

# GASTROESOPHAGEAL REFLUX DISEASE AS A FACTOR ASSOCIATED WITH BRONCHIAL ASTHMA IN THE PEDIATRIC POPULATION

ENFERMEDAD POR REFLUJO GASTROESOFÁGICO COMO FACTOR ASOCIADO A ASMA BRONQUIAL EN POBLACIÓN PEDIÁTRICA

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## ABSTRACT

**Objective:** To determine the relationship between gastroesophageal reflux disease and bronchial asthma in the pediatric population of the National Children's Hospital Breña headquarters between the years 2017-2018.

**Methods:** An analytical observational study of cases and controls was not matched, with a ratio of 1 case to 2 controls, with a total of 45 cases and 90 controls, a simple random probability sampling was performed, with a retrospective collection for the variables bronchial asthma, GERD, GERD-induced esophagitis, prematurity, interrupted breastfeeding, sex and age. A bivariate and multiple logistic regression model was performed to obtain the Odds Ratio for the strength of association. **Results:** A statistically significant difference was found for GERD ( $p = 0.002$ ), being 33.33% and 11.11% for cases and controls, as well as for interrupted lactation ( $p = 0.013$ ); by multiple logistic regression analysis the variables GERD (OR 4.27,  $p = 0.003$ , CI 1.64-10.92) and interrupted breastfeeding (OR 2.74,  $P = 0.011$ , CI 1.26-5.97 ) presented a relationship for bronchial asthma.

**Conclusion:** A relationship was found between GERD and bronchial asthma which can be extrapolated to the pediatric population of the city of Lima, this is the first article published in this regard at the national level, prospective studies are recommended to determine causality.

**Key words:** Gastroesophageal reflux disease; Bronchial asthma; Pediatrics (source: MeSH NLM).

## RESUMEN

**Objetivo:** Determinar la relación entre enfermedad por reflujo gastroesofágico y asma bronquial en población pediátrica en el hospital Nacional del Niño entre los años 2017-2018. **Métodos:** Se realizó un estudio observacional analítico tipo casos y controles no emparejado de razón 1 caso para 2 controles, con un total de 45 casos y 90 controles, se realizó un muestreo probabilístico aleatorio simple, con una recolección retrospectiva para las variables asma bronquial, ERGE, esofagitis inducida por ERGE, prematuridad, lactancia materna interrumpida, sexo y edad. Se realizó un modelo de regresión logística bivariado y múltiple para la obtención del Odds Ratio para la fuerza de asociación. **Resultados:** Se encontró una diferencia estadísticamente significativa para ERGE ( $p=0,002$ ), siendo 33,33% y 11,11% para los casos y controles, así como para lactancia interrumpida ( $p=0,013$ ); por análisis de regresión logística múltiple las variables ERGE (OR 4,27,  $p=0,003$ , IC 1,64-10,92) y lactancia materna interrumpida (OR 2,74,  $P=0,011$ , IC 1,26-5,97) presentaron relación para asma bronquial. **Conclusión:** Se encontró una relación entre ERGE y asma bronquial la cual puede ser extrapolada a la población pediátrica de la ciudad de Lima, este es el primer artículo publicado al respecto a nivel nacional, se recomiendan estudios prospectivos para determinar causalidad.

**Palabras clave:** Enfermedad por reflujo gastroesofágico; Asma bronquial; Pediatría (fuente: DeCS BIREME).

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as the flow of gastric contents into the esophagus associated with symptoms and/or complications that may be esophageal or extra-esophageal. GERD represents a frequent gastrointestinal pathology around the globe with estimated prevalence between 10-20% in America and Europe; and 5% in Asia<sup>(1, 2, 3, 4)</sup>.

Currently, its diagnosis has increased particularly in the pediatric population, where it occurs more frequently in males. GERD may present physiologically even before the first year of life due to immaturity of the gastroesophageal junction, a condition that decreases after the first year of life<sup>(3)</sup>.

Its prevalence is higher in children suffering from obesity, neurological diseases, congenital heart disease, gastrointestinal tract abnormalities, congenital diaphragmatic hernia, and chromosomal abnormalities. Preterm infants are also at risk of developing GERD due to immaturity of the lower esophageal sphincter, alterations in esophageal peristalsis, high milk intake, and delayed gastric emptying<sup>(3,4)</sup>. On the other hand, exclusive breastfeeding is a protective factor for GERD<sup>(3)</sup>.

Respiratory complications of GERD are common in the pediatric population, asthma being the most widely studied and whose occurrence is mainly attributed to vagal mechanisms, neurogenic inflammation, acid microaspiration, and increased bronchial reactivity<sup>(5, 6, 7, 8, 9)</sup>.

In recent years, multiple studies have demonstrated the existence of a relationship between asthma and GERD. A systematic review of 18 articles reported an average prevalence of 23.4% of GERD in patients with asthma<sup>10</sup>. Another systematic review that reviewed a total of 20 articles found a 22.0% prevalence of GERD in patients with asthma with a cumulative OR of 5.6 (95% CI: 4.3-6.9)<sup>(11)</sup>. However, many of these studies indicate a bidirectional relationship between these two variables<sup>(10, 11, 12, 13)</sup>. Therefore, we assume an association between these variables and present the following study in order to determine the association between gastroesophageal reflux disease (GERD) and bronchial asthma in pediatric population of the National Institute of Children Health during the period 2017-2018. This is the first national work to mention this association.

## METHODS

### Design

An observational, analytical, retrospective, and

unmatched case-control study was designed from a ratio of 1 case to 2 controls. The present study was carried out at the Instituto de Nacional del Niño - Breña in 2018, where data was collected on patients treated between 2017 and 2018. The target population was pediatric patients aged over 5 years with clinical manifestations of the respiratory tract treated in external consultation of the general pediatric service, where the cases were those patients with bronchial asthma and controls those patients without bronchial asthma. The exposure factor was taken at gastroesophageal reflux diagnosed by esophageal PH-metria.

### Procedures and variables

Within the selection criteria for the cases and controls were taken as inclusion criteria PH-metria test, high endoscopy, clinical history with complete data; as exclusion criteria were taken infantile cerebral palsy, organic abnormalities of the upper respiratory and digestive tract, invasive instruments to the respiratory and digestive tract, neoplasms and rheumatic pathologies.

The independent variables in the study were gastroesophageal reflux disease, whose diagnostic instrument was PH-metria and esophagitis whose diagnostic instrument was biopsy obtained by high digestive endoscopy, which were taken and evaluated by specialists in gastroenterology and pathology respectively. The dependent variable, bronchial asthma used as a diagnostic instrument to the spirometer according to the recommendations of the GINA guide<sup>(14)</sup>, which was given by pediatric outpatient specialists. As other variables, the patient's age, gender, prematurity and interrupted breastfeeding and premature birth were recorded, which were taken from the anamnesis and antecedents present in the secondary information source, the clinical history.

The data for each of the mentioned variables were recorded in a data collection sheet for each subject of study which were stored for subsequent emptying and statistical analysis.

### Population and sample

Para el cálculo del tamaño muestral se tomó un intervalo de confianza del 95%, una potencia estadística del 80%, una proporción de 1:2 para casos y controles respectivamente, tomaron los resultados obtenidos por Debley et al.<sup>(15)</sup> con una proporción de casos expuestos de 19,3%, proporción de controles expuestos 2,5% y un Odds ratio de 9,2, se empleó el paquete epidemiológico OpenEpi de acceso libre para el cálculo muestral donde For the calculation of

the sample size a 95% confidence interval was taken, a statistical power of 80%, a ratio of 1:2 for cases and controls respectively, they took the results obtained by Debley et al<sup>(15)</sup> with a proportion of exposed cases of 19.3%, proportion of exposed controls 2.5% and an Odds ratio of 9.2, the free-access epidemiological Openepi package was used for sampling where a total of 135 patients were obtained, 45 cases and 135 controls respectively using the Fleiss formula with continuity correction. A probabilistic joined tapestry sampling was performed where the population was stratified in patients with bronchial asthma and without bronchial asthma, a simple random sampling was performed in each of the strata, without replenishment.

### Ethical issues

In this study, the anonymity of each of the study subjects was not revealed, names or identity documents were not disclosed, and the institution's authorities approved the execution.

### Statistical analysis

The data collection sheets were emptied into an Excel spreadsheet, where through the program Stat-Transfer, they were transported to the statistical package STATA version 15 for further statistical analysis

The descriptive statistics will be presented for the cases and the controls with the mean and standard deviation for the quantitative variable age, as well as the absolute and relative frequency for each qualitative variable, this is sex, esophagitis and breastfeeding interrupted.

For inferential statistics, the nonparametric chi-square statistical test was performed to contrast qualitative variables and a contrast test of means for quantitative variables with respect to cases and controls, later a bivariate logistic regression model will be realized, for obtaining the Odds ratio and confidence intervals to 95%. To conclude, a multivariate logistic regression model will be executed to obtain an adjusted odds ratio with their respective 95% confidence intervals, with those variables that are considered as risk factors for bronchial asthma.

## RESULTS

Of the total sample of 135 pediatric patients none of the patients studied presented missing data for the variables studied, 45 were patients with asthma and 90 patients did not have asthma, the mean and standard deviation of age for both groups was 10.73 +/- 1.95 and 10.79 +/- 1.76 respectively, with no statistically significant differences. The percentage of males was higher in patients with asthma 60% than in patients without asthma 48.89%, with no statistically significant difference between the groups  $p=0.223$ . The percentage of interrupted breastfeeding was lower in asthmatic patients 44.44% than in non-asthmatic patients 66.67%, with a statistically significant difference between the groups  $p=0.013$ . The percentage of prematurity was higher in asthmatic patients 15.56% in relation to non-asthmatic patients 8.89%, with no statistically significant difference between the groups with a  $p=0.245$ . The percentage of GERD was higher in patients with asthma 33.33% than in patients without asthma 11.11%, with a statistically significant difference between the groups  $p=0.002$ . The percentage of esophagitis associated with GERD was higher in patients with asthma 17.78%, compared to non-asthmatic patients 7.78%, with no statistically significant difference between groups with a  $p=0.081$  (Table 1).

A bivariate logistic regression model was performed for the variables sex (OR 1.57,  $p=0.244$ , CI 0.76-3.24) interrupted breastfeeding (OR 2.5,  $p=0.014$ , CI 1.20-5.21), prematurity (OR 1.89,  $p=0.251$ , CI 0.64-5.59), GERD (OR 3.99,  $p=0.003$ , CI 1.62-9.87), esophagitis induced by GERD (OR 2.56,  $p=0.089$ , CI 0.87-7.60), only the variables GERD and interrupted breastfeeding were statistically significant (Table 2).

A multiple logistic regression model was performed to adjust the odds ratio of GERD for variables that had a demonstrated effect on bronchial asthma, GERD (OR 4.27,  $p=0.003$ , CI 1.64-10.92), gender (OR 1.61,  $p=0.235$ , CI 0.74-3.50), interrupted breastfeeding (OR 2.74,  $p=0.011$ , CI 1.26-5.97), prematurity (OR 1.92,  $p=0.274$ , CI 0.60-6.18) (Table 3). GERD and breastfeeding were the only variables with statistical significance.

**Table 1.** Univariate analysis.

	Controls (N:)% (n)	Cases (N:)% (n)	P Value
GERD	11.11% (10)	33.33% (15)	0.002
Interrupted breastfeeding	33.33% (30)	55.56 (25)	0.013
Premature birth	8.89% (8)	15.56% (7)	0.245
Male sex	48.89% (44)	60% (45)	0.223
Esophagitis induced by GERD	7.78% (7)	17.78% (8)	0.081

P values obtained from the non-parametric chi square test.

**Table 2.** Analysis with bivariate logistic regression.

Variables	Odds Ratio	P value	Confidence Intervals
GERD	3.99	0.003	1.62 – 9.87
Interrupted breastfeeding	2.50	0.014	1.20 – 5.21
Premature birth	1.89	0.251	0.64 – 5.59
Male sex	1.57	0.224	0.76 – 3.24
Esophagitis induced by	2.56	0.089	0.87 – 7.59

**Table 3.** Multiple logistic regression analysis.

Variables	Odds Ratio	P value	Confidence Intervals
GERD	4.24	0.003	1.64 – 10.93
Interrupted breastfeeding	2.74	0.011	1.26 – 5.97
Premature birth	1.92	0.274	0.60 – 6.18
Male sex	1.61	0.235	0.74 – 3.50

## DISCUSSION

The present study demonstrated an association between GERD and bronchial asthma in the pediatric population, as well as a high prevalence of GERD in patients with asthma. However, no statistically significant relationship was found between esophagitis and bronchial asthma. This finding could be explained by the fact that GERD symptomatology may exist without the presence of endoscopic findings and that the severity of these symptoms is also not correlated with endoscopic findings, as indicated in the studies by Zuberi BF et al. and Arul P. et al.<sup>(16,17)</sup>. On the other hand, there are studies such as that of Ashraf K et al. which suggest that, if there is an association between these variables, our result remains controversial<sup>(18)</sup>.

The study has design limitations. One of them lies in the fact that it is a single-center study, which affects its external validity. In addition, previously generated information was used and the available source of information did not have sufficient data to assess other variables such as anthropometric measurements and nutritional status of pediatric patients, with obesity being an important risk factor for both asthma and GERD<sup>(19,20)</sup>. Nor were other variables evaluated, such as the use of bronchodilators for asthma in children who had been diagnosed with GERD, the use of which has been shown to increase the risk of developing asthma in patients with GERD.<sup>(8,21,22,23)</sup> In addition, our study did not evaluate the correlation between asthma severity and a high prevalence of GERD or the effect of GERD treatment on asthma patients.

This study provides evidence of the association between GERD and asthma in accordance with previously published studies<sup>(8,23,24)</sup>. Also, systematic reviews such as those of Thakkar K et al demonstrate a high prevalence of GERD in patients with asthma (22.0%) compared to controls (4.8%)<sup>(11)</sup>. Similarly, studies such as those by Havemann B. et al show a statistically significant association with a cumulative OR of 5.5 (95% CI: 1.9-15.8) between GERD and asthma variables<sup>(12)</sup>.

There is pathophysiological evidence of this association that maintains that the presence of acid reflux can enter the tracheobronchial tree and alter its functioning by various mechanisms, one of them is stimulating vagal reflexes that increase airway resistance. Others are based on the stimulation of nociceptive afferent fibers that through the release of neurokinins such as substance P or neurokinin A cause bronchospasm and increased mucus secretion at the bronchial level. Another mechanism proposed is the increase in bronchial reactivity induced by the presence of acid<sup>(8,9,25)</sup>. Despite the existence of this relationship that postulates GERD as a potential cause of asthma in children, there are also studies that show an inverse relationship, suggesting a possible bidirectional relationship between these variables<sup>(8,9,21)</sup>. Finally, the present study can be extrapolated to pediatric populations at the level of metropolitan Lima.

## CONCLUSION

We concluded that there is a relationship between the variables GERD and interrupted breastfeeding for the variable bronchial asthma. This is the first nationwide study to realize this association. Prospective studies are recommended to determine a risk association.

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