Original

Association and Interacting Factors between Bronchial Asthma and Attention-deficit Hyperactivity Disorder in Children: Meta-analysis and Systematic Review

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Abstract

Background: This study aims to systematically assess the possible link between bronchial asthma usage and attention-deficit hyperactivity disorder (ADHD) in children.

Methods: PubMed, Web of Science, ScienceDirect, CNKI, Wanfang, and the China Biological Medicine Database (CBM) were searched for relevant articles published from database inception until September 28, 2023. The statistical analyses were conducted using Stata 15.1 software, followed by a quantitative meta-analysis to synthesize the results of the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs).

Results: A total of 10 articles involving 729,375 participants were included in the meta-analysis. The overall analysis revealed a statistically significant association between ADHD and an increased likelihood of having bronchial asthma, as indicated by a pooled odds ratio (OR) of 1.46 and a 95% confidence interval (CI) ranging from 1.41 to 1.51, $p < 0.001$, $I^2 = 58\%$. Potential associated factors linking bronchial asthma and ADHD in children include demographic characteristics, healthcare access, socioeconomic factors, comorbidities, genetic susceptibility, immune dysregulation, chronic conditions, growth and development factors, and parental/environmental influences.

Conclusion: This systematic review and meta-analysis presents convincing evidence for a notable link between bronchial asthma and ADHD in children. The results indicate an increased likelihood of bronchial asthma among children with ADHD compared to those without the condition. Additionally, various potential factors can underlie the association between bronchial asthma and ADHD in children, necessitating further research to fully comprehend their complex relationship. These findings have implications for clinical practice, highlighting the need for an integrated approach in managing asthma and ADHD.

Keywords

bronchial asthma; ADHD; child health; risk factors; systematic review; meta-analysis

Introduction

Bronchial asthma, commonly referred to as asthma, is a chronic respiratory disease characterized by persistent inflammation and narrowing of the airways, resulting in recurrent bouts of wheezing, coughing, difficulty breathing, and chest tightness [1,2]. Attention-deficit hyperactivity disorder (ADHD) is a neurobiological condition marked by enduring symptoms of poor concentration, hyperactivity, and impulsiveness, leading to substantial impairments in a child's day-to-day activities and broader growth and development [3–6]. Both bronchial asthma and ADHD are prevalent chronic conditions among children and can have profound effects on their well-being and quality of life [7,8].

Moreover, the interaction between bronchial asthma and ADHD can have detrimental effects on children [9]. The coexistence of bronchial asthma and ADHD may lead to increased healthcare visits and hospitalizations. Managing both chronic physical and neurodevelopmental conditions simultaneously present challenges that can contribute to feelings of frustration, stress, and emotional distress [10]. Previous studies have examined the potential association between bronchial asthma and ADHD; however, the results

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have been inconsistent, making it difficult to establish a clear understanding of the relationship between these two conditions [11–15]. These inconsistencies may arise from variations in study designs, sample sizes, diagnostic criteria, and measurement methods employed across different studies.

The existing literature on the association between bronchial asthma and ADHD is limited by several factors. Firstly, previous studies have primarily focused on individual cross-sectional investigations or case-control studies, which may not provide a comprehensive understanding of the complex relationship between these conditions. Secondly, the available evidence has often been derived from single-center studies, potentially limiting its generalizability. Additionally, there is a lack of consensus regarding the specific associated factors underlying the co-occurrence of bronchial asthma and ADHD in children. Therefore, there is a need for a systematic review and meta-analysis that encompasses a larger body of evidence to derive more robust conclusions.

To bridge the gaps identified in previous research, this study's objective is to systematically evaluate the potential link between bronchial asthma and ADHD in children through a thorough examination and quantitative meta-analysis of pertinent studies. By synthesizing data from multiple studies, this study will provide a more precise estimation of the overall association, considering potential sources of heterogeneity. Moreover, this investigation will explore potential associated factors linking these two conditions. By identifying the underlying associated factors, this study will contribute to a better understanding of the shared etiological factors and pathways involved in bronchial asthma and ADHD.

Materials and Methods

Literature Search

Two researchers conducted computerized searches in PubMed, Web of Science, ScienceDirect, CBM, Wanfang and CNKI from the inception of the databases until September 8, 2023, to retrieve all relevant literature. Other sources included internet searches and reference lists of included studies and relevant reviews. The search terms used were "Bronchial asthma", "Asthma", "Attention-Deficit Hyperactivity Disorder", "ADHD", "attention deficit disorder with hyperactivity (ADDH)", "Children", "Child". The search was conducted utilizing a blend of medical subject headings, free-text phrases, and Boolean operators. The PubMed literature search methodology is outlined in Table 1.

Inclusion and Exclusion Criteria

The criteria for study inclusion were as follows: (1) studies investigating the association between bronchial asthma and ADHD, encompassing both cross-sectional and case-control designs; (2) participants ranging in age from 3 to 18 years; (3) reliable assessments of bronchial asthma and ADHD; and (4) unambiguous statistical measures, such as odd ratios (ORs), illustrative of the association's magnitude. Conversely, the exclusion criteria were: (1) articles lacking accessible data; (2) studies involving participants with both bronchial asthma and other respiratory ailments; and (3) research not published in English or Chinese, or where the full text was unavailable.

Literature Screening and Data Extraction

All search results were merged, and duplicate citations were removed. Title and abstract screening were conducted to exclude clearly irrelevant citations. Full-text screening was performed, and any disagreements were resolved through discussion between the two researchers. Data extraction was independently conducted by the two researchers to ensure accuracy. The extracted data primarily included study basic information, risk of bias assessment data, and outcome data.

Following the screening of pertinent studies, data and vital information were independently extracted from qualified articles. A pre-defined Excel form was utilized during the data extraction process. Any inconsistencies encountered during data extraction were resolved through consensus with a third reviewer. The extracted data comprised: (1) study-specific details such as the first author, year of publication, country of origin, and sample size; (2) participant demographics including age and gender distribution; (3) definitions utilized for bronchial asthma and ADHD; (4) variables adjusted in statistical models; and (5) statistical outcomes represented by ORs along with their respective 95% confidence intervals (CIs). If multiple ORs were presented for the same metric, only the most comprehensive results, adjusted for the widest range of confounding factors, were extracted.

ADHD and Asthma Diagnosis

Diagnosing asthma involves parent reports, health and hospital records, and prescribed asthma medications (meds). The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire helps assess asthma in children. Clinical diagnosis includes questionnaires, physi-

Table 1. Search strategy of PubMed.

Search procedure	Search query
#1	(bronchial asthma [MeSH Terms]) OR (bronchial asthma) OR (Asthma)
#2	(attention deficit disorder with hyperactivity) OR (attention deficit disorders with hyperactivity) OR (attention deficit hyperactivity disorders) OR (hyperkinetic syndrome) OR (hyperkinetic syndrome) OR (ADDH) OR (ADHD)
#3	((children [MeSH Terms]) OR (children)) OR (child)
#4	#1 and #2 and #3

ADHD, attention-deficit hyperactivity disorder; ADDH, attention deficit disorder with hyperactivity.

cal exams, IgE level tests, eosinophil counts, and skin prick tests. Hospital records with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes help identify asthma cases.

Diagnosing ADHD uses various methods: parental phone interviews with the other Comorbidities (A-TAC) inventory, parent reports of doctor diagnoses, and child psychiatrist diagnoses based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or International Classification of Diseases 10th Edition (ICD-10) criteria. Questionnaires, health and hospital records, and prescribed ADHD meds provide valuable information.

Literature Quality Evaluation

The quality of cross-sectional studies was evaluated using the evaluation criteria of the Agency for Healthcare Research and Quality (AHRQ) in the United States, which included a total of 11 items with a maximum score of 11. The quality of case-control studies was assessed using the Newcastle-Ottawa Scale (NOS), which consisted of 8 items and had a maximum score of 9. Studies with a literature quality score of 6 or higher were included in this research. This process was independently conducted by two researchers, and in case of disagreement, consensus was reached through discussion or consultation with a third party.

Statistical Analysis

A meta-analysis was conducted to assess the ORs and corresponding 95% CIs, utilizing Review Manager 5.4 (Cochrane Collaboration, London, UK) and Stata 16 (StataCorp, College Station, TX, USA) for statistical analysis. To assess heterogeneity among studies, the Q test and I^2 statistic were utilized. In cases where $p > 0.1$ and $I^2 < 50\%$, it was deemed that there was no significant heterogeneity among the studies, and a fixed-effect model was employed for analysis. Conversely, if $p \leq 0.1$ or $I^2 \geq 50\%$, it was inferred that there was substantial heterogeneity among the studies, and a random-effects model was used for analysis. Sensitivity analysis was conducted to identify potential sources of heterogeneity. Both graphical (funnel plots) and statistical (Egger linear regression tests) methods were used to assess potential publication bias. $p < 0.05$ was considered statistically significant.

Results

Literature Retrieval and Screening

This meta-analysis was carried out in accordance with PRISMA as shown in **Supplementary File 1**. Fig. 1 presents a PRISMA flow diagram that summarizes the process of selecting relevant studies. After removing duplicates, a total of 631 articles were initially reviewed. Following the screening of titles and abstracts, 312 articles were identified as potentially eligible. After a thorough review of the full-text articles, 10 studies satisfied the pre-set inclusion criteria.

Basic Characteristics of the Literature

Table 2 (Ref. [16–25]) presents a comprehensive summary of the key characteristics of the 10 included studies, encompassing a total participant pool of 729,375 individuals. Among these eligible studies, three were conducted in the United States [16,17], three were conducted in Taiwan [18–20], and one study each originated from Sweden, Australia, the Netherlands, and Korea [21–24]. Among the 10 articles, there are 3 case-control studies and 8 cross-sectional studies. 6 articles received a quality rating of 6, 2 articles received a rating of 7, and the remaining 2 articles received a rating of 8. In this study, the control groups refer to children without ADHD, and the experimental groups comprise children diagnosed with ADHD.

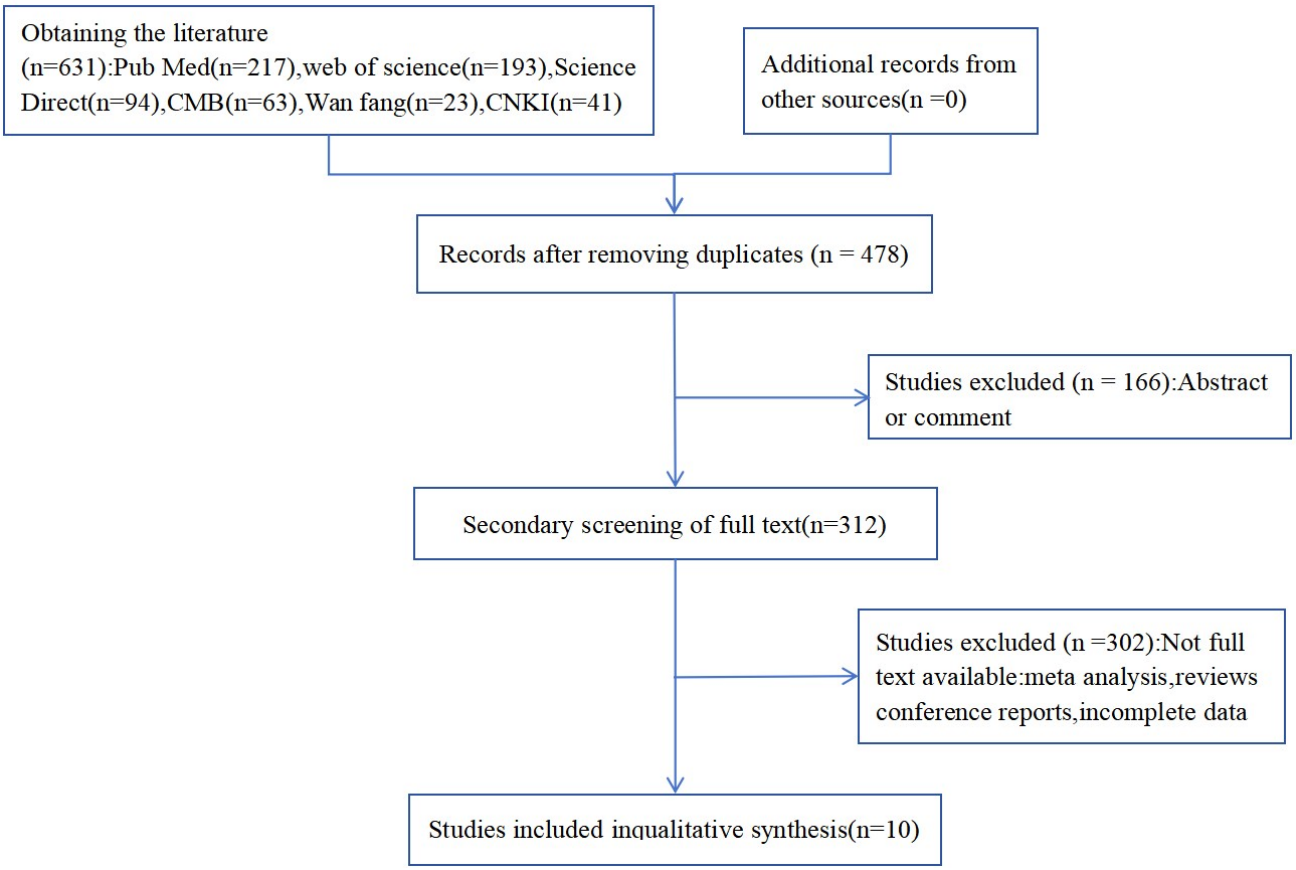

Fig. 1. Flowchart of study selection.

Meta-analysis Results

The meta-analysis demonstrated a clear association between ADHD and an increased likelihood of having bronchial asthma. The pooled odds ratio (OR) was calculated to be 1.46 with a 95% confidence interval (CI) ranging from 1.41 to 1.51, indicating a statistically significant result, as depicted in Fig. 2. A funnel plot was constructed to assess the potential presence of publication bias in the study results, as depicted in Fig. 3. Quantitative analysis, performed using the Egger's test, indicated no significant evidence of publication bias ($p > 0.05$).

Discussion

The meta-analysis demonstrates a significant positive correlation between bronchial asthma and ADHD in children. The OR is 1.46, with a 95% Cl of 1.41 to 1.51. This suggests that children with ADHD have a 46% higher risk of developing bronchial asthma compared to those without ADHD. These findings provide strong evidence for a link between bronchial asthma and ADHD in children. They are consistent with previous research that has also reported a connection between ADHD and respiratory disorders such as asthma [26,27]. These results enhance our comprehension of the potential connection between bronchial asthma and ADHD in children. Previous studies have also offered valuable insights into this association [14,28,29]. However, they have certain limitations. Many of these studies have utilized cross-sectional or small longitudinal designs, which may not adequately capture the dynamic nature of the association. These design limitations can limit the generalizability of the findings and may not provide a comprehensive understanding of the relationship. To assess publication bias in the study results, a funnel plot was analyzed. Fig. 3 displayed the distribution of effect sizes plotted against sample size or precision. In our analysis, the funnel plot indicated no significant evidence of publication bias. The symmetrical distribution of studies around the vertical line suggests that there is no systematic bias towards publishing only studies with positive or significant results. This strengthens the validity and reliability of our findings. By addressing the limitations of previous studies and incorporating a larger sample size, our systematic review and meta-analysis provide more robust evidence

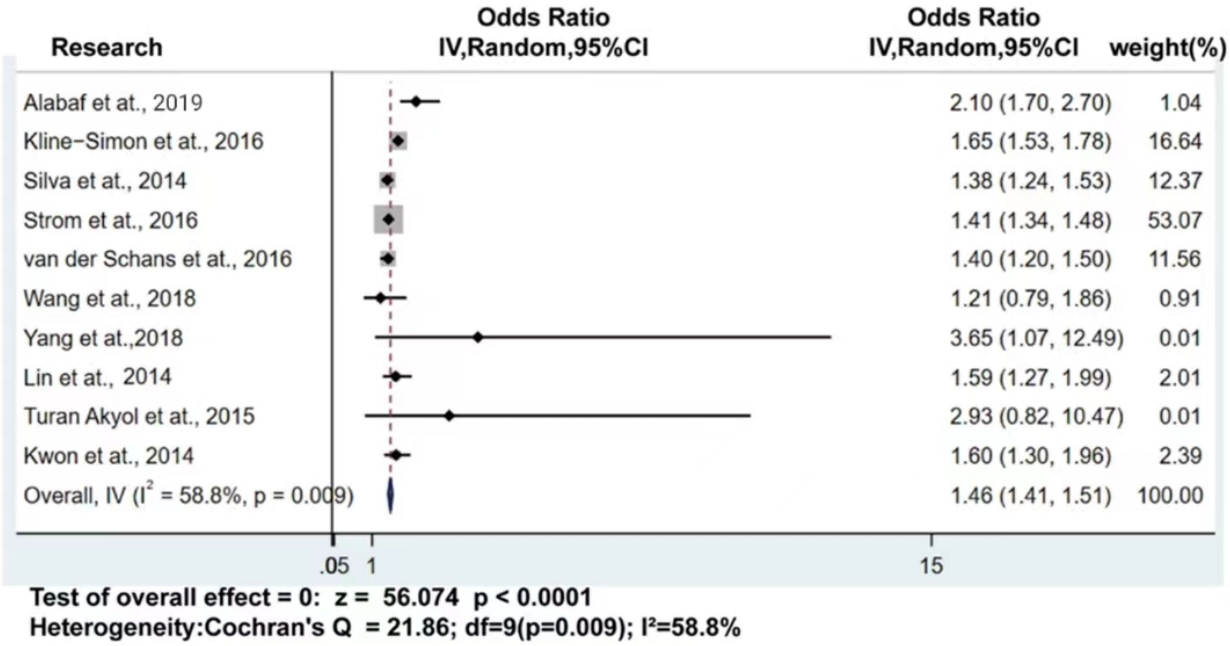

Fig. 2. Forest plot of the associations between bronchial asthma and ADHD. IV, independent variable.

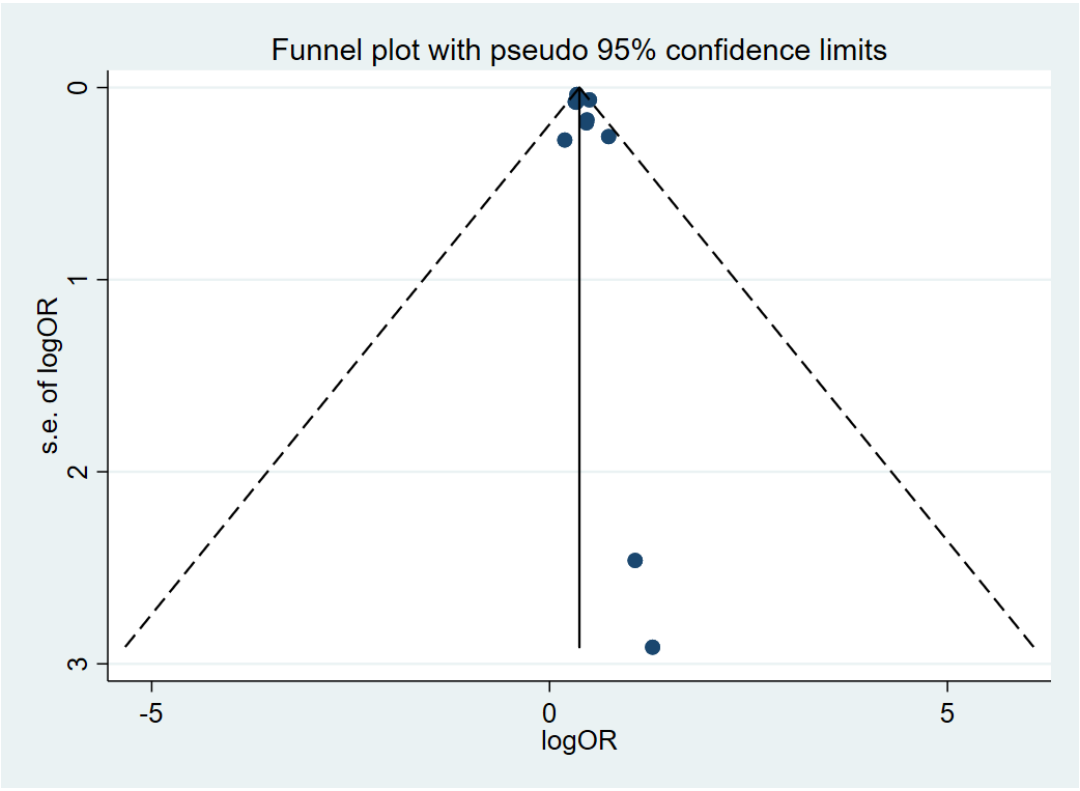

Fig. 3. Funnel plot of the associations between bronchial asthma and ADHD.

for the association between bronchial asthma and ADHD in children. The findings suggest that respiratory health should be considered in the management of ADHD in children, and highlight the need for further research.

Table 2. Basic characteristics of studies.

Study	Country/region	Study design	Sample size	Male (%)	Participants age	Definition of bronchial asthma	Definition of ADHD	Effect size	NOS/AHRQ score
Alabaf *et al.*, 2019 [21]	Sweden	Cross-sectional	22,028	64.86	9 or 12	Parent-reported diagnosis	Parental telephone interview using A-TAC	OR	6
Kline-Simon *et al.*, 2016 [16]	USA	Cross-sectional	11,888	69.9	13–18	Electronic health records' ICD-9 codes	ICD-9 codes from electronic health record	OR	7
Silva *et al.*, 2014 [22]	Australia	Cross-sectional	14,259	78	<18	Hospital records containing extracted ICD-9-CM codes	Diagnosis by a pediatrician or psychiatrist using DSM-IV/ICD-10 criteria and ADHD medication prescriptions from medical records.	OR	6
Strom *et al.*, 2016 [17]	USA	Cross-sectional	264,237	unknown	2–17	Parent-reported	Parent-reported physician diagnosis or parent-reported without physician verification.	OR	6
van der Schans *et al.*, 2016 [23]	Netherlands	case-control	21,285	76.7	6–12	Record of drug prescription	Record of drug prescription	OR	8
Wang *et al.*, 2018 [18]	Taiwan	Case-control	532	86.11	8–10	Parent-reported diagnosis utilizing the ISAAC questionnaire	Child psychiatrist diagnosed ADHD according to DSM-IVTR	OR	8
Yang *et al.*, 2018 [19]	Taiwan	Cross-sectional	2772	unknown	3–6	Parent-reported physician diagnosed asthma	Parent-reported physician-diagnosed ADHD	OR	6
Lin *et al.*, 2014 [20]	Taiwan	Cross-sectional	2896	unknown	9–10	Parent-reported diagnosis utilizing the ISAAC questionnaire	Chinese SNAP-IV 26 questionnaire for parent reports	OR	7
Turan Akyol *et al.*, 2015 [25]	nr	Nested case-control	105	52	7–12	Clinical diagnosis relies on the ISAAC questionnaire, physical exam, IgE levels, eosinophil count, and skin prick testing.	Child psychiatrist diagnosis based on DSM-IV	OR	6
Kwon *et al.*, 2014 [24]	Korea	Cross-sectional	4113	47.9	7–8	Parent-reported diagnosis utilizing the ISAAC questionnaire	Child psychiatrists diagnose based on DSM-IV criteria, epidemiological questionnaires, the Computerized Attention Deficit-Hyperactivity Disorder Diagnostic System, the abbreviated Conner's Parent Rating Scale (CPRS), and DuPaul's ADHD Rating Scales.	OR	6

NOS, Newcastle-Ottawa Scale; AHRQ, Agency for Healthcare Research and Quality; A-TAC, other Comorbidities; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD-10, International Classification of Diseases 10th Edition; ISAAC, International Study of Asthma and Allergies in Childhood.

The potential correlation between bronchial asthma and ADHD has been investigated in previous studies. Some studies have reported a positive association between these two conditions [12,30], while others have found no significant link [14,15]. This disparity in findings has posed challenges in establishing a definitive understanding of the relationship between bronchial asthma and ADHD. However, recent investigations with larger sample sizes and more comprehensive methodologies have suggested a potential connection between these conditions. We anticipate that this study will address the need for further supportive evidence and contribute to a better understanding of the relationship between bronchial asthma and ADHD. Potential associated factors underlying the relationship between bronchial asthma and ADHD in children can be explored through various methods [31]. Matching by age, sex, and medical facility suggests common demographic characteristics and healthcare access as potential shared risk factors [16]. Socioeconomic factors, such as socioeconomic index of disadvantage for areas, marital status, household income, and highest level of household education, may influence both asthma and ADHD development [22]. Comorbidities like eczema, allergic rhinitis, and atopic dermatitis can serve as mediators linking asthma and ADHD, possibly through shared genetic susceptibility or immune dysregulation [17]. The presence of chronic conditions such as type 1 diabetes mellitus (DM1), epilepsy, or depression can also impact the asthma-ADHD relationship [23]. Factors related to growth and development, including height, weight, BMI, gestational age, birth weight, and maternal history of atopic disorders, might play a role [18]. Additionally, parental and environmental influences, such as parental marriage status, family income, tobacco exposure, maternal smoking during pregnancy, preterm status, and city of residence, can contribute to the co-occurrence of asthma and ADHD. Overall, the interplay between these factors may enhance our understanding of the association between bronchial asthma and ADHD in children, although further research is needed for a comprehensive understanding.

A key strength of our study lies in its comprehensive approach to synthesizing available evidence. By including a wide range of studies and conducting quantitative analysis, we obtained a more precise estimation of the association while identifying potential sources of heterogeneity. Moreover, we explored underlying associated factors by highlighting the comprehensive literature review conducted prior to our research, which served as the foundation for identifying potential links between bronchial asthma and ADHD. These associated factors include demographic characteristics, healthcare access, socioeconomic factors, comorbidities, genetic susceptibility, immune dysregulation, chronic conditions, growth and development factors, and parental/environmental influences.

Although there have been meta-analyses analyzing the relationship between asthma and ADHD, it is important to note that the studies included in these analyses only focused on articles published in English. This selective criterion may have led to the exclusion of relevant studies published in other languages, thus limiting the scope of the search. Furthermore, the articles included in this meta-analysis varied in terms of study design (cross-sectional, cohort) and population characteristics. This heterogeneity in methodologies and participant demographics may introduce variability, and potentially affect the generalizability of the findings. However, one main advantage of our meta-analysis is that the majority of the included studies adjusted for relevant confounders. This adjustment helps to enhance the reliability of the findings by controlling for potential factors that could influence the association between asthma and ADHD.

The potential molecular mechanisms underlying the association between asthma and ADHD remain an active area of research. Genetic studies have identified several shared genetic variants between asthma and ADHD, suggesting common genetic basis for these conditions [32]. Immunological research has implicated immune dysregulation and inflammation as key players in both asthma and ADHD pathophysiology [33]. These molecular mechanisms are likely influenced by environmental factors, such as exposure to allergens, pollutants, and stress, which can modulate immune responses and brain development. The interaction between genetic and environmental factors may explain the variable expression of asthma and ADHD symptoms in different individuals. However, it is crucial to acknowledge certain limitations when interpreting our findings. Firstly, the included studies exhibited heterogeneity in terms of study design, population characteristics, and diagnostic criteria for bronchial asthma and ADHD, which may introduce bias and affect generalizability. Secondly, many of the studies were observational, limiting our ability to establish causality. Future prospective cohort studies or randomized controlled trials are needed to elucidate the temporal relationship between these conditions and explore potential causal associated factors.

Despite these limitations, our study provides significant insights for clinical practice and future research. The observed association between bronchial asthma and ADHD emphasizes the need for comprehensive assessment and management of both conditions in children. Clinicians should be aware of the increased risk of respiratory symptoms in children with ADHD and consider appropriate in-

terventions. Furthermore, future studies should focus on unraveling the underlying biological, genetic, and environmental associated factors that contribute to the association between bronchial asthma and ADHD.

Conclusion

In conclusion, our study contributes to the existing literature by conducting a systematic review and meta-analysis to examine the association between bronchial asthma and ADHD in children. The findings highlight a significant correlation between these conditions and underscore the importance of early detection and integrated management. Further research is warranted to address the limitations of our study and investigate potential causal pathways, ultimately leading to improved strategies for prevention, diagnosis, and treatment.

Availability of Data and Materials

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author Contributions

YD: Conception, Design, Supervision, Materials, Data Collection and Processing, Analysis, Literature Review, Writing. NJ: Supervision, Materials, Data Collection and Processing, Analysis, Literature Review, Writing, Critical Review. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://actaspsiquiatria.es/index.php/actas/article/view/1538.

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