



Association Between Mouth Breathing and Asthma: a Systematic Review and Meta-analysis

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Abstract

Purpose of Review This systematic review and meta-analysis evaluated the association between asthma and mouth breathing. We performed a systematic search in the PubMed, SCOPUS, Lilacs, Web of Science, Google Scholar and OpenThesis databases.

Recent Findings Asthma is defined as a heterogeneous disease characterized by variable symptoms of wheezing, shortness of breath, chest oppression and/or cough, and limitation of expiratory airflow. Although several studies have examined the association between asthma and mouth breathing, there are no systematic reviews or meta-analyses that synthesize the available bodies of evidence.

Summary We used the odds ratio as a measure of the association between asthma and mouth breathing. Summary estimates were calculated using random-effects models, and the risk of bias was estimated using the Newcastle-Ottawa Scale for case-control studies and the National Institutes of Health tool for cross-sectional studies. Nine studies were included in the present systematic review. Data from 12,147 subjects were analyzed, of which 2083 were children and adolescents and 10,064 were adults. We found an association between mouth breathing and asthma in children and adolescents (OR 2.46, 95% CI 1.78–3.39) and in adults (OR 4.60, 95% CI 1.49–14.20). However, limitations were found in the methodological description of the included studies, as well as high heterogeneity among studies evaluating adult populations. This meta-analysis showed an association between mouth breathing and asthma in children, adolescents and adults, but the results should be interpreted with caution. Further studies with standardized criteria for the investigation of mouth breathing are needed.

Keywords Asthma · Mouth breathing · Child · Adolescent · Adult

Introduction

Asthma is a heterogeneous disease that encompasses several clinical phenotypes and is characterized by recurrent episodes of wheezing, dyspnea, chest oppression, and cough that result from chronic airway inflammation [1]. Studies have shown a

higher prevalence of mouth breathing patterns in asthmatic individuals than in non-asthmatic individuals [2, 3]. Hallani et al. [4] observed that patients with mild asthma change their nasal breathing pattern to oronasal breathing at a significantly lower inspiratory nasal load than that used by healthy controls. These same authors showed a reduction in

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FEV1 (forced expiratory volume during the first second) in resting asthmatic patients caused by sudden mouth breathing. Thorstensen et al. [5] detected significantly smaller nasal cavity area and volume in asthmatic adults than in controls.

One of the main causes of nasal obstruction in asthmatics is associated with chronic rhinitis. Studies show a high prevalence of rhinitis in patients with asthma, even constituting one of the factors associated with difficult control [6, 7]. Both diseases share epidemiological, pathophysiological, and clinical characteristics, which has justified the term “united airway disease” [8••]. In addition, other clinical conditions of upper airway involvement present asthma as a highly prevalent comorbidity [9].

However, in a population-based study, Izuhara et al. showed that mouth breathing was significantly associated with asthma regardless of the presence of rhinitis [2•]. The pathophysiological mechanisms involved with predominantly oral breathing in an individual with asthma without a diagnosis of other upper airway diseases are still unclear. On the other hand, mouth breathing compromises the heating, humidification, and filtration of inspired air and may aggravate asthma by increasing allergen exposure or triggering the nasobronchial neural reflex [10, 11].

It is estimated that there is a 15.5% prevalence of mouth breathing patterns among children aged 9 to 14 years [12]. Laine-Alava et al. [13] evaluated nasal resistance among children and adolescents aged 8 to 17 years without respiratory disease and observed that nasal resistance decreased with age but temporarily increased in the prepubertal and pubertal phases, possibly due to hormonal changes. With respect to asthmatic children followed in a tertiary service, the three most common morbidities that affect the upper airways are allergic rhinitis, nasopharyngeal tonsil hypertrophy, and anomalies of intranasal structures [14]. Mouth breathing in school-age children with asthma has been estimated to occur in 31 to 42.8% of cases [15, 16•].

Oral breathing in asthmatics has a negative impact on the periodontal health of children [15, 17] and adults [18•, 19•], as well as its repercussions on lower airway reactivity [20•]. Airway cooling and dehydration resulting from exercise-associated mouth breathing may trigger bronchoconstriction mechanisms [21]. On the other hand, in a randomized controlled trial, Sue Cooper et al. [22] found no impairment in asthma control in patients who had mouth closure at night.

Although several studies have examined the association between asthma and mouth breathing, there are no systematic reviews or meta-analyses that synthesize the available bodies of evidence. It is important to verify the association between mouth breathing and asthma using the available scientific evidence to guide the teams of professionals who care for these patients. Thus, in the present study, we performed a systematic review and meta-analysis to verify the association between mouth breathing and asthma in children, adolescents, and adults.

Methods

This study was conducted following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement [23]. Institutional review board approval and informed consent were not required for this systematic review and meta-analysis.

Research Question and Eligibility Criteria

The present study focused on the following question: Is there an association between mouth breathing and asthma? Studies were considered eligible if they satisfied the following criteria: (i) they were observational studies; (ii) participants were diagnosed with asthma regardless of age and gender; (iii) they reported mouth breathing verified by questionnaires, interviews, or clinical diagnosis; and (iv) sufficient raw data were provided to evaluate the association between mouth breathing and asthma.

In this review, we excluded editorials, comments and opinions, articles of reflection, projects, reports and technical reports, reviews, and articles addressing other changes that were not related to mouth breathing and asthma.

Search Strategy

A systematic search using the PubMed, SCOPUS, Lilacs, and Web of Science databases was performed to identify studies that evaluated the association between mouth breathing and asthma. A gray literature search was conducted using Google Scholar and OpenThesis. The first 100 results of the Google Scholar search were analyzed. The search was performed in September 2019 and was limited to studies published in full-text versions, without language restrictions. The reference lists of all eligible studies and reviews were manually scanned to identify additional studies for inclusion. For articles not available in electronic databases or for data not available in the articles included in this review, the authors were contacted to obtain the necessary information. The structured search strategy used the following terms: (“mouth breathing” OR “oral breathing” OR “oral respiration”) AND (asthma OR asthmatic). To expand the number of eligible articles retrieved, no filters were used in the search.

Study Selection

Two reviewers (B.C.L.A. and V.T.G.S.) independently screened the search results and identified studies that were potentially relevant based on the paper’s title and abstract. Relevant studies were read in full and selected according to the eligibility criteria. Disagreements between the two reviewers were resolved by consensus or by a third reviewer.

Data Extraction and Risk of Bias Assessment

Two independent investigators (B.C.L.A. and V.T.G.S.) extracted data from published reports using a predefined protocol. Information on the study design, population, age and sex distribution, asthma diagnosis, and mouth breathing through a report, questionnaire, or clinical diagnosis were checked, as well as the main results. Outcome data included crude estimates. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (NIH) (nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to grade the quality of each individual study. This tool is composed of 14 items that evaluate the representativeness and selection of the sample, description and measurement of exposure, follow-up of participants, and treatment of confounding. After critical appraisal of each item, the studies were rated as good, fair, or poor, and the findings were discussed qualitatively. Disagreements were resolved by discussion. To assess the risk of bias in case-control studies, the Newcastle-Ottawa Scale (NOS) was used [24]. This instrument judges the study from three broad perspectives: the selection of the study groups, the comparability of the groups, and the determination of the outcome of interest. The assessment is made through a “star system,” in which a study can get a maximum of ten stars. The higher the number of stars, the higher the quality of the study.

Data Analysis

The odds ratio (OR) was used as the measure of association between mouth breathing and asthma. The OR was pooled using a random-effects model. Forest plots were used to graphically present the pooled ORs and the 95% CIs. *P* values lower than 0.05 were statistically significant. Heterogeneity was investigated using Cochran's *Q* test with a cut-off of 10% for significance [25] and were quantified using the I^2 index [$100\% \times (Q - df)/Q$] [26]. To explore potential sources of heterogeneity, a subgroup analysis was performed according to age (children/adolescents and adults). Publication bias was assessed by inspecting the funnel plot. Visual inspection of the funnel plot yields an indication of publication bias when larger and smaller studies are non-symmetrically distributed across the combined effect size. A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled results. The analyses were performed using Review Manager Version 5.3 software (Cochrane Collaboration, Copenhagen).

Results

Study Selection

The initial search located 2973 reports, 780 of which were collected from PubMed, 279 from Web of Science, 905 from SCOPUS, 483 from Lilacs, 100 from Google Scholar, and 426 from OpenThesis. Fifteen studies were potentially relevant and were analyzed in full. After a complete reading, six studies were excluded: five due to outcome data and one due to population. Finally, nine studies [2•, 3•, 12, 15, 16•, 18•, 19•, 27, 28•, 29•] satisfied the eligibility criteria and were included in the present systematic review and meta-analysis. A flowchart depicting the selection process of references at each stage is provided in Fig. 1.

Study Characteristics

The included studies were conducted in Europe (Sweden and Norway) [16•, 19•, 29•], Japan [2•, 28•], Iran [27], and Brazil [3•, 12, 18•], and they presented a nested design reporting cross-sectional [3•, 12, 28•] results from cohorts [2•] or were designed as case-control studies [16•, 18•, 19•, 27, 29•]. The majority of the participants were recruited from population-based samples of the Nagahama Study [2•], Basic Health Units of the Grupo Hospitalar Conceição (GHC) [3•], and Tokushima city [28•].

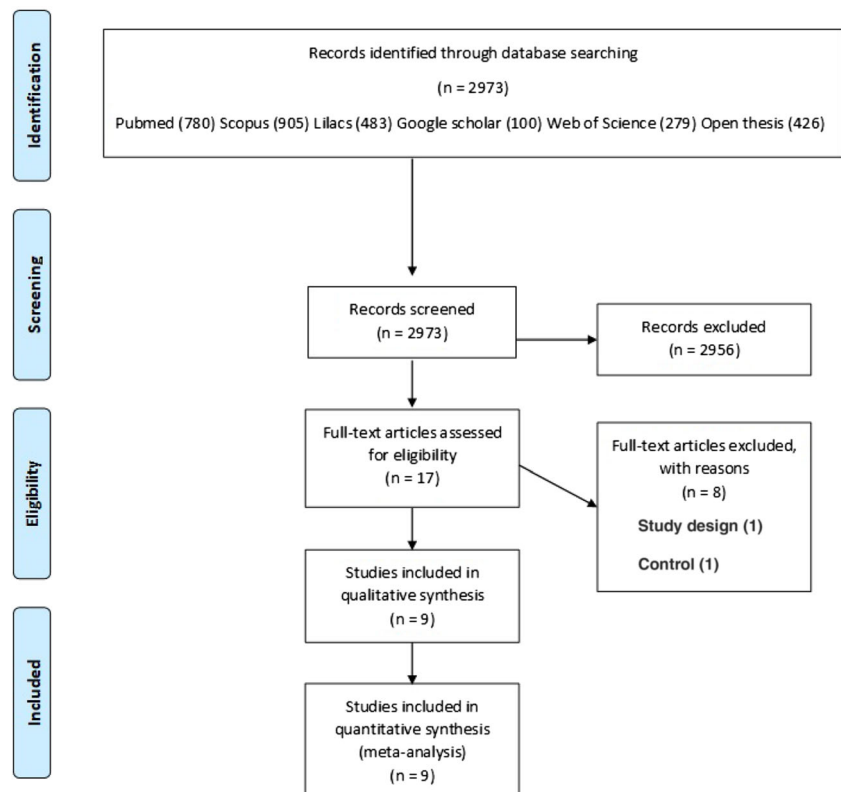
Data from 12,147 subjects were analyzed in this systematic review: 2083 of the subjects were children and adolescents [3•, 12, 16•, 27, 28•, 29•], and 10,064 were adults [2•, 18•, 19•]. Most studies sought information from participants through questionnaires to parents when the population comprised children or interviews when the population was composed of adults. The research scenario included schools, primary health centers, day care centers, and university hospitals.

Quality of the Studies

Studies included in this systematic review stated a research question, clearly described information related to the eligibility criteria, and had a low risk of selection bias. The evaluation measures were not clearly valid and reliable among the study participants. The criteria for assessing mouth breathing were similar among many authors, although there was no standard for the most accurate and standardized method for identifying this condition. Non-validated questionnaires, including patient reports, were used to identify mouth breathing (Tables 1 and 2).

Results of Individual Studies

In the cross-sectional study by Petry et al. [12], the authors identified 15.5% of Brazilian children and adolescents (out of

Fig. 1 Flowchart of literature search and screening process

a total of 998 asthmatic and non-asthmatic individuals) who reported via questionnaires that they had daytime mouth breathing. Bivariate analysis showed that several factors were significantly associated with daytime breathing: mother smoking (OR = 1.9; 95% CI 1.1–3.3; $p < 0.05$); active asthma (OR = 2.7; 95% CI 1.3–5.4; $p < 0.001$); and a positive marginal relationship with active rhinitis (OR = 1.7; 95% CI 0.9–3.2).

The Izuhara et al.'s [2•] study found 17% of mouth breathing adults in a population of 9804 in Nagahama City in the Shiga Prefecture, Japan, through a cohort study. Mouth breathing was assessed by self-report. In this study, the odds ratio for asthma morbidity was 1.85 (95% CI, 1.27–2.62) in

subjects with mouth breathing alone and 2.20 (95% CI, 1.72–2.80) in subjects with allergic rhinitis alone, which additively increased to 4.09 (95% CI, 3.01–5.52) when mouth breathing, and allergic rhinitis coexisted.

In Dos-Santos et al. [3•], a cross-sectional study with 228 children located in the city of Porto Alegre, Rio Grande do Sul, Brazil (112 asthmatic and 116 healthy), 66.3% of children with asthma reported mouth breathing, while in the non-asthmatic group, this percentage was 33.8%. Asthma was associated with mouth breathing (OR = 2.03; 95% CI 1.38–2.98; $p < 0.001$). The assessment of mouth breathing was determined by assessing orofacial changes related to mouth breathing syndrome, such as the following: frontal head

Table 1 Risk of bias of the included studies using the quality assessment tool for observational cohort and cross-sectional studies

Questions Studies	1	2	3	4	5	6	7	8	9	10	11	12	13	14	(–) bias	(+) bias
Petry et al. [12]	S	S	N	N	S	N	NA	N	S	N	S	N	NA	S		X
Izuhara et al. [2•]	S	S	NR	S	N	N	NA	N	N	NA	N	NA	NA	S	X	
Dos-Santos et al. [3•]	S	S	S	S	S	N	NA	N	N	N	S	N	NA	S	X	
Yamaguchi et al. [28•]	S	S	S	S	S	S	NA	N	S	N	S	N	NA	S	X	

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported. (1) objective clearly stated; (2) eligibility criteria clearly described; (3) representative sample of clinical population of interest; (4) all eligible participants enrolled; (5) sample size calculation; (6) exposure measured prior to the outcome; (7) timeframe sufficient; (8) examination of different levels of the exposure; (9) exposure clearly described; (10) exposure(s) assessed more than once over time; (11) outcome clearly described; (12) outcome assessors blinded to the exposure; (13) loss to follow-up less than 20%; (14) adjusted statistics performed

Table 2 Risk of bias of the included studies using the tool Newcastle-Ottawa (NOS) quality assessment scale case-control studies

Questions Studies	Selection				Comparability 1(**)	Exposure			(–) bias	(+) bias
	1*	2*	3*	4*		1**	2*	3*		
Ehsani et al. [27]	*	*	*	*	**	-	*	-	X	
Gomes-Filho et al. [18•]	*	-	*	*	*	-	*	-	X	
Steinsvåg et al. [16•]	*	-	*	*	-	*	*	-	X	
Stensson et al. [19•]	*	-	*	*	**	-	*	-	X	
Stensson et al. [29•]	*	-	*	*	-	-	*	-		X

Selection: 1. Is the case definition adequate?; 2. Representativeness of the cases; 3. Selection of controls; 4. Definition of controls. Comparability: 1. Comparability of cases and controls on the basis of the design or analysis. Exposure: 1. Ascertainment of exposure; 2. The same method of ascertainment for cases and controls; 3. Non-response rate. - A study can be awarded a maximum of one star (*) for each numbered item within the selection and exposure categories. A maximum of two stars (**) can be given for comparability

posture; dark circles under the eyes; narrow and long face; flat nose with narrow nostrils; hypotonic and dry, open, or semi-open lips; hypotonic and lowered tongue; atresic maxilla; ogival palate; and hypotonic orofacial muscles [3•].

In the 2015 population-based cross-sectional study by Yamaguchi et al., asthmatic and non-asthmatic preschool children who attended day nurseries in Tokushima City were subdivided into classifications that reported whether daytime or nighttime mouth breathing was conducted using a questionnaire. In the positive daytime breathing subgroup, 14.5% were asthmatic and 85.5% were non-asthmatic. Among the children who breathed through their mouths during sleep, 10.7% were asthmatic and 89.3% were non-asthmatic. There were significant associations between daytime mouth breathing and asthma (OR = 2.2; 95% CI 1.2–4.0; $p < 0.05$) [28•].

A case-control study [27] evaluated 44 asthmatic children and 46 healthy preschool children from Tehran University of Medical Sciences and other clinics in Tehran, between 3 and 6 years. Mouth breathing was diagnosed through clinical observation during the dental appointment. The proportion of mouth breathers among asthmatic children was 90.9%, while among healthy children, it was 9.1%.

In a case-control study, Gomes-Filho et al. [18•] investigated the ratio between mouth breathing and asthma in 113 adults diagnosed with asthma (case group) and 107 adults without a diagnosis of asthma (control group) assisted by the Program for Control of Asthma in Bahia (ProAR), Bahia, Brazil. Mouth breathing was reported through a questionnaire. The results showed the presence of mouth breathers in the asthma group (87.6%) and in the control group (54.2%). There was an association between mouth breathing and asthma (adjusted OR = 5.21, 95% CI 2.40–11.29) [18•].

In 2007, the Steinsvåg et al.'s case-control study investigated 27 asthmatic children and 29 children in the control group from the Department of Pediatrics, Haukeland University Hospital, Bergen, Norway. Mouth breathing was verified by a visual analogue scale indicating the extent of mouth

breathing. The presence of mouth breathing in the group of children with asthma and in the control group was 42.8% and 25.6%, respectively ($p = 0.04$) [16•].

Stensson and colleagues in 2008 evaluated 127 asthmatic children and 117 healthy controls at 3 and 6 years of age from the Department of Paediatrics at the County Hospital, Ryhov, Jönköping, Sweden, and from three child welfare centers in the Municipality of Jönköping, Sweden. Mouth breathing was assessed using a semi-structured questionnaire. The prevalence of mouth breathing in asthmatic children aged 3 years was 26%, and in children aged 6 years, it was 31%. In the control groups, the prevalence in children aged 3 and 6 years was 8% and 17%, respectively [29•]. Another case-control study by Stensson and colleagues in 2011 investigated the mouth breathing and asthma ratio in 40 adults (living in the city of Jönköping, Sweden), 20 asthmatic patients and 20 non-asthmatic patients. In the asthma group, 65% reported on a questionnaire the presence of frequent mouth breathing, compared with 10% of the control group ($p = 0.01$) [19•].

Regarding the outcomes of studies that verified mouth breathing and oral diseases, there was no significant relationship between asthma and oral health indices in the study by Ehsani et al. [27], highlighting the limitation of the small sample size in this study. Gomes-Filho et al. [18•] demonstrated the influence of periodontal disease on severe asthma, since the frequency of periodontitis is higher in individuals with this respiratory disease. Asthmatic individuals had a higher prevalence of caries than healthy individuals did in studies conducted by Stensson et al. [29•] (children) and by Stensson et al. [19•] (young adults). In the latter, individuals also presented higher rates of gingival inflammation and a lower rate of stimulated salivary secretion [19•, 29•].

The studies by Petry et al. [12] and Yamaguchi et al. [28•] did not evaluate the relationship between asthma/mouth breathing. The former obtained data on sleep-disordered

breathing and the marked risk of learning problems in children. The latter found that mouth breathing is significantly associated with atopic dermatitis in preschoolers.

Five studies [3•, 18•, 19•, 27, 29•] included in this meta-analysis did not clearly report the presence of upper airway disease in asthmatic patients.

Meta-analysis

The overall results of this meta-analysis revealed an association between asthma and mouth breathing (OR = 2.75; 95% CI 1.94–3.91; $p < 0.00001$), with a moderate degree of between-study heterogeneity ($I^2 = 46\%$). Subgroup analysis suggested an association between asthma and mouth breathing in children and adolescents (OR 2.46, 95% CI 1.78–3.39, $I^2 = 0\%$, $p < 0.00001$) and adults (OR 4.60, 95% CI 1.49–14.20, $I^2 = 85\%$, $p = 0.008$). Between-study heterogeneity was influenced by the age factor (Fig. 2).

To evaluate the robustness of the pooled results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary estimate. The summary estimate remained stable, indicating that our results were not driven by any single study. There was no potential for publication bias (Fig. 3).

Discussion

Asthma is a heterogeneous disease that encompasses several clinical phenotypes and is characterized by recurrent episodes of wheezing, dyspnea, chest oppression, and cough that result from chronic airway inflammation [1]. The presence of nasal

obstruction in asthmatics is due to the associated chronic rhinitis, as asthma and rhinitis are considered “united airway diseases.” Some studies have shown a higher prevalence of mouth breathing patterns in asthma patients than in control groups [2•, 3•].

The results of this systematic review and meta-analysis suggest a significant association between mouth breathing and asthma. Oral breathing may be present in up to 87.6% of patients with severe asthma compared with healthy patients [18•]. However, the studies in this review did not clarify the factors that influence mouth breathing in asthmatics.

In addition, although we found an association between mouth breathing and asthma in adults, high heterogeneity was observed among the studies included in this analysis. This finding may be the result of the population profiles studied with different clinical characteristics, including severity level, asthma duration and control, associated comorbidities, and age variability. The association between mouth breathing and asthma in adults can be attributed to the persistence of this breathing pattern even after resolution of the anatomical or functional abnormality that caused the mouth breathing [30]. Neural adaptations, changes in central upper airway control, muscle function, and skeletal alterations are justifications mentioned in the literature for this finding [31]. Importantly, the repercussions of mouth breathing in childhood and adolescence may perpetuate into adulthood [32, 33].

The results of our study also showed an association between mouth breathing and asthma in children and adolescents. Thus, children with asthma may be more likely to breathe through their mouths. Early multidisciplinary diagnosis of this population can prevent the development of mouth breathing syndrome, characterized by frontal head posture,

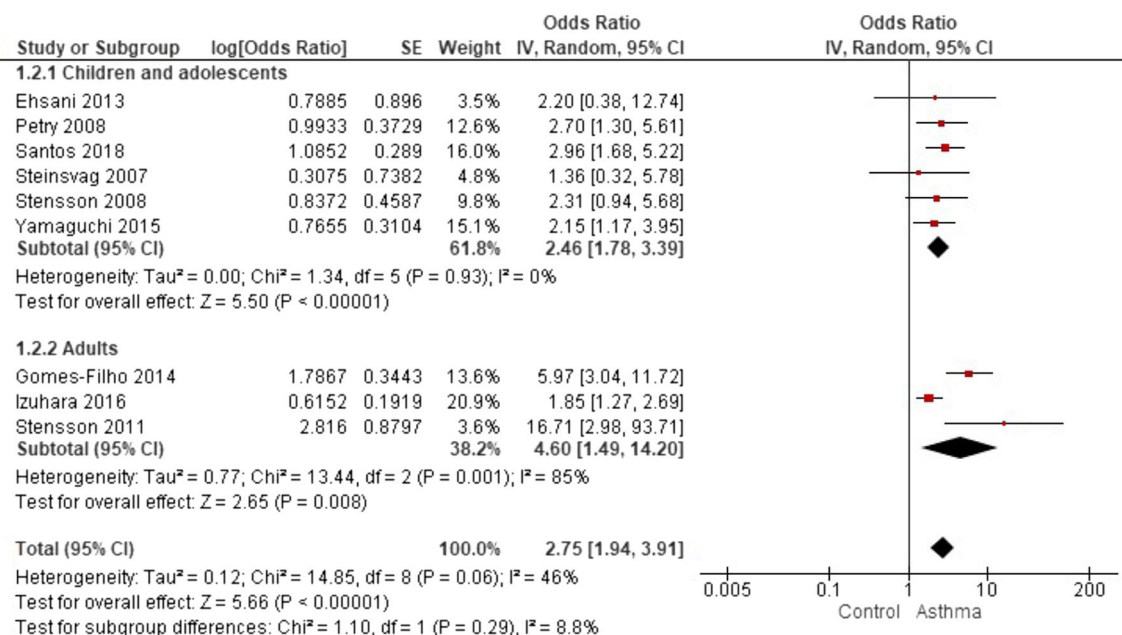
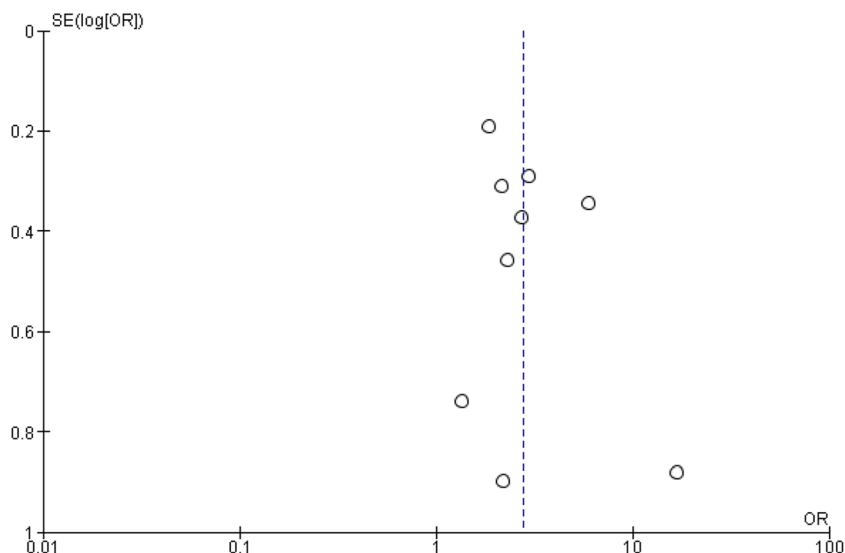


Fig. 2 Forest plot showing association between mouth breathing and asthma

Fig. 3 Funnel plot for the association between asthma and mouth breathing



dark circles under the eyes, narrow and long faces, flat nose with narrow nostrils, hypotonic open or semi-open lips, hypotonic and lowered tongue, atresic maxilla, ogival palate, and hypotonic orofacial muscles [33].

Therefore, health professionals should be aware of the association between these two conditions, and the use of screening tools [34] among children, adolescents, and adults with asthma by the multiprofessional team is suggested. Consequences of mouth breathing include the following: craniofacial, orofacial [3•, 35], pulmonary [36], postural changes [37]; attention problems associated with sleep disorders [38]; and reduced quality of life [39]. Anatomical changes are also found, such as enlargement of the lower third of the face, deep and narrow palate, posterior crossbite, anterior open bite, shortened upper lip, everted lower lip, and functional alterations, including atypical swallowing and speech alteration [3•, 33, 40–43].

Some studies included in this review did not address the possible presence of upper airway diseases in the asthmatic population, which would clarify the relationship between mouth breathing and asthma [3•, 18•, 19•, 27, 29•]. Allergic rhinitis is one of the most frequent diseases responsible for nasal obstruction in individuals with asthma, causing a persistent oral breathing pattern [6, 7, 44].

On the other hand, there is evidence of poor quality and limitations in the methodological description of the studies included in this systematic review, such as reliability analysis, validity of the instruments used, blinding of the examiners, random sampling, and participant eligibility criteria. These factors may limit the quality of evidence.

In the studies of this review, information on mouth breathing was not collected systematically but rather was collected via semi-structured interviews and reports from parents and/or caregivers. Standardized criteria should be used for more accurate investigation of mouth breathing [34]. Oral breathers

may be investigated by observing the lack of lip sealing and other typical signs and symptoms, such as elongated faces, dark circles under the eyes, ogival palate, presence of halitosis, and recurrent upper airway infection [42, 45], and complementary examinations, including nasal aeration measures [46], water retention tests, study of smell and taste [47], and surface electromyography [48]. Multidisciplinary assessment is therefore striking in these cases [33].

Some studies in this systematic review have analyzed preschool-aged children with asthma [16•, 27, 28•, 29•]. The diagnosis of asthma in this age group is doubtful due to other possible etiologies for recurrent wheezing [49]. Although most studies used medical diagnosis as asthma criteria, it was not clear how this diagnosis was made or which phenotypic profile of wheezing characterized the populations [50].

Our review should be interpreted with caution. It is possible that there are variations in mouth breathing according to age. The results of this meta-analysis show high heterogeneity among adults. The studies differ in geographical location, socioeconomic characteristics, and clinical profiles of populations and are therefore susceptible to patient selection bias. We conclude, therefore, that further studies on the subject with greater methodological rigor are needed. Several studies have addressed the heterogeneity of asthma with respect to its clinical manifestations, epidemiological and pathophysiological characteristics, and treatment response profile [51, 52]. For future studies, we suggest the evaluation of the oral breathing pattern as a characteristic of clinical asthma phenotypes, as well as their possible clinical outcomes.

Conclusion

The current evidence suggests an association between mouth breathing and asthma.

These findings can guide the development of targeted interventions to identify individuals at early risk of mouth breathing, as well as health promotion and prevention efforts among multidisciplinary professionals working with children, adolescents, and adults with asthma. Long-term follow-up is necessary to monitor outcomes associated with the development of mouth breathers in this population, such as prevention of orofacial, craniofacial, and pulmonary disorder.

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Authors' Contributions Brenda Carla Lima Araújo participated in the idealization of the study; data collection, analysis, and interpretation; and the writing of the article. Vanessa Tavares de Gois-Santos, Brenda Carla Lima Araújo, and Paulo Ricardo Saquete Martins-Filho participated in data collection. Silvia de Magalhães Simões and Paulo Ricardo Saquete Martins-Filho participated in guiding the idealization of the study; data analysis and interpretation; and the writing of the article.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication as stated by the International Committee of Medical Journal Editors (ICMJE): Ms. Brenda Araújo had full access to all the data and the accuracy of the data analysis.

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- Of importance
- Of major importance

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