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Neurodevelopmental Comorbidities in Children with Asthma

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ABSTRACT

Asthma is one of the most prevalent chronic diseases in childhood, contributing substantially to global morbidity. Comorbidities are common and may complicate management, impair asthma control, and increase the disease burden. While allergic, metabolic, and psychological conditions are well recognized, neurodevelopmental disorders (NDDs) have recently emerged as comorbidities of particular concern. To review current evidence on the association between childhood asthma and NDDs, with emphasis on attention deficit-hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). A narrative synthesis of the literature was undertaken, focusing on epidemiological studies, proposed biological mechanisms, and clinical implications of co-occurring asthma and NDDs. Children with asthma show consistently higher prevalence rates of ADHD and ASD compared with the general pediatric population. Reported associations are supported by large-scale epidemiologic studies across diverse populations. Potential mechanisms include shared genetic susceptibility, immune dysregulation, systemic inflammation, and early-life environmental exposures. Neurodevelopmental comorbidities may adversely affect asthma outcomes by reducing treatment adherence, impairing symptom perception, and increasing psychosocial burden. Conversely, recurrent respiratory symptoms and chronic inflammation may contribute to neurodevelopmental vulnerability. The coexistence of asthma and NDDs represents a clinically significant and bidirectional relationship. Recognition of these comorbidities is essential for comprehensive care, as they influence both disease management and long-term outcomes. Multidisciplinary approaches integrating pediatric pulmonology, allergy, and neurodevelopmental care are needed. Further research is warranted to clarify causal pathways and develop targeted interventions that address the dual burden of asthma and NDs in children.

Keywords: Neurodevelopmental disorders, attention deficit hyperactivity disorder, autism spectrum disorder, child, comorbidity

Asthma stands as one of the most prevalent chronic inflammatory diseases of childhood globally, impacting millions of children with varying prevalence across geographical regions and socioeconomic conditions (1). Asthma is often associated with various comorbidities. Among the comorbid conditions most frequently reported in patients with asthma are rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders, and various psychopathologies; additionally, several other conditions—sometimes lacking a clearly defined mechanistic link to asthma—have also been documented as highly prevalent in this population (2). Understanding comorbidities in children is important because these comorbidities not only impose a significant burden on the patient and family but can also impair asthma control and lead to asthma persistence (3).

The most common comorbidities of asthma in children are allergic rhinitis, sinusitis, atopic dermatitis, gastroesophageal reflux, food allergy, obesity, obstructive sleep apnea, and psychological disturbances. In recent years, neurodevelopmental disorders (NDDs) have garnered increasing attention among these comorbidities (4,5). Neurodevelopmental disorders are a heterogeneous group of conditions that typically emerge early in life and often persist across the lifespan. Common NDDs diagnoses include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability,

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communication disorders, learning disabilities, and motor disorders (6).

Among these conditions, ADHD and ASD are the most prevalent and best-characterized NDDs in childhood and they account for the majority of the clinical and epidemiological literature on asthma-NDDs comorbidity. Several large-scale studies and meta-analyses have demonstrated that children with asthma have significantly higher odds of ADHD compared with those without asthma, and that asthma and ADHD show a bidirectional association over time. Likewise, population-based data indicate a higher prevalence of asthma among children with ASD than among typically developing controls, supporting a non-random co-occurrence of these two conditions (4,5,7).

This review aims to comprehensively examine the complex relationship between asthma and NDDs, focusing specifically on ADHD and ASD. The clinical significance of this relationship, potential pathophysiological mechanisms, and integrated management strategies will be reviewed.

EVIDENCES OF ASSOCIATION

Numerous studies have identified a significant correlation between childhood asthma and NDDs (Table I). Large-scale epidemiological research has shown that children with asthma are more likely to be diagnosed with ADHD, ASD, and other NDDs compared to their non-asthmatic peers. A study, based on data from the U.S. National Survey of Children's Health, has shown that children with asthma had a 1.7-fold increased risk of ADHD. These associations remain robust even after controlling for variables such as age, gender, and socioeconomic status, indicating a specific link between asthma and neurodevelopmental outcomes (8).

Studies investigating the link between asthma and NDDs generally found a significant association between asthma and ADHD. Two studies in Germany and Taiwan with over a million participants found associations of OR 2.19 and OR 1.53 respectively (9,10).

Longitudinal studies have provided valuable information about the temporal relationship between asthma and NDDs. For example, maternal asthma was found to increase the risk of developing ADHD symptoms in a cohort of Norwegian children (11).

Systematic reviews and meta-analysis present convincing evidence for a notable link between bronchial asthma and ADHD in children. In a Swedish meta-analysis that screened 2,649 potentially eligible citations, a significant

Table I: Epidemiological Studies on the Association Between Asthma and Neurodevelopmental Disorders

Author	Year	Country	Study design	Sample size	Main Findings
Blackman & Conaway (8)	2013	USA	National survey (NSCH)	91,642	Asthma-ADHD risk OR 1.7 (1.7-2.1)
Kotey et al. (17)	2014	USA	National survey	77,951	ASD-Asthma OR 1.35 (1.18-1.55); adj OR 1.19 (1.03-1.36)
Holmberg et al. (22)	2015	Sweden	Twin + cohort	Large twin dataset	Asthma→ADHD OR 1.53 (1.16-2.02)
Zheng et al. (20)	2016	Multi-country	Meta-analysis	175,406	ASD-asthma ns: OR 1.26 (0.98-1.61)
Chen et al. (10)	2017	Taiwan	Claims database	>1.7M	Asthma-ADHD OR 1.53 (1.44-1.63)
Instanes et al. (11)	2017	Norway	Birth cohort	>2.3M	Maternal asthma → ADHD OR 1.5 (1.4-1.6)
Miyazaki et al. (13)	2017	Multi-country	Meta-analysis	5 studies 59,646 children	Pooled OR 1.80 (1.57-2.07)
Cortese et al. (12)	2018	Sweden + Multi	Meta-analysis + registry	Meta: 3M+; Sweden:1.5M	Pooled OR 1.53 (1.41-1.65)
Xie et al. (18)	2020	USA	National survey	>70,000	ASD-Asthma OR 2.25; (1.48-3.41)
Akmatov et al. (9)	2021	Germany	Insurance claims	ADHD 258k; controls 2.3M	Asthma-ADHD OR 2.19 (2.16-2.22)
Kaas et al. (19)	2021	Multi-country	Meta-analysis	Large pooled	ADHD-asthma OR 1.52 (1.42-1.63); ASD-asthma OR 1.12 (0.93-1.34)
Dai & Jin. (14)	2023	Multi-country	Meta-analysis	10 studies 729,375	OR 1.46 (1.41-1.51)

association between asthma and ADHD was demonstrated (12). A meta-analysis by Miyazaki et al., found a combined odds ratio for ADHD in children with asthma of 1.80, indicating a moderate but consistent association (13).

Another meta-analysis, including 729,375 participants, revealed a statistically significant association between ADHD and an increased likelihood of having bronchial asthma. 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 influence (14).

In a study using the Conners Parent Rating Scale-48, a 48-question multiple-choice questionnaire completed by mothers to identify symptoms of ADHD in their children, the attention deficit score was found to be significantly higher in the asthma group than in the control group (15).

Like ADHD, ASD represents a prevalent disorder that appears to be on the rise (16). In cross-sectional, population-based studies, parents of children with ASD were more likely to report asthma in their offspring than parents of children without ASD (17). The largest study on ASD-asthma comorbidity, using data from the U.S. National Survey of Children's Health, found that children with ASD (aged 0-17 years) had a two-fold increased risk of asthma (18)

However, the evidence for the relationship between asthma and ASD is not very strong. Indeed, another systematic review with meta-analyses investigating the association between asthma and ADHD or ASD in children shows a significant overlap between asthma and ADHD but not between asthma and ASD in children (19). A comprehensive meta-analysis that included ten studies encompassing 175,406 participants and 8,809 ASD cases found no evidence supporting an association between asthma and ASD (20). In contrast, a study conducted in Sweden that employed several genetically informed designs found evidence of familial co-aggregation between asthma and ASD, suggesting that the modest association between the two disorders may be influenced by shared genetic factors (21).

Childhood asthma, especially severe asthma, is associated with ADHD. Studies have also been conducted examining the relationship between asthma severity and ADHD. In a twin study to evaluate genetic and environmental risk factors on the asthma-ADHD relationship, asthmatic children had a higher risk of also having ADHD. In this study, the magnitude of the association increased with asthma severity [OR 2.84, (95% CI: 1.86-4.35)] for ≥ 4 asthma attacks in the last 12 months and was not affected by asthma treatment (22).

PATHOPHYSIOLOGY

The relationship between asthma and neurodevelopmental comorbidities is not attributed to a single cause but rather emerges from a complex interplay of numerous biological, environmental, and psychosocial factors within a bio-psycho-social model. Potential mechanisms are explained below.

Neuroinflammation

As one of the most prevalent chronic respiratory inflammatory diseases in children, childhood asthma has been implicated in potential neurodevelopmental impacts: emerging evidence suggests that asthma-related chronic inflammation, hypoxia, and immune dysregulation may disrupt central nervous system development, thereby implying a potential connection to the pathogenesis of NDDs (23).

While asthma is primarily characterized by chronic airway inflammation, this inflammatory response frequently becomes systemic, leading to elevated levels of circulating pro-inflammatory cytokines and chemokines. These inflammatory mediators can cross the blood-brain barrier or increase its permeability, thereby gaining access to the central nervous system (23,24). These molecules can trigger microglial activation and subsequent neuroinflammation. Neuroinflammation can disrupt synaptic plasticity, impair neuronal survival, and inhibit neurogenesis (25,26).

The model that most effectively explains neuronal inflammation is the association between maternal asthma and NDDs. Epidemiological studies have demonstrated that maternal asthma during pregnancy confers an increased risk of NDDs such as ASD and ADHD in the offspring. Maternal systemic inflammation may alter the fetal environment, leading to both short- and long-term consequences on the developing brain (25). Mouse models have shown that offspring of mothers with allergic asthma exhibit behavioral and neuroimmune alterations, which are

thought to occur in response to elevations in inflammatory cytokines associated with maternal allergic asthma (i.e., IL-4, IL-5, IL-6, and IL-17). Consistently, mid-pregnancy elevations of IL-4 and IL-5 have been reported in mothers of children diagnosed with ASD (23, 25).

Crucially, chronic inflammation in early life has been shown to adversely affect the development and function of brain regions vital for cognitive functions, attention, impulse control, and social behavior, such as the prefrontal cortex, hippocampus, basal ganglia, and cerebellum. Inflammatory and developmental disruptions in these regions could contribute to executive dysfunction observed in ADHD and the social-communicative deficits characteristic of ASD (27-29).

Chronic Hypoxia

Recurrent or chronic hypoxia, occurring during severe or poorly controlled asthma exacerbations, can have detrimental effects, especially on the developing brain. The immature brain is considerably more vulnerable to oxygen deprivation than the adult brain (30). Hypoxia disrupts neuronal energy metabolism, triggers neuronal apoptosis, leads to myelination abnormalities, and compromises the integrity of synaptic connections (31). These cellular and structural alterations can result in lasting impairments in cognitive functions (attention, memory, learning ability, processing speed), motor coordination, and emotional regulation, thereby contributing to the emergence or exacerbation of NDDs (32).

Sleep Disturbances

Sleep disturbances are remarkably common in children with asthma due to nocturnal symptoms and potential side effects of asthma medications (33). Chronic sleep deprivation or fragmented sleep is a significant factor adversely impacting cognitive functions (attention, concentration, learning, memory), emotional regulation, and behavior. ADHD symptoms (inattention, hyperactivity, impulsivity) can be significantly worsened by sleep deprivation, and sleep problems are a highly prevalent comorbidity in children with ADHD (34,35). Similarly, sleep disturbances are common in children with ASD, potentially exacerbating social-communicative difficulties and repetitive behaviors (36).

Psychosocial Stress due to Chronic Illness

As a chronic illness, asthma imposes significant psychosocial stress on both the child and their family. Anxieties related to disease management (fear of exacerbations, medication concerns, treatment costs), school absenteeism, difficulties in peer relationships, social restrictions, and parental burden can negatively affect the child's stress levels and mental well-being (37). Chronic or toxic stress can influence the brain's stress response systems, particularly the hypothalamic-pituitary-adrenal (HPA) axis, and neurotransmitter systems (e.g., dopamine, serotonin), thereby interfering with neurodevelopmental processes (38).

Socioeconomic status

Socioeconomic status (SES) influences the risk of both physical diseases, such as asthma, and NDs, including ADHD. Using Causal Mediation Analysis on French birth cohort data, a causal pathway from SES to ADHD symptoms, in part mediated by asthma, was found. An increase in family income at age 3 by one unit resulted in lower ADHD symptoms at age 5, by -0.37 [95% CI: -0.50, -0.24] SDQ-score-points, with additional -0.04 [95% CI: -0.08, -0.01] points reduction indirectly via asthma at age 3 (39).

Genetic and Epigenetic Factors

Both asthma and many NDDs are known to have genetic predispositions (40,41). Research suggests that shared genetic variants or pathways involved in regulating inflammatory responses, immune functions, and neuronal development could influence susceptibility to both asthma and NDDs. For instance, polymorphisms in major histocompatibility complex (MHC) genes, cytokine gene polymorphisms, and genes associated with neurotransmitter pathways may play a role in the pathogenesis of both conditions. Furthermore, epigenetic mechanisms (DNA methylation, histone modifications), where environmental factors (allergen exposure, diet, maternal stress, foetal distress, birth injury or trauma or small for gestational age) can modify gene expression, may also play a crucial role in this relationship (3, 42,43).

Firstly, evidence for a shared familial risk of ASD or ADHD with asthma has been identified in several family design studies. For example, Sun et al., through Swedish register linkages, demonstrated elevated ADHD risk among relatives of individuals with asthma, with stronger

associations observed in those with closer genetic relatedness (44). A single large-scale genomic analysis demonstrated a significant association between asthma and ADHD, supported by shared genetic architecture and potential causal pathways (42) However, in vitro gene expression studies using tissues from patients with asthma and ASD have found gene polymorphisms which are involved in inflammation and immune regulation. These may provide an insight into a genetic predisposition for asthma and ASD (3).

Potential Effects of Medication Use

Ongoing research is investigating the neurodevelopmental effects of certain medications used in asthma treatment. Specifically, long-term and high-dose use of systemic corticosteroids has been associated with neuropsychiatric side effects in children, such as irritability, sleep disturbances, mood swings, and, rarely, psychotic symptoms. However, inhaled corticosteroids generally have much lower systemic side effects, and there is no significant evidence of long-term neurodevelopmental impacts (45,46). Neuropsychiatric side effects associated with montelukast use have long been recognized. In 2020, the U.S. Food and Drug Administration acknowledged these potential harms and issued a boxed warning specifically for montelukast regarding the risk of serious mental health side effects. In a large population-based cohort study conducted in Taiwan, the use of leukotriene receptor antagonists was associated with a 6% increased risk of neuropsychiatric adverse events, an 88% increased risk of psychotic disorders, a 10% increased risk of anxiety disorders, and a 27% increased risk of behavioral and emotional disorders compared with inhaled corticosteroids (46).

CLINICAL CONSEQUENCES OF ASTHMA AND NEURODEVELOPMENTAL DISORDERS ASSOCIATION

Asthma hospitalizations reflect significant morbidity, with contributing factors including inadequate asthma control, exposure to environmental triggers, and adherence to treatment regimens. Children with disorders such as ASD and ADHD may experience additional challenges in managing asthma, given the complex interplay between their behavioral and physical health needs (47). Among adolescents with severe ADHD symptoms, poorer adherence to daily asthma controller therapy has been demonstrated, which in turn has been indirectly associated with increased asthma-related emergency department visits (48). In children with asthma, comorbid ASD has similarly been linked to suboptimal asthma control and a higher likelihood of hospitalization, largely attributable to behavioral barriers to treatment adherence, communication difficulties, and increased sensitivity to environmental triggers (47,49).

Asthma and Attention-Deficit/Hyperactivity Disorder

Attention deficit-hyperactivity disorders are some of the most common NDDs of childhood, characterized by a triad of inattention, hyperactivity, and impulsivity. Most epidemiological studies consistently demonstrate a two to three times higher prevalence of ADHD in children with asthma compared to the general pediatric population (5,50). This relationship is considered bidirectional: asthma may increase the risk of ADHD, and ADHD, in turn, can negatively impact asthma management (51).

Children with ADHD may struggle with consistent adherence to asthma medications, proper inhaler technique, or compliance with asthma action plans due to inattention and impulsivity (50). This can lead to worsening asthma symptoms and an increased risk of exacerbations.

Asthmatic children with ADHD may experience higher rates of emergency department visits and hospitalizations for asthma exacerbations. Delayed recognition of symptoms, medication non-adherence, or risky behaviors could contribute to this trend (49,52).

The co-occurrence of both chronic conditions can significantly impair the child's academic performance, social relationships, and overall quality of life. These children may face more academic struggles, peer rejection, and behavioral problems at school.

Asthma and ASD

Autism spectrum disorder (ASD) is a complex NDD characterized by repetitive, restricted, and stereotyped behaviors, along with persistent difficulties with social interaction and communication (53). Recent large-scale cohort studies and meta-analyses have provided evidence suggesting an increased risk of ASD in children with asthma and/or a history of allergic diseases (5,54). This association is often explained through the lens of early life immune dysregulation and neuroinflammation mechanisms (5,55).

Sensory processing differences and communication difficulties common in children with ASD can make it challenging for them to perceive, express, or react appropriately to asthma symptoms (e.g., shortness of breath, chest tightness). This could delay the recognition of asthma exacerbations and hinder timely intervention (56).

Children with ASD's intolerance to routine changes or specific sensory sensitivities (e.g., taste/smell of an inhaler, feel of a face mask) can make adherence to asthma medications or regular follow-up appointments challenging. Asthma symptoms or treatment procedures may lead to increased anxiety, meltdowns, or repetitive behaviors in children with ASD (47, 56).

Other Neurodevelopmental and Psychiatric Comorbidities

Anxiety Disorders and Depression

The prevalence of anxiety disorders and depression is higher in children with asthma, particularly those with chronic and poorly controlled asthma, compared to the general population (57,58). This can be attributed to both the inherent stress of living with a chronic illness and the impact of asthma-related inflammatory processes on mood regulation.

Learning Disabilities

Factors such as the burden of chronic illness, frequent school absenteeism, sleep disturbances, and co-occurring ADHD can increase the risk of learning disabilities in children with asthma (59).

Sensory processing disorder

Sensory processing disorder, a neurodevelopmental condition characterized by atypical responses to sensory stimuli, may also be linked to asthma through shared inflammatory mechanisms. In a recent study, asthma was associated with increased risk of atypical sensory processing, particularly in the tactile (OR: 5.716, 95% CI: 2.9-11.) and balance/movement (OR: 8.8, 95% CI: 2.5-30.7) domains (60).

MANAGEMENT STRATEGIES

The presence of neurodevelopmental comorbidities in children with asthma highlights that traditional approaches focusing solely on asthma management may be insufficient. An integrated and multifaceted clinical approach is essential to optimize the health and development of these children:

Early Diagnosis

Systematic and regular screening for neurodevelopmental problems is critically important for every child diagnosed with asthma, especially those presenting with ongoing behavioral, cognitive, or social-emotional difficulties. Screening tools (e.g., Vanderbilt ADHD Diagnostic Rating Scale, Childhood Autism Rating Scale (CARS), developmental screening inventories) and standardized scales can be utilized. Positive screening results necessitate a detailed diagnostic evaluation by a child psychiatrist, developmental pediatrician, or pediatric neurologist (61).

Multidisciplinary Approach

Multidisciplinary team collaboration is vital when asthma and NDDs co-occur. This team should ideally include a pediatrician, pediatric allergist, child psychiatrist, developmental pediatrician, child neurologist, psychologist, special education specialist, physiotherapist, speech and language therapist, and school nurse among other relevant healthcare and educational professionals. Regular communication and coordination among team members ensure effective management of both conditions and support for all areas of the child's development.

Optimizing Asthma Treatment

One particular challenge for children with concurrent asthma and ADHD and their parents is adequate disease management, such as appropriate use of inhalers, as well as stress and anxiety management to avoid asthma exacerbations. Effective control of asthma symptoms can have a positive impact on neurodevelopmental manifestations by reducing detrimental factors such as chronic inflammation, hypoxia, and sleep disturbances. Prioritizing regular medication adherence (especially inhaled corticosteroids) and compliance with asthma action plans is crucial (3).

Parent Education, Support, and Empowerment

Providing parent education, access to psychosocial support services (counseling, therapy), and referrals to support groups can empower families and strengthen their coping mechanisms. Reducing parental stress and enhancing well-being directly and positively impacts the child's overall health and development.

School and Environmental Accommodations

It is essential to ensure that the child's needs for both asthma and NDs are met within the school environment. School nurses and teachers should be informed about the child's asthma action plan and behavioral support plans for ADHD/ASD. Academic accommodations, special education support, and strategies to foster positive peer relationships should be implemented.

CONCLUSION

While asthma is a significant chronic disease of childhood, its strong comorbidity with NDDs underscores the necessity of a holistic approach to disease management. A multitude of mechanisms, including chronic inflammation, hypoxia, sleep disturbances, psychosocial stress, and genetic predispositions, form the bedrock of this complex relationship. The rising prevalence of ADHD, ASD, and other NDDs in asthmatic children mandates clinicians to possess a high level of awareness regarding these comorbidities, perform systematic screening, and implement integrated treatment plans within a multidisciplinary team framework.

Early diagnosis and timely intervention are critically important to optimize both the respiratory health and the cognitive, behavioral, and social development of children with asthma. This holistic approach will not only target symptom control but also aim to enhance the child's overall well-being, academic success, and quality of life, enabling these children to reach their full potential. Greater awareness and tailored clinical management strategies are crucial for addressing the needs of this at-risk population. Further research is warranted to elucidate the underlying biological and behavioral pathways driving these associations, thereby guiding the development of more effective therapeutic interventions.

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