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The influence of asthma on neuroinflammation and neurodevelopment: From epidemiology to basic models

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ABSTRACT

Asthma is a highly heterogeneous inflammatory disease that can have a significant effect on both the respiratory system and central nervous system. Population based studies and animal models have found asthma to be co-morbid with a number of neurological conditions, including depression, anxiety, and neurodevelopmental disorders. In addition, maternal asthma during pregnancy has been associated with neurodevelopmental disorders in the offspring, such as autism spectrum disorders and attention deficit hyperactivity disorder. In this article, we review the most current epidemiological studies of asthma that identify links to neurological conditions, both as it relates to individuals that suffer from asthma and the impacts asthma during pregnancy may have on offspring neurodevelopment. We also discuss the relevant animal models investigating these links, address the gaps in knowledge, and explore the potential future directions in this field.

1. Introduction

Asthma represents one of the leading chronic illnesses among children and affects approximately 24 million people in the United States (CDC, 2021). Prevalence of asthma is on the rise, with rates of asthma estimated at 3.1 % in 1980 increasing to 7.8 % by 2020 (CDC, 2021; Gans and Gavrilova, 2020). Of the populations most impacted, minority groups and those living below the poverty level are disproportionately more susceptible to asthma and asthma-related morbidity (Cardet et al., 2022; Ganti et al., 2022; Matsui et al., 2008; Milligan et al., 2016). Asthma mortality rates are estimated to be over 3000 deaths each year in the US. In addition, those living with asthma face an increased risk of hospitalization and are reported to miss more work and school days than those without asthma (Baek et al., 2022; Jean et al., 2019; Loftus and Wise, 2015). As such, asthma represents a serious chronic disease with a substantial impact on the personal lives of asthmatic individuals as well as a heavy economic burden placed on the healthcare system.

Asthma is a heterogeneous disease most often characterized by airway inflammation and bronchial hyperresponsiveness leading to constriction, obstruction, and remodeling of the airways (Gans and Gavrilova, 2020; Mims, 2015). A T-helper 2 (T_H2) immune response plays a significant role in the development of asthma through the release of pro-inflammatory cytokines and recruitment of granulocytes (Deo et al., 2010; León & Ballesteros-Tato, 2021; Yu et al., 2014). Asthma often occurs in response to an allergic trigger which begins with an initial sensitization to an allergen followed by an IgE immunoglobulin response where subsequent exposures to the allergen, or challenges, lead to inflammation (Sonntag et al., 2019). Allergic asthma is not the only type of asthma, however, and several factors in addition to allergen exposure can lead to the development of asthma.

The exact cause for asthma is unknown, but genetic, epigenetic, and environmental risk factors have been identified. Hundreds of gene variants and epigenetic translational variations have been associated with an increased risk of asthma (Harb and Renz, 2015; Wang et al., 2022). Environmental contributors, such as viral infections, air pollution, and sensitization to allergens have all been associated with development of asthma and disease severity (Acevedo et al., 2021; Castillo et al., 2017; Mims, 2015; Rosário Filho et al., 2021). Furthermore, pollutants such as particulate matter (PM), tobacco smoke, diesel exhaust, and ozone can exacerbate disease and symptom expression in individuals already diagnosed with asthma resulting in increased inflammatory response and airway hyperresponsiveness (Castañeda et al., 2018; Castillo et al.,

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2017; Hansel et al., 2008; Samoli et al., 2011; Trasande & Thurston, 2005).

In addition to these contributors to asthma and asthma severity, comorbidities alongside asthma are also highly prevalent and can further increase the burden of the disease. In total, 60 % of adults living with asthma have one or more comorbidities which may include other respiratory disorders, cardiovascular disease, immune disorders, cancer, and neurological conditions (Boulet & Boulay, 2011). Moreover, an increase in psychiatric conditions is seen both in adults and children with asthma. For instance, depression and anxiety disorders are frequently seen in adults with asthma, and children with asthma may also show increased symptoms of behavioral disorders as well as anxiety and depression (Cooley et al., 2022; Fasmer et al., 2011; Licari et al., 2022). Furthermore, individuals with asthma have an increased risk of cognitive deficits (Kroll & Ritz, 2023). While asthma can have neurological impacts on the individual patient, asthma during pregnancy can also disrupt the outcome of pregnancy and disease in the offspring. Maternal asthma is associated with increased complications and risk during pregnancy and delivery (Baghlaf et al., 2019; Shaked et al., 2019; Sheiner et al., 2005). Moreover, children of asthmatic mothers are more likely to develop asthma themselves, especially if the mother's asthma is uncontrolled during pregnancy (Lim et al., 2010; Liu et al., 2018). Another consequence of maternal asthma is an increased risk of neurodevelopmental disease in offspring (Abdallah et al., 2011; Ali & Ulrik, 2013; Croen et al., 2019; Croen et al., 2023; Fasmer et al., 2011; Gong et al., 2019; Hisle-Gorman et al., 2018; Lyall et al., 2014; Patel et al., 2020). Peripheral inflammation can lead to neuroinflammation and lifelong changes in brain function , and maternal inflammation can have an impact on offspring neurodevelopment through structural and functional changes in the offspring brain that occur in response to a neuroinflammatory environment. Together, these impacts of asthma represent not only an important disease that can affect the neuropsychiatric balance of the individuals suffering from asthma themselves, but also pose a potential risk for the neurodevelopment and wellbeing of offspring of mothers suffering from the disease. Here, we will provide a detailed overview of the current literature on asthma and impacts on behavior and neuroimmune interactions.

2. Asthma

Asthma is a heterogeneous disease that can present with a varying severity of symptoms depending on the person and external stimuli. These symptoms include chest tightness, difficulty breathing, cough, and airway hyperresponsiveness, (Gans and Gavrilova, 2020; Holgate et al., 2015; Lange et al., 1998). A spectrum of genetic risk factors can interact with environmental risks leading to the variation of symptoms and phenotypes present in the population (Kumar and Ghosh, 2009). The phenotype typically associated with asthma is allergic asthma, an atopic disease that occurs due to sensitization to allergens (Schatz and Rosenwasser, 2014). Atopic diseases are conditions in which the immune system is predisposed to becoming sensitized towards allergens and mounting an allergic, IgE mediated response (Vaillant et al., 2022). Non-atopic, or non-allergic, asthma is less common and more severe (Peters, 2014). Development of allergic asthma is characterized by a sensitization phase and a challenge phase (Sonntag et al., 2019). Briefly, sensitization to allergen occurs when dendritic cells (DC) phagocytose an allergen in the lung. The DC then carries the allergen to the draining lymph node where it can present it to naive T cells and elicit a type 2 immune response resulting in the differentiation of T helper 2 (T_H2) cells (León, 2017). T_H2 effector cell functions are responsible for the common pathologies and symptoms seen in asthma as T_H2 cells regulate allergen specific IgE production, eosinophil recruitment, inflammatory cytokine secretion, chronic inflammation, and expansion of memory T cells (Holgate et al., 2015; León, 2017; Schatz and Rosenwasser, 2014). Upon subsequent allergen challenge these memory T cells can be reactivated to perform effector functions and cause further inflammation (León, 2017). In both allergic and non-allergic asthma, airway remodeling is common and consists of airway wall thickening, increases in smooth muscle, and increased presence of mucous cells and mucous production which subsequently results in airway hyperresponsiveness, mucus plug formation, and the characteristic symptoms of asthma (Boucherat et al., 2013; Holgate et al., 2015).

The initiation of an allergic asthma response results from an increase in T_H2 cytokines interleukin-4 (IL-4), IL-5, and IL-13, an observation seen in both human patients with asthma and animal models of the disease (Barnes, 2001; Choy et al., 2015). IL-4 drives the differentiation of naive T cells into T_H2 cells after encountering inhaled allergen presented by DC in the lungs (Gans and Gavrilova, 2020; Chapoval et al., 2010). T_H2 cells then produce IL-5, IL-9, and IL-13, leading to eosinophil recruitment, mast cell degranulation, and resulting airway remodeling and obstruction (Hazlewood et al., 2011; Lambrecht et al., 2000; Spencer and Weller, 2010). Lung epithelial cells and fibroblasts secrete eotaxins in high amounts during allergic airway inflammation, assisting in the recruitment of eosinophils to the lungs (Adar et al., 2014; Conroy & Williams, 2001) (Fig. 1). Classically, a phenotype of high circulating IgE and eosinophil infiltration in the lungs has defined asthma (Lloyd and Saglani, 2013). However, asthma is a highly heterogeneous disease and some patients do not show evidence of high levels of IgE or respond to T_H2 repression as treatment, highlighting the need to investigate other mechanisms that may be driving airway hyperresponsiveness (Choy et al., 2015; Cosmi et al., 2011). For example, some cases of asthma are induced by a T_H17 response characterized by neutrophil invasion of the lungs and high levels of IL-17. Neutrophilic asthma is non-atopic and typically non-eosinophilic. Higher levels of IL-17 and neutrophil invasion of the lungs are associated with increased disease severity (Cosmi et al., 2011). In some patients, both a T_H2 and T_H17 response is seen, suggesting that although neutrophilic asthma is non-allergic, the added T_H17 response can exacerbate allergic airway inflammation and lead to an imbalance in regulatory T cells (T_{regs})/T_H17 cells (Liu et al., 2020; Newcomb & Peebles, 2013).

Other cytokines that have also been identified in asthma include interferon-γ (IFN-γ), which is upregulated in severe cases of asthma in mice and humans (Magnan et al., 2000; Raundhal et al., 2015). T cells in the context of asthma also upregulate IL-2 which can further induce production of IL-13 (Hashimoto et al., 2006). Tumor necrosis factor alpha (TNFα) is also suspected to contribute to asthma through increasing the inflammatory response, recruiting neutrophils and eosinophils, and increasing their cytotoxic effects (Berry et al., 2007). Mononuclear cells isolated from asthma patients with varying severity of the disease showed increased baseline levels of the chemokine MIP-1α (Rojas-Dotor et al., 2013). Taken together these data demonstrate that once asthma is initiated a cascade of immune responses and cytokines are induced that propagate the disease.

3. Asthma and the central nervous system (CNS)

3.1. Asthma and neuropsychiatric conditions

The underlying inflammatory response in asthma is suspected to play a role in associated neurological comorbidities, including depression, anxiety, and attention deficit hyperactivity disorder (ADHD) (Boulet & Boulay, 2011; Jiang et al., 2014; King-Dowling et al., 2019). Compared to non-asthmatic individuals, asthmatic patients are twice as likely to develop depressive symptoms or anxiety disorders (Lavoie et al., 2006; Kewalramani et al., 2008). This relationship between asthma and depression is bidirectional; individuals suffering from asthma or depression have an increased likelihood of having the other as a comorbidity (Choi et al., 2019; Liu et al., 2023; Loerbroks et al., 2010;). In a study of 245,727 individuals spanning 57 countries, it was shown that asthma and depression are comorbid (Loerbroks et al., 2012). Furthermore, asthmatics with depression have a higher mortality rate than asthmatics without depression (hazard ratio: 1.87) (Walters et al.,

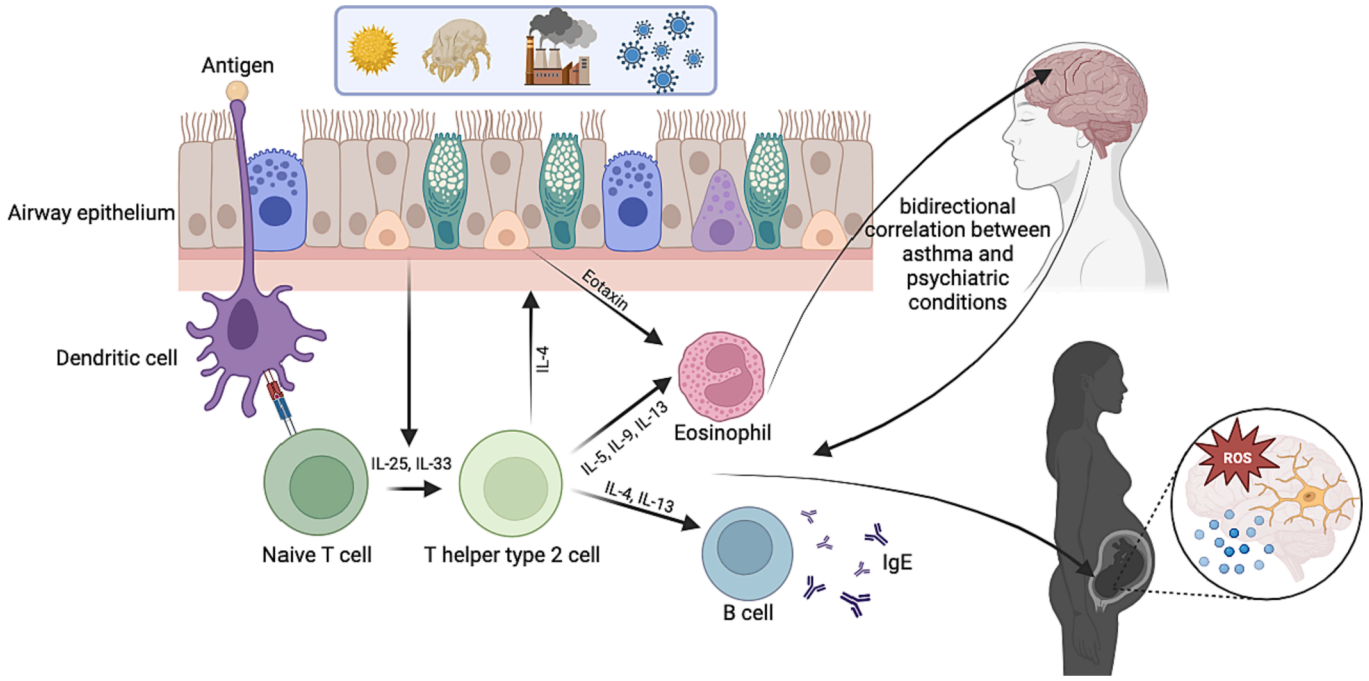

Fig. 1. The airway responds to stimuli from allergens, pollutants, or infection. Dendritic cells (DC) are recruited by chemokines secreted by the airway epithelial cells and migrate to the airways to take up and process antigen. DC then present the antigen to naive T cells. Epithelial cell secretion of cytokines IL-33 and IL-25, along with antigen presentation via DC, stimulate the development of a naive T cell to a T_H2 cell. T_H2 cells secrete cytokines IL-4, IL-5, IL-9, and IL-13. IL-4 stimulates airway epithelial cells to produce eotaxin and promote eosinophil recruitment. IL-4 also promotes IgE production by B cells, and IL-13 promotes IgE class switching. IL-5 is crucial for promoting eosinophil maturation, activation, and survival. IL-9 promotes T cell and mast cell proliferation. Pro-inflammatory cytokines and eotaxins can cross the BBB, resulting in neuroinflammation. Inflammation in the brain is noted in several neurological disorders comorbid with asthma. Inflammation during pregnancy is associated with neurodevelopmental disorders in the offspring, including ASD and ADHD. Pregnancy can also exacerbate asthma and cause increases in pro-inflammatory cytokines IL-4, IL-5, and IL-13. Comorbidities of depression, anxiety, and ADHD are common in asthmatics. Maternal allergic asthma is associated with an increased risk of neurodevelopmental disorders in the offspring.

2011). There is evidence that immune dysfunction and increased systemic inflammatory molecules can be associated with depression (Blume et al., 2011; Slavich & Irwin, 2014). Specifically, increased levels of IL-6 and TNF-α have been observed in individuals with depressive disorders (Slavich & Irwin, 2014). Similarly, elevations in IL-6 levels are seen in patients with anxiety, independent of depressive disorders; however, it is unknown whether this is a cause or a result of anxiety (O'Donovan et al., 2010; Salim et al., 2012). Importantly, elevated IL-6 and TNF-α have also been identified in cases of severe asthma and asthma exacerbations (Berry et al., 2007; Cui et al., 2017; Dimitrova et al., 2019).

Panic disorders and anxiety are also common among asthma patients, with both general symptoms of anxiety and anxiety disorders appearing at higher rates in asthmatics than non-asthmatic individuals (Hasler et al., 2005; Ye et al., 2021). The prevalence of anxiety is increased even more in individuals with difficult to treat, or treatment-resistant, asthma (Chee Kiang et al., 2015). Similar to the relationship between asthma and depression, there is evidence of a bidirectional relationship between asthma and anxiety (Lee et al., 2016), with asthma increasing risk of associated anxiety, and anxiety disorders leading to increased asthma incidence, deterioration, and severity (Lee et al., 2016). Psychosocial stress has been identified as a risk factor for asthma and increased asthma morbidity, potentially through immune mechanisms (Kemeny & Schedlowski, 2007; Mathews et al., 2011; Slattery et al., 2012; Yonas et al., 2012).

The exact mechanisms by which asthma influences neuropsychiatric disorders and the CNS, and vice versa, are not known. However, there is evidence that chronic inflammatory conditions, such as asthma, can lead to a disruption in the homeostasis of the neuroimmune environment. For example, during peripheral inflammation, inflammatory mediators cross the blood–brain barrier (BBB) and subsequently can alter brain chemistry and function (Di Benedetto et al., 2017; Varatharaj and Galea, 2017). Peripheral inflammation leads to a breakdown of tight junctions in the endothelial cells of the BBB, allowing for cytokine entry into the brain (Galea, 2021; Pan et al., 2011). Once across the barrier, cytokines can lead to functional changes in microglia and astrocytes, contributing to a neuroinflammatory environment (Kaur et al., 2019; Norden et al., 2016; Riazi et al., 2008; Riester et al., 2020). Under neuroinflammatory conditions, microglia can produce additional cytokines, reactive oxygen species, and participate in elimination of synapses, having an overall neurotoxic effect (Kim et al., 2007; Marttinen et al., 2018; Schafer and Stevens, 2010; Sousa et al., 2017; Xu et al., 2023). Astrocytes can also have modulatory effects on synapses and are important in BBB integrity (Allen et al., 2012; Chung et al., 2013; Heithoff et al., 2021;). Eotaxins present in a T_H2 response can cause neuronal cell death via microglial excitation (Kroll & Ritz, 2023; Parajuli et al., 2015). In mice, ithe main regions of the brain affected by asthma during periods of difficulty breathing are the hippocampus and frontal cortex. In humans, adults with asthma tend to have decreased volumes of the hippocampus and poor integrity of the hippocampal neurons (Carlson et al., 2017; Kroll et al., 2018). These reductions in the hippocampus are hypothesized to contribute to the cognitive deficits often associated with asthma (Kroll & Ritz, 2023). Moreover, in mouse models of asthma, dendritic spine density is decreased in the hippocampus in response to asthma, a phenomenon often associated with altered behavior and disrupted neurodevelopment (Fiala et al., 2002; Hering and Sheng, 2001; Sala and Segal, 2014). Hypoxia as a result of severe asthma attacks also poses significant risk to brain function leading to depression (suppressed brain activity) of the CNS that could impact behavior and brain functioning (Eckert et al., 2004).

Asthma can occur in an individual throughout a lifetime affecting multiple neuronal functions such as synaptogenesis, myelination and synaptic pruning, at different developmental times. When these impacts

occur may affect which neuronal circuits become altered and ultimately what behavioral impairments are presented. The allergic response itself in each individual can be diverse as discussed above (e.g., allergic, neutrophilic, medication resistant, etc.) and may thus elicit differential effects on neural circuits and behaviors. Moreover, developmental changes such as release of hormones during adolescence, genetic vulnerabilities or epigenetic changes could affect behavioral outcomes. Asthma may not only cause disruption of neural circuits and pathways through a general increase in peripheral immune responses, but it is also possible that asthma responses exacerbate already existing CNS diseases. The general inflammation caused by allergic or neutrophilic asthma could also interact with genetic or epigenetic susceptibilities to worsen existing CNS diseases or vulnerabilities. In fact, asthma and neuropsychiatric conditions/neurodevelopmental conditions could share common gene-environment vulnerabilities. These are areas of research that warrant further investigation.

3.2. Asthma and neurodevelopmental disorders

Autism spectrum disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are two highly prevalent neurodevelopmental disorders that often co-occur with an asthma diagnosis and individuals are frequently prescribed medications for both conditions (Fasmer et al., 2011). Environmental factors such as exposure to smoking and psychosocial stress appear to play a role in this relationship (Holmberg et al., 2015), and those with inflammatory disorders and atopic diseases are more often diagnosed with ADHD (Leffa et al., 2018; Chuang et al., 2022). In a recent *meta*-analysis that included studies of more than 25,000 individuals, a positive association between atopic diseases, such as asthma, with ADHD diagnosis and severity of ADHD symptoms was noted (Chuang et al., 2022). Similarly, in a Swedish study of 1,575,377 individuals, a significant association between asthma and ADHD was observed (odds ratio: 1.60) (Cortese et al., 2018).

Like ADHD, ASD represents a prevalent disorder that appears to be on the rise (Maenner et al., 2021), and asthma and ASD represent two of the most common childhood afflictions. Altered immune function is suspected to be involved in both ASD and asthma (Hughes et al., 2023; Jónsdóttir et al., 2017; Torpy et al., 2010), with both diagnoses more prevalent in boys (Jónsdóttir et al., 2017). Like asthma, ASD places increased financial, social, and mental health burdens on diagnosed individuals and their surrounding community, especially for those with more severe cases of the disorder (Patel et al., 2018). It was observed in three cross-sectional population-based studies that parents of individuals with ASD were more likely to report asthma among their children than those without ASD (odds ratios, 1.35–1.74) (Chen et al., 2017; Kotey et al., 2014; Schieve et al., 2012). Interestingly, branching anomalies of subsegmental airways have been described among ASD individuals (Stewart & Klar, 2013), which could impact asthma severity. In addition, children with ASD and asthma were more frequently prescribed asthma controller medications (Jónsdóttir et al., 2017). Lyall et al. found that food allergies were more common in children with ASD and observed a modest association between allergies and higher stereotypy scores in children with ASD (Lyall et al., 2015). Higher frequency of food allergies among individuals with ASD were also reported by Jyonouchi et al. in 2008 (Jyonouchi et al., 2008). This group found that non-IgE mediated allergies are more frequently found among autistic individuals (Jyonouchi, 2010). Of note, non-IgE-mediated asthma, or non-atopic asthma, accounts for approximately 20 % of asthma cases, and is mediated by antibodies other than IgE (Quirce, 2009).

Some researchers have found T_H2 skewed cytokine levels in individuals with ASD (Gupta et al., 1998; Molloy et al., 2006), and there is also evidence of mast cell activation in ASD children (Theoharides, 2009). Two of the main cytokine mediators of an allergic response, IL-5 and IL-13, were found to be elevated in serum samples of high-functioning ASD males (Suzuki et al., 2011). In a case control study, peripheral blood mononuclear cells (PBMC) from children with ASD produced higher IL-4, IL-5, and IL-13 at baseline when compared to controls (Molloy et al., 2006). Also related to asthma, two chemokines associated with neutrophil and eosinophil recruitment, eotaxin and IL-8, were found to be elevated in neonatal blood spots of children later diagnosed with ASD (Heuer et al., 2019). Moreover, IL-8 and eotaxin were found to be significantly elevated in plasma samples of ASD children, with eotaxin elevations being associated with more impaired behaviors (Ashwood et al., 2011a; Ashwood et al., 2011b).

Neutrophils and eosinophils play a significant role in airway and lung inflammation (Pease & Williams, 2001; Pease & Sabroe, 2002), and increased levels of the chemoattractants eotaxin and IL-8 in ASD suggests the potential for worsening of asthma symptoms in these individuals. Research suggests that individuals with ASD are more prone to a pro-inflammatory status, with significant elevations of IL-1β, IL-6, and IL-12p40 in plasma from children ages 2–5 (Ashwood et al., 2011b), as well as IL-1β, IL-6, IL-12, IL-23, and TNF-α found in serum samples of ASD individuals ranging from 2 to 21 years of age (Ricci et al., 2013). These elevated cytokines were observed on a background of decreased regulatory cytokines such as transforming growth factor (TGF) beta 1 and IL-35, indicating heightened inflammation without concomitant suppression from regulatory mechanisms (Ashwood et al., 2008; Rose and Ashwood, 2019). After activation, T_H2 cellular responses were associated with more severe impairments in children with ASD (Careaga et al., 2017). Moreover, PBMC stimulated by gliadin, cow's milk protein or soy, from individuals with ASD produced twice as much TNFα compared to controls (Jyonouchi et al., 2001). Antibodies against gliadin and cow's milk were increased in ASD patients, and these antibodies shared cross-reactivity with cerebellar peptides (Vojdani et al., 2004). Although not directly linked to asthma, food allergies and associated gastrointestinal abnormalities are significantly linked to ASD in many epidemiology and animal studies (de Theije et al., 2014; Jyonouchi et al., 2008; Jyonouchi, 2010; Nemet et al., 2022; Rose et al., 2018; Rose et al., 2020; Xu et al., 2018). With T_H2 skewed cytokine elevations and cellular responses associated with ASD, and the epidemiology links to allergy and asthma among ASD individuals, the potential for allergy related immune dysfunction in ASD is considerable.

3.3. Asthma during pregnancy and developmental impacts to offspring

Asthma is a common disease during pregnancy impacting an estimated 8–13 % of pregnant women worldwide (Murphy, 2022). Asthma symptoms worsen during pregnancy for approximately 40 % of individuals causing changes in the respiratory system and a shift from T_H1 immune dominance in the first trimester to T_H2 immune dominance during the second and third trimester (Bravo-Solarte et al., 2023). Asthma symptom changes can be unpredictable and are likely related to whether the asthma is IgE mediated or has a cellular basis (Grosso et al., 2018; Kircheret al., 2002). Exacerbations can occur frequently and may require medical intervention for up to 45 % of pregnant women (Murphy et al., 2010; Schatz et al., 2003). There also appears to be a link between women with increased risk of having uncontrolled asthma and neuropsychiatric disorders during pregnancy, particularly regarding anxiety and depression (Grzeskowiak et al., 2017). For example, a Danish study of 1,000 pregnant women with asthma enrolled between 2007 and 2014 reported that 6.1 % suffered with a new onset psychiatric condition (Ali et al., 2016). Asthma can also increase complications in pregnancy such as preeclampsia, gestational diabetes, premature contractions, placenta previa and premature ruptures of membranes (Dombrowski et al., 2004; Källén et al., 2000; Rejnö et al., 2014; Wen et al., 2001; Whalen et al., 2019). Postnatal complications in offspring have been identified as well, with some studies identifying associations between maternal asthma and low birth weight in offspring and/or being small for gestational age (Breton et al., 2009; Rejnö et al., 2014). These associations to low birth weight and small gestational age are stronger in cases of severe asthma and where there is poor asthma control (Namazy et al., 2013).

There have been recent investigations into the link between maternal asthma and increased risk of neurodevelopmental disorders in offspring. For instance, a Norwegian study of 2,322,657 residents found 50 % higher odds of ADHD among children whose mothers had asthma during pregnancy (Instanes et al., 2017). Additionally, a Danish population-based study of 961,202 individuals found associated risk of ADHD among children born from mothers or fathers with asthma, but higher associated risk among those children from mothers with asthma (Hazard ratio: 1.41) (Liu et al., 2018). Leonard et al. reported that asthma was associated with an increased odds of mild to moderate risk for offspring intellectual disability in a cohort of 2,865 subjects (odds ratio: 1.52; confidence intervals: 1.26–1.83) (Leonard et al., 2006).

Another neurodevelopmental disorder in offspring with strong links to maternal allergic asthma exposure is ASD (Abdallah et al., 2011; Ali & Ulrik, 2013; Croen et al., 2005; Croen et al., 2019; Croen et al., 2023; Fasmer et al., 2011; Gong et al., 2019; Hisle-Gorman et al., 2018; Langridge et al., 2013; Lyall et al., 2014; Murphy, et al., 2005; Murphy et al., 2006; Patel et al., 2020). Moreover, maternal asthma was found to be linked to increased risk for ASD even when treated (Croen et al., 2019). In a population-based study of 407 cases of ASD, Croen et al. found a two-fold elevated risk of ASD in offspring when mothers experienced new onset diagnosis of maternal allergy and asthma during pregnancy (Croen et al., 2005). Data collected from the Study to Explore Development (SEED), which was a study of children born 2003–2006 in the US, reported that history of maternal asthma increased odds of both ASD and developmental disorders by 20%-40% (Croen et al., 2019). In particular, maternal asthma was associated with increased risk of ASD with intellectual disability and developmental regression (Croen et al., 2019). This finding of symptom severity is supported by a study performed using data from the Western Australian Autism Biological Registry (WAABR), where asthma and allergies during pregnancy were found to be associated with a twofold elevated risk of ASD (Patel et al., 2018) Symptom severity was worse in ASD children whose mothers had asthma during pregnancy (Patel et al., 2018). A recent study of 363 ASD children from the Autism Phenome Project (APP) and Girls with Autism Imaging of Neurodevelopment (GAIN) study, found that asthma was the most common maternal immune condition or maternal infection linked to ASD cases (23.95 %). Maternal asthma during pregnancy was twice as common among male children diagnosed with ASD than with female children diagnosed with ASD. However, the female children with ASD that were born to mothers with maternal asthma during pregnancy showed increased scores on the Child Behavior Checklist and greater ASD impairment (Patel et al., 2020). In addition, maternal asthma was found to increase risk of autism with gastrointestinal disturbances (odds ratio 1.39; confidence intervals 1.17–1.67) relative to ASD with no gastrointestinal issues (Carter et al., 2022).

As with asthma itself, there does not appear to be a single etiology associated with ASD. However, inflammation during gestation has been strongly linked with having a child that will go on to develop a neurodevelopmental disorder. Specifically, the elevation of several cytokines has been implicated, and many of these are directly linked to an allergic response. For instance, elevations of three cytokines associated with a human allergic asthma response IFN-γ, IL-4 and IL-5, during mid-pregnancy were found to be associated with mothers bearing a child with ASD (Goines et al., 2011). In the large prospective study of Early Markers in Autism (EMA), several cytokines were reported to be elevated in mothers during mid-gestation whose children were later diagnosed with ASD and included granulocyte–macrophage colony-stimulating factor (GM-CSF), IFNγ, IL-1α, IL-6, IL-8 and monocyte chemoattractant protein-1 (MCP-1) (Jones et al., 2017). In the same study, Jones et al. also identified that higher levels of maternal IL-4 were associated with ASD severity and an increased risk of ASD with intellectual disability (ID) when compared to ASD without ID (Jones et al., 2017). In the amniotic fluid of individuals with ASD, elevated levels of IL-4, IL-10, TNFα and TNFβ have been noted compared to controls with no psychiatric comorbidities (Abdallah et al., 2013). MCP-1 was found to be significantly elevated in amniotic fluid of ASD cases compared to age and gender matched controls (Abdallah et al., 2012). Moreover, the Childhood Autism Risks from Genetics and the Environment (CHARGE) study found that IL-4 and IL-1β were elevated in newborn blood spots of children later diagnosed with ASD, with IL-4 associated with increased odds of severe ASD (odds ratio 1.40; confidence intervals 1.03–1.91) (Krakowiak et al., 2017). Together these case-control studies identified several asthma-associated cytokines are elevated in pregnancy and newborn tissue of offspring at increased risk for ASD.

Most studies on asthma and the CNS focus on allergic asthma, and little is known on how neutrophilic asthma may impact the brain. Patients with neutrophilic asthma often respond poorly to typical asthma treatments and have more severe asthma than those with allergic asthma who have no neutrophilic invasion of the lungs (Seys et al., 2019). T_H17 cytokines are an important factor in neutrophilic asthma and increased asthma severity (Margelidon-Cozzolino et al., 2022; Newcomb and Peebles, 2013). T_H17 cytokines have also been implicated in neurodevelopment and neuroinflammation (Choi et al., 2016). In the serum of ASD patients, IL-17a is increased (Al-Ayadhi and Mostafa, 2012), and IL-17 production and T_H17 are more numerous in children with ASD and inflammatory co-morbidities (Akintunde et al., 2015; Rose et al., 2020). These data suggest that the T_H17 pathway and neutrophilic asthma should be investigated in comparison to allergic asthma in studies of neurodevelopmental outcomes.

4. Animal models of maternal asthma and neurodevelopment

Several animal studies have found underlying mechanisms by which maternal immune activation (MIA) leads to neurodevelopmental disorders. Infections, mimics of infections and single cytokines have been studied in the context of MIA. IL-6 administration on its own has been shown to cross the placental barrier and alter fetal brain development in models of MIA (Dahlgren et al., 2006; Smith et al., 2007). IL-6 is considered a differentiating factor for IL-17 producing cells and IL-17 pathways have also been shown to contribute to behavioral outcomes of MIA (Choi et al., 2016). In a mouse model of MIA, Choi et al (2016) found that IL-17a and T_H17 cells are necessary for the model's altered behavioral phenotype and altered cortical development in fetal brains. It has been postulated that systemic maternal inflammation "programs" the offspring to be more susceptible to altered neurodevelopment through inflammatory signaling and epigenetic mechanisms (Han et al., 2021; Straub & Schradin, 2016). The potential mechanisms require signaling through Toll-like receptor pathways either by pathogen associated molecular patterns or by damage associated molecular patterns produced as a result of maternal immune responses. Fetal tissue and immune cell development are also affected by MIA leading to increased immune responses in the offspring tissue (Boktor et al., 2022; Onore et al., 2014; Rose et al., 2017; Tamayo et al., 2022) This includes innate immune cells in the brain such as microglia that also appear to be programmed by MIA, exhibiting altered phenotypes than those in control mice (Loayza et al., 2023). Altered microglia priming by maternal inflammation could lead to altered synaptic pruning that impacts healthy neural connections and brain growth. Animal models have also shown structural changes in the brains of MIA offspring. In an MRI study, it was found that the size of the cerebellum, olfactory bulb, thalamus, and parts of the cortex were decreased and interhemispheric connections were altered (Kreitz et al., 2020).

Considering the growing body of research demonstrating links between maternal asthma and offspring neurodevelopment deficits, we developed a novel model of maternal allergic asthma (MAA) where altered behaviors were exhibited in offspring of dams whose immune system was challenged by MAA during gestation. The dams were sensitized to ovalbumin (OVA) and later challenged with maternal asthma during pregnancy. The dams display elevations in the cytokines associated with a typical allergic response, such as IL-4, IL-5, and IL-13, but also those associated with severe chronic and neutrophilic asthma

such as IL-6 and IL-17 (Church et al., 2021; Tamayo et al., 2022). The offspring from these MAA mice display two core characteristic behaviors associated with ASD, specifically a decrease in social interaction and increase in repetitive-like behaviors (Church et al., 2021; Schwartzer et al., 2015; Schwartzer et al., 2017). Neurobiological changes in the offspring that echo phenotypic changes associated with human ASD cases were also observed. For instance, Vogel-Ciernia et al. found that adult microglia taken from offspring of MAA dams have altered DNA methylation patterns compared to wild-type microglia (Vogel Ciernia et al., 2018). Many of these changes were in immune regulatory genes shared with ASD individuals and in risk factor genes associated with autism as listed on the Simons Foundation Autism Research Initiative (SFARI) (Vogel Ciernia et al., 2018). Using a model of allergic asthma in rats, Lenz et al showed that maternal allergic asthma resulted in altered mast cells and microglia in the offspring brain as well as differences in dendritic spine patterning on neurons in neonates. The authors suspect that these findings may be linked to the social impairments, hyperactivity, and cognitive inflexibility behaviors in their model (Breach et al., 2021; Lenz et al., 2019). Breach et al further reported that dendritic spine densities varied by region in MAA offspring (Breach et al., 2022). Moreover, after MAA there were changes in the neuroimmune environment in offspring fetal brains such as increased proinflammatory cytokines GM-CSF, IFNγ, IL-1α, and IL-6 (Tamayo et al., 2022; Tamayo et al., 2023). Importantly, MAA also appeared to alter the brain neuroimmune environment into adulthood, as cytokine differences were also identified in the hypothalamus in adult offspring (Church et al., 2021). Together, these studies recapitulate findings in human postmortem ASD studies where neuroinflammation and functional differences in microglia have been observed (Li et al., 2009; Koyama and Ikegaya, 2015; Morgan et al., 2010; Morgan et al., 2014).

5. Asthma exacerbations and where to look next

As mentioned previously in this review, worsening of asthma symptoms can often occur during pregnancy, and exacerbations can worsen associated comorbidities, including those that occur in offspring of mothers with asthma. As such, it is important to investigate the myriad environmental factors that contribute to asthma and asthma exacerbations. Allergens, respiratory infections, fungus, air pollution, and particulate matter are well known triggers for asthma attacks (Del Giacco et al., 2017; Herr et al., 2010; Holgate et al., 2015; Zhuang et al., 2018). Common indoor allergens such as house dust mite (HDM), cat and dog dander, and cockroaches also pose a significant risk (Baxi & Phipatanakul, 2010; Custovic et al., 1998). Importantly, these allergens often co-occur in our environment resulting in multi-allergen exposures that can exacerbate asthma expression. Studies to date have focused on the impact of a single allergic insult on maternal and offspring health. While these studies are important for identifying the mechanistic links between asthma and brain health, they are limited in modeling the cocktail of environmental factors that likely impart converging, additive or synergistic outcomes.

Animal models of asthma exacerbation most often use allergic asthma models of OVA or HDM sensitization, and frequently investigate the contribution of viral infections and environmental pollutants to asthma exacerbations. Although exposure to a sensitizing allergen alone can trigger exacerbations, research suggests that these cases are relatively uncommon (Maltby et al., 2017). Mouse models investigating the link between viral infection and asthma exacerbation are limited, however, due to the inability of human rhinovirus (HRV) to infect mouse cells (Maltby et al., 2017). Due to this limitation, investigators will often use viral analogs, such as double-stranded RNA, or the HRV minor group human rhinovirus 1B (HRV1B), as the major group HRV cannot readily infect mouse cells (Maltby et al., 2017). There are far fewer studies investigating fungal related asthma exacerbations but among these, one investigation using Alternaria extract exposure to chronically challenged allergic mice identified increased airway hyperresponsiveness, immune cell infiltration of the lungs, as well as an increased T_H2 response (Snelgrove et al., 2014). The link between contributing factors such as viral infections and MAA on behavioral outcome in the offspring is an area warranting more research.

Obesity is another factor that can lead to asthma exacerbations. Severe asthma and asthma exacerbations have been associated with obesity in population studies (Barros et al., 2017; Schatz et al., 2013). Hospitalizations for asthma were also increased in obese patients, as well as the length of hospital stay (Hasegawa et al., 2014; Luthe et al., 2018). Obesity, like asthma, is associated with an increased risk of neurodevelopmental and neuropsychiatric disorders in the offspring (Edlow, 2017; Li et al., 2016; Reynolds et al., 2014; Sullivan et al., 2015). The neurodevelopmental impact of combined asthma and obesity has not yet been studied in depth; however, a recent report showed a link between maternal asthma combined with obesity and increased risk of ASD, with the risk increasing as obesity became more profound (Croen et al., 2023).

Perhaps more easily modeled in rodents are exposures to environmental pollutants and the impacts of these exposures on allergic asthma. It was demonstrated in a model of allergic asthma that concentrated ambient particle administration and ozone exposure increased airway hyperresponsiveness and increasing allergy-associated cytokine release (North et al., 2011; Kierstein et al., 2008). In a model of chronic asthma via OVA sensitization, PM_{10} exposure following asthma challenge resulted in increased lung inflammation. Similarly, diesel exhaust exposure resulted in increased airway inflammation, mucus secretion, and increased inflammatory cytokine production (Maltby et al., 2017). An understudied question is how asthma exacerbation via other environmental factors impacts pregnancy outcomes and what impacts this may have on offspring neurodevelopment. Research using animal models of prenatal PM exposure have identified evidence of neurodevelopmental delays associated with prenatal PM exposure (Church et al., 2018; Zheng et al., 2019). Moreover, models of asthma and PM exposure identify heightened allergic responses, such as upregulated IL-4, IL-5, IL-6, and IL-13 (Wu et al., 2018), the same cytokine profile associated with maternal inflammation and offspring neurodevelopmental deficits. Together, these studies illustrate the utility of animal models in the investigation of mechanisms underlying asthma exacerbation with environmental pollutants and their links to brain health and neurodevelopment.

6. Conclusion

Asthma represents a pervasive chronic disease that negatively impacts behavior in individuals and their offspring. The immune mechanisms underlying this heterogenous disease are not well understood, but various types of inflammation play an important role. This inflammation and the severity of the asthma response can vary dramatically depending on several factors including sensitized allergens, comorbidities, age, genetic susceptibility, infection, and environmental factors. Comorbid neuropsychiatric disorders appear to have a particular importance given their high prevalence among asthmatic individuals. Additionally, the risk factors for asthma exacerbation can confer increased risk for pregnant mothers and their offspring. Pregnancy outcomes can be worsened by asthma and there are also potential long-term impacts on offspring that can result in a significant risk of childhood asthma and neuropsychiatric disorders, such as ASD and ADHD. This is an important gap in the literature considering that individuals are rarely exposed to only a single environmental insult. Importantly, to our knowledge, there are no studies investigating the combined impact of maternal allergic asthma and exacerbating exposure during pregnancy on neurodevelopmental outcomes in the offspring. More likely, individuals are exposed to multiple asthma-associated environmental triggers concurrently and the combined effects contribute to later life and transgenerational impacts to mental health. As such, it is necessary for researchers to explore these questions to uncover the impacts of multiple inflammatory insults, such

as PM exposure and asthma combined, may have on offspring, and how these concomitant triggers may be contributing to the rise in neurodevelopmental disorders such as ASD and ADHD.

Data availability

Data will be made available on request.

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