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Original Article

Association between Serum Ferritin and Total IgE among Pediatric Patients with Recurrent Wheeze: Hospital-based study in Libya

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Abstract

Background: The "iron allergy hypothesis" suggests insufficient iron stores drive T-helper 2 polarisation and promote IgE sensitisation. We studied the association between serum ferritin and total IgE categories among Libyan children with recurrent wheeze. **Methods:** This cross-sectional study was conducted at Ali Omar Asker Hospital (Tripoli, Libya) from January 2023 to February 2026.Investigated 150 children aged 2-16 years diagnosed with recurrent wheezing. Serum ferritin and total IgE levels were classified as normal, low, or high based on laboratory ranges. Statistical analysis was performed using **Pearson's** Chi-square, Fisher's exact and Spearman's rank correlation tests. **Results:** Among the 150 children, 23.8% had low ferritin, 76.2%were normal, and none were high. Overall, 54.7% had high IgE levels. The results showed IgE levels were nearly the same in both the normal and low ferritin groups (55.6% vs. 54.8%). This difference was not significant ($\chi^2 = 0.089$, $p = 0.912$). Also, Spearman's test confirmed no correlation between thetwo measures (rho = 0.012, p = 0.883).In subgroups, boys had a significantly higher rate of high IgE than girls (62.5% compared to 43.5%; p = 0.032). Regarding age, high IgE wasfound in 47.7% of children aged 2-6 years, 56.9% aged 7-11 years, and 58.5% aged 12-16 years. However, these variations were not statistically significant (p = 0.645). Finally, patient atopy and family history showed no significant links to ferritin or IgE levels.
Conclusion: Our study found no association between serum ferritin and total IgE levels in Libyan children with recurrent wheeze. However, the finding of male predominance in elevated IgE warrants more investigation. Further studies are needed to clarify nutrition-immunity interactions in pediatric respiratory diseases.

Keywords: Wheezing, Immunoglobulin , Ferritins, Hypersensitivity, Libya

Introduction

Recurrent wheezing is a major pediatric respiratory symptom and an important clinical indicator for developing childhood asthma [1]. It affects 11% to 21% of school-aged children globally, carrying a particularly high burden in low and middle income counties where dietary and environmental factors worsen disease outcomes [2].While immunoglobulin E (IgE) mediated sensitisation drives airway inflammation, the nutritional factors regulating IgE remain unclear [3, 4]. Recently, iron homeostasis has been documented as a main immunomodulator in allergy pathophysiology [5, 6]. In the "iron allergy hypothesis", low iron stores stimulate T-helper 2 (Th2) polarisation and raise IgE levels [5, 6]. The iron deficiency prolongs Th2 lymphocyte survival and upregulates activation-induced cytidine deaminase (AID), shifting the immune response toward an allergic phenotype [7, 8]. Preclinical studies show that iron deficiency worsens allergen-induced airway eosinophilia, while iron supplementation reverses these changes [9]. Clinically, children with atopic diseases have an eightfold higher risk of iron deficiency anaemia, and maternal iron deficiency during pregnancy is related to childhood atopy [10]. However, a major challenge in current research is data interpretation; instead of using raw continuous numbers, paediatricians must use age and sex specific reference thresholds to accurately diagnose real iron deficiency [11]. Libyan and North African pediatric populations are seriously underrepresented in research involving nutrition and respiratory allergies [1].To address this clinical gap, we conducted a hospital-based, cross-sectional study to evaluate the association between serum ferritin categories and total IgE categories in Libyan children aged 2-16 years with recurrent wheeze [1]. Following the STROBE guidelines, this study aims to define whether iron status is related to allergic sensitisation in this population, or if demographic and atopic factors play a more dominant role [1].

Material and Method

Study Design cross-sectional study was conducted at the Department of Pediatrics, Ali Omar Asker Hospital, a

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tertiary care pediatric centre in Tripoli, Libya. The study examined the association between serum ferritin and total IgE levels in the pediatric population aged 2-16 years in

Reporting Guidelines

This study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for cross-sectional studies, ensuring transparency, completeness, and methodological rigour.

Study Population

Identification of Participants

Eligible participants were identified from hospital medical records of the pediatric respiratory clinic. Children were included if they met the following criteria.

Selection Criteria

Inclusion criteria:

- Age 2–16 years at the time of evaluation.
- Documented history of recurrent respiratory wheeze (≥3 episodes of physician-diagnosed respiratory wheezing within the previous 12 months, or as recorded in the clinical notes).
- Availability of laboratory measurements for both serum ferritin and total IgE, performed during the same clinical encounter or within a maximum of four weeks.
- ***Exclusion criteria:***
- Incomplete or missing data on serum ferritin or total IgE.
- Presence of documented chronic conditions known to significantly alter iron metabolism (e.g., thalassemia major, chronic kidney disease, malignancy, or inflammatory bowel disease), when explicitly noted in the medical record

Participant Flow

A total of 167 medical records were initially screened. Of these, 150 children (90.4%) had complete data on the primary variables and were included in the final analysis

Variables and Definitions

All study variables were extracted from the hospital-recorded database.

Primary Variables Serum ferritin..... categorised as 1 = low, 2 = normal, or 3 = high. Total serum IgE... categorised as 1 = low, 2 = normal, or 3 = high. Both primary variables were treated as ordinal categories for statistical purposes.

- : equal to or more than 3 episodes of physician-diagnosed respiratory wheezing within the previous 12 months.

Secondary and descriptive variables:

- Age: grouped as 2–6 years, 7–11 years, or 12–16 years.
- Gender: recorded as 1 = male or 2 = female.
- Patient atopy: coded as 1 = absent, 2 = allergic rhinitis, 3 = eczema,
- Family atopy (among first-degree relatives): coded as 1 = absent, 2 = bronchial asthma, 3 = allergic rhinitis, 4 = eczema.
- Haematological parameters (red blood cell count, haemoglobin, and platelet count): each categorised as 1 = low, 2 = normal, 3 = high based on standard pediatric reference values used by the hospital laboratory.
- Recurrent wheeze: equal to or more than 3 episodes of physician-diagnosed respiratory wheezing within the previous 12 months.

Data Sources and Measurement

Data were collected from the hospital's paper-based medical record. Serum ferritin and total IgE levels were measured using standard immunoassay techniques available within different laboratories. Haematological parameters were obtained from automated complete blood count analysers. All tests were performed as part of routine clinical care, and laboratory methods remained consistent throughout the period from January 2023 to February 2026.

Statistical Analysis

Statistical analyses were conducted using R software (version 4.5). Categorical and ordinal variables were summarised as frequencies and percentages. To analyse the primary outcome, the association between serum ferritin categories (low, normal, high) and total IgE categories (low, normal, high), **Pearson's Chi-square test of independence** was applied. In instances where contingency table cells had an expected frequency of less than 5, **Fisher's exact test** was utilised. Additionally, **Spearman's rank correlation coefficient (rho)** was computed to evaluate the strength and direction of the monotonic relationship between the ordinal categories of ferritin and IgE. Stratified subgroup analyses (by age, gender, and atopy status) were also evaluated using the **Chi-square test**. Missing data were managed with complete-case analysis, meaning only records with

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complete information on the variables of interest were included in each analysis. No multiple imputation was performed.A two-sided p-value <0.05 was considered statistically significant. No adjustment for multiple testing was applied, given the exploratory nature of subgroup analyses. Sensitivity analyses were not required due to the categorical nature of all variables and the absence of sampling strategy adjustments.

Ethical Considerations

The study was approved by the Training Centre and the Head of the Department of Paediatrics at Ali Omar Asker Hospital. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki. Patient confidentiality was strictly maintained, and all identifying information was removed prior to analysis. Because the study involved secondary use of routinely collected clinical data, individual informed consent was waived. Participants (or their guardians) retained the right to request withdrawal of their data at any time without any negative consequences

Results

Regarding atopic status, patient atopy was absent in 60% of children. Allergic rhinitis was present in 35. 3%, and eczema was documented in 4. 7%. A strong family history of atopy was observed among first-degree relatives, withof the sample (58.9%), while females accounted for 41.1%.

only 11.3% reporting no atopic disease. Bronchial asthma in the family was the most common (51. 3%), followed by allergic rhinitis (34%) and eczema (3.3%). These baseline characteristics are summarised in Table 1

Table 1. Baseline characteristics of the study population

Characteristic	Category	n (%)
Age group	2–6 years	44 (29.1)
	7–11 years	66 (43.7)
	12–16 years	40 (27.2)
Sex	Male	88 (58.9)
	Female	62 (41.1)
Patient atopy	None	90 (60)
	Allergic rhinitis	53 (35. 3)
	Eczema	7 (4. 7)
Family atopy	None	17 (11.3)
	Bronchial asthma	77 (51. 3)
	Allergic rhinitis	51 (34)
	Eczema	5 (3.3)
Total IgE	Low	4 (2.7)
	Normal	64 (42.7)
	High	82 (54.7)
Serum ferritin	Low	35 (23.3)
	Normal	115 (76.7)
	High	0 (0.0)
RBC	Low	3 (2.0)
	Normal	147 (98.0)
	High	0 (0.0)
Hemoglobin	Low	7 (4.7)
	Normal	143 (95.3)
	High	0 (0.0)
Platelet	Low	0 (0.0)
	Normal	149 (99.3)

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	High	1 (0.7)

Data are presented as n (%). Total analyzed patients = 150.

Distribution of Serum Ferritin and Total IgE Levels

Serum ferritin was categorised as low in 35 patients (23.3%) and normal in 115 patients (76.7%). No patients were classified in the high ferritin category according to the hospital's reference ranges.

The distribution of total IgE levels across serum ferritin categories is presented in Table 3. Among the 35 children with low ferritin, 19 (54.3%) had high total IgE, 15 (42.9%) had normal levels, and only 1 (2.9%) had low levels. In the group of 115 children with normal ferritin, 63 (54.8%) had high total IgE, 49 (42.6%) had normal levels, and 3 (2.6%) had low levels.

Overall, high total IgE was the most prevalent category in both ferritin groups (approximately 54–55%), indicating a consistent pattern of elevated IgE irrespective of ferritin status.

Table 3. Distribution of Total IgE Levels According to Serum Ferritin Categories (N = 150)

Serum Ferritin	Total IgE Category		
	Low	Normal	High
Low (n =35)	1 (2.9%)	15 (42.9%)	19 (54.3%)
Normal (n =115)	3 (2.6%)	49 (42.6%)	63 (54.8%)
Data presented as n. Categories defined according to hospital pediatric reference ranges.			

Primary Analysis: Association between Serum Ferritin and Total IgE Levels

The primary objective of this study was to examine the association between serum ferritin categories and total IgE categories in Libyan children with recurrent wheeze. As shown in Table 4, the distribution of total IgE levels was similar between the two groups.

Among the 35 children with low serum ferritin, 19 (54.3%) had high total IgE, 15 (42.9%) had normal levels, and 1 (2.9%) had low levels. In the 115 children with normal serum ferritin, 63 (54.8%) had high total IgE, 49 (42.6%) had normal levels, and 3 (2.6%) had low levels.

The Pearson's Chi-square test of independence revealed no statistically significant association between serum ferritin categories and total IgE categories ($\chi^2 = 0.089$, $p = 0.912$). Similarly, Spearman's rank correlation coefficient demonstrated no meaningful monotonic relationship between the ordinal categories of serum ferritin and total IgE (rho 0.012 p 0.883).

Table 4. Association Between Serum Ferritin Categories and Total IgE Levels (N = 150)

Serum Ferritin	Total IgE Category		
	Low	Normal	High
Low (n =35)	1 (2.9%)	15 (42.9%)	19 (54.3%)
Normal (n =115)	3 (2.6%)	49 (42.6%)	63 (54.8%)
Note: p-values were determined using Pearson's Chi-square test; Fisher's exact test was applied where expected cell counts were less than 5."			

Exploratory and Subgroup Analyses

Exploratory subgroup analyses were conducted to evaluate potential effect modification by demographic and atopic variables on the proportion of high total IgE levels. As shown in Table 5A, the proportion of high total IgE did not differ significantly across age groups (p = 0.645). High IgE was observed in 47.7% of children aged 2–6 years, 56.9%

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of those aged 7–11 years, and 58.5% of those aged 12–16 years.

Table 5A. Proportion of high total IgE levels by age group.

Age Group	n	High IgE n (%)	p-value (Chi-square)
2- 6 years	44	21 (47.7%)	0.645
7–11 years	66	37 (56.9)	0.645
12–16 years	40	24 (58.5%)	0.645
*Note: p-values were determined using **Pearson's Chi-square test**; **Fisher's exact test** was applied where expected cell counts were less than 5."*			

A statistically significant difference was found by gender (Table 5B). Males had a higher proportion of high total IgE (62.5%) compared to females (43.5%; p = 0.032).

Table 5B. Proportion of high total IgE levels by gender

Gender	n	High IgE n (%)	p-value (Chi-square)
Female	62	27 (43.5%)	0.032
Male	88	55 (62.5%)	0.032
*Note: p-values were determined using **Pearson's Chi-square test**; **Fisher's exact test** was applied where expected cell counts were less than 5."*			

No significant associations were observed with patient atopy status (Table 5C), although children with allergic rhinitis showed the highest rate of high total IgE (64.2%; p = 0.118).

Table 5C. Proportion of high total IgE levels by patient atopy status

Patient Atopy	n	High IgE n (%)	p-value (Chi-square)
Allergic rhinitis	53	34 (64.2%)	0.118
Eczema	7	4 (57.1%)	0.118
None	90	44 (48.9%)	0.118
*Note: p-values were determined using **Pearson's Chi-square test**; **Fisher's exact test** was applied where expected cell counts were less than 5."*			

Similarly, family history of atopy was not significantly associated with high IgE levels (Table 5D), with proportions ranging from 20.0% (family history of eczema) to 60.8% (family history of allergic rhinitis; p = 0.475).

Table 5D. Proportion of high total IgE levels by family history of atopy (first-degree relatives).

Family Atopy	n	High IgE n (%)	p-value (Chi-square)
Allergic rhinitis	51	31 (60.8%)	0.475
Bronchial asthma	77	43 (55.8%)	0.475
Eczema	5	1 (20%)	0.475
None	17	7 (41.2%)	0.475
*Note: p-values were determined using **Pearson's Chi-square test**; **Fisher's exact test** was applied where expected cell counts were less than 5."*			

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Discussion

This hospital based cross sectional study examined the association between total IgE categories and serum ferritin levels in 150 Libyan children with recurrent respiratory wheeze. In contrast to expectations based on the iron allergy hypothesis, no statistically significant association was found between serum ferritin categories and total IgE categories ($p > 0.05$). High total IgE levels were prevalent in both low and normal ferritin groups (approximately 55%), indicating that allergic sensitization is common in this population irrespective of iron status when assessed using categorized ferritin measures.

The minimal difference in proportions between ferritin groups suggests a negligible effect size, reinforcing the absence of a clinically meaningful association. These findings differ from several studies supporting the iron allergy hypothesis. Some studies suggest that iron deficiency may promote Th2-skewed immune responses and enhance IgE class switching through upregulation of activation induced cytidine deaminase and modulation of transcription factors [13].

Preclinical models demonstrate that iron administration can reduce airway hyper reactivity and eosinophilic inflammation, whereas iron restriction exacerbates allergen induced responses [14]. Epidemiological evidence further links lower serum ferritin with increased risk of atopic diseases, and iron supplementation in deficient children has been associated with reductions in total IgE levels [15].

Maternal iron deficiency during pregnancy has also been linked to impaired lung function and higher atopic risk in offspring [16]. The absence of an expected inverse relationship in our cohort may be explained by the categorical nature of the laboratory data, which likely reduced statistical power to detect subtle associations. The “low” ferritin group may not have represented severe functional iron deficiency sufficient to drive a strong Th2 bias. Additionally, unmeasured confounders such as subclinical inflammation, parasitic infections, and nutritional heterogeneity may have obscured potential associations in this cohort.

Contextual factors specific to North African populations, including dietary patterns, genetic background, and environmental exposures, could also modulate the iron allergy axis [17].

A notable finding was the statistically significant gender difference revealed by the Pearson's Chi-square test, with males showing a higher proportion of high total IgE (62.5%) compared to females (43.5%; $\chi 2 = 4.58$, $p = 0.032$) (Table 5B).

This aligns with established patterns in pediatric allergy, where pre pubertal boys often exhibit higher total and allergen specific IgE levels and greater asthma prevalence, potentially due to differences in airway caliber, sex hormone influences, or genetic factors [18].

No significant differences were observed across age groups ($p = 0.645$, Table 5A), patient atopy status ($p = 0.118$, Table 5C), or family history of atopy ($p = 0.475$, Table 5D). The high overall prevalence of elevated total IgE (~55%) in our cohort is consistent with the substantial atopic burden reported in Libyan school-aged children, where asthma prevalence is approximately 12.3%, allergic rhinitis 13.3%, and eczema 8.3% [19].

Comparative Analysis of Findings

The present study exposes a significant atopic condition among Libyan pediatric patients with recurrent wheeze, with high total IgE (54.7%) of the group. This finding is consistent with the high prevalence of allergic diseases reported in North Africa. With results documenting a significant prevalence of asthma (12.3%) and allergic rhinitis (13.3%) among school-aged children in Al-Beyda, Libya [19]. While prior research focused on epidemiological prevalence, our study provides a deeper immunological perspective by confirming a high rate of IgE-mediated sensitization within a clinical setting in Tripoli.

Regarding the 'iron allergy hypothesis', our study found no significant association between serum ferritin levels and total IgE levels using Pearson's Chi-square test ($p = 0.912$) and Spearman's rank correlation ($rho = 0.012$, $p = 0.883$)."

These results contrast with several international studies that have reported a functional link between iron deficiency and allergic sensitization. For instance, research conducted in South Korea observed an inverse relationship where lower iron stores were correlated with increased risk of atopy and elevated IgE levels [15]. Similarly, A Study made in Netherlands (Europe) suggested that higher maternal transferrin concentrations during pregnancy (decreased serum iron levels) were associated with an increased risk of inhalational allergy but not respiratory outcomes (lung function, asthma, or inhalant allergic sensitization) [16].

Also A study in Iraq suggested that low ferritin levels may aggravate asthma symptoms and inflammation [20].

The difference between our findings and these global researches could be attributed to factors related to the severity of the ferritin deficiency group in our study (23.3%) might not have reached the level of severe deficiency required to stimulate a strong T-helper 2 (Th2) polarization

Strengths and Limitations

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Strengths of our study include its focus on an underrepresented North African pediatric population, use of real world clinical data, and adherence to STROBE reporting guidelines.

Limitations include the retrospective single center design, reliance on pre categorized laboratory values, absence of specific IgE or lung function measurements, limited power in small subgroups, which restricted assessment of potential dose response relationships.

Conclusion

This study did not support a significant association between serum ferritin categories and total IgE levels in Libyan children with recurrent respiratory wheeze. The observed male predominance in high IgE warrants further investigation. Prospective studies using continuous iron biomarkers, component resolved diagnostics, and interventional designs are needed to clarify the role of iron status in allergic Respiratory disease among Libyan and North African children and to inform potential nutritional interventions.

Conflict of Interest

The authors declare no conflict of interest

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