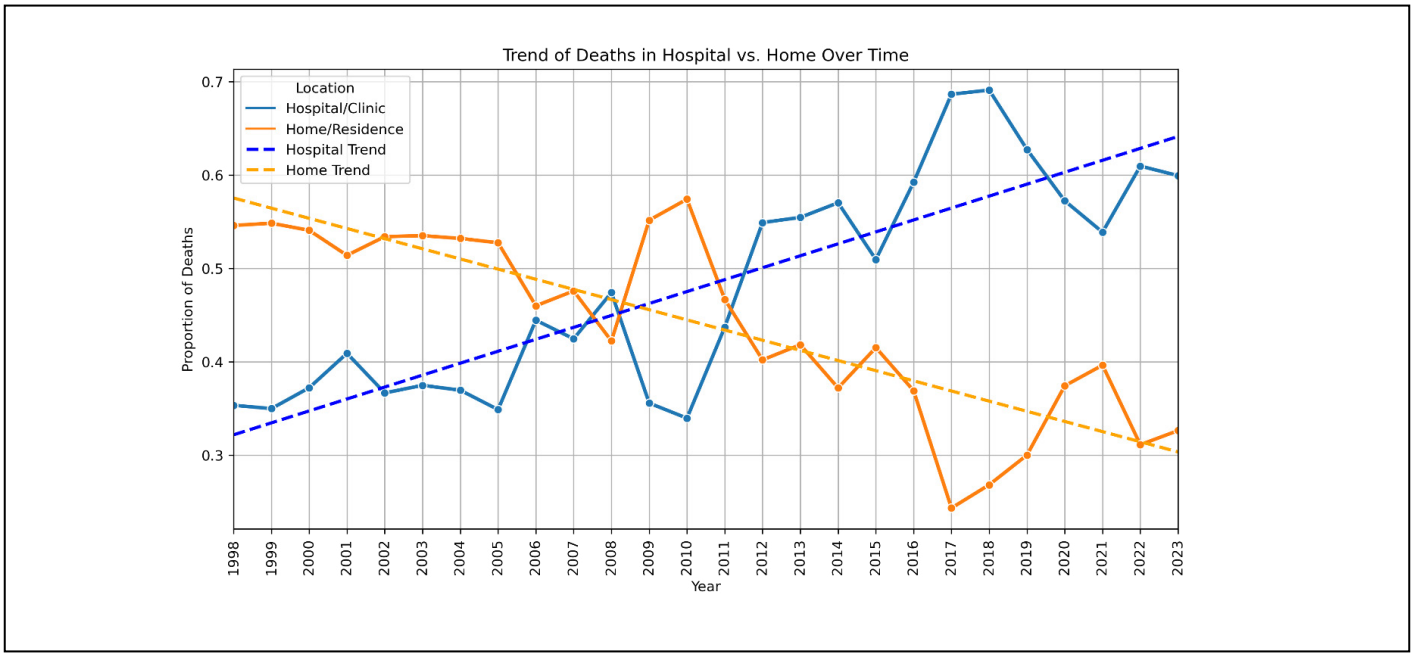
Department	2015	2016	2017	2018	2019	2020	2021	CMR Before	CMR 2020-21	Dif	APC
Boyacá	1	2	-	1	1	8	5	0.08	0.52	0.44	538.5%
Chocó	1	-	1	-	2	5	5	0.19	0.91	0.73	393.6%
Norte de Santander	9	11	10	2	4	12	13	0.19	0.77	0.57	293.2%
Caquetá	3	1	2	1	1	2	3	0.25	0.61	0.36	144.5%
Cauca	12	6	6	6	5	12	10	0.37	0.73	0.36	96.4%
Arauca	-	1	-	-	3	3	3	0.54	1.01	0.47	88.2%
Antioquia	26	30	29	28	27	48	52	0.42	0.74	0.32	74.9%
Quindío	1	2	1	2	2	5	2	0.37	0.63	0.26	70.8%
Bolívar	23	14	20	20	21	35	38	0.98	1.66	0.69	70.2%
Cesar	2	5	5	6	6	14	7	0.49	0.81	0.32	64.5%
Risaralda	1	1	1	5	5	5	11	0.53	0.83	0.30	57.0%
Valle del Cauca	27	16	17	26	27	41	42	0.59	0.91	0.32	54.8%
Sucre	5	4	4	3	6	9	5	0.49	0.73	0.25	50.2%
Santander	5	6	7	5	7	9	9	0.27	0.39	0.12	44.9%
Cundinamarca	13	6	6	6	12	13	14	0.30	0.41	0.11	37.3%

...continuation supplementary table 2.

Department	2015	2016	2017	2018	2019	2020	2021	CMR Before	CMR 2020-21	Dif	APC
Caldas	4	5	7	4	4	7	4	0.40	0.54	0.14	35.0%
La guajira	3	3	2	4	3	1	9	0.39	0.51	0.12	30.5%
Córdoba	7	8	5	10	9	14	9	0.53	0.63	0.10	18.5%
Atlántico	11	5	18	25	10	25	18	0.68	0.78	0.10	14.9%
Magdalena	8	9	6	3	8	7	6	0.40	0.45	0.05	13.1%
Bogotá, D.C.	27	18	16	27	30	25	35	0.38	0.38	0.01	1.3%
Casanare	-	1	1	3	1	2	1	0.47	0.34	- 0.13	-27.4%
Meta	1	5	2	2	4	2	2	0.29	0.19	- 0.10	-34.6%
Huila	8	4	3	8	8	4	6	0.72	0.44	- 0.28	-38.7%
Nariño	7	10	5	14	6	3	9	0.61	0.37	- 0.24	-39.9%
Tolima	1	6	6	8	7	5	4	0.56	0.34	- 0.23	-40.4%
Putumayo	1	-	2	1	1	1	-	0.28	0.14	- 0.15	-51.1%
Guainía	-	-	-	-	-	1	-	-	0.99	-	-
Vichada	-	-	1	-	-	-	1	-	0.44	-	-



Supplementary Figure 1. Relative distribution of death locations reported in DANE for asthma.



Supplementary Figure 2. Proportion of deaths reported at home or hospital during 1998 to 2023. Continuous lines report relative proportion of deaths about the total number of events; dashed lines represent linear trends derived from linear regression models.

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Original article

Spanish translation and cross-cultural adaptation of a new severity scale to measure activity in patients with chronic prurigo: Prurigo Control Test (PCT)

Traducción al español y adaptación transcultural de una nueva escala de severidad para medir la actividad en pacientes con prurigo crónico: Prurigo Control Test (PCT)

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Abstract

OBJECTIVE: Perform the translation and cross-cultural adaptation of the severity scale to measure activity in patients with chronic prurigo: Prurigo Control Test (PCT) for the locality of Río de la Plata, Argentina.

METHODS: A cross-sectional study using a mixed-methods (qualitative and quantitative) approach was performed. The process involved seven stages: translation, expert reconciliation, back-translation into English, equivalence review, expert evaluation, cognitive interviews with patients, and development of the final version.

RESULTS: A Spanish version of the questionnaire was obtained. Eleven patients were interviewed. The median age was 70 years (IQR 59-75), and the median disease duration was 24 months. Correct comprehension of all items was achieved by 90% of the patients. The only modification made was the addition of the clarification "(de la piel)" [of the skin] following the term "cutánea" [cutaneous] to ensure comprehension across all educational levels.

CONCLUSIONS: The translated and adapted version of the PCT constitutes a simple, objective, and valuable tool for assessing disease control and therapeutic response in the daily clinical care of Spanish-speaking patients.

KEYWORDS: Chronic prurigo; Severity scale; Prurigo control test (PCT); Comprehension; Educational levels; Patients; Argentina.

Resumen

OBJETIVO: Realizar la traducción y adaptación transcultural de la escala de severidad para medir la actividad de la enfermedad en pacientes con prurigo crónico: Prurigo Control Test (PCT) para la región del Río de la Plata, Argentina.

MÉTODOS: Estudio de corte transversal, con metodología cuali-cuantitativa, que comprendió un proceso de siete pasos: traducción, conciliación por expertos, retro-traducción al inglés, revisión de equivalencias, evaluación por expertos, entrevistas cognitivas a pacientes y elaboración de la versión final.

RESULTADOS: Se obtuvo una versión en español del cuestionario. Se entrevistaron 11 pacientes. La mediana de edad fue de 70 años (RIC 59-75) y la mediana de duración de la enfermedad de 24 meses. El 90% comprendió correctamente todos los ítems. La única modificación realizada fue la inclusión de la aclaración "(de la piel)" a continuación del término "cutánea" para asegurar la comprensión en todos los niveles educativos.

CONCLUSIONES: La versión traducida y adaptada del Prurigo Control Test (PCT) constituye un método simple, objetivo y valioso para evaluar el control de la enfermedad y su respuesta terapéutica en la práctica cotidiana en pacientes de habla hispana.

PALABRAS CLAVE: Prurigo crónico; Escala de gravedad; Prueba de control del prurigo (PCT); Comprensión; Nivel educativo; Pacientes; Argentina.

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BACKGROUND

Chronic prurigo is a neuroinflammatory skin disease characterized by intense pruritus and the appearance of skin lesions as a consequence of it.[1,2]

The onset of the disease most frequently occurs between the ages of 50 and 60. It is more common in women and in the Black race.[2-4] Worldwide prevalence is variable, with 6.5, 72, and 111 cases per 100,000 inhabitants in Poland, United States, and Argentina, respectively.[3-5]

Chronic prurigo has a high impact on patients' quality of life. Its approach must be holistic and comprehensive, and treatment multimodal, with the goal of controlling the disease and reducing morbidity and mortality.[1,2] Currently, clinical evaluation of treatment response and assessment of disease control are complex and present difficulties. To perform an objective evaluation of treatment response, according to research studies, scales such as: IGA (Investigator Global Assessment score), Peak Pruritus NRS (Peak Pruritus Numerical Rating Scale), and DLQI (Dermatology Life Quality Index) are typically used, which may be impractical for outpatient care.[6-8] Recently, Metz and colleagues developed a new scale: Prurigo Control Test (PCT). This measurement instrument was designed and validated in 2024 in English.[9] It consists of a direct patient-reported outcome, brief and simple, which allows for understanding the global perception of the chronic prurigo status and its control with the established treatment. It includes a scale from 0 to 20 points that evaluates 5 aspects (0 to 4 points for each): *1)* severity of skin lesions, *2)* frequency of scratching, *3)* impact on sleep, *4)* impact on quality of life, and *5)* treatment efficacy.[9]

With the intention of having this questionnaire available in Spanish, the objective of this study was: to perform the translation and cross-cultural adaptation of the severity scale to measure disease activity in patients with chronic prurigo: Prurigo Control Test (PCT) for the Río de la Plata region, Argentina.

METHODS

Study design

Cross-sectional study whose methodology includes qualitative and quantitative components.

Methodology for translation and cross-cultural adaptation

The translation and cross-cultural adaptation process included seven steps: *1)* translation of the original questionnaire into the target language carried out by two bilingual translators, whose native language was Spanish, one with experience in medicine or medical terms and the other with knowledge of everyday language terms; *2)* comparison and reconciliation of the first two translated versions into the target language by a committee of bilingual experts; *3)* back-translation into the original language by two bilingual translators (native English speakers), blinded to the original questionnaire; *4)* review of the back-translated version into the original language by a bilingual committee, consisting of the four translators and the expert committee from step 2, by comparing the two back-translations with each other and with the original questionnaire; *5)* evaluation of the first version by a committee consisting of two researchers with experience in chronic prurigo, who assessed conceptual, semantic, grammatical, and content equivalences of the translated instrument; *6)* cognitive interviews with patients of both genders with chronic prurigo and a wide age range, using the "think aloud" format, conducted according to the proposal by Eardley et al., and audio-recorded for subsequent analysis. This technique consists of asking the participant to verbalize in real time the thoughts that arise while reading and responding to each item, allowing the interviewer to identify comprehension difficulties, ambiguous terms, or misinterpreted questions without needing to infer them from the final answers.[10,11] For each question in the questionnaire, the evaluation was performed item by item, recording three dimensions: *a)* global comprehension (yes/no), *b)* identification of words or phrases that were difficult, confusing, or disturbing, and *c)* correct paraphrasing of the concept (yes/no), where the participant was asked to reformulate in their own words what the question was inquiring. This last dimension constitutes the most robust way to verify that the concept was correctly interpreted, as a participant may answer affirmatively when asked if they understood, even when their understanding is incorrect or partial.[11] In step *7* of the translation and cross-cultural adaptation process, the analysis of the recorded interviews was performed, registering relevant observations and creating the final version of the translated and adapted Spanish questionnaire.[10,11]

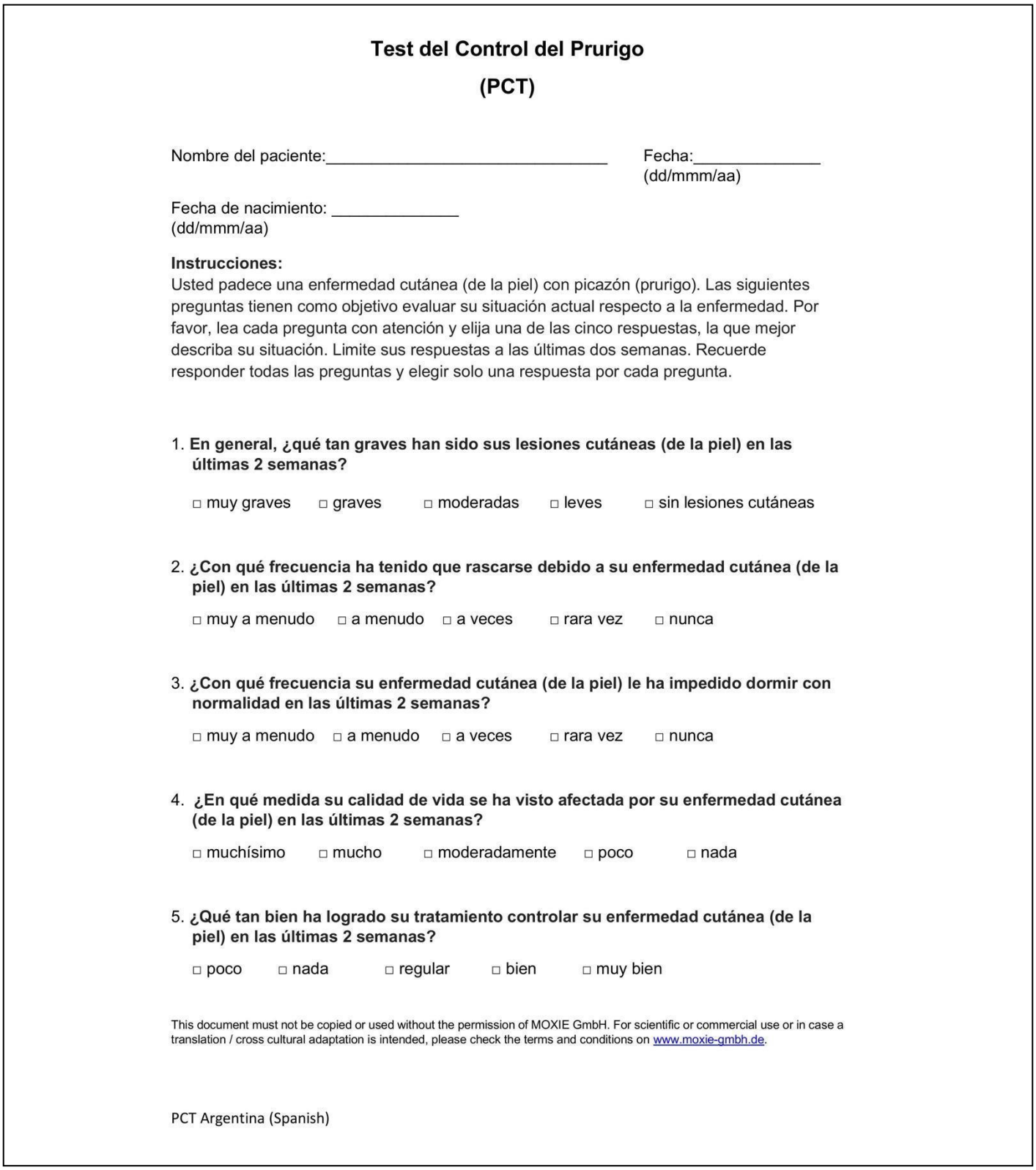
Authorization was obtained from the developers of the original English questionnaire, who also participated by providing comparative feedback between the original version and the back-translation from Spanish to English, as well as suggestions on the observations obtained from the cognitive interviews. For reporting the results, the methodology proposed by Streiner et al. was followed.[11]

The study complied with the ethical standards of the institutional and national research committee, and with the 1964 Declaration of Helsinki and its subsequent amendments, as well as with comparable ethical standards. The interviewed individuals provided written informed consent. The protocol was approved by the ethics committee for research protocols of the Hospital Italiano de Buenos Aires (protocol 7467).

RESULTS

The translation process, with its 7 steps, allowed for obtaining a questionnaire in the Spanish language (**Figure 1**).

Cognitive interviews were conducted with 11 patients diagnosed with CP, 9 of whom were female. Their demographic characteristics are detailed in **Table 1**. All patients resided in urban areas at the time of the study. The median age was 70 years (IQR 59–75), and the median disease duration was 24 months (IQR 18–60). Educational levels were: primary (n=1), secondary (n=4), tertiary (n=3), and university (n=2). The median time for completing the interviews was 8 minutes (IQR 7–11).



Test del Control del Prurigo

(PCT)

Nombre del paciente:_____ Fecha:_____
(dd/mmm/aa)

Fecha de nacimiento: _____
(dd/mmm/aa)

Instrucciones:
Usted padece una enfermedad cutánea (de la piel) con picazón (prurigo). Las siguientes preguntas tienen como objetivo evaluar su situación actual respecto a la enfermedad. Por favor, lea cada pregunta con atención y elija una de las cinco respuestas, la que mejor describa su situación. Limite sus respuestas a las últimas dos semanas. Recuerde responder todas las preguntas y elegir solo una respuesta por cada pregunta.

1. **En general, ¿qué tan graves han sido sus lesiones cutáneas (de la piel) en las últimas 2 semanas?**

□ muy graves □ graves □ moderadas □ leves □ sin lesiones cutáneas

2. **¿Con qué frecuencia ha tenido que rascarse debido a su enfermedad cutánea (de la piel) en las últimas 2 semanas?**

□ muy a menudo □ a menudo □ a veces □ rara vez □ nunca

3. **¿Con qué frecuencia su enfermedad cutánea (de la piel) le ha impedido dormir con normalidad en las últimas 2 semanas?**

□ muy a menudo □ a menudo □ a veces □ rara vez □ nunca

4. **¿En qué medida su calidad de vida se ha visto afectada por su enfermedad cutánea (de la piel) en las últimas 2 semanas?**

□ muchísimo □ mucho □ moderadamente □ poco □ nada

5. **¿Qué tan bien ha logrado su tratamiento controlar su enfermedad cutánea (de la piel) en las últimas 2 semanas?**

□ poco □ nada □ regular □ bien □ muy bien

PCT Argentina (Spanish)

Figure 1. Format of the test to measure prurigo control.

All patients (11/11) stated that they correctly understood the 6 items (the instructions and the five questions) that make up the questionnaire. When asked to paraphrase them, 1/11 patients was unable to do so for questions 1, 2, and 3. The most frequent observations were: the term "cutánea" [cutaneous] was pointed out as potentially confusing by one patient (question 1); the distinction between the options "muchísimo" [very much] and "mucho" [a lot] generated an isolated observation (question 4); and the term "calidad de vida" [quality of life] was questioned by one participant (question 4). No observations were recorded regarding the questions that implied a lack of understanding of the central concept. Based on the item-by-item analysis of all interviews, it was decided to incorporate the clarification "(de la piel)" [(of the skin)] after the term "cutánea," in order to improve comprehension without altering the original meaning of the instrument. The results of the cognitive interviews by item are presented in **Table 2**.

Table 1. Patient demographic information.

Patient	Age (years)	Gender	Disease duration (months)	Highest educational level reached	City of residence	Interview duration (minutes)
1	74	F	24	University degree completed	CABA	7
2	76	F	12	University degree completed	CABA	7
3	52	M	48	Secondary school completed	CABA	10
4	75	F	18	Secondary school incomplete (up to 3rd year)	Merlo, Buenos Aires	8
5	70	F	60	Secondary school completed	Mercedes, Buenos Aires	15
6	81	M	24	Primary school completed	San Fernando, Buenos Aires	10
7	69	F	25	Tertiary degree completed	Caseros, Buenos Aires	5
8	70	F	15	Secondary school completed	Wilde, Buenos Aires	17
9	48	F	108	Tertiary degree completed	CABA	11
10	73	F	4	Tertiary degree completed	CABA	5
11	59	F	24	Secondary school completed	San Juan	8

F: female; M: male; CABA: Autonomous City of Buenos Aires.
All patients resided in Argentina.

DISCUSSION

This study carried out the translation and adaptation of the questionnaire developed by Metz et al.[9] The resulting questionnaire provides a new, potentially useful method for objectifying chronic prurigo activity in Spanish-speaking patients.[1,2]

The translation process and subsequent analysis through cognitive interviews revealed that no significant cultural differences were observed in the use of vocabulary for this particular questionnaire. Each item of the questionnaire was evaluated individually and systematically in three dimensions: 1) global comprehension (did you understand?), 2) identification of difficult or ambiguous words or phrases, and 3) correct paraphrasing of the concept (yes/no). This item-by-item approach is recommended by methodological literature specialized in scale adaptation. Streiner, Norman, and Cairney, in Health Measurement Scales in 2015, establish that the goal of cognitive interviews is to detect ambiguous items, incomprehensible terms, or double-meaning questions, and that the central evaluation criterion is the respondent's ability to correctly paraphrase the concept, not just to report whether they "understand" or not. The same text points out that asking whether a phrase or word was difficult and requesting the participant to reformulate the item in their own words constitutes the standard way to assess comprehensibility at the level of each individual item. Through the completed steps, it was determined that

Table 2. Detail of cognitive interviews.

Source text	Patient	Comprehension	Words or phrases found difficult or confusing	Correct paraphrasing / concept understood	Patient or interviewer comments and suggestions for rephrasing
Instructions: You suffer from a skin disease with itching (prurigo). The following questions aim to evaluate your current situation regarding the disease. Please read each question carefully and choose one of the five responses that best describes your situation. Limit your responses to the last two weeks. Remember to answer all questions and choose only one response per question.	**1**	Yes	None	Yes	Suggests clarifying that responses should be considered according to the current therapeutic status (in treatment if so, or without treatment if not).
	2	Yes	None	Yes	-
	3	Yes	None	Yes	-
	4	Yes	None	Yes	-
	5	Yes	None	Yes	-
	6	Yes	None	Yes	-
	7	Yes	None	Yes	-
	8	Yes	None	Yes	-
	9	Yes	None	Yes	-
	10	Yes	None	Yes	-
	11	Yes	None	Yes	-

...continuation table 2.

Source text	Patient	Comprehension	Words or phrases found difficult or confusing	Correct paraphrasing / concept understood	Patient or interviewer comments and suggestions for rephrasing
In general, how severe have your skin lesions been in the last 2 weeks? *(Very severe, Severe, Moderate, Mild, No skin lesions)*	**1**	Yes	None	Yes	-
	2	Yes	None	Yes	-
	3	Yes	None	Yes	Considers that the word “cutaneous” could cause comprehension problems.
	4	Yes	None	Yes	-
	5	Yes	None	Yes	-
	6	Yes	None	Yes	-
	7	Yes	None	Yes	-
	8	Yes	None	Yes	-
	9	Yes	None	Yes	Considers that the word “severe” can be understood in several ways, depending on what each patient is used to.
	10	Yes	None	No	-
	11	Yes	None	Yes	-

...continuation table 2.

Source text	Patient	Comprehension	Words or phrases found difficult or confusing	Correct paraphrasing / concept understood	Patient or interviewer comments and suggestions for rephrasing
How often have you had to scratch yourself due to your skin disease in the last 2 weeks? *(Very often, Often, Sometimes, Rarely, Never, No skin lesions)*	**1**	Yes	None	Yes	-
	2	Yes	None	Yes	-
	3	Yes	None	Yes	-
	4	Yes	None	Yes	-
	5	Yes	None	Yes	-
	6	Yes	None	Yes	-
	7	Yes	None	Yes	-
	8	Yes	None	Yes	-
	9	Yes	Yes, Frequency	Yes	-
	10	Yes	None	No	-
	11	Yes	None	Yes	-

...continuation table 2.

Source text	Patient	Comprehension	Words or phrases found difficult or confusing	Correct paraphrasing / concept understood	Patient or interviewer comments and suggestions for rephrasing
How often has your skin disease prevented you from sleeping normally in the last 2 weeks? *(Very often, Often, Sometimes, Rarely, Never)*	**1**	Yes	None	Yes	-
	2	Yes	None	Yes	-
	3	Yes	None	Yes	-
	4	Yes	None	Yes	-
	5	Yes	None	Yes	-
	6	Yes	None	Yes	-
	7	Yes	None	Yes	-
	8	Yes	None	Yes	-
	9	Yes	None	Yes	-
	10	Yes	None	No	-
	11	Yes	None	Yes	-

...continuation table 2.

Source text	Patient	Comprehension	Words or phrases found difficult or confusing	Correct paraphrasing / concept understood	Patient or interviewer comments and suggestions for rephrasing
To what extent has your quality of life been affected by your skin disease in the last 2 weeks? *(Very much, A lot, Moderately, A little, Not at all)*	**1**	Yes	None	Yes	-
	2	Yes	None	Yes	-
	3	Yes	None	Yes	Suggests modifying response options, as “very much” and “a lot” can be confusing.
	4	Yes	None	Yes	-
	5	Yes	None	Yes	-
	6	Yes	None	Yes	-
	7	Yes	None	Yes	-
	8	Yes	None	Yes	-
	9	Yes	None	Yes	-
	10	Yes	None	Yes	-
	11	Yes	None	Yes	Considered the term “quality of life” may be confusing for some people.

...continuation table 2.

Source text	Patient	Comprehension	Words or phrases found difficult or confusing	Correct paraphrasing / concept understood	Patient or interviewer comments and suggestions for rephrasing
How well has your treatment managed to control your skin disease in the last 2 weeks? *(None, A little, Fair, W ell, Very well)*	**1**	Yes	None	Yes	-
	2	Yes	None	Yes	-
	3	Yes	None	Yes	-
	4	Yes	None	Yes	-
	5	Yes	None	Yes	-
	6	Yes	None	Yes	-
	7	Yes	None	Yes	-
	8	Yes	None	Yes	-
	9	Yes	None	Yes	-
	10	Yes	None	Yes	-
	11	Yes	None	Yes	-

the global comprehension rate for each item studied was 100%, and the correct paraphrasing rate was 91% to 100% depending on the item. This highlights the clarity and correct interpretation of the questions, in accordance with the exploratory objective of each of them, as well as clarifying that each item of the questionnaire can measure what it intends to. This is what is called cross-cultural adaptation.[10,11] This methodology is consistent with what is described by Streiner et al., who emphasize that for the cross-cultural adaptation stage (unlike formal psychometric validation), qualitative item-by-item evaluation through cognitive interviewing is the appropriate method, and that quantitative difficulty analyses (such as difficulty indices from Item Response Theory) correspond to later phases of psychometric validation, which are currently underway.

However, based on the observations made by the interviewees, a directed review of the literature on self-administered instruments and educational materials in Spanish intended for patients was carried out. In methodologically comparable works, such as the cross-cultural adaptation into Spanish of the Dermatology Life Quality Index (DLQI), a consistent use of accessible terminology for the general population is observed, using the term "piel" [skin] instead of using technical vocabulary such as the term "cutánea" [cutaneous].[12] Based on this precedent, it was decided to keep the original term but add the clarification "(de la piel)" immediately after "cutánea," in order to improve patient comprehension.

This research was conducted at a private university hospital where the care of middle-class patients living in an urban environment predominates, which could introduce socioeconomic and cultural biases to this work and limit the possibility of extrapolating the utility of the questionnaire to a different population. On the other hand, and in line with the higher prevalence of this disease in females (also documented in our population by our research group)[5], women predominated in our sample.

Since the Spanish language of the Río de la Plata region has its linguistic peculiarities, it would be advisable to carry out separate cross-cultural adaptations before administering this scale on a massive scale in other Spanish-speaking contexts.

CONCLUSIONS

We consider that the translated and adapted Spanish version of the PCT constitutes the initial stage of work to provide a potentially useful tool that will contribute to objectifying disease activity and treatment response in the daily care of Spanish-speaking CP patients. Although the translation and adaptation were performed considering the Spanish of the Río de la Plata (Argentina) as the target language, we consider that this tool will be adaptable for use in other Spanish-speaking countries and will help counteract the communication deficit between non-Spanish-speaking professionals and Spanish-speaking patients.

Formal psychometric validation is required to determine the construct validity, internal consistency, and reproducibility to determine that it adequately measures prurigo control in the Spanish-speaking population. This work is currently under development by our research group.

DECLARATIONS

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

Ana Clara Torre, Agustin Wagner, Sergio Adrián Terrasa, and Luis Daniel Mazzuoccolo conceived and designed the study and supervised the overall development of the project. Anama Di Prinzio, Nadia Bejar, and María Valeria Angles conducted the cognitive interviews. Ana Clara Torre and Sergio Adrián Terrasa performed the data analysis and interpretation of the results. Ana Clara Torre and Agustin Wagner drafted the initial manuscript. All authors participated in the critical revision of the text, provided key intellectual commentary, and approved the final version for publication.

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Review article

Prebiotics and asthma: current insights and future directions from a bibliometric analysis

Prebióticos y asma: perspectivas actuales y direcciones futuras a partir de un análisis bibliométrico

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Abstract

BACKGROUND: Prebiotics have gained attention as a microbiome-modulating strategy in asthma because they may influence immune regulation through the gut–lung axis. However, evidence on prebiotics and asthma remains distributed across allergy, immunology, nutrition, microbiology, and respiratory medicine.

OBJECTIVES: This study aimed to map global research trends, influential contributors, and thematic development in prebiotics–asthma research using bibliometric analysis.

METHODOLOGY: This bibliometric study analyzed English-language articles and reviews indexed in Scopus. Prebiotic-related and synbiotic-related terms were combined using OR and then linked with asthma-related terms using AND. Eligible records were screened for relevance to prebiotics and asthma. Bibliometric analyses and visualizations were performed using Biblioshiny and VOSviewer to evaluate publication output, leading contributors, citation impact, keyword co-occurrence, and temporal research trends.

RESULTS: A total of 296 publications from 166 sources were included. The earliest eligible publication was published in 2002. Annual scientific production increased over time, with an annual growth rate of 13.66% and the highest output in 2024. Review articles outnumbered original articles. The United States was the leading contributor, followed by Australia, the Netherlands, Italy, and China. Keyword analysis identified three major domains: mechanistic and immunologic studies, early-life allergy prevention, and microbiota-focused modulation. Trend analysis showed a shift toward gut microbiome, short-chain fatty acids, immune dysregulation, and gut–lung axis.

CONCLUSION: Prebiotics–asthma research is a relatively recent but steadily growing field with increasing emphasis on microbiome-mediated and mechanistic pathways. However, asthma-specific translational evidence remains limited, supporting the need for standardized clinical studies and integrative multi-omic approaches.

KEYWORDS: Asthma; Allergy; Bibliometrics analysis; Prebiotics; Symbiotics; United States; Australia; Netherlands; China; Gut microbiome; Short-chain fatty acids; Gut-lung axis; Multi-omic approaches.

Resumen

ANTECEDENTES: Los prebióticos han recibido atención como estrategia de modulación del microbioma en pacientes con asma, debido a su influencia en la regulación inmunitaria a través del eje intestino-pulmón. Sin embargo, la evidencia relacionada con los prebióticos y el asma permanece distribuida entre diferentes disciplinas.

OBJETIVO: Mapear las tendencias globales de investigación, influencias de los contribuyentes y desarrollo temático en la investigación acerca de los prebióticos y el asma mediante un análisis bibliométrico.

METODOLOGÍA: Se analizaron artículos y revisiones en inglés indexados en Scopus. Los términos relacionados con prebióticos y simbióticos se combinaron mediante OR y luego se vincularon con términos asociados con asma mediante AND. Los registros elegibles se evaluaron por su relevancia para prebióticos y asma. El análisis bibliométrico se llevó a cabo con Biblioshiny y VOSviewer para evaluar la producción científica, influencia de los contribuyentes, efecto de la citación, co-ocurrencia de palabras clave y tendencias temporales.

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RESULTADOS: Se incluyeron 296 publicaciones de 166 fuentes. La primera publicación elegible apareció en 2002. La producción anual aumentó con el tiempo, con una tasa de crecimiento de 13.66%, y la mayor cantidad de publicaciones se registró en 2024. Las revisiones superaron a los artículos originales. Estados Unidos fue el principal país contribuyente, seguido de Australia, Países Bajos, Italia y China. El análisis de palabras clave identificó tres dominios: *1)* estudios mecanísticos e inmunológicos, *2)* prevención temprana de alergias y *3)* modulación centrada en la microbiota. El análisis de tendencias mostró un cambio en el microbioma intestinal, los ácidos grasos de cadena corta, la desregulación inmunitaria y el eje intestino-pulmón.

CONCLUSIÓN: La investigación acerca de prebióticos y asma es reciente, pero creciente. La evidencia traslacional específica para asma sigue siendo limitada, por lo que se requieren estudios clínicos estandarizados y enfoques multiómicos integrativos.

PALABRAS CLAVE: Asma; Alergia; Análisis bibliométrico; Prebióticos; Simbióticos; Estados Unidos; Australia; Países bajos; China; Microbioma intestinal; Ácidos grasos de cadena corta; Eje intestino-pulmón; Enfoques multiómicos.

INTRODUCTION

Asthma remains a major global health problem, affecting more than 260 million people worldwide and contributing substantially to morbidity and mortality.[1] Beyond airway inflammation and bronchoconstriction, increasing attention has been directed toward the role of the microbiome in chronic inflammatory disease, including asthma, particularly through the gut–lung axis.[2,3] Early-life microbial perturbations have been linked to aberrant immune maturation and subsequent susceptibility to allergic airway disease, supporting the concept that asthma may be influenced, at least in part, by microbiota-dependent immune programming.[2,4] Among the proposed mechanisms, short-chain fatty acids (SCFAs) have emerged as key mediators, as they may attenuate allergic airway inflammation by enhancing regulatory immune pathways and maintaining epithelial homeostasis.[5,6]

Microbiome-modulating interventions have therefore become an important area of interest in asthma and allergic disease research. These interventions include related but distinct concepts. Probiotics are live microorganisms that may provide health benefits, whereas prebiotics are substrates that selectively support beneficial endogenous microbes and their metabolic activity, including short-chain fatty acid production. Symbiotics combine live microorganisms with substrates intended to support microbial persistence or activity.[7,8] In this study, the focus was the prebiotics–asthma research landscape, while symbiotics and related microbiome concepts were considered when they appeared within the retrieved literature.

Despite increasing interest in this area, research on prebiotics and symbiotics in asthma remains dispersed across allergy, immunology, nutrition, microbiology, and respiratory medicine. This fragmentation makes it difficult to identify how the field has developed, which contributors and publications have shaped the literature, and which themes are emerging. Bibliometric mapping can help address this gap by summarizing publication patterns, citation structures, leading contributors, and keyword evolution in a multidisciplinary research field.[9] Accordingly, this study aimed to map global research trends, influential contributors, and thematic development in prebiotics–asthma research using bibliometric analysis.

METHODOLOGY

This bibliometric study was conducted through four sequential stages: search source and strategy, eligibility criteria and screening, data extraction and quality control, and data analysis and synthesis. The complete study selection and analysis workflow, including the number of records identified, excluded, and included in the final analysis, is presented in **Figure 1**.

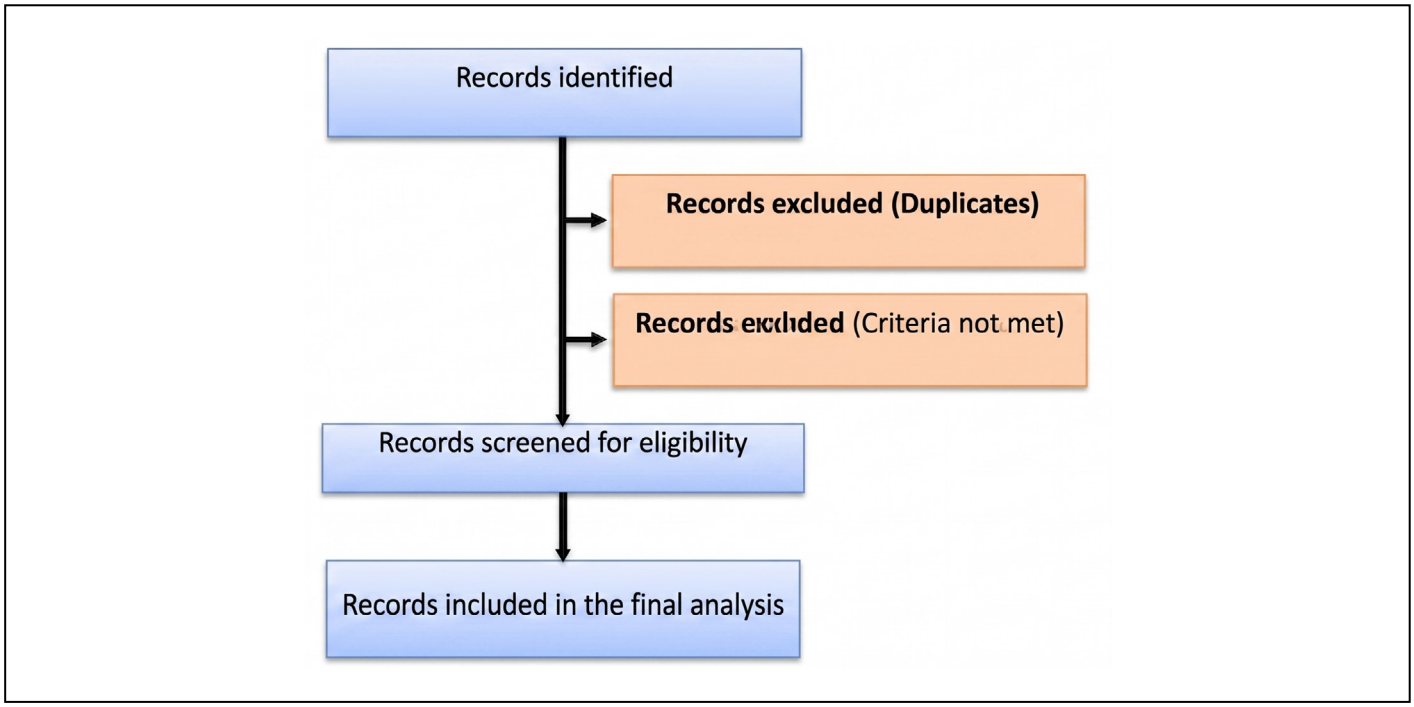

Figure 1. Flowchart of study selection and analysis process.

Search source and strategy

Bibliographic records were retrieved from the Scopus database because of its broad coverage of biomedical and life sciences literature and its compatibility with bibliometric analysis tools. The search was applied to the TITLE-ABS-KEY fields without a publication year restriction. Prebiotic-related terms and symbiotics-related terms were combined using OR, and the resulting set was combined with asthma-related terms using AND. The initial Scopus search identified 678 records. After applying database filters for the final publication stage, English language, and document type limited to articles or reviews, 114 records were excluded. The remaining records were screened using predefined title/abstract and full-text eligibility criteria. Disagreements during screening were resolved by consensus among the three reviewers; if consensus was not reached, the final decision was made by majority vote based on the predefined eligibility and exclusion criteria. A total of 296 records met the eligibility criteria and were included in the final bibliometric analysis.

Data extraction and analysis

Data extraction was based on standardized bibliometric variables, including authorship, article title, institutional affiliations, keywords, source journal, citation count, and publication year. Bibliometric visualization and analysis were performed using Biblioshiny from the Bibliometrix R package (version 4.1.3) and VOSviewer (version 1.6.18).[10,11] The analyses included descriptive bibliometric mapping of publication output, citation patterns, leading contributors, and source characteristics, together with keyword co-occurrence mapping and trend topic analysis. Keyword co-occurrence analysis was performed in VOSviewer using full counting, a minimum keyword occurrence threshold of 15, and association strength normalization. A thesaurus file was applied to harmonize synonymous and variant terms, and a remove-list file was used to exclude non-informative terms. Interpretation followed established bibliometric procedures while considering the limitations inherent to bibliometric indicators.[12]

RESULTS

Main information

A total of 296 publications on asthma and prebiotics were retrieved from 166 sources. Although no time restriction was applied during the search, the earliest publication identified in the dataset was published in 2002. Annual scientific production (**Figure 2A**) showed an overall increase over time, with an annual growth rate of 13.66% and the highest output recorded in 2024 (32 articles). The dataset included 1,249 authors, with an international co-authorship rate of 25.68% and an average of 5.13 co-authors per document. Review articles (n = 188) outnumbered original articles (n = 108). Average citations per year (**Figure 2B**) fluctuated across the study period and reached their highest level around 2010, whereas publication output continued to increase in later years.

Productivity of key authors, countries, institutions, and sources

Figure 3 presents the leading contributors in terms of authors, countries, institutions, and sources. Johan Garssen was the most prolific author, followed by Gert Folkerts and Susan L. Prescott, while the remaining top authors contributed within a narrower publication range. At the country level, the United States led research output, followed by Australia, the Netherlands, Italy, and China. The other top contributing countries included Canada, Germany, the United Kingdom, Spain, and France. At the institutional level, Utrecht Institute for Pharmaceutical Sciences ranked first, followed by the University of Rochester School of Medicine and Dentistry and Universiteit Utrecht. Other highly productive institutions included The University of British Columbia, The University of Western Australia, and Università degli Studi di Milano. In terms of source productivity, *Journal of Allergy and Clinical Immunology, Nutrients*, and *Frontiers in Immunology* were the leading sources, followed by *Allergy, Clinical* and *Experimental Allergy, Frontiers in Pediatrics,* and *World Allergy Organization Journal*.

Most cited publications and citation impact

Presents the 10 most-cited publications on prebiotics, symbiotics, and asthma research, ranked by total citations, citations per year, and normalized total citations. The most cited publication was *The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota*, with 1,466 total citations and 162.89 citations per year. The second-ranked publication was *Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: A randomized, double-blind, placebo-controlled trial*, with 643 total citations and 33.84 citations per year. Several publications also showed high normalized citation values. *The First Microbial Colonizers of the Human Gut* had a normalized total citation score of 9.48, followed by *Bifidobacteria-mediated immune system imprinting early in life* (8.88) and *Postbiotics—A Step Beyond Pre- and Probiotics* (6.35). Other highly cited publications included *The Gastrointestinal Microbiome: A Review* (520 citations), *Production of Chitooligosaccharides and Their Potential Applications in Medicine* (518 citations), and *Inflammatory Disease Processes and Interactions with Nutrition* (483 citations).

Overall, the top-cited publications addressed infant gut microbiota, prebiotic and probiotic interventions, postbiotics, bifidobacteria, nutrition, gastrointestinal microbiome composition, and immune regulation. Across the top 10 publications, total citations ranged from 414 to 1,466, citations per year ranged from 18.82 to 162.89, and normalized total citations ranged from 1.54 to 9.48.

Keyword structure and temporal evolution

The co-occurrence network and trend topic analysis of prebiotics–asthma research is shown in **Figure 4.** The co-occurrence network was organized around three major domains: mechanistic and immunologic studies (blue cluster), early-life allergy prevention (green cluster), and microbiota-focused modulation (red cluster). The blue cluster included *asthma*, *animals*, *oligosaccharides*, *short-chain fatty acids*,

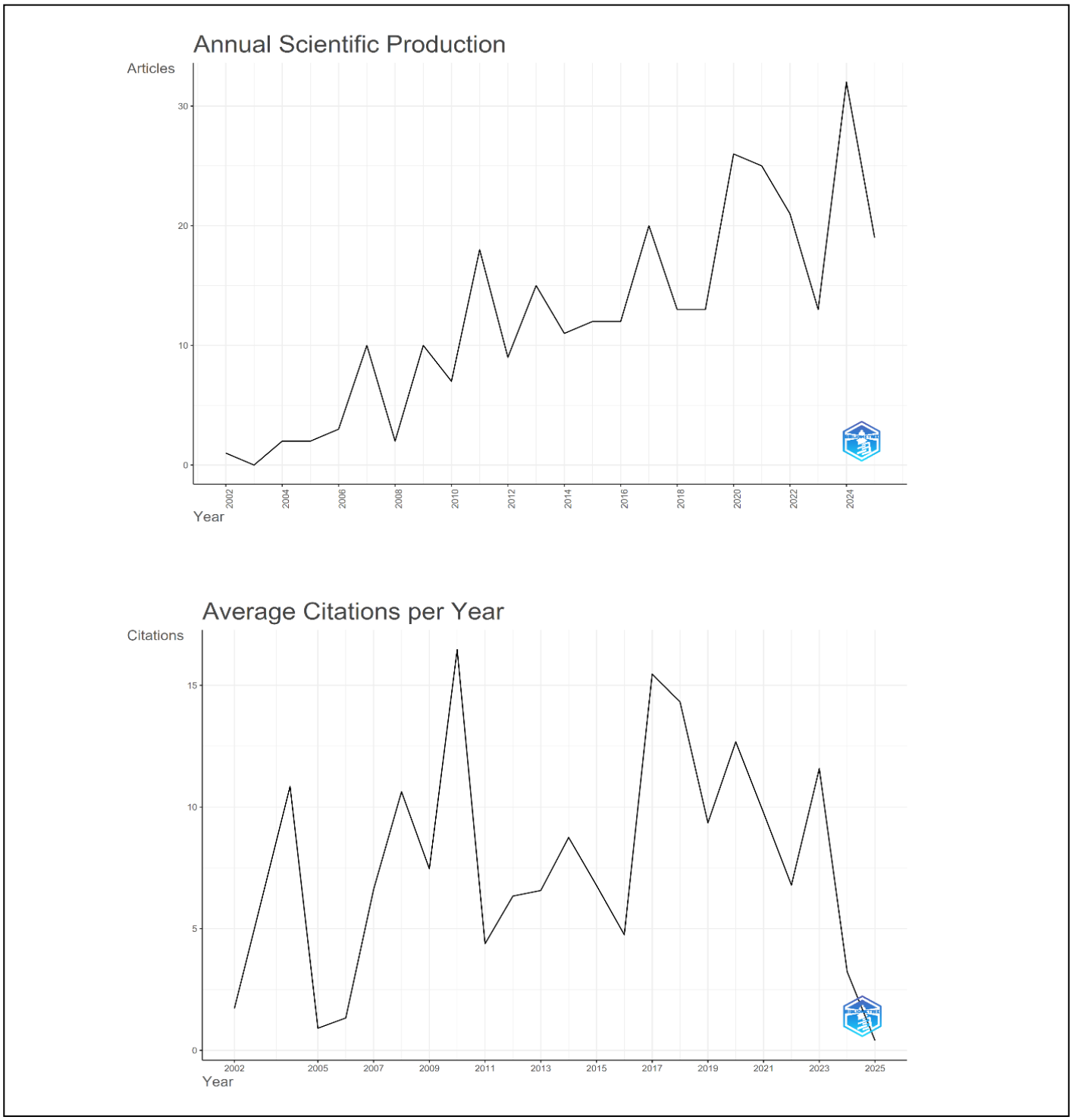

Figure 2. General characteristics of the bibliometric dataset. **A)** Annual scientific production on prebiotics and asthma from 2002 to 2025. **B)** Average citations per year across the study period.

respiratory tract inflammation, *cytokines*, and *regulatory T lymphocytes*. The green cluster linked *allergic disease*, *food allergy*, *pregnancy*, *infant*, and *prevention*. The red cluster was anchored by *prebiotics*, *probiotics*, *microbiome*, *gut microbiome*, *dysbiosis*, and *microbiology*. Peripheral nodes included *gut–lung axis*, *high-risk population*, *infant feeding*, *macrophage*, *eosinophil*, *Th17 cells*, and *CD4⁺ lymphocyte*.

Trend topic analysis showed a temporal progression in prebiotics–asthma research from 2005 to 2024. Early studies (2005–2010) mainly emphasized antioxidants, vitamins (*ascorbic acid*, *beta-carotene*, *selenium*, *alpha-tocopherol*), and antineoplastic or anti-inflammatory activity. Between 2011 and 2016, frequently appearing terms included *randomized controlled trial*, *clinical study*, *infant*, *allergic disease*, *immunoglobulin*, and *cesarean section*. From 2017 onward, dominant terms included *gut microbiome*, *short-chain fatty acids*, *Faecalibacterium*, *Bacteroides*, *gut–lung axis*, *immune dysregulation*, and *cytokine*. More recent keywords also included *fecal microbiota transplantation*, *phenotype*, and *air pollution*.

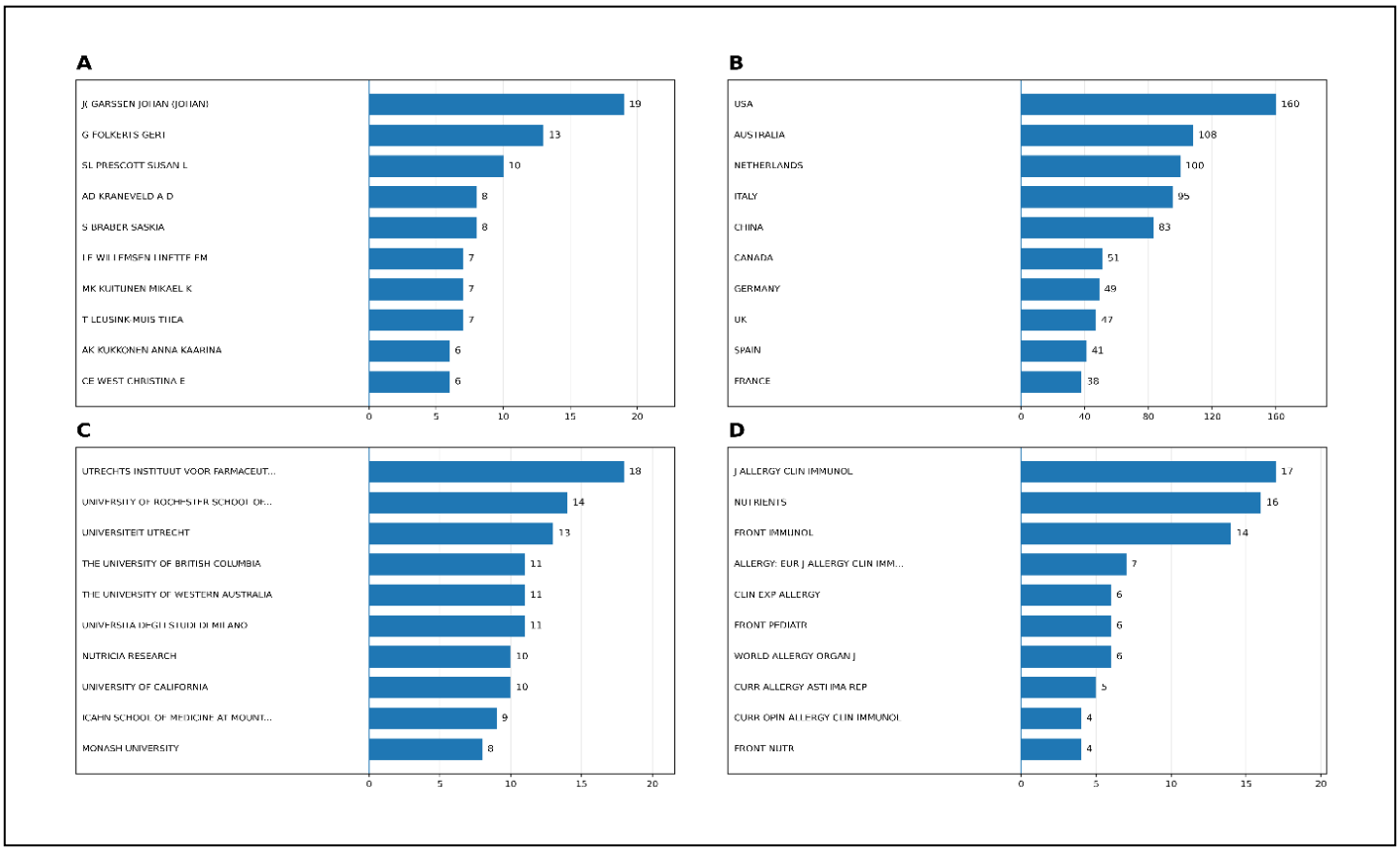

Figure 3. Most productive authors (**A),** countries (**B),** institutions (**C),** and sources (**D)** in the bibliometric dataset, ranked by number of publications.

DISCUSSION

General description

This bibliometric analysis provides an updated overview of global research trends on prebiotics and asthma, highlighting a field that is relatively recent but expanding steadily. Although no time restriction was applied, the earliest eligible publication in the present dataset appeared in 2002, and annual scientific production increased gradually over time, with year-to-year fluctuations, peaking in 2024. This pattern is consistent with growing scientific interest in the gut–lung axis as a biologic framework linking diet, microbial metabolites, and airway inflammation.[2,3,13]

Another notable finding is that review articles outnumbered original articles. This pattern suggests that the field remains in a consolidative phase, with substantial effort directed toward synthesizing mechanistic and translational evidence while asthma-specific interventional research remains comparatively limited. The citation profile further indicates that the intellectual foundation of this field is strongly shaped by broader microbiome, nutrition, and immune-regulation literature. Several highly cited publications addressed infant gut microbiota, bifidobacteria, postbiotics, gastrointestinal microbiome composition, nutrition, and immune maturation, rather than asthma-specific prebiotic interventions. Therefore, citation impact in this dataset should be interpreted as reflecting foundational concepts that informed prebiotics–asthma research, not as direct evidence of advances in asthma-specific intervention studies. This distinction is important because asthma-specific translational evidence remains comparatively limited, despite the strong mechanistic rationale linking microbial metabolites, immune regulation, and airway inflammation.[4,14-16] These citation-based findings should be interpreted within the scope of Scopus-indexed literature, as citation accumulation may vary across bibliographic databases and indexing histories.

From a geographic perspective, research productivity was led by the United States, followed by Australia, the Netherlands, Italy, and China. At the institutional level, Utrecht Institute for Pharmaceutical Sciences, the University of Rochester School of Medicine and Dentistry, and Universiteit Utrecht were the most productive affiliations, while *Journal of Allergy and Clinical Immunology*, *Nutrients*, and *Frontiers in Immunology* were the leading publication sources. This distribution reflects the multidisciplinary character of the field, which has also been described across the broader literature at the interface of allergy, immunology, microbiome science, and nutrition.[7,8,15] The contribution of North American and European centers may reflect the presence of established microbiome research infrastructure, including large collaborative initiatives in the United States and dedicated translational microbiome networks in the Netherlands. Meanwhile, the presence of China among the leading contributors may suggest ongoing geographic diversification in this area. However, this pattern should be interpreted as a representation of Scopus-indexed literature. The prominence of specific countries, institutions, and jour-

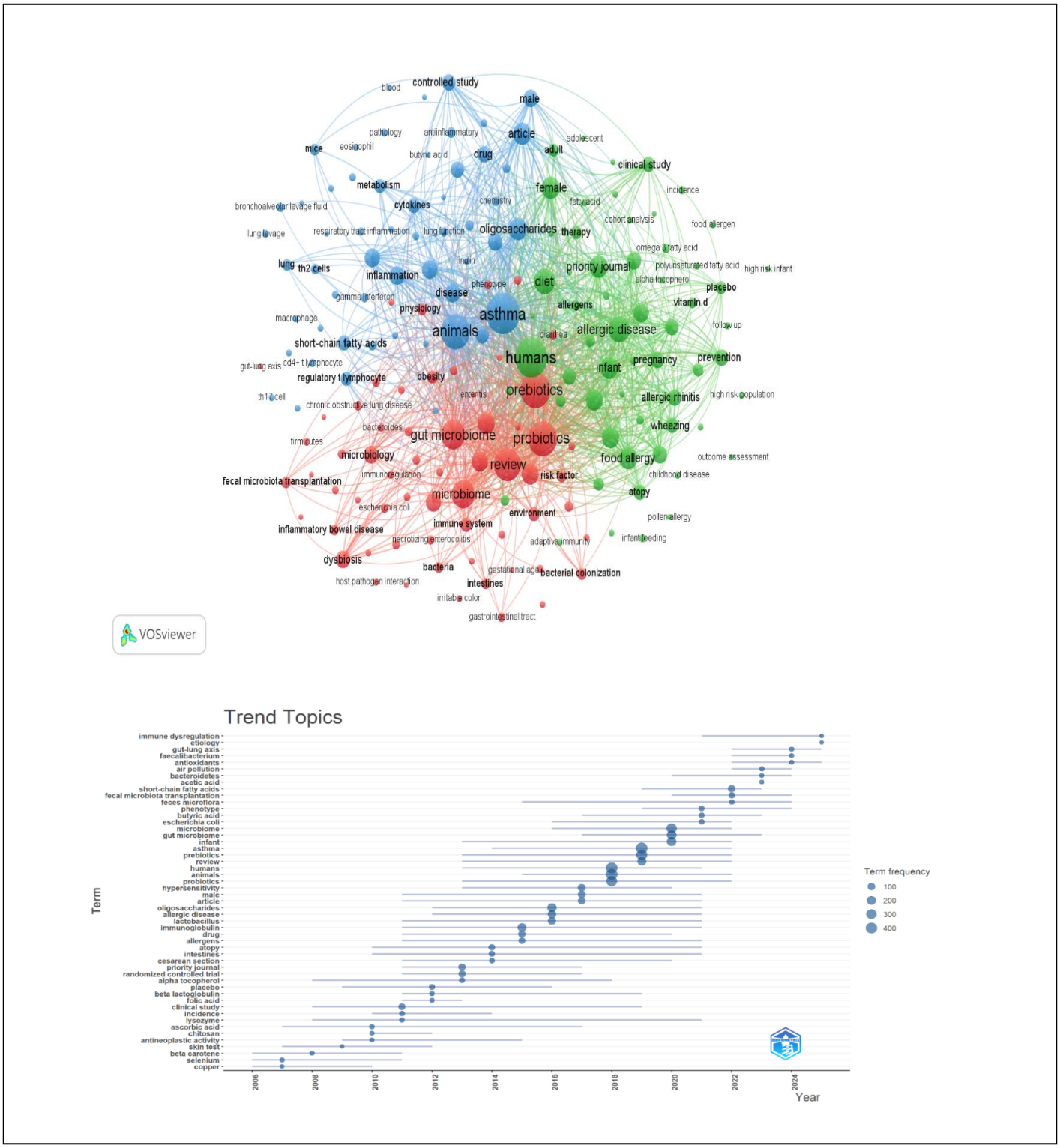

Figure 4. Keyword structure and temporal evolution in prebiotics–asthma research. **(A)** Co-occurrence network mapping of author keywords, showing major thematic clusters related to asthma, microbiome modulation, allergic disease, and prebiotic/probiotic research. **(B)** Trend topics analysis showing the temporal distribution of recurrent terms and the shift in research focus from early nutrition- and antioxidant-related topics toward gut microbiome, immune dysregulation, and microbiota-based interventions.

nals may partly reflect their stronger visibility within Scopus-indexed publication networks, whereas regional, local, non-English, or non-indexed journals may be less represented.

Mechanistic and translational evidence on prebiotic modulation in asthma

The thematic shift toward gut microbiome, short-chain fatty acids, immune dysregulation, and the gut–lung axis is biologically plausible and supported by current mechanistic literature. Prebiotics are increasingly

discussed not only as dietary substrates, but also as modulators of host–microbe interaction through their capacity to stimulate beneficial endogenous microbes and enhance short-chain fatty acid production.[6,8,16,17] Among these metabolites, acetate, propionate, and butyrate are particularly relevant because they have been linked to regulatory immune pathways involved in allergic airway inflammation.[5,6,17-19] Experimental studies have shown that SCFAs may attenuate airway inflammation through effects on regulatory T cells, cytokine balance, epithelial homeostasis, and macrophage polarization.[17-22] These mechanisms provide a biologic rationale for the increasing prominence of microbiome- and metabolite-related themes in the present bibliometric analysis.

However, the translation of these mechanistic findings into asthma-specific clinical practice remains limited. Compared with probiotics, prebiotics and symbiotics are less extensively studied in asthma-specific clinical settings, despite their conceptual advantage of modulating microbial function without relying solely on persistent colonization by exogenous live organisms.[16,17,23] Current clinical evidence is difficult to synthesize because studies vary in prebiotic formulation, dose, intervention duration, timing of exposure, comparator groups, and outcome definitions. In addition, asthma itself is heterogeneous, with differences in age group, allergic status, inflammatory phenotype, disease severity, and background therapy potentially modifying the response to microbiome-directed interventions.

Microbiome heterogeneity further complicates clinical translation. Baseline microbial composition, diet, antibiotic exposure, geography, and early-life environmental factors may influence whether a given prebiotic substrate produces consistent metabolic or immunologic effects across populations. As a result, findings from mechanistic studies or selected clinical cohorts may not be directly generalizable to broader asthma populations. This gap between mechanistic plausibility and clinical applicability is consistent with the bibliometric profile observed in this study, where review articles outnumbered original studies and highly cited publications were dominated by foundational microbiome and nutrition literature rather than asthma-specific intervention trials.[16,23,24]

Strengths, limitations, and future directions

This study has several strengths. It provides an updated bibliometric overview of publication growth, leading contributors, influential publications, and thematic development in prebiotics–asthma research using standardized mapping tools. By combining descriptive indicators with keyword co-occurrence and trend topic analysis, it captures both the structural and temporal dimensions of the literature, which is particularly useful in a field distributed across multiple disciplines and publication sources.

Several limitations should also be acknowledged. First, the analysis was restricted to the Scopus database and English-language publications, which may have excluded relevant studies indexed elsewhere or published in other languages. Second, bibliometric indicators are influenced by publication age, citation lag, and indexing practices, which can favor older or broader conceptual papers over newer translational studies. Third, the present analysis describes the structure and evolution of the literature but does not evaluate the methodological quality of individual studies or permit causal conclusions regarding clinical efficacy. Fourth, the observed growth in publication output may partly reflect the broader expansion of microbiome research across medicine, rather than a uniquely accelerated increase in asthma-specific prebiotic research.

Future research should therefore focus on stronger clinical integration. More asthma-specific trials of prebiotics and symbiotics, better standardized intervention protocols, and clearer characterization of asthma phenotypes will be necessary to improve comparability across studies and strengthen translational relevance. In addition, multiomic approaches integrating metagenomics, metabolomics, and immunophenotyping may help clarify how microbial function, rather than taxonomic composition alone, shapes allergic airway disease. Greater geographic diversification will also be important, because microbiome composition, diet, and asthma epidemiology vary across populations and may affect the generalizability of current findings.

CONCLUSION

This bibliometric analysis demonstrates that prebiotics–asthma research has evolved into a growing multidisciplinary field spanning allergy, immunology, microbiome science, and nutrition. The literature has shifted from general nutritional and allergy-related themes toward mechanistic investigation of gut microbiome modulation, short-chain fatty acids, and immune dysregulation. Although the field is supported by a substantial mechanistic foundation, asthma-specific translational and interventional evidence remains comparatively limited. Therefore, the observed bibliometric trends should be interpreted as indicators of research development rather than evidence of clinical efficacy. Future studies should prioritize rigorous clinical validation, standardized intervention protocols, and multiomic investigation.

DECLARATIONS

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Conflict of interest statement

The authors declare that they have no conflicts of interest related to this manuscript. Each author's conflict of interest declaration is provided below: A. Farih Raharjo, Sp.P(K) declares no conflict of interest related to this manuscript. Hamzah Haryo Prakoso, MD declares no conflict of interest related to this manuscript. Andre Setiawan, MD declares no conflict of interest related to this manuscript. Lisana Sidqi Aliya, MD declares no conflict of interest related to this manuscript. Tika Tazkiya Tasnim, MD declares no conflict of interest related to this manuscript.

Ethics approval statement

This study was based exclusively on bibliographic data from published literature indexed in Scopus. It did not

involve human participants, patient data, biological samples, animal subjects, or any intervention. Therefore, ethics committee approval was not required.

Informed consent statement

Not applicable. This study did not involve human participants, patient data, or identifiable personal information.

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Editorial board membership statement

The authors declare that none of the authors is a member of the journal's Editorial Board.

Declaration regarding the use of AI and AI-assisted technologies

During manuscript preparation, the authors used ChatGPT (OpenAI) to support language editing, sentence clarity, manuscript flow, and formatting consistency. All AI-assisted outputs were reviewed, verified against the original data and manuscript content, and manually revised by the authors as needed. The authors take full responsibility for the final content of the manuscript.

Data availability statement

The data analyzed in this study were obtained from Scopus. The final bibliometric dataset and analysis outputs are available upon reasonable request.

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Supplementary Table 1. Stepwise Scopus search strategy, filter details, and screening criteria.

Stage	Details	Records
Search 1	TITLE-ABS-KEY (prebiotic* OR inulin OR “galactose oligosaccharide” OR “galactose oligomer” OR oligogalactose OR fructan* OR fructooligosaccharide* OR “fructo-oligosaccharide*” OR oligofructose OR galactooligosaccharide* OR “galacto-oligosaccharide*” OR oligosaccharide* OR lpdolax OR “Raftilose P95”)	127,919
Search 2	TITLE-ABS-KEY (synbioti* OR synbiotic*)	6,453
Search 3	TITLE-ABS-KEY (asthma*)	332,224
Search 4	#1 OR #2	129,452
Search 5	#3 AND #4	678
Search 6	#5 AND (LIMIT-TO (PUBSTAGE, “final”)) AND (LIMIT-TO (DOCTYPE, “re”) OR LIMIT-TO (DOCTYPE, “ar”)) AND (LIMIT-TO (LANGUAGE, “English”))	564
	• Excluded by publication stage: article in press (n = 1).	1 excluded
	• Excluded by language: Chinese (n = 5), German (n = 4), Spanish (n = 3), French (n = 3), Czech (n = 2), Ukrainian (n = 1), Russian (n = 1), Polish (n = 1), Japanese (n = 1).	21 excluded
	• Excluded by document type: book chapters (n = 35), editorials (n = 17), conference papers (n = 27), notes (n = 9), short surveys (n = 5), letters (n = 4), errata (n = 2), books (n = 1).	100 excluded
Duplicates removed	No duplicates were identified.	0 excluded
Title/abstract and full-text screening	Records were excluded if they were not related to asthma, or if asthma was mentioned only as family history. Records were also excluded if interventions were limited to probiotics, inulin or other oligosaccharides used as markers of intestinal permeability, endogenous/complex oligosaccharides such as mucin, heparin, Le□, and sulfated glycans that were not considered prebiotics, or herbal products not meeting prebiotic criteria. Full-text screening used the same content-based criteria with confirmation from the complete article content.	268 excluded
Disagreement resolution	Disagreements during screening were resolved by consensus among the three reviewers; if consensus was not reached, the final decision was made by majority vote based on the predefined eligibility and exclusion criteria.	—
Final dataset	Records included in the final bibliometric analysis.	296

TITLE-ABS-KEY: title, abstract, and keyword fields in Scopus; PUBSTAGE: publication stage; DOCTYPE: document type.

The category-specific details under Search 6 describe records excluded by Scopus database filters. These categories may overlap and should not be summed as mutually exclusive exclusion counts.

Supplementary Table 2A. Network construction parameters**.**

Component	Parameter	Setting / Description
Software	Software used	VOSviewer
Software version	Version	1.6.18
Analysis type	Type of analysis	Co-occurrence analysis
Unit of analysis	Unit analyzed	Keywords
Data source	Bibliographic metadata	Scopus export file
Keyword source	Keyword field	Author keywords and indexed keywords available in Scopus metadata
Counting method	Counting approach	Full counting
Keyword inclusion threshold	Minimum number of keyword occurrences	15 occurrences
Normalization	Normalization method	Association strength
Clustering	Random starts	10
Clustering	Iterations	10
Clustering	Random seed	0
Clustering	Minimum cluster size	1
Network line display	Minimum line strength	0
Network line display	Maximum number of lines	10,000
Visualization	Node weight	Occurrence
Term harmonization	Thesaurus file	Applied to merge synonymous, spelling, singular/plural, and variant keyword terms before visualization
Term exclusion	Remove-list file	Applied to exclude the generic non-substantive term “article” before visualization

VOSviewer: visualization of similarities viewer.

Supplementary Table 2B. Thesaurus mapping used for term harmonization.

Standardized label	Original labels replaced
allergens	allergen
allergic disease	allergic disease; allergic disorders; allergy
animals	animal; animal cell; animal experiment; animal model; animal tissue; disease models, animal; nonhuman
antibiotics	anti-bacterial agents; antibiotic agent; antibiotic therapy
antiinfective	antiinfective agent
antiinflammatory	antiinflammatory activity; antiinflammatory agent
asthma	allergic asthma
atopic dermatitis	atopic dermatitis; dermatitis, atopic
bacteria	bacterium
bifidobacterium	bifidobacteriaceae; bifidobacterium bifidum; bifidobacterium breve; bifidobacterium longum
breast feeding	breast milk; breastfeeding; human milk; milk, human
children	child; child, preschool; preschool child
clinical study	clinical article; clinical trial; controlled clinical trial; major clinical study
cytokines	cytokine; cytokine production
diabetes mellitus	insulin-dependent diabetes mellitus
diet	diet supplementation; diet therapy; dietary fiber; dietary intake; dietary supplement; dietary supplements
disease	disease association; disease exacerbation; disease model; disease predisposition; disease severity
drug	drug effects; drug efficacy; drug safety; drug effect; drug therapy; drug mechanism
dysbiosis	microbial imbalance
environment	environmental; environmental exposure; environmental factor
food allergy	food allergy; food hypersensitivity
formula feeding	artificial milk; formula milk; infant formula

...continuation supplementary table 2B.

Standardized label	Original labels replaced
gut microbiome	gastrointestinal microbiome; gut microbiota; gut microflora; intestinal flora; intestinal microbiota; intestine flora
humans	human
hypersensitivity	hypersensitivity, immediate
immunity	immune response; innate immunity
immunoglobulin	immunoglobulin a; immunoglobulin blood level; immunoglobulin e; immunoglobulin g
infant	infancy; infant, newborn; newborn
inflammatory bowel disease	ibd
interleukins	interleukin 10; interleukin 13; interleukin 17; interleukin 1beta; interleukin 33; interleukin 4; interleukin 5; interleukin 6
intestines	intestine
lactobacillus	lactobacillus acidophilus; lactobacillus casei; lactobacillus paracasei; lactobacillus rhamnosus
mice	bagg albino mouse; mice, inbred balb c; mouse
microbiology	microbiological; microbiology
microbiome	microbial colonization; microbial community; microbial diversity; microbial immunity; microbiota; microflora
oligosaccharides	fructose oligosaccharide; galactose oligosaccharide; oligosaccharide
prebiotics	prebiotic; prebiotic agent
prevention	prevention and control; primary prevention
probiotics	probiotic; probiotic agent
randomized controlled trial	controlled clinical trial; double blind procedure; double-blind method; randomized controlled trial; randomized controlled trial (topic); RCT
review	review article
short-chain fatty acids	short-chain fatty acid; volatile fatty acid; fatty acids, volatile
synbiotics	synbiotic agent
systematic review	meta-analysis; meta-analysis (topic); systematic literature review

...continuation supplementary table 2B.

Standardized label	Original labels replaced
th2 cells	th2 cell
therapy	treatment duration; treatment outcome
toll like receptor	toll like receptor 4
vitamin d	vitamin D supplementation

Standardized labels are shown in the left column, while original keyword variants merged into each standardized label are shown in the right column. A remove-list file was used to exclude the term “article” because it is a generic document-related term rather than a substantive research concept.

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Brief commnications

Food allergy in the context of the 2026 FIFA World Cup in Mexico

Alergia alimentaria en el contexto de la *Copa Mundial de la FIFA 2026* en México

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Abstract

BACKGROUND: Food allergy is an immune reaction that occurs after ingesting food allergens. In Mexico, the "milpa diet" is the basis of the diet and has health benefits; however, it has been reported that these foods contain allergens that can induce food allergies. In the context of the World Cup being held in Mexico, visitors with food allergies are a vulnerable group, so it is important to provide both them and healthcare personnel with general information about the allergens present in the milpa diet.

OBJECTIVE. Describe the main allergens identified in native Mexican foods, particularly from the milpa diet, that may represent a potential risk for travelers/fans with food allergies in the context of the *2026 FIFA World Cup* in Mexico.

METHODS: A descriptive and retrospective study was conducted by searching the NIH/PubMed portal for reports of food allergies related to the milpa diet, selecting those that included allergens identified on the WHO/IUIS website. A descriptive analysis was then performed, considering only the most frequently implicated proteins associated with food allergies.

RESULTS: The Milpa diet includes 71 foods; 51/71 (68%) have food allergy reports, and only 13/51 (25.49%) have an identified allergen (peanut, tomato, sunflower seeds, corn, pea, lentil, pumpkin, chili, papaya, pineapple, amaranth, avocado, and green bean). The most frequently reported allergens were profilins 8/13 (61.53%), nonspecific lipid transfer proteins 7/13(53.84%) and PR-10 2/13(15.38%). 6/13% (46.15%) of these foods share at least two proteins. The main association of proteins was between nonspecific lipid transfer proteins and profilins reported in the same food, 4/13 (30.76%).

CONCLUSION: Many foods in the Milpa diet contain profilins, which are associated with oral symptoms. However, this diet includes some foods with nonspecific lipid transfer proteins, like peanuts, which can induce anaphylaxis.

KEYWORDS: Allergens; Diet; Food allergy; PubMed; WHO; Peanut; Tomatoes; Sunflower seeds; Corn; Pea; FIFA world cup; Profilins; Lipids; Anaphylaxis.

Resumen

ANTECEDENTES: La alergia alimentaria es una reacción inmunológica que ocurre posterior a la ingesta de alérgenos alimentarios. En México, la "*Dieta de la milpa*" es la base de la alimentación, que posee beneficios para la salud; sin embargo, se ha informado que estos alimentos contienen alérgenos que pueden inducir alergia alimentaria. En el contexto del mundial de fútbol con sede en México, un grupo vulnerable son los visitantes con alergia alimentaria, por lo que es importante ofrecer, tanto a ellos como a al personal de salud, información general del repertorio alérgico de la dieta de la milpa.

OBJETIVO: Describir los principales alérgenos identificados en alimentos locales de México, particularmente de la dieta de la milpa, que pueden representar un riesgo potencial para viajeros o aficionados con alergia alimentaria en el contexto de la *Copa Mundial de la FIFA 2026* en México.

MÉTODOS: Estudio descriptivo y retrospectivo, llevado a cabo a partir de la búsqueda de información de reportes de alergia alimentaria relacionada con la dieta de la milpa en el portal NIH/PubMed, seleccionando aquellos que mostraban el reporte de alérgenos identificados en el sitio web WHO/IUIS. Posteriormente, se realizó un análisis descriptivo, considerando solo las proteínas de mayor frecuencia implicadas con alergia alimentaria.

RESULTADOS: Se identificaron 71 alimentos conformados en la dieta de la milpa: 68% (51 de 71) tuvieron reporte de alergia alimentaria y solo 25.49% (13 de 51: cacahuate, tomate, semillas de girasol, maíz, guisante, lenteja, calabaza, chile, papaya, piña, amaranto, aguacate, ejote) tienen identificado un alérgeno, principalmente profilinas (61.53%; 8 de 13), subsecuentemente proteínas de transferencia de lípidos no específicas (53.8%; 7 de 13) y PR-10 (15.38%; 2 de 13). El 46.15% (6 de 13) de los alimentos comparten al menos dos proteínas; la principal combinación se evidenció entre alimentos que contienen proteínas de transferencia de lípidos no específicas y profilinas (30.76%; 4 de 13 para cada uno).

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CONCLUSIÓN. La mayor parte de los alimentos incluidos en la dieta de la milpa contienen profilinas, que se asocian a síntomas orales. No obstante, esta dieta contiene alimentos que comparten proteínas de transferencia de lípidos no específicas (por ejemplo, cacahuate), que pueden inducir anafilaxia.

PALABRAS CLAVE: Alérgenos; Dieta; Alergia alimentaria; PubMed; OMS; Cacahuate; Tomates; Semillas de girasol; Maíz; Chicharos; Copa mundial de la FIFA; Profilinas; Lípidos; Anafilaxia.

BACKGROUND

Football is the most popular sport worldwide, and the *Fédération Internationale de Football Association (FIFA)* has been its main governing body, overseeing and promoting its development at all levels. Its central event is the *FIFA World Cup,* a tournament whose growth has steadily increased global viewership, sponsorship, and economic impact in host countries.[1,2]

The *FIFA World Cup* is held every four years, and the 2026 edition will be the first organized by three countries (Mexico, the United States of America, and Canada). A significant number of visitors is expected in Mexico, predominantly men aged 18 to 44, coming from regions such as South America, East Asia, and Central Europe.[3] It is estimated that fans will stay for approximately 12 days, spending an average of $416 USD per day, with nearly 30% of this budget allocated to food.[4]

During the *2026 FIFA World Cup,* it is likely that many visitors will consume traditional Mexican cuisine.[5] Although this represents a cultural opportunity, it also poses a challenge for individuals with food allergies, particularly when exposed to unfamiliar local ingredients. In this scenario, food education, clear labeling, training for food staff, and the preparation of the health system become especially relevant.[6]

A food allergy is an adverse immunological reaction triggered by proteins present in seemingly harmless foods, which occurs in susceptible individuals.[7] Manifestations can appear immediately and range from mild symptoms (oral pruritus) to severe anaphylaxis, particularly in previously sensitized patients.[8]

Anaphylaxis is the most severe manifestation of allergy; symptoms typically appear within the first 30 minutes after consuming the allergen and include manifestations in at least two systems, including: cutaneous (urticaria, pruritus, angioedema), digestive (abdominal pain, nausea, vomiting, diarrhea), respiratory (wheezing, laryngeal obstruction, rhinorrhea), and/or hemodynamic (hypotension, syncope, tachycardia)(9); therefore, it represents a potentially life-threatening condition and is resolved by the administration of intramuscular adrenaline (0.5 mg) (0.5 mL from a 1 mg/mL ampoule, the only presentation available in Mexico).[10]

Food allergy is a major public health problem that affects all aspects of life, and travel is no exception.[11] The prevalence of food allergy is approximately 10% worldwide.[12] Furthermore, various allergens show cross-reactivity with a wide variety of foods, increasing the risk of exposure during international travel.[13]

Travelers with food allergies may experience allergic reactions at any stage of their journey. For example, it has been reported that the prevalence of food-related allergic reactions during flights varies ~3%, while the prevalence of reactions occurring during the trip increases to 10%. Likewise, most of these manifestations occurred in countries where the predominant language was not English.[14]

Various food reactions are explained by cross-reactivity, that is, the recognition of shared epitopes between different allergens by the same IgE antibody. Molecular sensitization corresponds to the coexistence of specific IgE antibodies directed against individual molecular allergenic components (genetically and immunologically defined proteins), detectable through *in vitro* tests.[15]

Based on the above, the objective of the study was to describe the main allergens identified in native Mexican foods, particularly from the *milpa* diet, that could represent a potential risk for travelers or fans with food allergies in the context of the *2026 FIFA World Cup* in Mexico, with the intention of providing useful information for first-contact physicians and subspecialists to establish an timely diagnosis.

MÉTHODOLOGY

A descriptive and retrospective study was carried out based on a bibliographic search in the United States National Library of Medicine (PubMed), using combinations of terms related to each food of the *milpa* diet and food allergy, with the keywords: *"X-food of the MILPA-D* (scientific name) AND *food allergy*"; [for example, *Solanum lycopersicum* (tomato) AND *food allergy*]. Articles from 2002 to 2025 were included, with an emphasis on plant-based foods, the main group that constitutes the *milpa* diet. Subsequently, only those that had an allergen described in the *World Health Organization/International Union of Immunological Societies* (WHO/IUIS) database were selected and, in turn, were classified by protein families. Finally, a descriptive analysis of the most frequently identified proteins was performed, and the results were expressed in percentages. **Supplementary Figure 1**

RESULTS

The "milpa" diet consists of 71 foods, and 51 of these have food allergy reports; however, at least one allergen was identified in only 13 vegetable foods: peanut, tomato, sunflower seeds, corn, pea, lentil, pumpkin, chili, papaya, pineapple, amaranth, green bean, and avocado. **Figure 1**

The most relevant protein families in vegetables were profilins, present in eight foods (peanut, tomato, sunflower seeds, corn, chili, pineapple, green bean, and amaranth), followed by nonspecific lipid transfer proteins (nsLTP), identified in seven foods (peanut, tomato, sunflower seeds, corn, pea, lentil, and amaranth), and PR-10, present in two foods (peanut and tomato).

Additionally, a broad group of other allergenic proteins was identified (n = 36 proteins in 13 foods), mainly:

endo-polygalacturonase in papaya, 2S-albumin in peanut, bromelain in pineapple, beta-fructofuranosidase in tomato, and vicilin in lentil. (**Table 1**)[16] 38.46% (5/13) of the foods shared at least two allergenic proteins. In particular, peanut and tomato shared the three main families described (2/13; 15.38%), while sunflower seeds, corn, and amaranth shared profilins and nsLTP (3/13; 23.07%). **Supplementary Figure 2**

DISCUSSION

In this descriptive analysis, profilins were the most frequent protein family in the foods of the milpa diet with identified allergens. These proteins are found in widely consumed and easily accessible foods, such as peanut, tomato, sunflower seeds, corn, chili, pineapple, green bean, and amaranth, which increases the probability of exposure in the local population and among tourists or fans.

Food allergy is a disease whose incidence has increased. Although milk and egg are among the most prevalent food allergens worldwide, various fruits, tree nuts, and peanuts also represent relevant sources of sensitization and clinical disease.[17]

In the present analysis, profilins and PR-10 stood out for their frequency. Both protein families are usually thermolabile and susceptible to digestion, so they have been associated mainly with mild manifestations: pruritus and edema in the lips, tongue, palate, and pharynx, in the context of oral allergy syndrome (OAS), which can appear after the consumption of raw fruits-vegetables in previously sensitized patients, although the risk of systemic reaction with these proteins is extremely low.[15,18,19] However, it is important to mention that, although several foods share common antigenic determinants, this phenomenon is not necessarily related to any allergic clinical manifestation.[20] In Mexico, various foods containing these proteins are consumed as snacks, traditional sweets, or ingredients commonly used in sauces, salads, and other preparations.

On the contrary, nsLTP are more stable proteins to heat and digestion, so they can induce reactions, even after cooking, and have been related to systemic reactions.[21] In this context, peanuts and tomatoes acquire special clinical relevance, because they are part of widely consumed preparations, including sauces and other typical dishes. Although peanut proteins were not of high frequency in this study, they represent one of the most relevant allergens worldwide, and have been related to systemic reactions (anaphylaxis), which is important because it is incorporated into a great variety of foods in Mexican culture.[22,23] **Figure 2A**

In Mexico, the ingestion of insects is common, for example, crickets, scorpions, ants, escamoles (ant eggs), and acociles (crustaceans), foods that are very attractive to foreign visitors; however, many of these contain tropomyosin (a protein related to anaphylaxis), which, despite not being a protein group evaluated in our analysis, the identification of this protein poses a risk in susceptible patients with previously known shrimp allergy, due to the probable phenomenon of cross-reactivity between these species.[24] **Figure 2B**

A significant proportion of the analyzed foods shared more than one allergenic protein family.[25] This finding supports

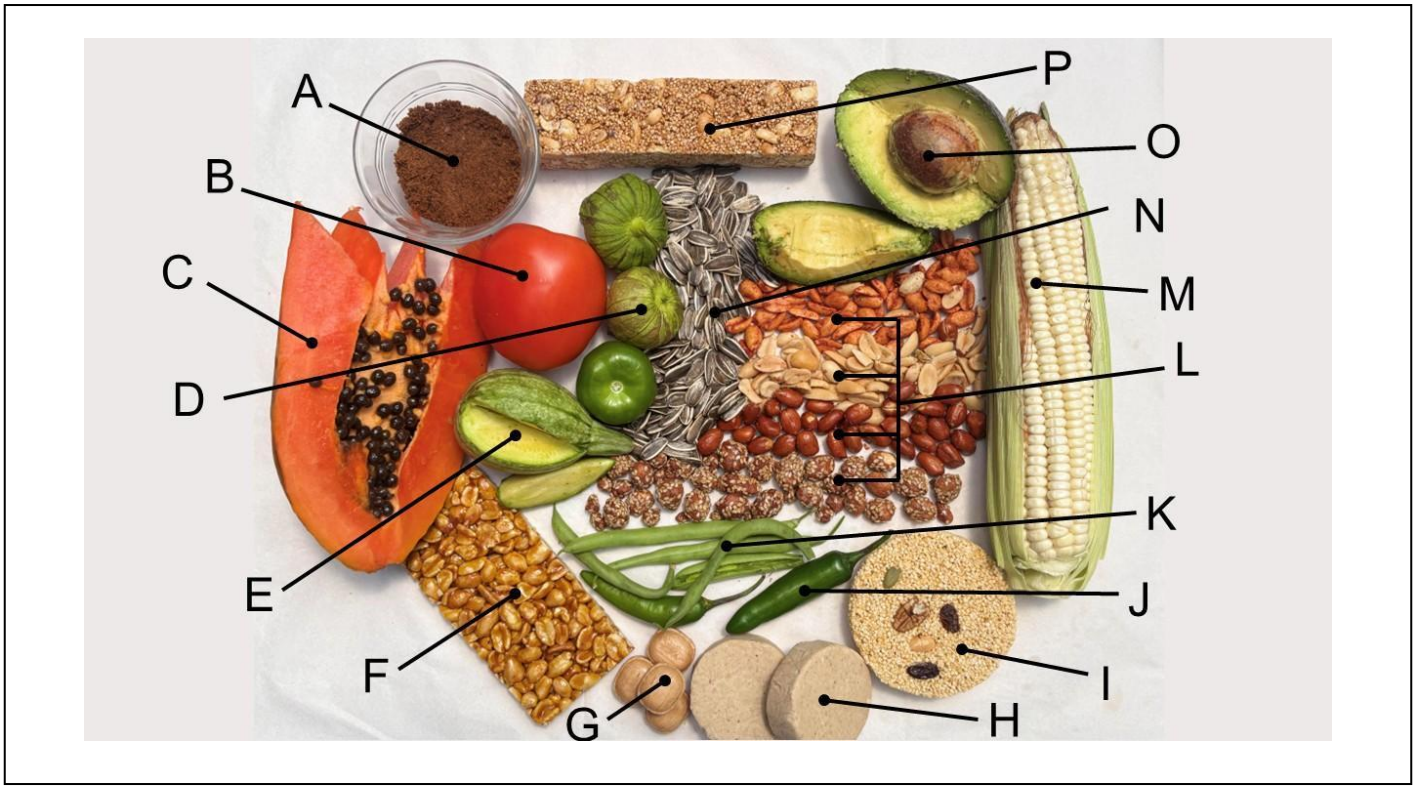

Figure 1. A) Mole; **B)** Tomato; **C)** Papaya; **D)** Tomatillo; **E)** Pumpkin; **F)** Peanut brittle (palanqueta); **G)** Peanut-based candy; **H)** Marzipan; **I)** Amaranth-based candy; **J)** Chile; **K)** Green bean; **L)** Different types of peanuts; **M)** Corn; **N)** Sunflower seeds; **O)** Avocado; **P)** Peanut and amaranth-based candy (Alegría).

Table 1. Clasificación de las proteínas como profilinas, nsLTP y PR-10 que contienen los alimentos externos y locales de la dieta de la milpa.

	Common name (Nombre común)	Profilin (profilina)	nsLTP	PR-10	Others proteins (Otras proteínas)
External foods- Alimentos externos a la dieta de la milpa	Kiwi (Kiwi)	Act d 9	Act d 10	Act d 8	Act d 2, Act d 3, Act d4, Act d5, Act d6, Act d 7, Act d 11, Act d 12, Act d1
	Celery (Apio)	Api g 4	Api g 2, Api g 6		Api g 1, Api g 3, Api g 5, Api g 7
	Bell pepper (pimiento morrón)	Cap a 2			Cap a 1, Cap a 7
	Watermelon (Sandia)	Citr l 2			
	Orange (Naranja)	Cit s 2	Cit s 3		Cit s 1, Cit s 7
	Hazel (Avellana)	Cor a 2	Cor a 8	Cor a 1	Cor a 6, Cor a 9, Cor a 10, Cor a 11, Cor a 12, Cor a 13, Cor a 14, Cor a 15, Cor a 16
	Melon (Melón)	Cuc m 2			Cuc m 1, Cuc m 2
	Carrot (Zanahoria)	Dau c 4		Dau c 1	Dau c 5
	Strawberry (Fresa)	Fra a 4	Fra a 3	Fra a 1	
	Soy (Soya)	Gly m 3		Gly m 4,	Gly m 1, Gly m 2, Gly m 5, Gly m 6, Gly m 7, Gly m 8
	Barley (Cebada)	Hor v 12			Hor v 5, Hor v 12, Hor v 15, Hor v 16, Hor v 17, Hor v 20
	Nut (Nuez de Castilla)	Jug r 7	Jug r 3, Jug r 8	Jug r 5	Jug r 1, Jug r 2, Jug r 4, Jug r 6, Jug r 9
	Lychee (Litchi)	Lit c 1			
	Mango (Mango)	Man i 4		Man i 2	Man i 1

...*continuation* table 1.

Common name (Nombre común)	Profilin (profilina)	nsLTP	PR-10	Others proteins (Otras proteínas)
Apple (Manzana)	Mal d 4	Mal d 3	Mal d 1	Mal d 2
Banana (Plátano)	Mus a 1	Mus a 3		Mus a 2, Mus a 4, Mus a 5, Mus a 6
Cherry (Cereza)	Pru av 4	Pru av 3	Pru av 1	Pru av 2, Pru av 7
Almond (Almendra)	Pru du 4	Pru du 3	Pru du 1	Pru du 5, Pru du 6, Pru du 8, Pru du 10
Peach (Durazno)	Pru p 4	Pru p 3	Pru p 1	Pru p 2, Pru p 7, Pru p 9, Pru p 10
Pear (Pera)	Pyr c 4	Pyr c 3	Pyr c 1	Pyr c 5
Yellow mustard (Mostaza amarilla)	Sin a 4	Sin a 3		Sin a 1, Sin a 2
Eggplant (Berenjena)	Sola m 1			
Wheat (Trigo)	Tri a 12	Tri a 14, Tri a 44		Tri a 15, Tri a 17, Tri a 18, Tri a 19, Tri a 20, Tri a 21, Tri a 25, Tri a 26, Tri a 27, Tri a 28, Tri a 29, Tri a 30, Tri a 31, Tri a 32, Tri a 33, Tri a 34, Tri a 35, Tri a 36, Tri a 37, Tri a 39, Tri a 40, Tri a 41, Tri a 42, Tri a 43 y Tri a 45.
Lemon (Limón)		Cit l 3		
Green beans (Ejote)		Pha v 3		
Grape (Uva)		Vit v 1		
Asparagus (Espárrago)		Aspa o 1		
Lettuce (Lechuga)		Lac s 1		

...*continuation* table 1.

	Common name (Nombre común)	Profilin (profilina)	nsLTP	PR-10	Others proteins (Otras proteínas)
Milpa diet-Dieta de la milpa	Peanut (Cacahuate)	Ara h 5	Ara h 9, Ara h 16, Ara h 17	Ara h 8	Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 6, Ara h 7, Ara h 10, Ara h 11, Ara h 12, Ara h 13, Ara h 14, Ara h 15, Ara h 18, Ara h 19, Ara h 20
	Tomato (Tomate)	Sola l 1	Sola l 3, Sola l 6, Sola l 7	Sola l 4	Sola l 2, Sola l 5
	Sunflower (Girasol)	Hel a 2 (aire)	Hel a 3		Hel a 6, Hel a 15, Hel a 16, Hel a 17
	Corn (Maiz)	Zea m 12	Zea m 14		Zea m 1, Zea m 8, Zea m 25
	Pea (Guisante)		Pis s 3		Pis s 1, Pis s 2
	Lentil (Lenteja)		Len c 3		Len c 1, Len c 2
	Pumpkin (Calabaza)				Cuc ma 4, Cuc ma 5
	Chile (Chile)	Cap a 2			Cap a 1, Cap a 7
	Papaya (Papaya)				Cari p 1, Cari p 2
	Pineapple (Piña)	Ana c 1			Ana c 2
	Amaranth (Amaranto)	Ama r 2	Ama r 1		
	Avocado (Aguacate)				Pers a 1
	Green beans (Ejote)		Pha v 3		

the possibility of cross-reactivity or concomitant sensitizations in susceptible individuals. For example, patients allergic to apples could also be allergic to carrots, due to the presence of PR-10 and/or profilins,[13,26] and this may suggest susceptibility to tomatoes when consumed raw.

In international events, such as the 2026 FIFA World Cup, tourists face an environment of great cultural and gastronomic diversity, which increases the probability of exposure to unfamiliar allergens. Therefore, it is essential to strengthen health education and promote specific preventive strategies for travelers with food allergies.[11] **Figure 3**

The present search focused mainly on foods of plant origin, due to their wide distribution in local foods and frequent incorporation into typical dishes, where their identification

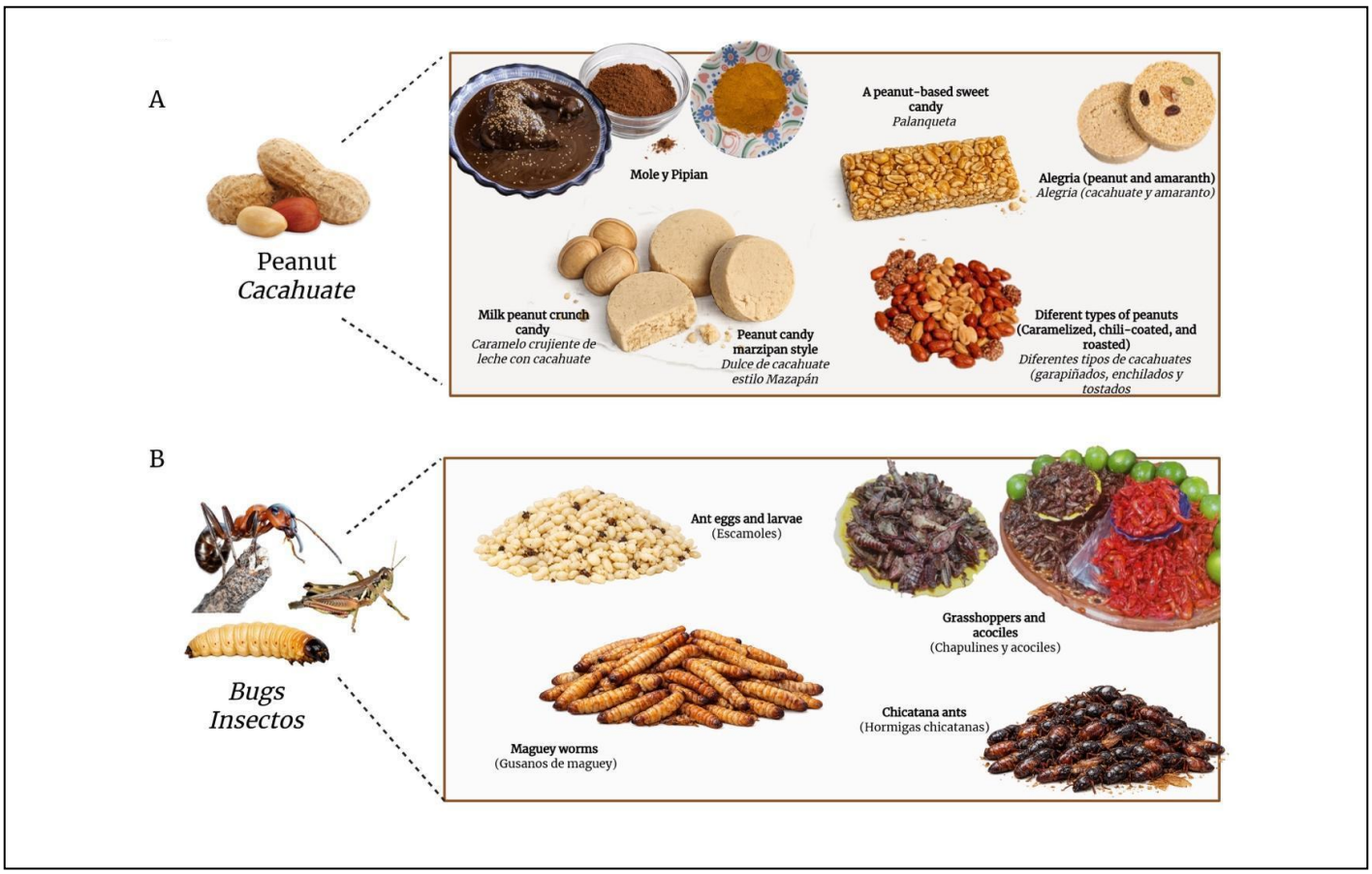

Figure 2. A) Different presentations of peanuts, including traditional products such as sweets (palanqueta, marzipan), processed peanuts (candied, spicy, toasted), and their use in typical dishes such as mole and pipian. **B)** Edible insects commonly consumed in Mexico, such as escamoles (ant eggs and larvae), maguey worms, grasshoppers (chapulines), and chicatana ants.

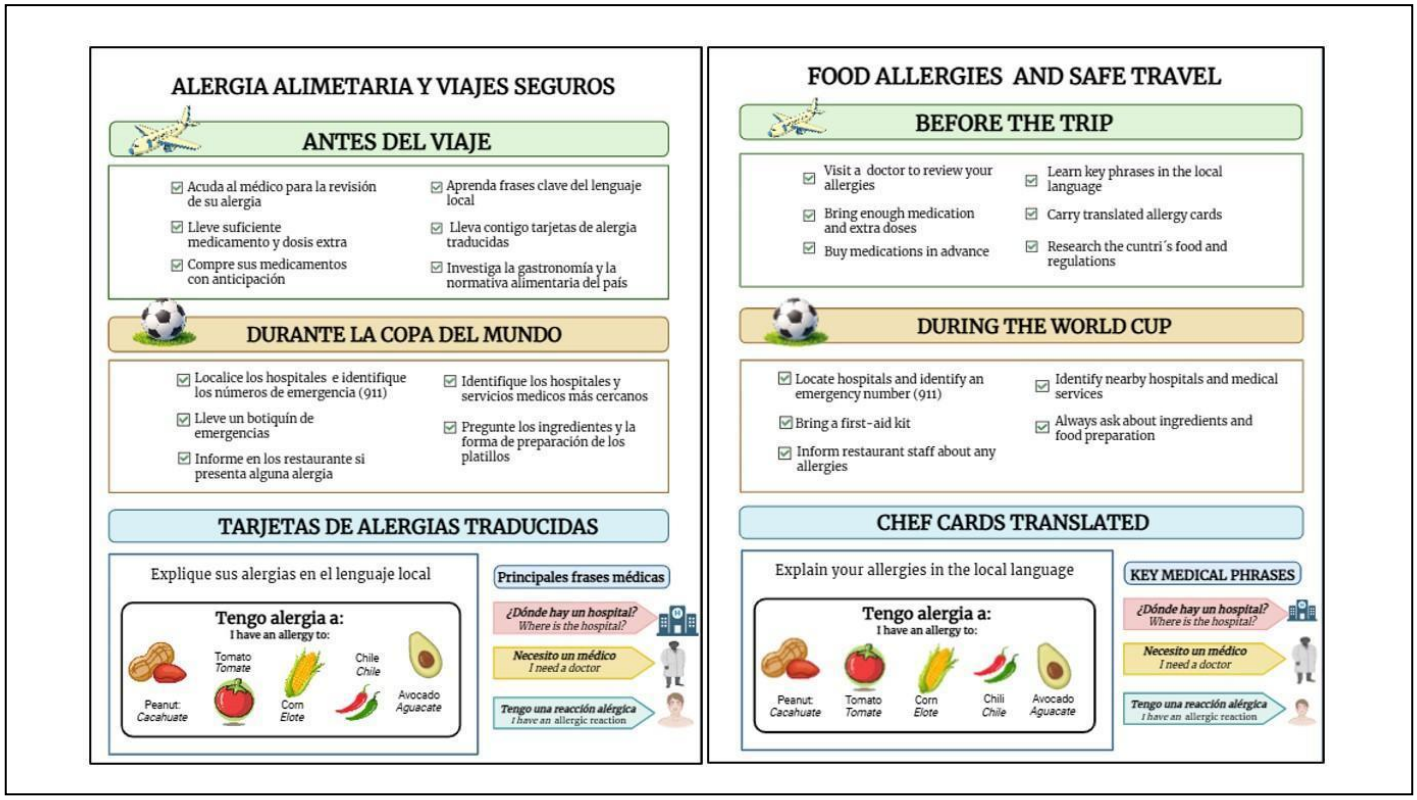

Figure 3. Infographic "Food allergies and safe travel": lists a series of recommendations for people with food allergies.

may not be evident to the tourist. This characteristic justifies the relevance of the approach adopted in our study. However, a limitation of this methodology is that the analysis of allergens or protein families contained in each food depends on the existing information in the WHO/IUIS database, which is updated intermittently and considers only validated allergenic proteins for consultation.

This research seeks to provide useful and accessible information for first-contact physicians and fan patients with food allergies who will travel to Mexico during the 2026 FIFA World Cup. Although the milpa diet is recognized for its nutritional value and metabolic and cardiovascular benefits, the foods can contain proteins with allergenic potential in susceptible individuals.[26,27]

In this context, it is recommended that travelers attending the 2026 FIFA World Cup with a diagnosis of food allergy identify nearby health services near the main sports venues in advance, and request detailed information on the ingredients and preparation of dishes, given the impossibility of preparing their own food.[17] In particular, it is advisable to take extreme precautions with foods containing nsLTP: peanut, tomato, sunflower seeds, corn, pea, lentil, and amaranth, due to their possible association with systemic reactions in previously sensitized patients and, therefore, with greater susceptibility.

Regarding labeling rules in Mexico, NOM-051-SCFI/SSA1-2010 establishes that the identification of allergens must be declared in a mandatory and visible manner on the label of manufactured products with the phrase "may contain".[28] However, it is important to mention that, in foods prepared in restaurants, markets, or on the public street, this identification may be limited, which represents an additional risk for tourists with food allergies at the time of consumption.

It is important to comment that among the main challenges for travelers with food allergies are language barriers, so effective communication is also key. Among the safety strategies when consuming food abroad are: 1) always ask about ingredients and the method of preparation, 2) notify the allergy in restaurants, 3) use translation cards in the local language, and 4) avoid environments with a high risk of cross-contamination (buffets). Additional measures, for example: carrying safe food during travel and cleaning contact surfaces, can also contribute to reducing complications.

CONCLUSIONS

Within the foods included in the "milpa" diet with identified allergens, profilins were the most frequent protein family; therefore, they may be primarily associated with local manifestations. However, some widely consumed foods also showed nsLTPs or tropomyosin, protein families of greater clinical relevance related to systemic reactions, including anaphylaxis. Together, these findings provide useful information to guide travelers with food allergies visiting Mexico during the *2026 FIFA World Cup*, as well as for the physicians involved in their care.

DECLARATIONS

QuillBot software was used exclusively for English language review.

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Author contribution

All authors contributed to the preparation of this manuscript.

Conflict of interest

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Human and animal rights declaration

This article does not report studies conducted on humans or animals.

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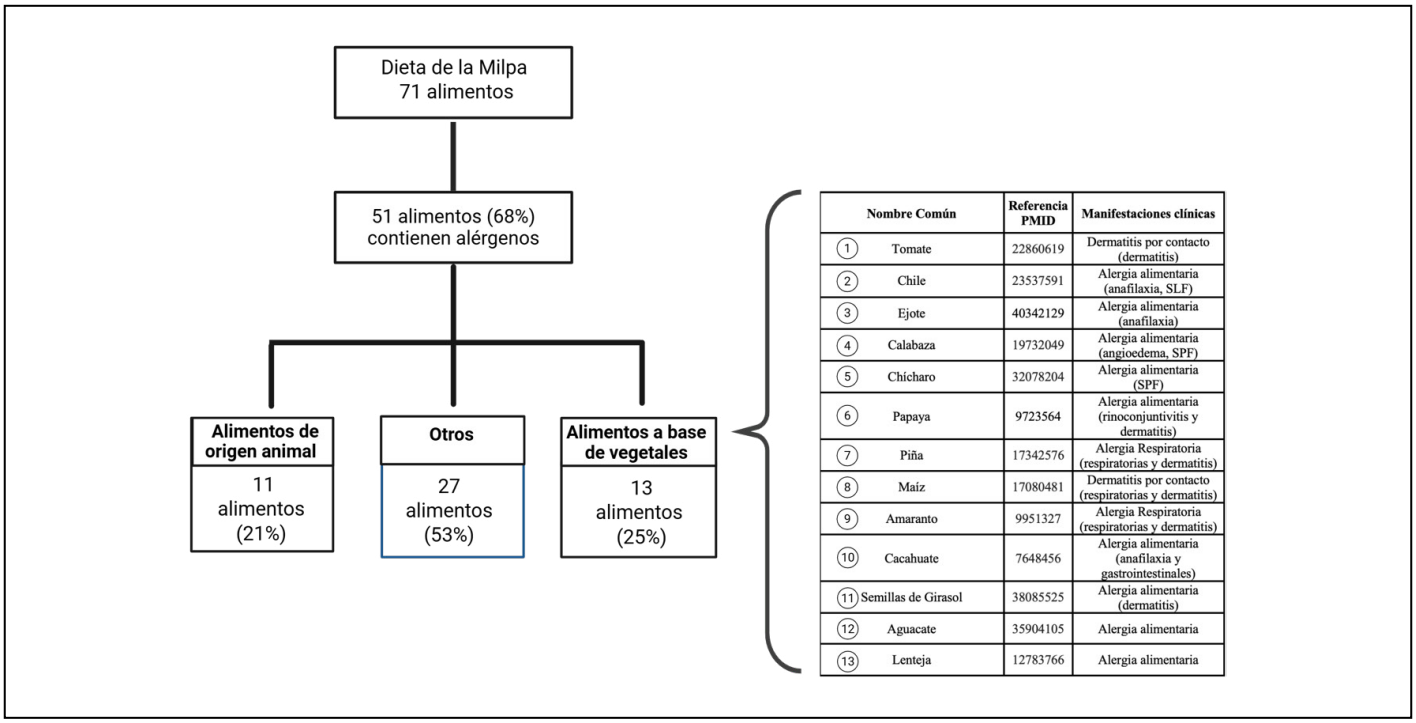
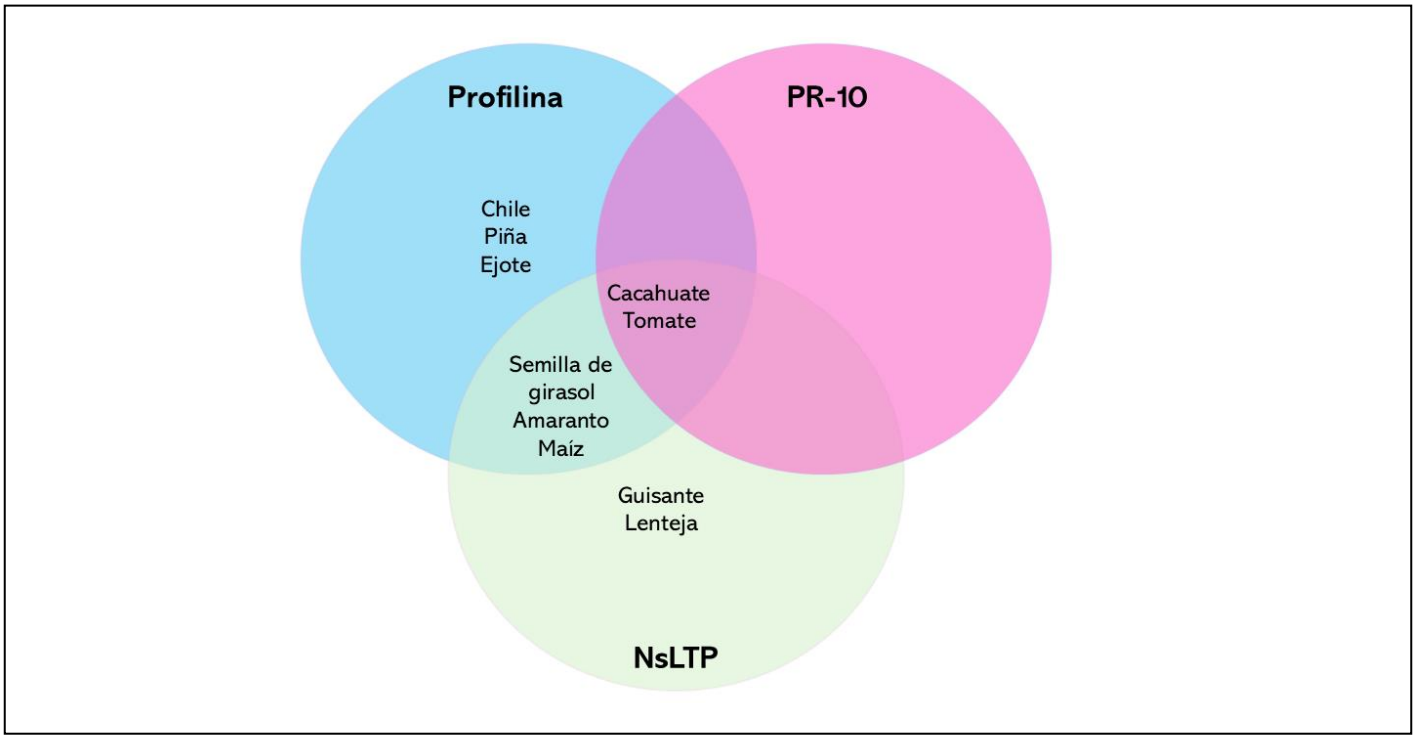


	Nombre Común	Referencia PMID	Manifestaciones clínicas
1	Tomate	22860619	Dermatitis por contacto (dermatitis)
2	Chile	23537591	Alergia alimentaria (anafilaxia, SLF)
3	Ejote	40342129	Alergia alimentaria (anafilaxia)
4	Calabaza	19732049	Alergia alimentaria (angioedema, SPF)
5	Chícharo	32078204	Alergia alimentaria (SPF)
6	Papaya	9723564	Alergia alimentaria (rinoconjuntivitis y dermatitis)
7	Piña	17342576	Alergia Respiratoria (respiratorias y dermatitis)
8	Maíz	17080481	Dermatitis por contacto (respiratorias y dermatitis)
9	Amaranto	9951327	Alergia Respiratoria (respiratorias y dermatitis)
10	Cacahuate	7648456	Alergia alimentaria (anafilaxia y gastrointestinales)
11	Semillas de Girasol	38085525	Alergia alimentaria (dermatitis)
12	Aguacate	35904105	Alergia alimentaria
13	Lenteja	12783766	Alergia alimentaria

Supplementary Figure 1. Distribution of foods that make up the "milpa" diet. The proteins registered in the WHO/IUIS platform were included and divided into food groups. Subsequently, foods of plant origin were selected, and the associated clinical manifestations were described: anaphylaxis, dermatitis, rhinoconjunctivitis, pollen-food syndrome (PFS), oral allergy syndrome (OAS), and latex-fruit syndrome (LFS).



Supplementary Figure 2. Venn diagram showing the distribution of the three most relevant allergen families in plant foods of the "milpa" diet and the relationship between allergen families.

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Brief commnications

Main trees in the Guadalajara Metropolitan Area and their relationship with pollen allergy

Principales árboles en el Área Metropolitana de Guadalajara y su relación con alergia al polen

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Abstract

OBJECTIVE: Identify the main tree species of the Guadalajara Metropolitan Area and their relationship with allergies.

METHODS: Observational, cross-sectional and descriptive study, carried out with the intention of identifying the trees. An inventory of the most frequent trees from the AMG urban tree database was carried out and the species with the highest relationship to allergic diseases were identified.

RESULTS: A total of 49,138 trees were identified; the most common species were the Ficus, Orange Tree, Palm, Cypress, Guava and Ash. Of the 15 most common species, Cypress, Ash, Casuarina, Eucalyptus, and Thunder are of greater allergology relevance.

CONCLUSIONS: Due to the increase in allergic diseases, such as allergy to tree pollen, it is important to have inventories that identify the species that may be related to these conditions, both for allergists and health authorities.

KEYWORDS: Species of trees; Allergies; Ficus; Orange tree; Cypress; Guava; Eucalyptus; Pollen.

Resumen

OBJETIVO: Identificar las principales especies de árboles del Área Metropolitana de Guadalajara y su relación con las alergias.

MÉTODOS: Estudio observacional, transversal y descriptivo, llevado a cabo con la intención de identificar el arbolado del Área Metropolitana de Guadalajara. Se realizó un inventario de los árboles más frecuentes de la base de datos del arbolado urbano del Área Metropolitana de Guadalajara y se identificaron las especies frecuentemente con enfermedades alérgicas.

RESULTADOS: Se identificaron 49,138 árboles y las especies más comunes fueron: Ficus, Naranjo, Palma, Ciprés, Guayaba y Fresno. De las 15 especies más frecuentes, el Ciprés, Fresno, Casuarina, Eucalipto y Trueno tuvieron mayor relevancia alergológica.

CONCLUSIONES: Debido al aumento de las enfermedades alérgicas, por ejemplo, la alergia al polen de árboles, es importante contar con inventarios que identifiquen las especies relacionadas con estos padecimientos, tanto para los alergólogos como para las autoridades de salud.

PALABRAS CLAVE: Especies de árboles; Alergias; Ficus; Naranjo; Ciprés; Guayaba; Eucalipto; Polen.

BACKGROUND

The expansion of cities is increasingly greater due to the increase in the percentage of people living in urban areas compared to rural areas, which generates challenges in the planning of services, environments, and health.[1] Cities with a greater amount of green areas offer a better quality of life due to their benefits to the urban ecosystem, such as the reduction of heat islands and noise, hosting biodiversity, among others.[2-4] The Food and Agriculture Organization of the United Nations (FAO) has a program called "Tree Cities of the World," which recognizes and encourages the creation and maintenance of urban forests,[5] and among the recognized cities are Guadalajara, Zapopan, and Tlajomulco de Zúñiga, in Jalisco, Mexico.

The Guadalajara Metropolitan Area is made up of nine municipalities: El Salto, Guadalajara, Ixtlahuacán de los Membrillos, Juanacatlán, Tlajomulco de Zúñiga, Tlaquepaque, Tonalá, Zapopan, and Zapotlanejo, with a territorial

extension of 3,265 km^2.[2] In 2020, a population of 5,268,642 inhabitants was counted, located in the Valley of the Santiago River basin, in the Atemajac Valley and the Tonalá plain. The Guadalajara Metropolitan Area includes 14 protected natural areas and 13 urban forests.[6]

In urban areas, trees represent the largest source of the total airborne pollen to which the population is exposed.[7] Pollen, from the Latin *pollen* (flour, dust), is one of the main allergens causing exacerbations of allergic diseases: asthma or rhinitis.

The increase in the prevalence of allergic diseases is a phenomenon occurring at both global and local levels.[8,9] In recent years, an increase in the prevalence of asthma has been identified in Guadalajara,[9] and a high prevalence of atopy (genetic tendency to develop allergic diseases) has even been documented in the Metropolitan Area population, especially to tree pollen.[10,11]

Although the origin of allergic diseases is multifactorial, it has a strong hereditary component, and various studies indicate that its contribution varies from 30 to 80%,[12] which shows that the increase in its prevalence is also due to other factors, such as the environment.

In the Guadalajara Metropolitan Area, public policy is directed towards strengthening programs that promote urban forestry; additionally, there are private initiatives, such as the Bosque Urbano de Extra A.C., which aims to make the Guadalajara Metropolitan Area the most forested in the country, with the goal of planting 5 million trees in the next 10 years.[13]

At the same time, there is also a growth in the size of the urban area and, within it, a greater density of buildings that concentrate materials such as asphalt, concrete, steel, and glass that hinder temperature dissipation and generate heat islands, affecting the microclimate of specific zones of the Guadalajara Metropolitan Area. This temperature increase is associated with meteorological phenomena: heat waves, intense rains, floods, and hailstorms.[14] Consequently, climate change can alter pollination patterns, generate an increase in pollen production, and increase its allergenic properties.[15]

The objective of this study was: to identify the main tree species in the Guadalajara Metropolitan Area and their relationship with allergies.

METHODS

Observational, cross-sectional, and descriptive study, carried out with the intention of identifying the trees of the Guadalajara Metropolitan Area. The census developed by the Metropolitan Planning Institute (IMEPLAN) was used, a public body dedicated to planning, managing, and coordinating projects and instruments for metropolitan development with the support of the municipalities of the Guadalajara Metropolitan Area and the state government of Jalisco.[16]

The census was created from satellite images available through QGIS® and Google Earth® from which tree crowns were identified, considering the criteria: shape, size, texture, and projected shadow, which allowed individual specimens to be distinguished within the urban environment. Using the Street View® tool, it was verified that the identified crowns corresponded to the morphometric characteristics of a tree and, once confirmed, a georeferenced point was digitized at the base of the trunk to register its precise location. The absence of duplicates was verified and the census of the nine municipalities of the AMG was integrated. Estimates were made of the number of trees by municipality, tree density per hectare and neighborhood. Finally, the collection of taxonomic, dasometric, urbanistic, and phytosanitary data was validated in the field.[2]

With the publicly available census database, a data sheet was prepared with the Excel® program. Quantification by families and genera of the total trees in the Guadalajara Metropolitan Area was carried out. From the list of most frequent tree species, a subclassification was made of the species with the greatest allergenic potential, both due to the presence of allergens recognized by the World Health Organization and the International Union of Immunological Societies (WHO/IUIS),[17] and due to their known allergenicity. Similarly, a list was prepared of the main tree species of the 13 urban forests of the AMG.

RESULTS

The most recent urban tree census, conducted in 2022, included 49,138 trees identified by botanical family, genus, scientific name, and common name; in addition, other variables such as coordinate location, municipality where it is located, whether it is classified as a native, exotic, or invasive species, and its endemism are reported. With this sampling, it was estimated, using inferential statistics, that the total number of trees in the Guadalajara Metropolitan Area was 1,379,306 trees.

A total of 192 different tree genera were identified in the urban tree inventory of the Guadalajara Metropolitan Area, and among the most frequent were: Ficus, Sour Orange, Palm, Cypress, Guava, and Ash. The most common tree families were: *Oleaceae, Cupressaceae* and *Myrtaceae*. From the list of the most frequent trees, only 4 species were considered native (Guava, Ash, Manila Tamarind, and Black Olive) and the rest, exotic species; in the case of Casuarina, Eucalyptus, and Thunder, they are considered invasive exotic species. **Table 1**

Of the 15 most common trees, 5 genera were reported to have greater interest for the development of allergic diseases, as they have allergens recognized by the WHO/IUIS, for example: Cypress, Ash, Casuarina, Eucalyptus, and Thunder.

The rest of the trees, although they can cause allergies to their pollen, are a less frequent cause, in addition to not having recognized allergens. The sour orange (*Citrus x aurantium*) does not show allergens recognized by the WHO/IUIS, unlike other genera of the same family, such as *Citrus limon* (lemon tree), *Citrus reticulata* (mandarin) and *Citrus sinensis* (sweet orange), which do have specified allergens.

In **Table 2** the 5 most common allergy-causing trees in the Guadalajara Metropolitan Area are listed, in addition to the proteins known or proposed as allergens by the WHO/IUIS allergen nomenclature subcommittee.

Of the 13 urban forests located in the Guadalajara Metropolitan Area, there is no inventory specifying which tree species

Table 1. Main trees of the Guadalajara Metropolitan Area.

Genus	Scientific Name	Common Name	Total
Ficus	*Ficus benjamina*	Ficus	11150
Citrus	*Citrus x aurantium*	Sour Orange	4949
Syagrus	*Syagrus romanzoffiana*	Plume Palm	2852
Cupressus	*Cupressus sempervirens*	Cypress	2078
Psidium	*Psidium guajava*	Guava	1910
Fraxinus	*Fraxinus uhdei*	Ash	1633
Pithecellobium	*Pithecellobium dulce*	Manila Tamarind	1348
Jacaranda	*Jacaranda mimosifolia*	Jacaranda	1216
Casuarina	*Casuarina equisetifolia*	Australian Pine	991
Terminalia	*Terminalia buceras*	Black Olive	951
Thuja	*Thuja occidentalis*	Northern White Cedar	734
Eucalyptus	*Eucalyptus camaldulensis*	Red Gum	717
Bougainvillea	*Bougainvillea sp.*	Bougainvillea	664
Mangifera	*Mangifera indica*	Mango	620
Ligustrum	*Ligustrum lucidum*	Glossy Privet	530

are present. From the urban tree census, they were not taken as part of the sampling because these blocks are found in only 4 municipalities, 10 of which are in the municipality of Guadalajara; however, there are estimates of the main tree species in these urban forests. In **Table 3** the characteristics of location, extension, and main species are shown, information obtained from the urban forests website of the Guadalajara Metropolitan Area.[18]

DISCUSSION

There are studies evaluating urban trees in specific areas of the Guadalajara Metropolitan Area, such as that of Gómez-Vega et al. 2024,[19] which characterized the urban trees of a linear green area (median strip of Acueducto Avenue) between Guadalajara and Zapopan, where a total of 897 trees were registered and the most abundant species were: *Syagrus romanzoffiana* (queen palm) 19.62%, *Pinus greggii* 10.81%, *Platanus mexicana* 10.26% and *Pithecellobium dulce K* (Manila Tamarind) 9.3%, which in the census reported in the present study include the palm and the manila tamarind among the most frequent; the genera *Pinus* and *Platanus* were also identified, where 414 and 42 specimens were counted, respectively.

Macías-Muro et al. 2022[20] evaluated the health of urban trees in the Guadalajara Metropolitan Area through satellite images, identifying 950 trees, whose most frequent species were Ash (n = 235), Casuarina (n = 202), Ficus (n = 143), Jacaranda (n = 129), Eucalyptus (n = 109), and Palm (n = 100), which are found in the present report as part of the most frequent species.

Hernández-Tovar et al. 2021[21] conducted an inventory model for the management of urban trees in a neighborhood of Guadalajara (Chapultepec Country), performing a census that included 1,386 trees; they recorded 81 species belonging to 32 families, with the most abundant trees being Ficus

Table 2. Most common allergy-causing trees in the Guadalajara Metropolitan Area.

Cupressus - Cypress	
Cup s 1	Pectate lyase
Cup s 2	Polygalacturonase
Cup s 3	Thaumatin-like protein
Cup s7	Gibberellin-regulated protein
Fraxinus - Ash	
Fra e 1	Ole e 1
Casuarina	
Cas e 1	Unknown
Eucalyptus	
Euc c 1	Unknown
Ligustrum - Privet	
Lig v 1	Ole e 1
Lig v 2	Profilin

(*Ficus benjamina*) with 326 individuals (23.52%), Thuja (*Thuja orientalis*) with 117 individuals (8.44%), Queen palm (*Arecastrum romanzoffianum*) with 107 individuals (7.72%), Sour orange (*Citrus aurantium*) with 101 individuals (7.28%) and Italian cypress (*Cupressus sempervirens*) with 74 individuals (3.39%) with a cumulative total of 698 trees representing 50% of the total census, all of these being part of the most frequent trees found in the present study.

Although there is agreement with the types of most frequent species in the previously cited studies, no studies are found that report the main species of the Guadalajara Metropolitan Area or that have this quantity of registered trees. It is important to mention that, according to the estimates from the data in the present study, there is approximately 1 tree for every 4 inhabitants in the Guadalajara Metropolitan Area.

Regarding the fact that most trees are of exotic origin, it may be because tree species are preferred for their appearance to favor the ornamentation and landscaping of the environment; however, the use of native species has the advantage of ecological adaptation and resistance to the environment.

Green areas and urban trees are important factors for the well-being of the population; they encourage physical activity, reduce stress, anxiety, and depression. In addition, they are meeting and recreation points that strengthen social cohesion, increase the perception of safety, and the sense of belonging.[22,23] However, for all the benefits they generate, they can also be a determinant for causing allergic diseases, which in conjunction with other components, such as genetic predisposition to atopy or climate change, can be associated so that allergic conditions are increasingly frequent. In **Figure 1** the aforementioned factors are reported.

There are studies that identify green areas as triggers of respiratory symptoms in urban settings, unlike their exposure in rural environments,[24,25] a hypothesis for this difference is

Table 3. Main trees of the urban forests of the Guadalajara Metropolitan Area.

Name	Municipality	Extension	Tree Species
Alcalde Park	Guadalajara	6.4 Ha	Ash, Casuarina, Guamúchil, Yucca, Laurel, Primavera, Lead tree, Rosy trumpet tree, Arrayan
Ávila Camacho Park	Guadalajara	3.6 Ha	Ash, Jacaranda, Grevillea, Ceiba, Montezuma cypress, White sapote, Ahuejote, Casuarina, Royal poinciana
Montenegro Park	El Salto	13.3 Ha	Ash, Jacaranda, Casuarina
Metropolitan Park	Zapopan	10.3 Ha	Ash, Ficus, Galeanas, Casuarinas
Los Colomos Forest	Guadalajara	93.29 Ha	Michoacan pine, Eucalyptus, Cedar, Oak, Ocote pine, Casuarina, Sweet acacia, Montezuma cypress
Agua Azul Park	Guadalajara	10.3 Ha	Ash, Jacaranda, Fan palm

...continuation table 3.

Name	Municipality	Extension	Tree Species
Urban Forest	Tlaquepaque	9.9 Ha	Lead tree, Primavera, Guamúchil, Rosy trumpet tree, Ash, Broom, Palo dulce, Tepozan, Mesquite
González Gallo Park	Guadalajara	17.3 Ha	Eucalyptus, Ash, Jacaranda, Palms
Luis Quintanar Park	Guadalajara	104.4 Ha	Casuarina, Jacaranda, Eucalyptus, Ash, Willow, Grevillea, Guava, Guamúchil, Ficus
La Liberación Park	Guadalajara	26.3 Ha	Ficus, Ash, Casuarina, Cedar, Walnut, Bottlebrush
Morelos Park	Guadalajara	4.7 Ha	Ash, Jacaranda, Casuarina, Arrayan, Clavellina, Privet, Guamúchil, Montezuma cypress
Puerta de la Barranca Park	Guadalajara	1.1 Ha	Jacaranda, Lead tree, Royal poinciana, Izote, Tabachin, Plumeria, Arrayán, White sapote
Huentitán Natural Park	Guadalajara	6.8 Ha	Guamúchil, Jacaranda, Casuarina, Thuja, Lead tree, Rosy trumpet tree, Primavera, Guava, Parota

Ha: Hectare

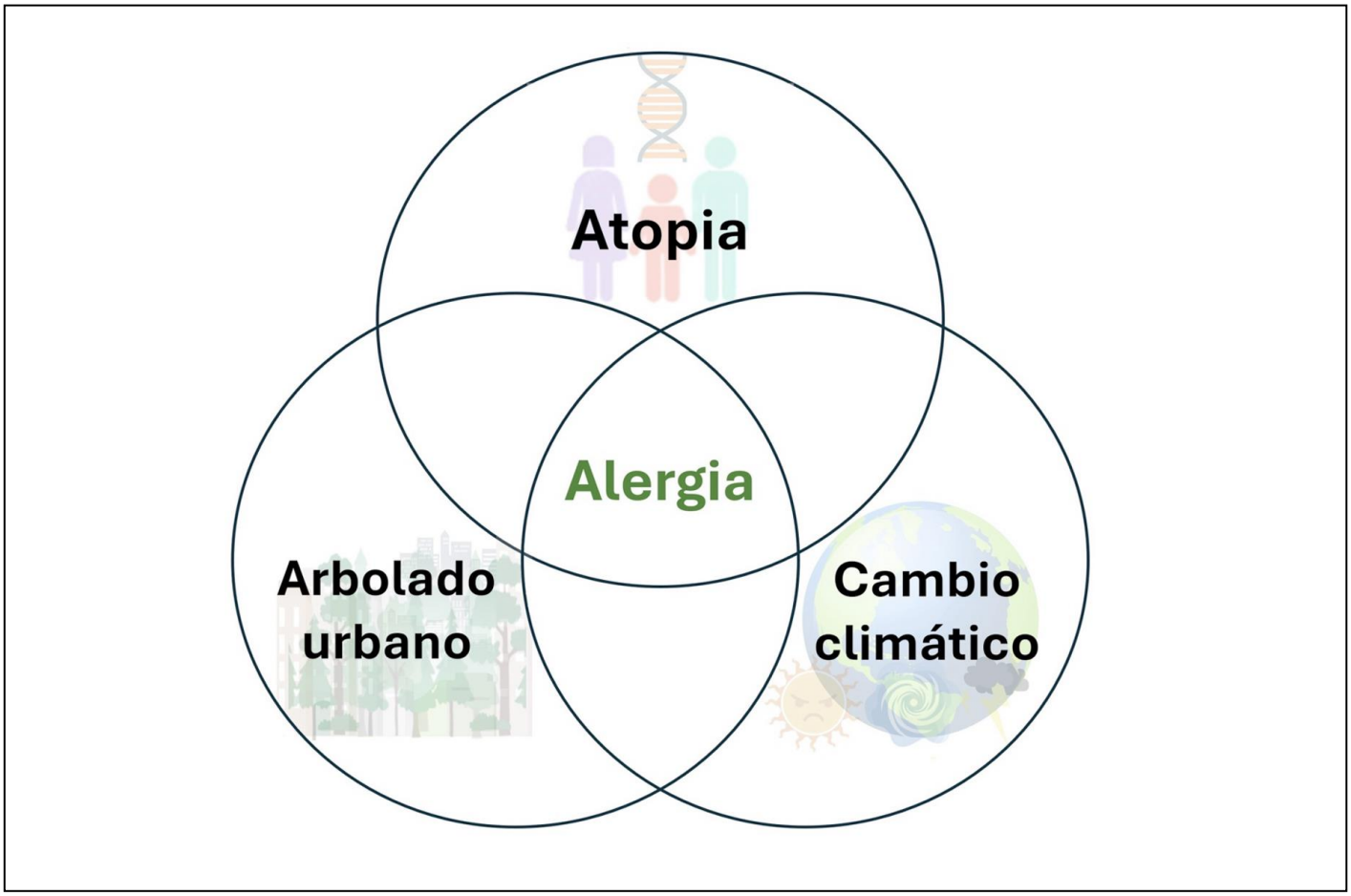

Figure 1. Pollen allergy triad in cities.

that environmental pollution is related to the increase in the prevalence of allergic diseases in two main ways: first, by increasing the allergenicity of pollen,[26,27] and second, through the inflammation that polluting particles can produce, by themselves, in the respiratory tract,[28] therefore, the beneficial effects of green areas and urban trees are greater in cities with little air pollution and population density.

In this sense, it can be proposed as a possibility that respiratory allergies will continue to increase in the population of the Guadalajara Metropolitan Area, so it is important to know which are the most common tree species and their characteristics, both for the allergist who treats patients with this type of disease and for governments, in order to guide public health policies.

Study limitations

The central axis of this work was to publicize the main species that make up the urban trees of the Guadalajara Metropolitan Area; however, due to the nature of the descriptive study, it was not possible to make causal implications.

The proposal of the association between urban trees, especially species with potential allergenic implication, and the effects of climate change with respiratory allergies cannot be affirmed with the evidence presented in this research, but it is important to mention that said hypothesis is valuable to be considered with caution.

CONCLUSIONS

Due to the increase in allergic diseases, such as allergy to tree pollen, it is important to have inventories that identify the species that may be related to these conditions, both for allergists and health authorities.

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Author contribution

The author carried out the entire preparation of this manuscript.

Conflict of interest

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Clinical case

Kikuchi-Fujimoto disease associated with systemic lupus erythematosus in an adolescent patient: case report and diagnostic challenges

Enfermedad de Kikuchi-Fujimoto asociada con lupus eritematoso sistémico en una paciente adolescente: reporte de caso y retos diagnósticos

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Abstract

BACKGROUND: Kikuchi-Fujimoto disease is a disorder that can mimic lymphoma and present with clinical and histopathological overlap with systemic lupus erythematosus in adolescent patients.

CASE REPORT: A 15-year-old female patient presented with recurrent upper respiratory tract infections. Concomitantly, she developed morning arthralgia in the bilateral metacarpophalangeal joints and a photosensitive malar rash. Subsequently, she developed persistent intermittent fever, anorexia, joint limitation, and cervical and inguinal lymphadenopathy, associated with normocytic normochromic anemia. Complete blood count revealed leukopenia and progressive anemia. Bone marrow biopsy showed increased cellularity with erythroid hypoplasia and reactive megaloblastic changes. Immunohistochemical staining revealed reactive polyclonal lymphoid hyperplasia. During her hospitalization, oral ulcers, jaundice, a skin rash, and elevated transaminases and direct bilirubin were detected. She developed bilateral pleural effusion, acute respiratory failure, and required mechanical ventilation. Positive antinuclear antibodies were documented: 1:640 (AC-20 pattern), leading to a diagnosis of systemic lupus erythematosus. Treatment was initiated with high-dose corticosteroids, intravenous immunoglobulin, and cyclophosphamide for refractory lupus pneumonitis, with initial clinical improvement. She was transferred to a tertiary care hospital; however, she experienced progressive multisystem deterioration and died despite the treatment.

CONCLUSIONS: Early recognition of the overlap between Kikuchi-Fujimoto disease and systemic lupus erythematosus is essential to avoid treatment delays and guide the timely prescription of immunosuppression in severe cases. Prolonged clinical surveillance and close follow-up are crucial for the timely detection of complications and to optimize patient prognosis.

KEYWORDS: Kikuchi-Fujimoto disease; Systemic lupus erythematosus; Lymphoma; Upper respiratory tract infections; Bone marrow biopsy; Corticosteroids; Lymphadenopathy.

Resumen

ANTECEDENTES: La enfermedad de Kikuchi-Fujimoto es una alteración que puede simular un linfoma y manifestarse con traslape clínico e histopatológico con lupus eritematoso sistémico en pacientes adolescentes.

REPORTE DE CASO: Paciente femenina de 15 años, que inició con infecciones recurrentes de vías respiratorias superiores. De manera concomitante, manifestó artralgias matutinas en las articulaciones metacarpofalángicas bilaterales y exantema malar fotosensible. Posteriormente, se agregó fiebre intermitente persistente, anorexia, limitación articular y linfadenopatía cervical e inguinal, asociadas con anemia normocítica normocrómica. La biometría hemática evidenció leucopenia y anemia progresiva. La biopsia de médula ósea mostró celularidad aumentada con hipoplasia eritroide y cambios megaloblásticos reactivos. El estudio de inmunohistoquímica concluyó hiperplasia linfoide policlonal reactiva. Durante su hospitalización aparecieron úlceras orales, ictericia, exantema cutáneo y elevación de transaminasas y bilirrubina directa. Evolucionó con derrame pleural bilateral, insuficiencia respiratoria aguda y requerimiento de ventilación mecánica. Se documentaron anticuerpos antinucleares positivos: 1:640 (patrón AC-20), por lo que se estableció el diagnóstico de lupus eritematoso sistémico. Se inició tratamiento con corticosteroides a dosis altas, inmunoglobulina intravenosa y ciclofosfamida por neumonitis lúpica refractaria, con mejoría clínica inicial. Fue enviada a un hospital de tercer nivel; no obstante, reportó deterioro multisistémico progresivo y falleció pese al tratamiento instaurado.

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CONCLUSIONES: El reconocimiento temprano del traslape de enfermedad de Kikuchi-Fujimoto–lupus eritematoso sistémico es fundamental para evitar retrasos terapéuticos y orientar oportunamente la prescripción de inmunosupresión en casos graves. La vigilancia clínica prolongada y el seguimiento estrecho son decisivos para la detección oportuna de las complicaciones y optimizar el pronóstico de los pacientes.

PALABRAS CLAVE: Enfermedad de Kikuchi-Fujimoto; Lupus eritematoso sistémico; Linfoma; Infecciones de las vías respiratorias superiores; Biopsia de médula ósea; Corticosteroides; Linfadenopatía.

BACKGROUND

Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is a rare disorder described primarily in adolescents and young adults. Clinically, it is characterized by lymphadenopathy, fever, and constitutional symptoms, and is often confused with infectious processes, lymphoma, or other autoimmune diseases due to its nonspecific clinical presentation.[1-3]

A particularly relevant aspect is its association with systemic lupus erythematosus. Kikuchi-Fujimoto disease may precede, coexist, or develop during the course of systemic lupus erythematosus, and there is significant clinical and histopathological overlap with lupus lymphadenitis, which represents a significant diagnostic challenge.[1,19] Both disorders can share paracortical necrosis, absence of neutrophils, and an abundance of histiocytes and plasmacytoid dendritic cells; however, the presence of hematoxylin bodies and the Azzopardi phenomenon favors a diagnosis of systemic lupus erythematosus.[4]

Correct interpretation of the lymph node biopsy, together with clinical and immunological correlation, is decisive for differentiating between isolated Kikuchi-Fujimoto disease, lupus-associated lymphadenitis, and hematological malignancies, as the therapeutic implications differ substantially. The following is the case of an adolescent with fever, lymphadenopathy, and multisystem deterioration, initially interpreted as lymphoma, in whom an excisional biopsy confirmed Kikuchi-Fujimoto disease and systemic lupus erythematosus was subsequently documented, highlighting the diagnostic and therapeutic challenges of the overlap between Kikuchi-Fujimoto disease and systemic lupus erythematosus.

CASE REPORT

A 15-year-old previously healthy female patient, with a complete vaccination schedule and appropriate weight and height for her age, began in March 2025 with recurrent upper respiratory tract infections treated on an outpatient basis. Concomitantly, she manifested morning arthralgia in bilateral metacarpophalangeal joints, initially treated with nonsteroidal anti-inflammatory drugs, as well as a photosensitive malar rash. In April, she manifested persistent intermittent fever, anorexia, joint limitation, and cervical and inguinal lymphadenopathy, associated with normocytic normochromic anemia. In June 2025, she was evaluated by staff from the Rheumatology service, who prescribed treatment with methotrexate, prednisolone, and hydroxychloroquine due to suspected autoimmune disease.

Subsequently, in the context of hospitalization for pneumonia and severe anemia, imaging studies showed bilateral ground-glass pulmonary infiltrates with areas of consolidation, as well as axillary and inguinal lymphadenomegaly. A complete blood count showed leukopenia and progressive anemia. Bone marrow biopsy showed increased cellularity with erythroid hypoplasia and reactive megaloblastic changes. The initial percutaneous lymph node biopsy suggested non-Hodgkin lymphoma; however, the immunohistochemical study concluded reactive polyclonal lymphoid hyperplasia. In July, a general urine examination reported proteinuria and an active urinary sediment (**Table 1**). Subsequently, an excisional biopsy of a right posterior cervical lymph node was obtained, the histopathological study of which revealed preserved architecture with foci of necrosis and cellular debris, without the presence of Reed-Sternberg cells or malignant atypia, compatible with

Table 1. Clinical timeline summarizing the evolution, diagnostic studies, and treatment.

Date - Period	Relevant clinical event
March 2025	Onset of recurrent respiratory infections, morning arthralgia in metacarpophalangeal joints, and photosensitive malar rash.
April 2025	Persistent fever, anorexia, joint limitation, and cervical and inguinal lymphadenopathy. Initial anemia documented.
June 2025	Evaluation by the Rheumatology service. Initiation of treatment with methotrexate, prednisolone, and hydroxychloroquine.
July 2025 (early)	Hospitalization for pneumonia and severe anemia. Persistent leukopenia. Percutaneous lymph node biopsy suggestive of lymphoma; immunohistochemistry consistent with reactive hyperplasia.

...continuation table 1.

Date - Period	Relevant clinical event
July 2025 (late)	Admission to a secondary care hospital. General urine examination reported proteinuria and an active urinary sediment.
August 2025 (early)	Excisional cervical lymph node biopsy: necrotizing lymphadenitis compatible with Kikuchi-Fujimoto disease.
August 2025 (mid)	Progressive respiratory deterioration with bilateral pleural effusion and acute respiratory failure; positive ANA 1:640 (AC-20 pattern) and establishment of concomitant diagnosis of systemic lupus erythematosus; initiation of treatment with high-dose corticosteroids, intravenous immunoglobulin, and cyclophosphamide for refractory lupus pneumonitis.
August 2025 (late)	Transfer to a tertiary care hospital. The patient reported progressive multisystem deterioration and died.

necrotizing lymphadenitis (Kikuchi-Fujimoto disease). The histological microphotographs were evaluated by a certified pathologist. **Figures 1 to 3**

During her hospitalization, the patient presented with oral ulcers, jaundice, a skin rash, and significant elevation of transaminases and direct bilirubin (**Figure 4**). She progressed with bilateral pleural effusion, acute respiratory failure, and the need for mechanical ventilation. Positive antinuclear antibodies were documented at a titer of 1:640 (AC-20 pattern), thus meeting the immunological and clinical criteria for systemic lupus erythematosus. Treatment was initiated with high-dose corticosteroids, intravenous immunoglobulin, and subsequently cyclophosphamide for refractory lupus pneumonitis, with initial clinical improvement. The patient was sent to a tertiary care hospital; however, she reported progressive multisystem deterioration and died despite the established treatment.

DISCUSSION

The main contribution of this case lies in the clinical, evolutionary, and histopathological overlap between

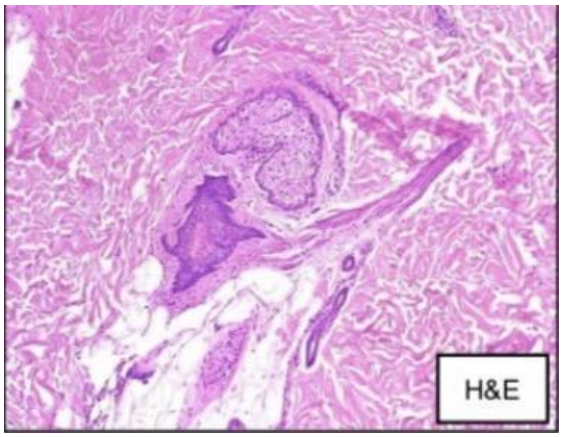

Figure 1. Histological section of a lymph node stained with hematoxylin and eosin (H&E). Partial preservation of the lymph node architecture is observed, with areas of paracortical necrosis and abundant cellular debris, without evidence of malignancy or atypia.

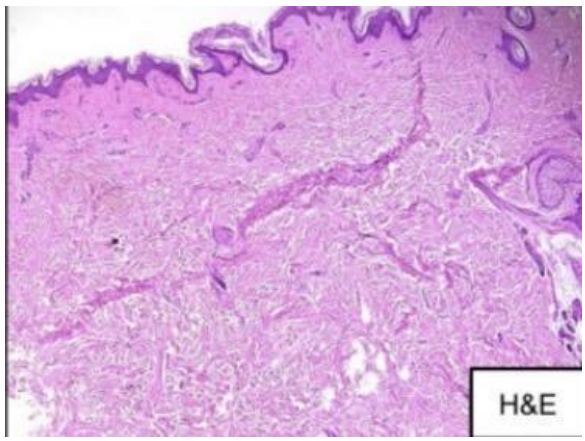

Figure 2. High-power histopathological detail (H&E) showing foci of necrosis with apoptotic material and a predominance of histiocytes, with an absence of neutrophils and no Reed–Sternberg cells, findings characteristic of histiocytic necrotizing lymphadenitis.

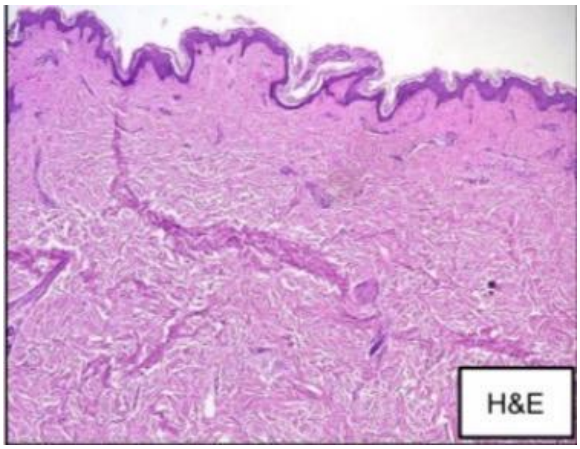

Figure 3. Panoramic view of the lymph node (H&E), showing a mononuclear inflammatory infiltrate and paracortical necrotic areas, with partial preservation of the lymph node architecture. The findings are compatible with Kikuchi-Fujimoto disease.

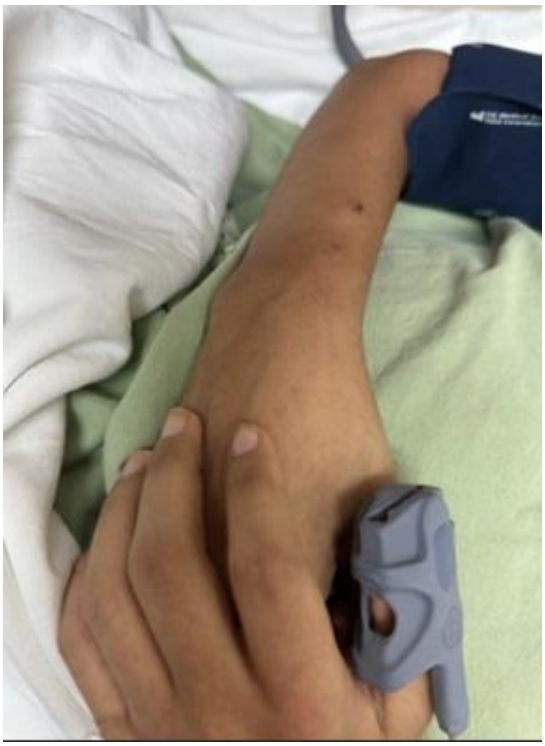

Figure 4. Cutaneous jaundice suggesting systemic involvement during the progression of Kikuchi-Fujimoto disease associated with systemic lupus erythematosus.

Kikuchi-Fujimoto disease and systemic lupus erythematosus. The excisional lymph node biopsy showed findings compatible with histiocytic necrotizing lymphadenitis, which initially allowed the diagnosis of Kikuchi-Fujimoto disease to be established and any hematological malignancy to be ruled out. However, the subsequent evolution, with multisystem involvement, positivity for antinuclear antibodies at high titers, and clinical progression, allowed the concomitant diagnosis of systemic lupus erythema-tosus to be confirmed. Although both diseases can share paracortical necrosis, absence of neutrophils, and an abundant concentration of histiocytes and plasmacytoid dendritic cells, in the patient in this study, no hematoxylin bodies or the Azzopardi phenomenon were documented— findings characteristic of lupus lymphadenitis—which ini-tially supported the diagnosis of Kikuchi-Fujimoto disease over lupus-associated lymphadenitis.[1,4]

Kikuchi-Fujimoto disease is an exceptional disorder, gener-ally benign and self-limiting, with a worldwide distribution and higher prevalence in Asian populations. It usually af-fects adolescent and young adult patients, typically with acute onset of painful cervical lymphadenopathy, fever, and constitutional symptoms.[1-3] Its clinical spectrum is heterogeneous and is frequently confused with infectious processes, autoimmune diseases, or hematological malig-nancies, particularly lymphoma, which leads to delays in diagnosis and unnecessary interventions.[3,4] Since its initial description in Japan in 1972, it has been documented in various regions of the world, affecting both children and adults, with a clear predominance in women, although in the pediatric population this gender difference may be less marked.[5-8]

The association between Kikuchi-Fujimoto disease and sys-temic lupus erythematosus has been widely described and represents one of the main diagnostic challenges of the dis-ease. Lupus may precede, coexist, or develop subsequent to Kikuchi-Fujimoto disease, and some authors consider that certain cases represent manifestations of lupus lymphad-enitis rather than isolated Kikuchi-Fujimoto disease.[1,4] This distinction is clinically relevant because, while isolated Kikuchi-Fujimoto disease usually resolves spontaneously and responds to supportive treatment or anti-inflammatory drugs, the coexistence with systemic lupus erythematosus implies a higher risk of severe organ involvement and the need for intensive systemic immunosuppression.[4] In our case, the progression toward respiratory failure, acute kid-ney injury, and liver involvement reflected high lupus activity that conditioned a torpid clinical course.

From a histopathological point of view, excisional lymph node biopsy remains the gold standard for establishing the diagnosis. Characteristic findings of Kikuchi-Fujimoto disease include apoptotic debris phagocytized by cres-cent-shaped macrophages, loss of follicular architecture, and mixed infiltrate of lymphocytes, histiocytes, and immu-noblasts, with an absence of neutrophils.[1,3] These findings allow it to be differentiated from lymphoma; however, the overlap with systemic lupus erythematosus requires careful interpretation and clinical-serological correlation. In patients with skin or other organ involvement, immunohistochem-istry and the clinical context are fundamental to guide the diagnosis.[1,4]

Regarding clinical manifestations, in addition to lymphade-nopathy, up to one-third of patients with Kikuchi-Fujimoto disease suffer from skin alterations: malar rash, erythema-tous papules, or macules, which increases confusion with systemic lupus erythematosus.[1,10] Also, neurological man-ifestations (aseptic meningitis and encephalitis) and rare but serious complications have also been described, for ex-ample, hemophagocytic syndrome, pulmonary hemorrhage, and multiple organ failure.[9,11-14] These complications explain the occasional deaths described in the literature, particularly in cases associated with autoimmune diseases.

Recently, cases of Kikuchi-Fujimoto disease associated with SARS-CoV-2 infection or COVID-19 vaccination have been described, supporting the hypothesis of immune activation triggered by viral or vaccine stimuli.[15-19]

In general, isolated Kikuchi-Fujimoto disease has a benign and self-limiting course (in weeks or months) and a low rate of recurrence. However, when associated with lupus, the prognosis depends on the degree of lupus activity and organ involvement; patients may even require aggressive immunosuppression and close long-term follow-up. Our case illustrates that the Kikuchi-Fujimoto disease–systemic lupus erythematosus overlap can be associated with severe outcomes, reinforcing the need for prolonged clinical sur-veillance, multidisciplinary care, and a high index of suspi-cion in patients with persistent fever, lymphadenopathy, and multisystem deterioration.

The limitations of this study are inherent to its nature as a case report, including its retrospective character and reli-ance on the electronic medical record, as well as the im-possibility of performing genetic studies (HLA or exome), which could have provided additional information. However, it shows relevant clinical evidence by highlighting the diag-nostic and therapeutic implications of the overlap between Kikuchi-Fujimoto disease and systemic lupus erythemato-sus in the pediatric population, particularly in public hospi-tals with limited resources.

CONCLUSIONS

The diagnosis and treatment of patients with Kikuchi-Fujimoto disease require a comprehensive approach and close multidisciplinary collaboration. Although it is considered a benign and self-limiting disease, the course can be complicated and life-threatening when associated with autoimmune diseases, such as systemic lupus erythemato-sus. In the case presented here, the overlap between Kikuchi- Fujimoto disease and systemic lupus erythematosus was accompanied by a torpid clinical course, with multisystem involvement and death, which underscores the importance of timely recognition of this association.

This report emphasizes the need to maintain a high index of suspicion in patients with persistent fever, lymphade-nopathy, and progressive organ deterioration, as well as to perform an exhaustive histopathological and serological evaluation for proper differential diagnosis.

Early recogni-tion of the Kikuchi-Fujimoto disease–systemic lupus ery-thematosus overlap is essential to avoid treatment delays and guide the timely prescription of immunosuppression in severe cases. Prolonged clinical surveillance and close follow-up are decisive for the timely detection of complica-tions and to optimize patient prognosis.

DECLARATIONS

Author contributions

Alan Orlando Morales Reyes: Data curation; formal analysis; writing—original draft; review and editing. *Karla Mitchell Ro-dríguez García:* Data curation; formal analysis; review and editing. *Anette Michelle Ávila Silva:* Visualization; review and editing. *Christian Jair Ramos Gómez:* Software; data cura-tion; review and editing.

Conflicts of interest

None of the authors declare any financial, personal, aca-demic, or institutional conflicts of interest.

Informed consent

Informed written consent was obtained from the family member responsible for the patient for the publication of this clinical case and the associated images.

Data confidentiality

The patient's identity was protected through the anonymiza-tion of clinical data. No personal data that would allow for identification are included.

Ethical approval

This case report was reviewed and approved by the corre-sponding institutional authority of the Hospital of the In-stitute for Social Security and Services for State Workers (ISSSTE), in accordance with current ethical regulations.

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Some figures and tables are original; the rest are adapted from the bibliography used in the article.

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RAM
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Clinical case

Hymenoptera allergy, difficulties in differential diagnosis: a case report

Alergia a himenópteros, dificultades en el diagnóstico diferencial: a propósito de un caso

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Abstract

BACKGROUND: The diagnosis of hymenoptera venom allergy can be particularly challenging, with the clinical history serving as a fundamental tool to guide the identification of the culprit insect. However, patient-reported visual recognition is often inaccurate and may lead to diagnostic errors unless supported by specific immunoallergological testing.

CASE REPORT: A 37-year-old man who, during a stay in Taramundi (Asturias, Spain), sustained an insect sting that he visually identified as *Nomada flava*. Ten minutes later, he developed Müller grade III anaphylaxis, with loss of consciousness, angioedema, and vomiting. The allergologic evaluation revealed double sensitization to *Vespula spp*. and *Polistes dominula* through skin testing and specific IgE measurement, with no evidence of sensitization to *Apis mellifera*. Immunoblot analysis demonstrated serum reactivity directed against *Polistes dominula* venom, mainly to component Pol d 1. Based on these findings, a diagnosis of *Polistes dominula* venom allergy was established, and species-specific venom immunotherapy was prescribed. The patient was also diagnosed with mast cell activation syndrome, confirmed by bone marrow examination.

CONCLUSION: This case underscores the need for a comprehensive allergologic workup to accurately identify the implicated species and guide appropriate venom immunotherapy, as patient-reported visual recognition of the stinging insect may be unreliable.

KEYWORDS: Hymenoptera venom; Allergy; Insect; Anaphylaxis; Angioedema; IgE; *Apis mellifera*; *Polistes dominula*; Specific immunotherapy; Mast cell activation syndrome; Bone marrow.

Resumen

ANTECEDENTES: El diagnóstico de alergia a himenópteros puede resultar especialmente complejo, y la historia clínica supone un pilar fundamental para orientar la identificación del insecto responsable. No obstante, el reconocimiento visual, por parte del paciente, suele ser inexacto y conducir a errores en el diagnóstico si no se realizan pruebas específicas de inmunoalergia.

REPORTE DEL CASO: Varón de 37 años, que durante su estancia en Taramundi (Asturias), sufrió una picadura de insecto que identificó visualmente como *Nomada flava*. Diez minutos después manifestó una reacción anafiláctica de grado III de Müller, con pérdida de la conciencia, leve angioedema y vómito. El estudio alergológico reveló doble sensibilización a *Vespula spp*. y *Polistes dominula* mediante pruebas cutáneas y determinación de IgE específica, sin evidencia de sensibilización a *Apis mellifera*. El inmunoblot mostró reconocimiento sérico dirigido contra el veneno de *Polistes dominula*, fundamentalmente al componente Pol d 1. Con estos resultados se estableció el diagnóstico de alergia a *Polistes dominula* y se indicó inmunoterapia específica frente a este veneno. El paciente fue además diagnosticado con síndrome de activación mastocitaria clonal, confirmado mediante estudio de médula ósea.

CONCLUSIÓN: Este caso destaca la necesidad del estudio alergológico completo, que permita identificar con precisión la especie implicada y seleccionar el tratamiento adecuado, pues el reconocimiento visual del insecto agresor puede ser limitado.

PALABRAS CLAVE: Veneno de himenópteros; Alergia; Insecto; Anafilaxia; Angioedema; IgE; *Apis mellifera*; *Polistes dominula*; Inmunoterapia específica; Síndrome de activación de mastocitos; Médula ósea.

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BACKGROUND

Hymenoptera venom allergy is a potentially life-threatening condition; therefore, an accurate diagnosis is essential to establish appropriate and effective treatment. This process presents several difficulties, including the heterogeneity in venom composition, the limitations of conventional diagnostic tests, the interpretation of double sensitizations, and the involvement of non-traditional species.[1,2] Furthermore, in patients with anaphylaxis due to Hymenoptera venom, especially in the most severe cases, it is fundamental to investigate the possible presence of clonal mast cell activation syndrome (CMAS), the detection of which is key for management and prognosis.[3]

This clinical case addresses and illustrates three of these difficulties: the identification of the insect, the management of double sensitizations, and the screening for CMAS.

CASE REPORT

A 37-year-old male, a gardener (a high-risk profession), presented in July 2023 with a systemic reaction following an insect sting in a public area in Taramundi (Asturias). The patient initially identified the insect as a bee (*Nomada flava*), reporting having seen a small nest on wood on the ground after being stung. Ten minutes after the event, he began to manifest clinical signs compatible with an anaphylactic reaction: cardiovascularly, loss of consciousness without sphincter relaxation; cutaneously, mild labial angioedema; and gastrointestinally, nausea and vomiting. He was attended by a mobile ICU, where blood pressure was observed at 60/35 mmHg, heart rate at 60 bpm, and a decreased level of consciousness. He received treatment with intramuscular adrenaline (0.5 mg in the anterolateral aspect of the thigh), dexchlorpheniramine (5 mg), and methylprednisolone (80 mg), with complete resolution of the clinical picture.

In the consultation, the patient completed the HiCaV (quality of life) test, obtaining a score of 3.78 (moderate impairment).[4]

An allergologic study was performed using skin tests and laboratory studies. Prick and intradermal (ID) skin tests against *Vespula spp*. showed positivity in ID 0.1 mg/mL (7 × 5 mm) and against *Polistes dominula* in ID 0.1 mg/mL (5 × 5 mm), while skin tests for *Apis mellifera* were negative. Specific IgE determination was performed using ImmunoCAP® (Thermo Fisher Scientific) and a blot study for venoms using IMMULITE® 2000/2000XPi 3gAllergy™, which reported double sensitization to *Vespula spp*. and *Polistes dominula*, with the absence of sensitization against *Apis mellifera* and absence of sensitization to cross-reactive carbohydrate determinants (CCDs). **Table 1**

Additionally, an immunoblot was performed against venoms of the main Hymenoptera of allergologic relevance (Hymnox®/Venenox®, Roxall Medicina España S.A.), which revealed a predominant immunoreactive band in the *Polistes dominula* extract in the range of ~34–38 kDa, consistent with Pol d 1, whose theoretical molecular weight is ~36 kDa, which may appear increased under electrophoretic conditions due to glycosylation. **Figure 1**

A diagnosis of *Polistes dominula* allergy was established, and species-specific immunotherapy (SIT) was prescribed, with good tolerance and clinical response. Medical treatment in the event of a new sting was explained to the patient, and he was instructed on the use of an adrenaline autoinjector. After one year of starting SIT, he suffered a new accidental wasp sting in a public area without manifesting a systemic reaction, which supported the clinical efficacy of the treatment.

Due to a REMA score (Spanish Network on Mastocytosis) of +3 (high probability of clonal mast cell syndrome), a bone marrow study was performed. Cytology showed mast cell hyperplasia, mostly with atypical morphology (88% of the total). Flow cytometry detected 0.016% of aberrant mast cells, findings compatible with CMAS. The D816V mutation of the KIT gene, analyzed by digital PCR, was negative. Likewise, bone marrow densitometry and abdominal ultrasound were performed, with no pathological findings. Treatment with disodium cromoglycate (200 mg every 12 hours) was prescribed, with good subsequent clinical progression.[5]

DISCUSSION

Nomada flava is a small cleptoparasitic bee belonging to the *Apidae* family, whose morphology can complicate visual identification and favor confusion with other hymenoptera of allergological relevance such as *Apis mellifera* or *Polistes dominula*. To date, there are no documented descriptions of allergic reactions to this species nor characterization of its allergens, which limits the availability of specific diagnostic tests. This situation forces reliance on integrating clinical

Table 1. ImmunoCAP® (Thermo Fisher Scientific). IgE values expressed in kU/L and IgG4 in mg/L.

Species	Total IgE (kU/L)	Ves v1 / Pol d1 / Api m1 (kU/L)	Ves v5 / Pol d5/ Api m2	IgG4 (mg/L)
Vespula spp.	**6.31**	**5.11**	**1.26**	0.27
Polistes dominula	**6.68**	–	**2.18**	0.35
Apis mellifera	<0.01	<0.01	<0.01	<0.01

Significant values are shown in bold. Basal parameters: total IgE 42.6 kU/L; basal tryptase 8.43 µg/L; CCD marker <0.35 kU/L.

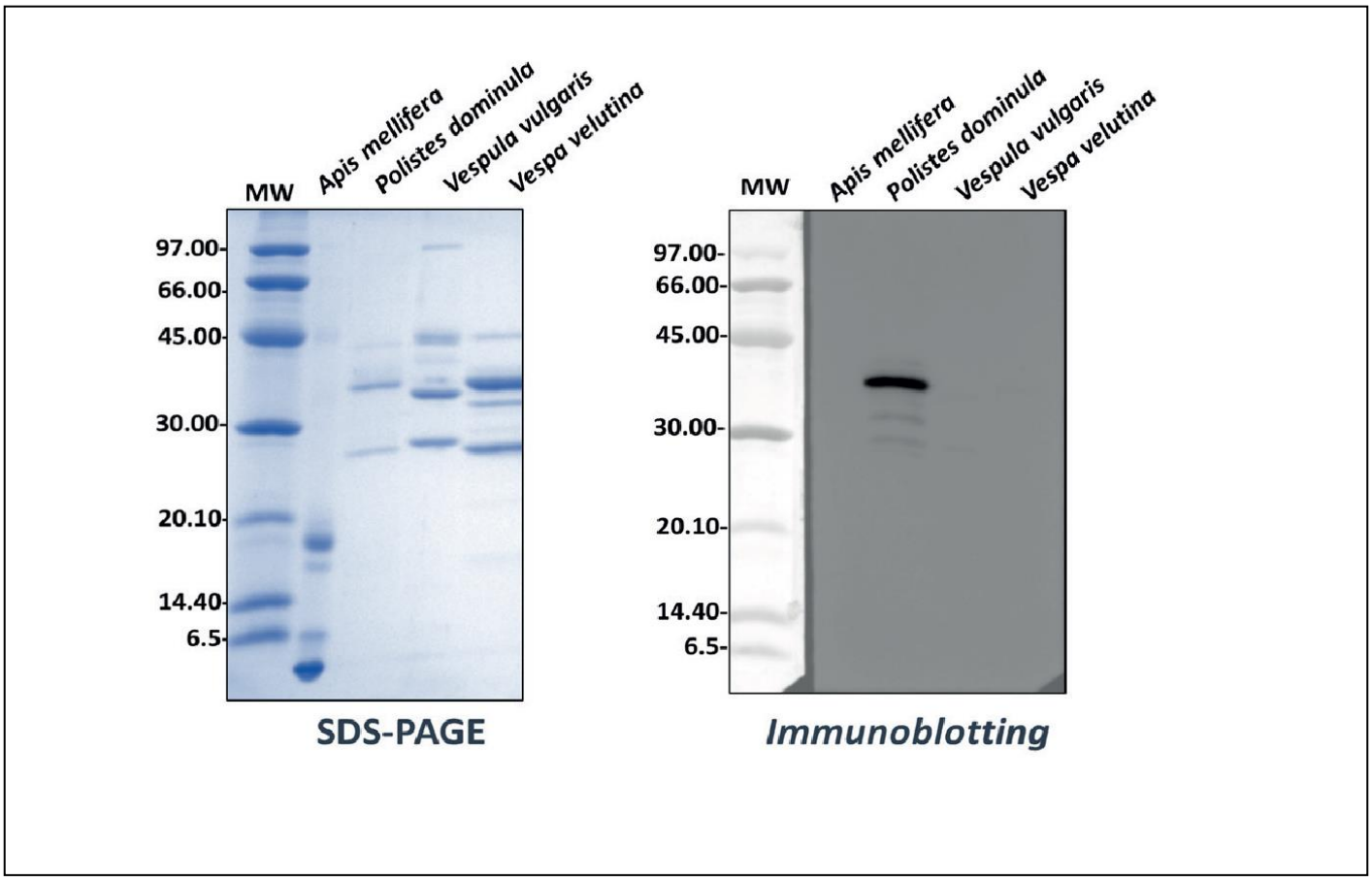

Figure 1. SDS-PAGE (left) and immunoblot (right) of Apis mellifera, Polistes dominula, Vespula vulgaris, and Vespa velutina venom extracts. The immunoblot shows a predominant immunoreactive band in P. dominula at ~34–38 kDa, consistent with Pol d 1, whose theoretical molecular weight is ~36 kDa. MW: molecular weight marker (kDa).

history and available immunological techniques to identify the culprit insect.[6–8]

In our patient, the initial suspicion of a *Nomada flava* sting was inconsistent with the immunological findings, which showed predominant recognition against Pol d 1. This is the main allergen of *Polistes dominula* venom, and its detection is associated with clinically relevant sensitization.

In the ImmunoCAP® currently available in Spain, it is not possible to determine Pol d 1; therefore, complementary techniques (IMMULITE® and immunoblot) were used. These showed detectable concentrations of Pol d 1 (0.54 kU/L) and a predominant band in the expected range.

The predominant identification of Pol d 1, together with the absence of CCD-mediated cross-reactivity and negative results against *Apis mellifera* allergens, allowed for differentiation between serological double sensitization and clinically relevant *Polistes dominula* allergy. Therefore, it was considered more likely that the sting was caused by *Polistes dominula*, visually confused with *Nomada flava* due to their morphological similarity (**Figure 2**). The characteristics of the nest, the insect's anatomy, and the immunological results support this hypothesis. The discovery of the stinger suggests the death of the insect after the sting, although this finding is not entirely specific. The visual difficulty in differentiating between species and the coexistence of double sensitization highlight the need for a comprehensive diagnostic approach that includes advanced techniques such as immunoblot, inhibition tests, or basophil activation tests to identify the correct species, thereby differentiating between primary sensitization and cross-reactivity.

The case presented in this study also shows that in patients with anaphylaxis due to Hymenoptera venom, especially in the most severe cases, clonal mast cell activation syndrome may coexist and go unnoticed, even with normal basal tryptase concentrations. Its detection is fundamental because it modifies clinical management, including the indication for prolonged or indefinite immunotherapy, carrying more than one adrenaline autoinjector, and the use of adjuvant treatments.

In our patient, the negative KIT D816V mutation, together with the absence of dense mast cell infiltration in the bone marrow, makes a diagnosis of indolent systemic mastocytosis less likely and supports the diagnosis of clonal mast cell activation syndrome, although both conditions can be part of a continuous spectrum and require longitudinal follow-up.

Among the limitations of the case presented is the impossibility of absolutely confirming the culprit species, since identification is based on indirect clinical and immunological findings. Likewise, as it is an isolated case, the extrapolation of the results should be performed with caution.

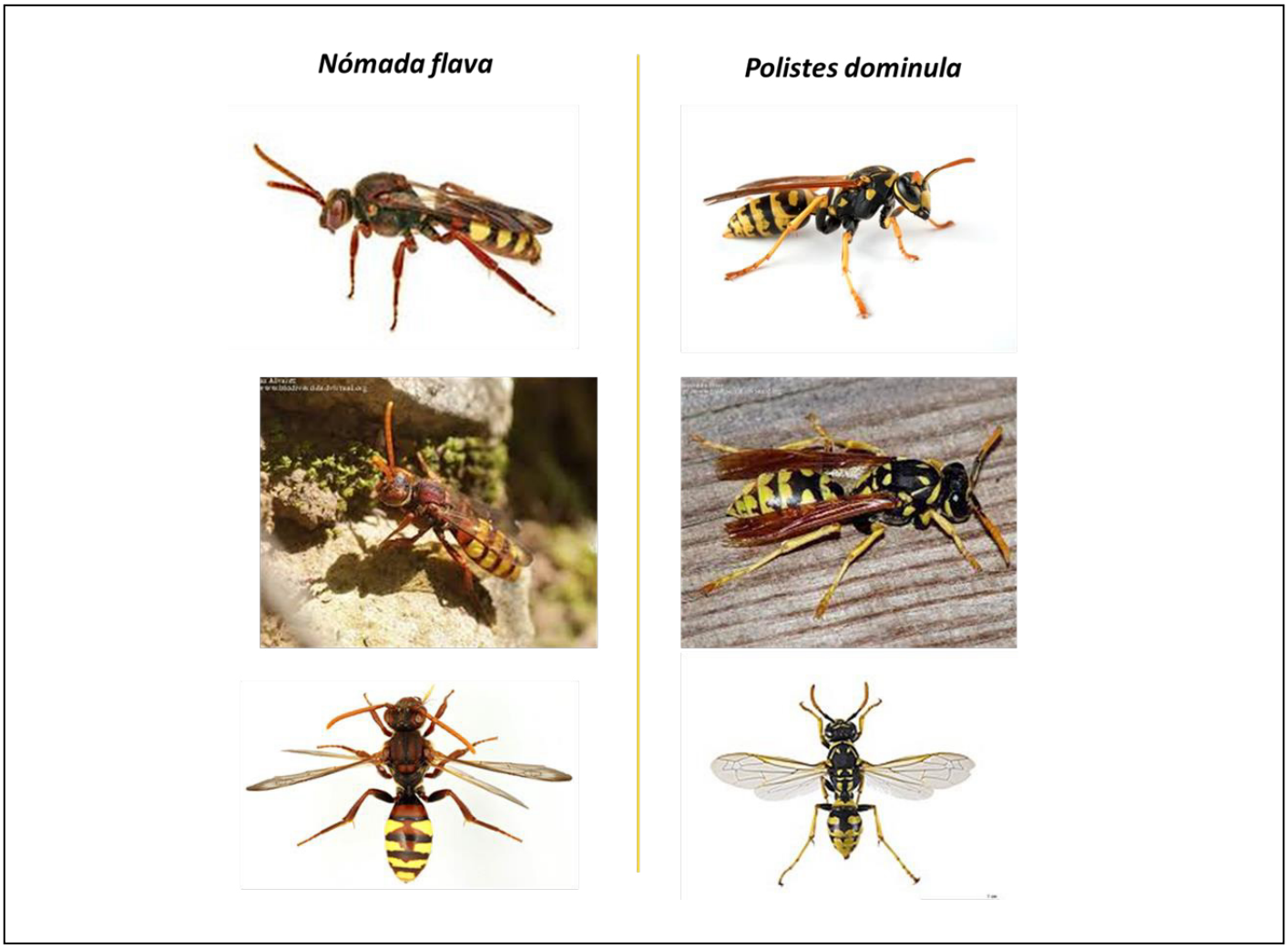

Figure 2. Morphological comparison between Nomada flava and Polistes dominula, highlighting the characteristics that can lead to confusion during visual identification.

CONCLUSIONS

This case highlights the diagnostic complexity of Hymenoptera venom allergy and the importance of a multidimensional approach that integrates insect identification, assessment of cross-sensitizations, and the use of advanced diagnostic methods to ensure appropriate and effective immunotherapy. It also highlights the need to rule out clonal mast cell activation syndrome in patients with severe systemic reactions, due to its impact on prognosis and treatment.

DECLARATIONS

Author contributions

Each of the signing authors declares to have made substantial contributions that meet the four authorship criteria approved by the International Committee of Medical Journal Editors (ICMJE).

Conflict of interest

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All figures and tables are original.

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RAM
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Letter to the Editor

Beyond scientific advances: delays, disparities, and opportunities in hereditary angioedema care across Latin America

Más allá de los avances científicos: retrasos, disparidades y oportunidades en la atención de pacientes con angioedema hereditario en América Latina

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Angioedema (AE) is a heterogeneous syndrome of episodic, self-limited swelling of subcutaneous and submucosal tissues. Its two principal mechanistic subtypes, mast-cell-mediated (histaminergic) and bradykinin-mediated, share clinical features but diverge entirely in pathophysiology and treatment. This distinction carries life-or-death consequences: bradykinin-mediated AE does not respond to antihistamines, corticosteroids, or epinephrine, and misclassification delays access to effective therapy in a disease capable of causing fatal laryngeal obstruction. Among bradykinin-mediated variants, hereditary angioedema (HAE) due to C1-inhibitor deficiency (HAE-C1INH) and with normal C1-inhibitor levels (HAE-nC1INH) remain among the most underdiagnosed conditions in the region. HAE is a devastating disease; in addition to being potentially life-threatening, its recurrent and unpredictable nature imposes a substantial burden, keeping patients in a state of constant alertness that drastically impairs their quality of life and is associated with high rates of anxiety and depression, as documented in studies of health-related quality of life in this population.[1] This letter offers a clinically grounded regional perspective that integrates epidemiological evidence and public health considerations to inform practice and policy at all levels of care.

Diagnostic delay is a primary obstacle; in Mexico, the time from symptom onset to confirmed diagnosis can extend up to 20 years.[2] Multinational data confirm that limited access to on-demand treatment is directly associated with longer therapeutic delays and impaired patient-reported outcomes.[3] The common denominator of this delay is diagnostic confusion: bradykinin-mediated angioedema is repeatedly and incorrectly managed as an allergic reaction, chronic urticaria, anaphylaxis, or a surgical abdominal emergency. The clinical signal that must not be missed is the following: recurrent angioedema without urticaria that does not respond to antihistamines, corticosteroids, or epinephrine. When bradykinin-mediated angioedema is suspected, measuring serum C4 and quantitative and functional C1-inhibitor levels represents a basic and widely accessible diagnostic strategy.

The barriers are structural and profoundly unequal. Of the thirteen countries in the region, only six (Argentina, Brazil, Chile, Colombia, Mexico, and Peru) have any degree of access to targeted therapies or on-demand treatments for HAE; access is defined here as the regulatory approval and availability of at least one specific HAE therapy through any mechanism, including public health coverage, hospital formulary, special access programs, or private market authorization. In the remaining countries, patients not only lack current therapeutic options but also remain unprotected against life-threatening attacks, representing an unacceptable gap in access to care for a treatable condition. In Brazil, a real-world study documented the widespread use of danazol in the public health system as a direct consequence of economic restrictions that limit access to newer therapies.[4] Long-term use of attenuated androgens is associated with significant adverse effects, including

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hepatotoxicity, dyslipidemia, and virilization, further underscoring the need for access to safer, targeted therapies. The Argentine and Mexican consensus documents have established recommendations adapted to resource-limited contexts,[5,6] but their implementation remains uneven across the region.

Faced with this fragmented reality, and in the absence of a regional health authority to coordinate common policies, collaborative work among national HAE patient organizations is a strategic necessity. Regional cooperation enables the replication of successful access models, the sharing of epidemiological data, the development of professional networks, peer-to-peer consultation among specialists, and the support of countries with less institutional development. Existing initiatives such as the Latin American guideline: Diagnosis and Management of Hereditary Angioedema in Latin America: International Recommendations and Regional Practice Realities, the ACARE network of reference centers, and binational consensus collaborations demonstrate that regional coordination is not only necessary but already underway in parts of the region.[7] The priority challenges and proposed strategies to address this regional crisis are summarized in **Table 1**.

CONCLUSION

Ultimately, HAE is a treatable condition, yet patients in our region still endure up to a two-decade diagnostic odyssey for a disease capable of causing fatal asphyxiation. The fundamental issue is no longer a lack of scientific progress but rather systemic inequities and a profound deficiency in clinical recognition. Leaving patients unprotected in countries without access to targeted therapies is not merely a healthcare gap; it is an unacceptable failure to act on available knowledge. We urgently call upon health authorities, medical societies, and policymakers across Latin America to implement simple diagnostic algorithms and establish a shared regional agenda. Our region possesses the inherent capacity to transform this reality through collective will, shared expertise, and the unwavering conviction that no patient should die from a treatable disease.

STATEMENTS

Conflicts of interest

The author declares being a speaker for Takeda, CSL Behring, Novartis, Sanofi, Pint Pharma, Panalab, AbbVie, and

Table 1. Priority challenges, clinical impact, regional scope, and proposed strategies in hereditary angioedema in Latin America.

Challenge	Clinical Impact	Regional Scope	Proposed strategy
Delayed and confused diagnosis	Unnecessary invasive procedures; inappropriate treatment with antihistamines, corticosteroids, or epinephrine; fatal laryngeal attacks	All 13 countries	Incorporate simple diagnostic algorithms in emergency departments, internal medicine, and pediatrics: recurrent angioedema without urticaria not responding to antihistamines or epinephrine warrants measurement of serum C4 and C1-INH.
Barriers to laboratory diagnosis	Missed or excessively delayed diagnosis of HAE-C1INH and HAE-nC1INH; prolonged diagnostic odyssey	All 13 countries; serum C4 unavailable in many public settings	Include serum C4 as initial screening; a persistently low C4 warrants quantitative and functional C1-INH measurement. Expand access to genetic testing for HAE-nC1INH.
Therapeutic inequity	Dependence on attenuated androgens with hepatotoxicity, dyslipidemia, and virilization; no on-demand treatment available for acute attacks	7 of 13 countries without access to any targeted therapy	Promote transition from attenuated androgens and fresh plasma toward targeted therapies (plasma-derived C1-INH, bradykinin antagonists, kallikrein inhibitors) through public health coverage, hospital formularies, or special access programs.
Challenge	**Clinical Impact**	**Regional Scope**	
Fragmentation of regional information	Absence of epidemiological data; isolated clinical decisions; inability to benchmark outcomes or replicate successful models	All 13 countries; registry data limited to Argentina, Brazil, and Mexico	Drive national and Latin American registries in collaboration with HAE patient organizations; strengthen the ACARE network of reference centers; consolidate referral pathways to specialists; replicate successful binational consensus models.

AstraZeneca; Advisor from Takeda, CSL Behring, AbbVie, KalVista, Pint Pharma, Pharvaris, and Bagó; and Investigator from Takeda, Sanofi, and Pharvaris.

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