REVIEW

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Associations and Related Mechanisms of Attention-Deficit Hyperactivity Disorder and Allergic Rhinitis in Children

Nannan Lin[1], **Rongwang Yang**[2], **Weijia Gao**[2]

[1]Department of Child Psychology, Childrens Hospital, Zhejiang University School of Medicine, Zhejiang, China
[2]Department of Child Psychology, Childrens Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Zhejiang, China

ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder that manifests in early childhood and often affects children's daily life and academic performance, impairing their psychological development and potentially influencing their personality. The concurrent yearly increase in the incidence of allergic diseases and ADHD among children has prompted researchers to explore the association between these 2 health issues. Allergic rhinitis (AR) is one of the most common allergic diseases and is characterized by chronic inflammation of the nasal mucosa. The prevalence of AR increases from infancy through adolescence and then decreases with further aging. The relationship between ADHD and AR has garnered significant attention from researchers recently, although it remains a topic of debate. Numerous studies have suggested a correlation, while some have reported conflicting results. Furthermore, the precise mechanisms underlying their coexistence have not been fully elucidated. This review summarizes the literature on ADHD and AR both domestically and internationally. It highlights their interrelationship and potential comorbid mechanisms, thereby providing new perspectives on the pathogenesis of ADHD and informing long-term treatment and management strategies.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder that manifests in early childhood and is characterized by persistent inattention, hyperactivity, and impulsivity. These symptoms often persist into adulthood, affecting children's daily life, academic performance, and relationships with parents, teachers, and peers. Attention-deficit hyperactivity disorder can impair children's psychological development and potentially influence their personality.[1,2] The global prevalence of ADHD in children and adolescents is estimated to be 6.8% (9.2% in boys and 3% in girls),[3] whereas the prevalence in China is 5.7% (approximately 7.5% in boys and 3.4% in girls).[4] Current research commonly contends that ADHD is the result of a combination of genetic and environmental factors; however, the precise etiology and pathogenesis remain elusive.

Although the relationship between ADHD and psychiatric comorbidities has received extensive attention and research, the health issues associated with ADHD are not confined to psychiatric disorders. ttention-deficit hyperactivity disorder is also linked to physical health issues such as obesity, enuresis, and allergies, which have garnered the attention of some researchers. The physical comorbidities of ADHD warrant further attention and investigation. The concurrent annual increases in the incidence of allergic diseases and ADHD among children and adolescents have prompted researchers to explore the associations between these 2 health issues. Allergic rhinitis (AR), one of the most common allergic diseases, is characterized by chronic inflammation of the nasal mucosa, which is caused primarily by elevated IgE protein levels. Immune lymphocytes and various cytokines are involved in this pathogenic process, and the symptoms include seasonal nasal congestion, runny nose, and sneezing. The prevalence of AR increases from infancy through adolescence, reaching 12.5%-43.6%, and then decreases with increasing age.[5]

This article reviews the literature on ADHD and AR from both Chinese and international sources. It explores their relationships and potential comorbid mechanisms, thereby providing new insights into the pathogenesis of ADHD and informing long-term treatment and management

Corresponding author: Rongwang Yang, e-mail: yangrw@zju.edu.cn

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strategies. The strategy for document retrieval is illustrated in Figure 1.

Figure 1 illustrates the search strategy and inclusion process for the literature references in this review. We incorporated 9 original research articles and 7 meta-analyses reporting on the epidemiological associations between ADHD and AR. Additionally, we included 44 articles exploring the mechanisms underlying co-occurring ADHD and AR, consisting of 19 original studies, 11 systematic reviews, and 14 meta-analyses. The exclusion criteria were as follows: 1) subjects over 18 years; 2) nonhuman subjects; 3) unreviewed studies; 4) single case reports; 5) articles not published in English; 6) studies focusing on treatment drugs rather than co-occurring disorders; and 7) publications diverging from our thematic focus.

Correlation Between Allergic Rhinitis and Attention Deficit Hyperactivity Disorder in Children

In the 1980s, researchers began to conduct small-sample studies to explore the relationship between ADHD and allergies. In addition to small samples, these studies did not utilize standardized diagnostic procedures.[6] Over the past 2 decades, interest in the relationship between ADHD and allergies has increased, resulting in a significant increase in related publications. Brawley et al[9] conducted physical examinations and skin prick tests (SPTs) in 23 children aged 5-18 years who were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria in a pediatric outpatient clinic. They reported that most patients exhibited symptoms of AR, with 43% showing typical signs of AR and 61% having positive SPTs, which indicated an increased incidence of AR among children with ADHD. A subsequent study in Taiwan utilizing a longitudinal health insurance database involving 4692 children with ADHD and a randomly selected control group of 18 768 children revealed a strong association between ADHD and allergies. The prevalence of allergic diseases was significantly greater in children with ADHD, and the presence of allergic diseases increased the risk of developing ADHD. Among these children, 40.6% had AR, which is the allergic disease most strongly associated with ADHD.[8] In mainland China, Qian et al[21] conducted a controlled experiment in which 278 children with ADHD and 278 control children were matched 1:1 by age (age gap < 1 year), sex, and ethnicity, revealing that the incidence of AR symptoms such as nasal congestion and runny nose over the past year was significantly greater in the ADHD group than in the control group. The prevalence of AR is notably elevated among children with ADHD.

Additionally, some researchers have investigated the prevalence of ADHD among children with AR. Shyu et al[10] collected data on 226 550 children younger than 18 years from an insurance database and divided them into a normal control group and an allergic disease group (AR, asthma, and allergic dermatitis). In comparison with the general population, allergic patients showed an overall higher risk for developing ADHD. When considering individual allergic disorders, AR and asthma, but not allergic dermatitis, showed higher risks of being associated with ADHD. A study by Chen's group involving 465 children aged 6-12 years with AR revealed that 26.7% met the ADHD scoring criteria. Group comparisons revealed that the severity, duration, and skin reaction index of AR were related to the incidence of ADHD, with the associations being particularly significant in boys.[11] A cross-sectional study from China using stratified cluster sampling randomly selected 22 018 primary school children in grades 1-6 for a parental questionnaire survey. The results indicated that the prevalence of ADHD in children with AR (7.7%) was significantly greater than that in children without AR (4.1%).[12] In a longitudinal study by Mindy and colleagues, 97 children underwent clinical assessments and provided blood samples for IgE testing. The findings revealed a robust correlation between AR and higher attention scores on the Swanson, Nolan, and Pelham Rating Scale-IV (SNAP-IV) scale at 12 years of age among children diagnosed with asthma, atopic dermatitis (AD), or allergic rhinitis at 6 years of age. Additionally, a positive association was noted between hyperactivity/impulsivity scores and increased IgE levels after 6 years of age.[13] Furthermore, a meta-analysis by Wang et al[14] incorporated data from 12 high-quality studies. The results demonstrated that the prevalence of AR was significantly greater in the ADHD group than in the control group. The risk of developing ADHD was substantially greater in the AR group than in the control group (OR = 3.96, 95% CI = 3.80-4.12), thus establishing a significant association between ADHD and AR. Subgroup analysis further indicated that girls aged 9-15 years were more likely to experience comorbid ADHD and AR. In a longitudinal birth cohort study conducted in Australia, Qu et al investigated the associations between allergic diseases and neurodevelopmental disorders. A total of 2580 children were enrolled at birth for this analysis. The results indicated a significantly greater prevalence of ADHD among children with asthma, AD, and AR than in their counterparts without allergic

MAIN POINTS

- The exact etiology and pathogenesis of ADHD remain elusive.
- Somatic comorbidities associated with ADHD warrant further investigation.
- Notably, the incidence rates of allergic diseases and ADHD among children and adolescents have risen concurrently over recent years, prompting researchers to explore potential links between these two health issues. Allergic rhinitis (AR) is one of the most prevalent allergic conditions.
- This study aims to elucidate the relationship between allergic diseases and ADHD, as well as the underlying comorbidity mechanisms, thereby offering new insights into the pathogenesis of ADHD and informing long-term treatment and management strategies.

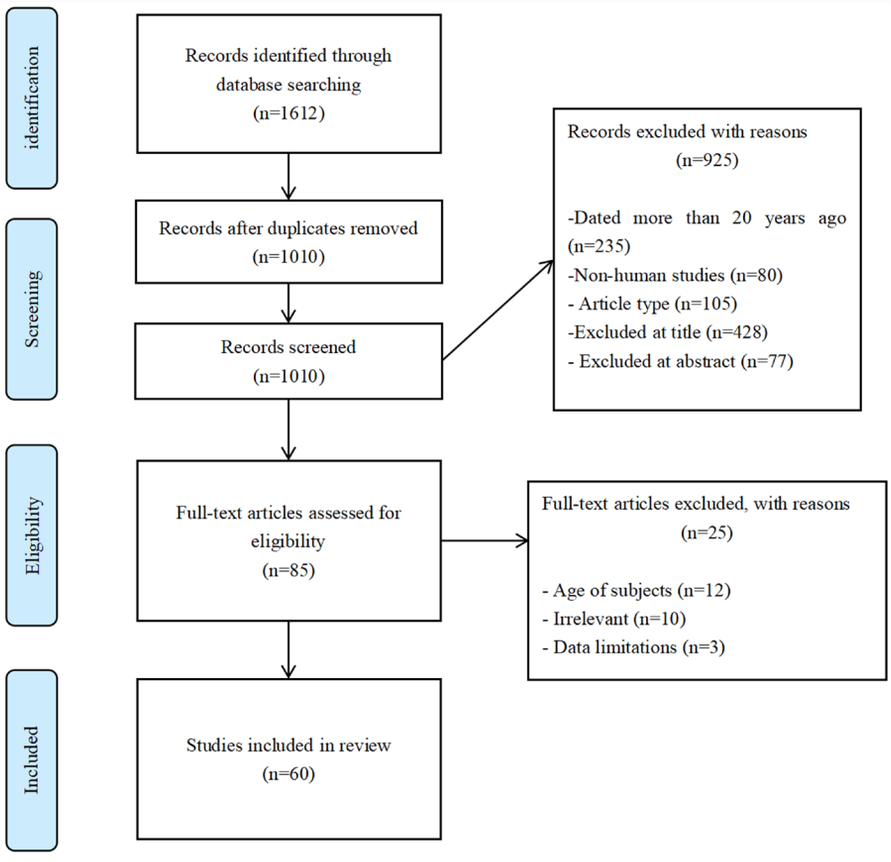

Figure 1. Flowchart for the Literature Search Process.

conditions. After adjusting for maternal and child factors, it was determined that the likelihood of ADHD in children increased when either the mother or child had an allergic disease, as opposed to neither having such conditions. Moreover, the correlation between both mothers and children with allergies demonstrated an even stronger association with ADHD (aRRR = 2.65 [1.84-3.82]) than when only one party was affected by allergies (aRRR = 1.54 [1.12-2.10]).[15]

The results of these studies confirmed a bidirectional relationship and common underlying mechanisms between AR and ADHD. Nonetheless, some research has offered differing perspectives. In a controlled study by Hak et al[16] involving 884 boys with ADHD and 3536 boys without ADHD, asthma and dermatitis increased the risk of ADHD, whereas other types of allergies were not linked to the incidence of ADHD. Similarly, a meta-analysis by Schmitt's group[7] using data from 20 studies concerning ADHD and allergies indicated that despite the relationship between ADHD and allergic conditions, only allergic dermatitis exhibited a clear correlation with ADHD, whereas no such connection was noted for AR. In summary, the preponderance of current research supports a correlation between AR and ADHD. Table 1 presents the findings of the investigation into the correlation between AR and ADHD.

Potential Comorbid Mechanisms

Research, both domestically and internationally, has attempted to explore the correlation between AR and ADHD in children. However, few empirical studies have investigated the mechanisms linking these 2 childhood disorders, and their relationship remains poorly understood. On the basis of previous research and hypotheses, we have organized and discussed the potential mechanisms of comorbidity between ADHD and AR.

Sleep Problems as Mediators: Previous studies have suggested that allergic symptoms such as nasal congestion, itching, and sleep-disordered breathing in children with AR lead to sleep disturbances, which mediate the occurrence of daytime cognitive dysfunction. This results in symptoms of ADHD, including fatigue, difficulty concentrating, irritability, and decreased self-control. Furthermore, AR is associated with sinusitis, eustachian tube dysfunction, and conductive hearing loss, all of which can contribute to learning disabilities.[17] Poor sleep quality has been posited as a potential cause of the increased incidence of ADHD in children with AR.[18,19] Dennis et al [20]reported that poor sleep attributable to allergies in early childhood affects early neural development.Nelson's group further elucidated that inadequate sleep affects the early development of the prefrontal cortex, particularly the functionality of the

Table 1. Summary of the Association Between Allergic Rhinitis and ADHD

No.	Authors	Recruiting Year	Country	Study Design	Recruiting Criteria	Sample Size	Outcome	Critical Review
1.	Brawley et al[9]	From August 2002 to May 2003.	America	Observational study	•Age: 5-18 years; •With psychiatrist -diagnosed ADHD who met DSM-IV criteria for ADHD.	23 children	•80% reported AR symptoms; •61% had at least 1 positive prick skin test result; •43% showed typical physical signs of AR; •100% had a positive atopic family history; •53% had other associated atopic disorders.	•Strength: a notable strength of this research is that participants were evaluated according to established diagnostic criteria prior to inclusion, thereby minimizing selection bias. •Limitations: as a cross-sectional study with a sample size of only 23 participants, it lacks sufficient power to generalize findings to the broader ADHD population. Additionally, since AR assessments were conducted by a single examiner, there remains a risk of selective bias. Merely calculating the prevalence of AR does not sufficiently elucidate the relationship between these 2 conditions.
2.	Tsai et al[8]	From 2002 to 2009	Taiwan, China	Population-based case-control study	• Age: <18 years; •The diagnosis of ADHD was based on at least 1 hospital admission or at least 2 outpatient department visits where the outcome was a diagnosis of ADHD. • AR diagnosed by International Classification of Diseases-9 (ICD-9);	4692 children with ADHD; 18768 controls	The children with ADHD had a higher rate of atopic diseases than controls, particularly AR and allergic conjunctivitis.	•Strength: the large sample size enhances the study's validity and generalizability. •Limitations: it is important to note that diagnoses are based exclusively on historical medical records within the database, which may introduce bias in diagnostic criteria. Moreover, individuals in the non-ADHD group cannot be entirely ruled out as potential ADHD cases since they might seek medical attention in the future without being documented. Additionally, the absence of data regarding clinical assessments and laboratory test results limits our ability to ascertain the severity of comorbidities or determine whether participants are in subclinical or advanced stages of their conditions; this limitation could potentially influence the overall findings.

(*Continued*)

Table 1. Summary of the Association Between Allergic Rhinitis and ADHD (Continued)

No.	Authors	Recruiting Year	Country	Study Design	Recruiting Criteria	Sample Size	Outcome	Critical Review
3.	Qian et al[21]	From January 2012 to September 2013.	China	Case-control study	• Age: <18 years; •Patient diagnosed with ADHD, excluding other conditions, and has a Wechsler Adult Intelligence Scale Intelligent Quotient above 70. •The control group exhibited negative results on the Conner's questionnaire, were not ranked among the lowest 4 students in final exam grades from the previous semester, and had no documented history of ADHD.	278 children with ADHD; 278 Controls	AR ,and often have a runny nose, eye itching, nasal congestion were risk factors for ADHD by conditional Logistic regression analysis.	•Strength: participants in the ADHD group underwent standardized evaluations based on DSM-IV diagnostic criteria. •Limitations: allergic diseases were assessed through a questionnaire, which may be subject to parental recall bias. The sample size of 278 cases in this study is insufficient to generalize findings to the broader population. Furthermore, there exists potential diagnostic criterion bias regarding AR. Additionally, prior medication history for allergic conditions was not excluded from consideration and may have further influenced the results.
4.	Shyu et al[10]	Between January 1 and December 31, 2005.	Taiwan, China	A nationwide, population-based cohort study	• Age: 0-17 years; • The allergic group consisted of all pediatric patients with at least 1 diagnosed case of Bronchial Asthma (BA), AR, or AD by ICD-9; • The diagnosis of ADHD was based on at least 1 hospital admission or at least 2 outpatient department visits where the outcome was a diagnosis of ADHD.	2 26 550 children	Pediatric patients with AR had a substantially increased rate of developing ADHD (QR = 1.71). This significance existed across various demographic groups.	•Strength: a notable strength of this study lies in its large sample size, which enhances representativeness and provides substantial reference value. •Limitations: it is important to note that the diagnostic criteria are based solely on past medical history recorded in the insurance database. Consequently, none of the included samples underwent standardized assessments, potentially introducing bias into these criteria. Furthermore, there is a lack of data regarding evaluations and laboratory test results for these samples, making it difficult to ascertain the severity of co-morbid conditions or determine whether participants are in subclinical or advanced stages—factors that may significantly influence the final outcomes.
5.	Chen et al[11]	From September 2016 to December 2018	China	A cross-sectional study	• Age between 6 and 12 years old; • Children have 2 out of 4 basic symptoms for more than 1 hour • SPT has clear allergens.	465 children	•Children with the inattention /hyperactivity scale (IHS) > 1.25 accounted for 26.4% of all children with AR. •Univariate analysis showed that age, gender, duration of AR symptoms, skin index, and Pediatric Rhinoconjuntivitis Quality of Life Questionnaire subscales were associated with symptoms of hyperactivity and attention deficit (IHS > 1.25).	•Strength: AR diagnosis underwent standardized evaluations based on the inclusion criteria outlined in the Allergic Rhinitis and its Impact on Asthma guidelines. •Limitations: this study relied solely on the SNAP-IV questionnaire for assessing ADHD, which may introduce diagnostic bias due to variations in parental education levels influencing their responses. Furthermore, as a cross-sectional investigation, it does not encompass the full spectrum of ADHD patients necessary for establishing causal relationships.

(*Continued*)

Table 1. Summary of the Association Between Allergic Rhinitis and ADHD (Continued)

No.	Authors	Recruiting Year	Country	Study Design	Recruiting Criteria	Sample Size	Outcome	Critical Review
6.	Jiang et al[12]	From November to December, 2005.	China	Population-based cross-sectional survey	•School—age children in 1-6 grade in primary schools; •The diagnoses of both ADHD and AR are established based on the parents' recollection of the child's past medical history as presented in a questionnaire.	22018 children	•The risk ratios of ADHD were 2.197 (95% CI: 1.823-2.648) and 13.150 (95% CI: 2.082-4.760) in children with single allergic disease and combined allergic diseases separately. •Airway allergic disorders augment the susceptibility to ADHD in children.	•Strength: this study ensured a substantial sample size and robust overall representativeness that effectively reflects the distribution and interrelationship between ADHD and airway allergic diseases among school-age children in China. •Limitations: as a cross-sectional survey, this study may be subject to biases related to parental recall of previous diagnoses and diagnostic criteria for both ADHD and airway allergic conditions. Furthermore, given its cross-sectional nature, additional longitudinal studies are warranted to validate these findings.
7.	Guo et al[13]	From birth to 6 and 12 years old.	Taiwan, China	Longitudinal follow-up study	•Age:6-12 years old; •Diagnosis of AR was determined by the presence of active symptoms within the past year; • The assessment of ADHD symptoms was conducted utilizing SNAP-IV.	97 children	• They found that AR at 6 years old was associated with a higher inattention score at 12 years old. • Higher specific IgE levels for peanuts at 6 years of age were correlated with higher hyperactivity /impulsivity scores.	•Strength: the strength of this study lies in its longitudinal design. •Limitations: a relatively small sample size and the inherent complexity of ADHD as a multifactorial disorder, which complicates the identification of all possible confounding factors contributing to ADHD symptoms at age 12. The assessment of ADHD relied exclusively on parental questionnaires rather than active investigations or structured interviews, potentially introducing biases related to parental educational levels and recall inaccuracies. Furthermore, individuals with allergic diseases may have been more inclined to participate in additional ADHD assessments at age 12, which could also influence the findings.

(*Continued*)

Table 1. Summary of the Association Between Allergic Rhinitis and ADHD (Continued)

No.	Authors	Recruiting Year	Country	Study Design	Recruiting Criteria	Sample Size	Outcome	Critical Review
8.	Qu et al[15]	From 2013 to 2015	Australia	A cohort study	• The study included all children born in New South Wales, Australia, from July 1, 2001 to December 31, 2011, who survived until their third birthday; • The cohort was followed from the age of 3 until December 31, 2014 via linkage to the New South Wales Pharmaceutical Drugs of Addiction System to identify ADHD stimulant treatment prescriptions.	2580 children	•The results indicated a significantly higher prevalence of ADHD among children with AR compared to their counterparts without allergic conditions. •The likelihood of ADHD in children increased when either the mother or child had an allergic disease, as opposed to neither having such conditions.	•Strength: the study was a birth cohort study. This longitudinal cohort study demonstrates considerable strength in drawing conclusions. •Limitations: due to its relatively small sample size, random errors may influence the findings, resulting in wide confidence intervals and lower precision, particularly concerning stratified analysis results. Additionally, diagnoses of neurodevelopmental disorders and atopic diseases were extracted from electronic medical record (EMR) data based on ICD codes rather than standardized diagnostic evaluations, which could introduce classification error bias into NDs' and atopic diseases' EMR data. Lastly, healthcare providers may closely monitor children diagnosed with NDs, leading to an increased likelihood of detecting atopic diseases within this population.
9.	Hak, et al[16]	From 1996 to 2006	United Kingdom	A matched case-control study using the General Practice Research Database	• Boys <15 years; • Each case of ADHD was required to have at least 1 recorded prescription of methylphenidate within 12 months after the date of their first diagnosis; • Controls were selected from the source population of male patients with no diagnosis of ADHD or treatment with either methylphenidate or atomoxetine; • AR diagnosis originates from medical records.	3388 ADHD boys; 3536 Controls	Asthma and dermatitis increased the risk of ADHD, whereas other types of allergies were not linked to the incidence of ADHD.	•Strength: the research utilizes a substantial UK sample database, ensuring an adequate sample size and robust representativeness, thereby enhancing its reference value. By focusing exclusively on male participants, the study mitigates potential biases stemming from gender differences. •Limitations: focusing exclusively on male participants restricts the generalizability of findings to female populations and does not encompass all children with ADHD. The inclusion criteria were based on receiving medication for ADHD diagnosis, excluding those untreated; it is posited that untreated children may exhibit symptoms in a subclinical state. Nonetheless, decisions regarding medication usage could be influenced by parental perceptions and physician judgments, potentially introducing selection bias into the sample. Additionally, pharmacological interventions for ADHD might also influence the incidence rates of allergic diseases, thus affecting overall research outcomes.

prefrontal cortex circuits, leading to executive function disorders and behavioral issues. Sleep problems are considered important modulating factors for reducing ADHD symptoms in children with AR.[22] Over the past decade, research has begun to investigate other potential mechanisms by which allergies might affect ADHD. A population-based survey analysis in the United States suggested that sleep disorders can influence the occurrence and development of ADHD, potentially synergizing with allergies. Allergies have independent health mechanisms that directly affect the emergence and progression of behavioral problems associated with ADHD, with sleep acting as an indirect factor.[23] A large-scale database analysis in China revealed no significant difference in the impact of allergic diseases on ADHD risk before and after adjusting for sleep factors, initially indicating that the influence of allergies on ADHD is not directly related to sleep.[24] This suggests that researchers should focus more on potentially more complex direct links between these conditions.

Mediation Through Immunoinflammatory Mechanisms: Several researchers have hypothesized that ADHD is an inflammation- and immune-related disorder and explored this idea at the molecular biology level. This hypothesis also provides a framework for understanding the comorbid mechanisms of AR and ADHD. One explanation is that allergic reactions in peripheral tissues increase peripheral serum IgE levels, which in turn increase the activity of T helper 2 (Th2) cells. Similarly, the influx of eosinophils into allergic tissues and Th2-related anti-inflammatory cytokines (IL-1, IL-4, IL-6, and TNF-*a*) can cross the blood-brain barrier, interfering with the secretion and uptake of neurotransmitters by neurons and microglia. Thus, an imbalance in neurotransmitters activates behavior and emotion-related circuits in the brain, thereby mediating the occurrence of comorbidities.[25] Alternatively, cytokines might activate vagal afferent signals in specific brain regions, affecting brain response functions.[26] Another explanation posits that the blood–brain barrier itself possesses immune functions. When exposed to allergens or allergic environments, the immune function of the blood-brain barrier is activated, leading to the secretion of inflammatory mediators such as nitric oxide and cytokines. These mediators enter the peripheral blood and the central nervous system, disrupting the release and metabolism of neurotransmitters in the prefrontal cortex and thereby increasing the risk of ADHD.[27] Although ADHD is generally accepted as an immune-related disorder, some studies have reported no significant differences in the levels of Th2-related cytokines such as IL-6 and TNF-*a* between children with ADHD and normal children, and elevated IgE levels were not associated with the occurrence of ADHD.[28] Pelsser et al[29] suggested that ADHD can be induced by both allergic and nonallergic reactions, with multiple mechanisms potentially triggering ADHD symptoms. Attention-deficit hyperactivity disorder might be a non-IgE-mediated hypersensitivity reaction occurring in brain tissue. This hypothesis is supported by evidence that dietary adjustments can improve ADHD symptoms, but the specific pathways involved unclear. More research is needed to confirm these findings. Additionally, Passarelli et al[30] reported a significant positive correlation between ADHD and the immunoreactivity of anti-Yo antibodies in Purkinje cells in the cerebellum in children. The discovery of functional lymphatic vessels in the meninges, connected to peripheral cervical lymphatics, suggests that these vessels influence neurological function by draining cerebrospinal fluid and immune cells.[31] These findings identify a neuroimmune mechanism in ADHD, offering new directions for future research on ADHD and allergic diseases such as AR.

The state of the gut microbiota is also intricately linked to the body's immune system. The gut microbiota interacts with intestinal epithelial cells and mucosal cells by exchanging cytokines, thereby helping to maintain homeostasis and ensure proper immune system function.[32,33] A study on airway disease-related microbiota revealed a close relationship between ciliated bacteria in airways and the presence of *Dorea* and *Ruminococcus* in feces. An imbalance in the proportion of ciliated bacteria increases the risk of AR. The occurrence of AR might also be associated with a reduction in Firmicutes, and the diversity of the gut microbiota in children with AR is lower than in normal children.[34] The state of the gut microbiota can also influence brain function through several mechanisms. (1) Gastrointestinal microbes can directly cross the blood–brain barrier to interfere with neurons. An imbalance in the microbiota composition can alter the body's immune response to external stimuli, thereby affecting the regulation of brain function.[35] (2) Dysbiosis of the gut microbiota affects the release of cytokines in the peripheral blood circulation. The immunoinflammatory mechanism triggered by cytokines can affect brain tissue function through the blood–brain barrier or by activating the vagal nervous system.[36] (3) An imbalance in the gut microbiota can disrupt gut barrier function. This disruption interferes with the metabolism of gut toxins, and accumulated endotoxins can interfere with vagal nervous system signaling, thereby disrupting the release of neurotransmitters such as dopamine, norepinephrine, and serotonin in the brain, ultimately affecting brain function.[37] Carlson et al[38] were the first to establish a correlation between the gut microbiome and cognitive development in human infants by analyzing the fecal microbiomes of 89 American infants at 1 year of age and evaluating their cognitive abilities at 2 years. These findings revealed a positive association between the Bacteroidetes phylum and the enhancement of infant cognitive skills, whereas a negative correlation was observed with the Clostridiales phylum. A controlled study by Jiang et al[39] revealed an imbalance in the proportion of *Faecalibacterium* in the gut of patients with ADHD

and a negative correlation between the proportion of *Faecalibacterium* and ADHD symptoms, indicating that the proportion of *Faecalibacterium* in children with ADHD was reduced. Zhang et al[40] performed 16S rRNA gene sequencing to analyze fecal samples from 24 children diagnosed with AR and 25 healthy control (HC). The findings revealed that the diversity index of the intestinal microbiota in AR children was significantly lower than that in HC, whereas the evenness index was markedly greater. Additionally, the abundance of Bacteroidetes was greater in AR children than in their HC counterparts. Furthermore, Wan et al[41] collected fecal samples from 23 children with allergic asthma, 18 with AR, and 19 healthy controls and employed high-throughput gene sequencing for microbiota analysis. Their results revealed an increase in both the abundance and diversity of the intestinal microbiota among children with allergic asthma and AR; however, no statistically significant differences were noted between the asthma group and the rhinitis group at the phylum level. In both the AR and asthma groups, the relative Firmicutes abundance surpassed that found in healthy controls. Compared with healthy children, those with AR presented an increased capacity for proinflammatory responses and increased production of proinflammatory molecules within their gut microbiome. Although research on the role of the gut microbiota in the comorbid mechanisms of ADHD and allergic diseases is limited, the potential correlations of the gut microbiota with both conditions suggest that their relationship can be mediated by an imbalance in the gut microbiota. This hypothesis provides a valuable direction for future research.

Nerve Growth Factor: Nerve growth actor (NGF) is a characteristic neurotrophic factor that includes 2 known receptors, TrkA and p75NTR. It was first discovered by Leonardo Levi-Montalcini in the 1950s. Nerve growth factor and its receptors are produced by various types of cells in both the central and peripheral nervous systems during development and adulthood.[42] Nerve growth factor plays a critical role in the growth and maturation of cholinergic neurons, which are closely associated with memory and cognitive processes in the brain.[43] Additionally, NGF is involved in regulating brain plasticity during early postnatal development.[44] Nerve growth factor has also been extensively studied and reported in the context of allergic reactions. Research has shown that serum NGF levels significantly increase during allergic reactions in children with allergies. The role of NGF in the pathogenesis of allergic reactions is supported by experimental evidence.[45] Nerve growth factor directly affects immune cells through multiple mechanisms, including stimulating mast cell degranulation, granulocyte and macrophage differentiation, and the proliferation and differentiation of B and T lymphocytes.[46] Moreover, an in vitro study confirmed that PHA activates and induces Th0 and Th2 clones to secrete NGF, whereas Th1 clones do not secrete NGF, supporting the role of NGF in allergic reactions.[47] Given the potential roles of NGF in the pathogenesis of both allergic reactions and ADHD, some scholars suggest that NGF might play a crucial role in the comorbidity of ADHD with AR and other allergic conditions. To support this hypothesis, researchers have conducted studies on patients with comorbid ADHD and AR using single-drug single-disease treatments and dual-drug dual-disease treatments. These studies revealed that single-disease treatments improved the symptoms of comorbid conditions and that both single-disease and combined treatments reduced serum NGF levels,[48,49] suggesting that increased serum NGF is a potential key mechanism in the comorbidity of these 2 diseases.

Epigenetic and Gene Expression: In a comparative study conducted by Dorota Stefanowicz, alterations in deoxyribonucleic acid (DNA) methylation were observed at CpG sites within blood monocytes and epithelial cells of children with allergies.[50] Additionally, research by Swamy et al[51] revealed that DNA methylation at the Foxp3 CpG site was diminished in patients with airway allergies following sublingual immunotherapy. Moreover, variations in CpG site methylation are correlated with changes in various immune cell populations, including eosinophils and T cells, as well as cytokines such as IL-33 and IgE.[52,53] Consequently, modifications in CpG site methylation may represent a crucial epigenetic mechanism contributing to the pathogenesis of AR.

In parallel, Michael's extensive investigation into DNA methylation in children diagnosed with ADHD identified several DNA methylation sites linked to the onset of ADHD, thereby elucidating the epigenetic molecular mechanisms underlying this condition.[54] Vin et al conducted a study involving umbilical cord blood DNA from 426 6-year-old children in the Netherlands and assessed the levels of DNA methylation across 11 regions within 7 genes. These findings indicated that lower levels of DNA methylation in these specific regions were negatively correlated with ADHD symptom scores, implying that diminished DNA methylation may be associated with the onset of ADHD.[55]

Consequently, we can postulate that epigenetic factors and gene expression could serve as potential mechanisms for the co-occurrence of ADHD and AR, warranting further investigation to validate this hypothesis.

Psychological Stress: Xie et al[56] reported that children with ADHD who also have allergic diseases experience lower self-esteem and higher anxiety levels. Another study suggested that children's allergic symptoms can induce maternal anxiety, which in turn exacerbates their psychological stress, leading to increased problems such as attention deficits and emotional instability.[57] These findings indicate that psychological stress is also a mediating factor in the comorbidity of AR and ADHD. Emotions and stress connect the brain and immune system through the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, and they influence the immune system and

brain neurotransmitter release via the autonomic vagus nerve system.[58]

Our study has several limitations. First, the research examining the correlations included in our review predominantly originates from Asia, with a limited representation from other countries and regions. Despite extensive efforts to identify relevant studies, we found a notable scarcity of research from other parts of the world that could contribute to global insights. This limitation constrains the generalizability of our conclusions, prompting us to advocate for further investigations across diverse cultural and regional contexts to determine whether differing outcomes may arise. Secondly, while there are a limited number of longitudinal cohort studies addressing this association, the majority remain cross-sectional in nature. This limitation hinders the ability to encompass the full spectrum of ADHD patients necessary for establishing causal relationships. Therefore, an increased emphasis on longitudinal study designs is essential to enhance the validity and reliability of research conclusions. Thirdly, although our investigation incorporates several population-based large sample studies, numerous others suffer from inadequate sample sizes, which restricts the representativeness of their findings. Consequently, further large-scale studies are warranted to corroborate these results. Fourthly, our analysis revealed that the inclusion criteria for diagnostic samples in numerous studies were predominantly based on historical medical records from databases or parental questionnaires. This reliance may introduce biases into the study conclusions due to potential inaccuracies in parental recall and variations in diagnostic standards. Furthermore, despite our comprehensive efforts to identify relevant literature, the overall number of studies investigating the relationship between ADHD and AR remains limited. Most existing research primarily focuses on establishing correlations between these 2 conditions rather than delving into the underlying mechanisms of their co-occurrence. We anticipate that future investigations will yield direct empirical evidence elucidating this co-occurrence mechanism, as such findings would significantly enhance clinical treatment strategies for both ADHD and AR.

CONCLUSIONS

In summary, although the mechanism of comorbidity between ADHD and AR remains unclear, their relationship has been extensively documented despite some differing research results, which might be attributed to varying research methodologies or the presence of confounding factors. Despite the significant correlation revealed in cross-sectional studies, the causal relationship remains elusive. Longitudinal data suggest that children with AR have a higher propensity to develop ADHD in later life.[13,15] Hence, identifying this cohort of subjects with potential AR issues might facilitate early intervention and treatment for ADHD. As an increasing amount of evidence implies a possible connection between AR and ADHD, comprehending the underlying mechanisms is pivotal for identifying novel treatment approaches and targets.

We explore the potential underlying mechanisms of AR and ADHD, encompassing sleep disorders, immune-inflammatory mechanisms, neurotrophic factors, genetic and epigenetic mechanisms, and psychological stress. Among these, the immunoinflammatory mechanism is the primary trend in current research, which could become an important direction for future updates in ADHD diagnosis and treatment. However, at present, there is a dearth of direct evidence to establish a connection between these factors and AR as well as ADHD. Hence, additional longitudinal studies are requisite to explore the association between these factors and the 2 disorders within the same population, and to investigate the mediating role of these factors in the relationship between AR and ADHD. To further illuminate the role of epigenetics in the connection and development of AR and ADHD, more in vivo studies are necessary to observe the methylation patterns in animal models that mirror these conditions.

In fact, in clinical practice, comorbid allergic diseases such as AR are insufficiently emphasized in ADHD diagnosis and treatment. In a controlled study, Yang et al[59] reported that ADHD symptoms in children with AR significantly improved following effective treatment for AR alone. Considering AR treatment at the beginning of ADHD treatment may be valuable. Yu et al[60] conducted systematic allergen immunotherapy (AIT) for 2-6 months for 27 children who had received long-term treatment for ADHD without improvement in behavior or medication and who were also diagnosed with AR. Improvements in both AR and ADHD symptoms were noted after AIT. Therefore, AIT might improve the prognosis of refractory ADHD patients with co-occurring AR symptoms. Consequently, further testing and treatment for AR in children with ADHD who have a family history of AR or who experience seasonal symptom exacerbation are recommended. Additionally, desensitization treatment targeting dust mites effectively improved ADHD symptoms, suggesting a potential link between mite sensitization and the occurrence of ADHD symptoms in individuals with AR, which warrants further research confirmation. However, it is important to note that not all cases of ADHD involve AR, and the etiology of ADHD can involve multiple mechanisms. Exploring the mechanisms of the comorbidity of ADHD with AR and allergies can further enhance our understanding of the pathogenesis of ADHD and provide new insights into its diagnosis and treatment. For example, could ADHD be classified into allergic and non-allergic types? Could new and more effective medications and treatment strategies be identified for allergic-type ADHD? This approach can

also aid in the comprehensive management of chronic diseases during follow-up.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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