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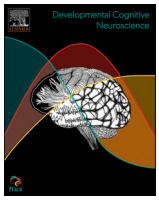

Neurocognitive risks of asthma during childhood

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ABSTRACT

The impact of chronic medical conditions on the developing brain has gained recent attention, but the neurocognitive risks associated with asthma, which has high prevalence in childhood, are still largely unknown. Recent findings have underscored that children with asthma may be at higher risk for developing cognitive difficulties. In this review, we examine the pathophysiology of asthma and its associations with brain and cognitive development based on rodent models and relatively scant research in humans. We also examine risk factors that may exacerbate asthma symptoms and neurocognitive outcomes, and we discuss why children may be particularly vulnerable to asthma-related neurocognitive consequences. We conclude by providing a framework for future research.

1. Neurocognitive risk of asthma during child development

Over the last decade, research into the impact of chronic medical conditions on the developing brain has been burgeoning (Compas et al., 2017; Ghetti et al., 2023, 2020, 2010; Myers et al., 2020; Nishat et al., 2023; Schmithorst et al., 2022; Schwartz et al., 2014). Advances in life-extending and disease-managing medications, paired with the development of cutting-edge investigative methods supporting in vivo neuroimaging and cognitive assessment, have afforded new insight into neurocognitive risks associated with chronic medical conditions. Although there is considerable research into neurological consequences of these conditions in adults (Chang and Shukla, 2018; Christopher-Hayes et al., 2021; Embury et al., 2018; Heaton et al., 2010), research in children lags behind (Compas et al., 2017). However, children with chronic medical illnesses, including but not limited to type 1 diabetes (Aye et al., 2018; Cameron et al., 2019; Ghetti et al., 2023, 2020; Schwartz et al., 2014), congenital heart disease (Aleksonis and King, 2023; Brossard-Racine and Panigrahy, 2023; Schmithorst et al., 2022) and obesity (Bantulà et al., 2021; Bozkurt et al., 2017; Liang et al., 2014; Tsai et al., 2016), may be at greater risk for developing neurocognitive difficulties.

Asthma is one of the most frequent chronic diseases in children in the US (Bitsko et al., 2014; CDC, 2024; Centers for Disease Control and Prevention, 2020; Lizzo et al., 2025; Miller et al., 2016; Nunes et al., 2017a; Pate et al., 2021), yet it is one of the least studied for its neurocognitive profile. Recent evidence from rodent models (Guo et al., 2013; Xia et al., 2014) and human studies (Christopher-Hayes et al., 2024; Rosenkranz et al., 2022) has highlighted putative mechanisms of neural injury (e.g., neuroinflammation) and cognitive impairment in asthma (Fig. 1). These risks and implications for neurocognitive development are still largely unknown.

The current review seeks to examine the extant body of research highlighting neurocognitive consequences of asthma, and to situate it within the broader context of child development. Specifically, we will: (1) outline the significance of studying asthma; (2) describe mechanisms of injury and associated cognitive effects; (3) highlight exacerbating factors (e.g., environmental variables) of neurocognitive risk; and (4) generate hypotheses regarding differential effects across developmental periods and to guide future research aimed at clarifying risk.

2. Why Study Chronic Asthma?

Asthma is a common disease accompanied by respiratory symptoms, such as limited expiratory airflow and bronchial hyperresponsiveness (Nunes et al., 2017a; Stanescu et al., 2019; Wenzel, 2012) and can affect people of any age (CDC, 2024; Nunes et al., 2017b). However, chronic asthma frequently emerges in childhood and currently affects about 5 million children in the United States with individual variability as far as whether symptoms persist throughout the lifetime (Bitsko et al., 2014; Lizzo et al., 2025; Nunes et al., 2017a; Stanescu et al., 2019).

The societal impact of asthma is vast. Although mortality rates have steadily declined, incidence rates have markedly increased (Nunes et al.,

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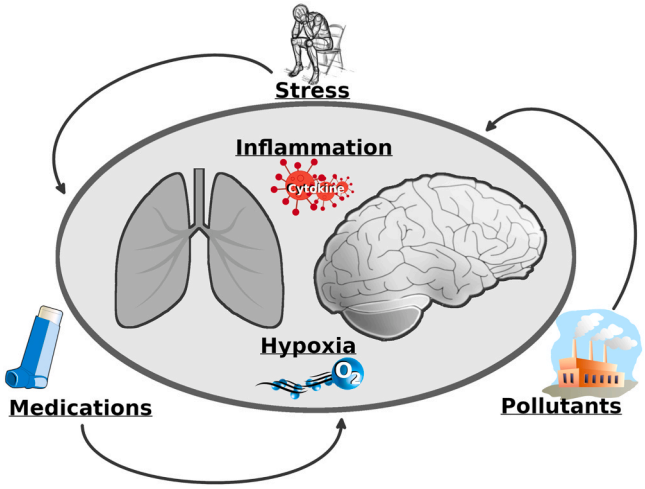

Fig. 1. Illustration of the key neurocognitive risk factors associated with asthma: inflammation, hypoxia, medications, and environmental factors including stress and pollutants.

2017a). These seemingly contradictory trends have been thought to reflect modernization in two ways. On the one hand, treatment and disease control has improved and lowered mortality; on the other hand, increased exposure to environmental risk factors has been associated with rising incidence (Nunes et al., 2017a). Overall, the current estimates suggest that asthma costs over ~$USD 70 billion annually in the United States (Nunes et al., 2017a).

In addition to problems with physical health due to respiratory symptoms, research has uncovered possible psychological and behavioral consequences of the disease, such as increased fatigue, anxiety and depression, occupational deprivation, and suicidal tendencies (Bitsko et al., 2014; Blackman and Gurka, 2007; Caulfield et al., 2021; Hoffman et al., 2022; Katon et al., 2007; Lahaye et al., 2012; McQuaid et al., 2001; Rosenkranz and Davidson, 2009; Stanescu et al., 2019; Yuksel et al., 2008). Despite these far-reaching consequences, research on the connection between asthma and neurological factors has primarily focused on neural substrates underlying breathing functions in search for novel treatments and therapeutics (Busse, 2012; Davenport et al., 2000; Fauroux et al., 2007; Vafaee et al., 2022; von Leupoldt et al., 2009a).

Recent studies involving rodent models and human adults have shown that asthma may be associated with neurological consequences (Guo et al., 2013; Hopkins, 2010; Hu et al., 2024; Irani et al., 2017; Kroll and Ritz, 2023; Nair et al., 2023; Rosenkranz et al., 2022; Wang et al., 2023; Y. Wang et al., 2023; Woodrow et al., 2023; Xia et al., 2014; Zhu et al., 2023). However, research has largely neglected their examination in children. Thus, many open questions remain about the consequences of chronic asthma on children's neurocognitive development.

3. Mechanisms of neural injury and related cognitive consequences

Neural injury in asthma is likely multi-determined. Here, we review research examining putative brain injury mechanisms due to either the pathophysiology of asthma or the medications used to treat it, including their associations with neurocognitive outcomes.

3.1. Asthma pathophysiology and consequences

Despite ongoing debates regarding the exact pathophysiology of asthma, respiratory symptoms such as shortness of breath, wheezing, and coughing are reportedly the result of ongoing inflammatory processes and airway remodeling (Bantulà et al., 2021; Michaeloudes et al., 2022; Page, 1991; Wenzel, 2012). Asthma has been shown to manifest as different phenotypes (Wenzel, 2012) which have been attributed to some combination of host (e.g., genetic predisposition, immune system function, inflammation regulation, oxidative stress) and environmental factors (e.g., air pollution)(Michaeloudes et al., 2022; Papi et al., 2018; Wenzel, 2012; Woodrow et al., 2023). However, the present review operationalizes asthma as an all-encompassing umbrella term because extant work does not make any such distinction due to the fact that inflammatory processes are a shared pathophysiology across phenotypes.

Importantly, there is evidence that inflammatory mechanisms may operate more systemically, involving both local inflammation in the lungs and neuroinflammation in the brain (Fig. 1) (Albéri, 2013; Busse, 2012; Chen and Miller, 2007; Hu et al., 2024; Kroll and Ritz, 2023; Rosenkranz et al., 2022; Y. Wang et al., 2023; Xia et al., 2014). Moreover, several asthma symptoms necessarily disrupt oxygen intake, known as asthma-induced intermittent hypoxia, which can result in hypoxic ischemic stroke and injury in the brain (Fig. 1) (Bierman et al., 1975; Feigin et al., 1973; Omata et al., 2003; CDC, 2024; Hopkins, 2010; Li et al., 2023; Nwaubani et al., 2022; Takada et al., 2015). If asthma is associated with either systemic inflammatory processes extending to the brain or hypoxic injuries, we would expect brain regions with high sensitivity to both neuroinflammation and oxygenation to be affected (Barrientos et al., 2015, 2009; Nwaubani et al., 2022). In the next sections, we examine available evidence that neuroinflammation may underlie neurocognitive difficulties in asthma.

3.1.1. Non-human animal studies

Research with rodent models has begun to elucidate putative mechanisms of neural injury in asthma. Moreover, a growing body of work illustrates cognitive deficits resulting from such injury. Both lines of work are reviewed in the following sections.

3.1.1.1. Neural indices. Research using rodent models of asthma has focused primarily on injury of the hippocampus (Guo et al., 2013; Ren et al., 2021; Xia et al., 2014; Zhuang et al., 2018). The hippocampus is a structure located in the medial temporal lobe and is comprised of histologically distinguishable subfields (Cornus ammonis, CA1–4; Dentate Gyrus, DG; Subiculum) (Duvernoy, 2005) which support our ability to encode, store, and retrieve episodic memories (Eichenbaum, 2017; Eichenbaum and Cohen, 2004; Ekstrom and Ranganath, 2018; Tulving, 1972). The hippocampus displays a dense microglial population (microglia are often used as a marker of neuroinflammatory response), as well as high expression of interleukin (IL) −1 receptors (regulating response to inflammation) on neurons and glia in the granule cells of the DG and the pyramidal cell layer of the hippocampus, making this structure particularly likely to exhibit neuroinflammatory responses and associated injury (Barrientos et al., 2015, 2009). To examine this possibility, Xia and colleagues (2014) used a mouse model of asthma by first sensitizing two-month-old mature animals (i.e., later-onset) to a foreign protein in the first 15 days after birth, followed by a consistent but subtle airway challenge of antigen exposure over the course of 9 weeks, with intermittent periods of additional and intensive repeated exposure to aggravate the airway. They found that the asthmatic mice compared to control mice exhibited significantly more microglia activation in the hippocampus. Moreover, this increased neuroinflammation was accompanied by neuronal loss, indicating that asthma not only produced a neuroinflammatory response, but also tissue damage in the hippocampus (Xia et al., 2014). The effects extended beyond the hippocampus as indicated by increased proinflammatory cytokine concentrations and neuronal loss in the prefrontal cortex (PFC). These results highlight that neuroinflammatory mechanisms may be at least in part responsible for neural injuries, thereby linking neuroinflammatory factors in asthma to changes in brain structure (Xia et al., 2014). Future studies are needed to determine the extent to which age at onset moderates

neuroinflammatory effects. This information would help ascertain developmental periods of increased risk for neural injury.

Hippocampal injury may also be associated with those asthma symptoms that disrupt oxygen homeostasis, such as is the case during events of cerebral hypoxia (Bierman et al., 1975; Guo et al., 2013; Ren et al., 2021; Takada et al., 2015; Zhuang et al., 2018). Using a mouse model of asthma following the same sensitization procedure described earlier (Guo et al., 2013; Xia et al., 2014; Zhuang et al., 2018), Guo and colleagues (2013) used adolescent mice, and compared two earlier-onset asthma groups (asthma with medication, asthma without medication) with one control group without asthma. The authors employed High-Frequency Stimulation (HFS), a neurostimulation protocol used in rodent studies to modulate synaptic function and induce Long Term Potentiation (LTP), to explore mechanisms of learning and memory within hippocampal subfields. Specifically, they investigated LTP in the CA1 both before and after HFS was applied to the CA3, and reported several notable results. First, hypoxia-inducible-factors which regulate cellular responses to hypoxia were significantly upregulated in the hippocampus of asthma groups, indicating asthma-induced hypoxia affected the hippocampal structure (Guo et al., 2013). Second, LTP maintenance after HFS was significantly reduced in the asthma groups as compared to controls, and was related to synaptic malfunction as demonstrated by asthma-related reductions in total CA3 synapses (Fig. 2), synaptic vesicles, and overall synapse densities, as well as damaged mitochondria (swollen or broken membranes) (Guo et al., 2013). Moreover, the effects of asthma extended beyond the synapse to affect neuronal morphology, such as reducing CA1 and CA3 dendritic length and branches, as well as DG dendritic spine density (Zhuang et al., 2018). These findings provide a critical link between incidents of cerebral hypoxia induced by chronic asthma and neural injury in the hippocampus (Guo et al., 2013; Zhuang et al., 2018). Collectively, these data suggest that neural injury in asthma may result from distinct and complementary mechanisms. Moreover, they indicate that earlier-onset asthma may increase susceptibility to deleterious neural effects associated with disruptions to oxygen homeostasis, Next we discuss the implication of these findings on behavioral outcomes.

3.1.1.2. Behavioral indices. The evidence of neural injury raises the question of whether tangible behavioral effects may be observed. In the study by Guo and colleagues (2013), rodents were also administered the Morris Water Maze task to examine learning and memory outcomes. The authors reported that the asthma and control groups took a similar amount of time to find the elevated platform on day 1 of training. However, asthmatic mice took significantly more time than control mice to find the target for days 2–4 of training (Fig. 2)(Guo et al., 2013), a pattern of results that were later replicated in an independent sample (Zhuang et al., 2018). Thus, rodents with asthma showed worse memory than controls, despite similar ability to perform the task. Notably, asthma-related reductions in learning rates and memory performance were associated with hippocampal injuries in adolescent and mature rodents (Guo et al., 2013; Ren et al., 2021; Zhuang et al., 2018). Results from these animal models converge in highlighting risk of hippocampal injury associated with asthma.

3.1.2. Human studies

Only a handful of studies have begun to examine neurocognitive

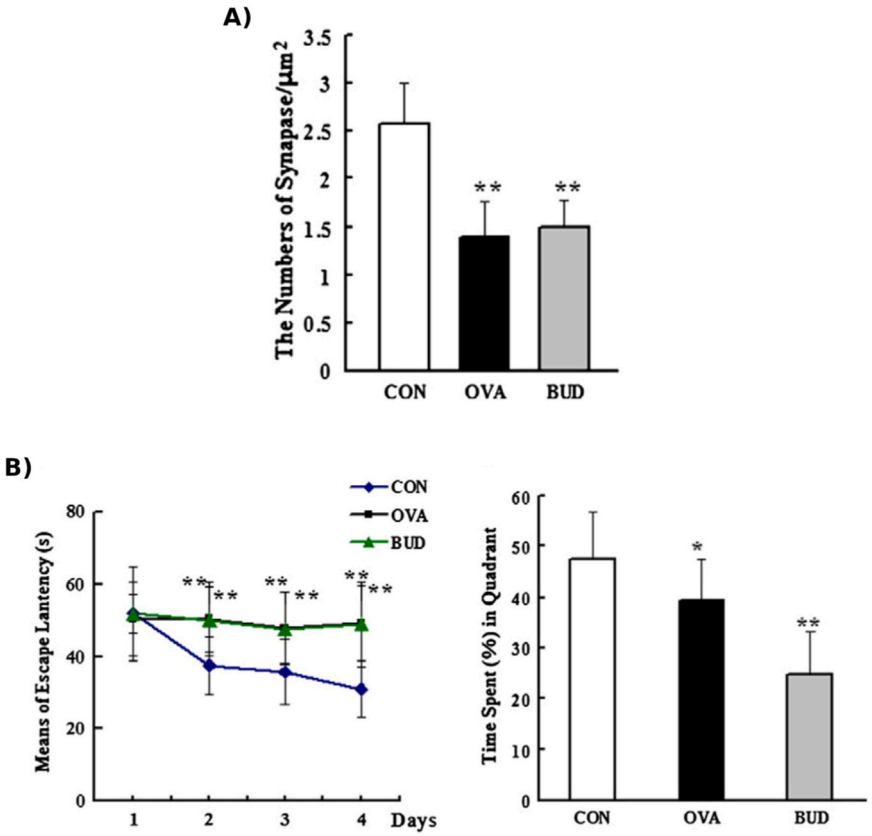

Fig. 2. A) Effects of chronic asthma on the CA3 ultra-structures of mouse hippocampus. Synapse numbers of CA3 in control group (CON), asthmatic group (OVA) and budesonide-treated asthmatic group (BUD). B) Effects of chronic asthma on the learning and memory ability of mice in the water maze test. A. Latency periods to find the hidden platform over 4 consecutive training days were shown. B. The percentage of time spent in target quadrant in three groups. *p < 0.05, * *p < 0.01 vs. control group. CON: control group; OVA: asthma model group; BUD: budesonide-treated asthma model group. Adapted from Guo, R.-B., Sun, P.-L., Zhao, A.-P., Gu, J., Ding, X., Qi, J., Sun, X.-L., Hu, G., 2013. Chronic asthma results in cognitive dysfunction in immature mice. Experimental Neurology 247, 209–217. https://doi.org/10.1016/j.expneurol.2013.04.008.

risks associated with asthma in humans, with the majority focused on adults with asthma, and very few examining asthma in children. This emerging literature is reviewed next.

3.1.2.1. Neural indices. Given the evidence from non-human animal models, it is reasonable to hypothesize asthma may be associated with neural changes in humans. The focus on hippocampal injury and memory in rodent models presents mechanistic hypotheses for human investigations. For example, Carlson and colleagues (2017) reported that among a large sample of adults (32–52 years), those who reported suffering from asthma compared to those who did not exhibited significantly smaller hippocampal volumes controlling for sex and education level, which aligns with findings in animal models showing hippocampal injury (Guo et al., 2013; Xia et al., 2014; Zhuang et al., 2018). In two smaller studies of adults (18–45 years) (Kroll et al., 2018a; Ritz et al., 2020), no group differences in hippocampal volumes were observed between adults with and without asthma. However, using Magnetic Resonance Spectroscopy, they found significantly reduced levels of several hippocampal metabolites – which represent neuronal viability and have been shown to predict disease progression and future cognitive decline (Fig. 3)(Kroll et al., 2018a). Given the difference in age groups between these studies, it is possible that changes in hippocampal metabolites in younger populations with asthma may be an early marker of neural injury, followed by structural volume changes evident later in adulthood. It is also possible this change in relevance of neuroimaging markers may indicate age-related susceptibility, or may depend on the duration or severity of the disease. For example, while the latter study did not observe group differences, asthma duration and control were negatively associated with striatal volumes (Ritz et al., 2020). These hypotheses require longitudinal designs to be fully assessed. Additionally, these hippocampal metabolites were correlated with medication use, and therefore may serve as a more sensitive measure than hippocampal volumetrics in tracking disease-related consequences (Kroll et al., 2018a). Several studies have also reported white-matter abnormalities among patients with asthma (Bian et al., 2018; Nair et al., 2023; Parker et al., 2011; Rosenkranz et al., 2022) which correlated with asthma severity and duration (Bian et al., 2018; Rosenkranz et al., 2022). Because white-matter abnormalities were observed in a wide age range (19–59 years), it is possible that they capture a feature of the disease and may be altered in individuals with any exposure to asthma, at any age.

In humans, evidence of altered neural function associated with asthma extends beyond the hippocampus, with several cortical regions implicated. For example, regions such as angular gyrus, precuneus and lingual gyrus, ventrolateral PFC, and inferior and middle temporal gyrus, are reportedly altered in asthma (Fig. 4) (Li et al., 2018, 2020; Ritz et al., 2024; T. Wang et al., 2023; Wang et al., 2024; Zhang et al., 2021). Although these results seem in apparent contrast to the research in rodents, the hippocampus operates at a network-level with cortical regions to support an array of cognitive processes in addition to memory; studies have demonstrated patterns of connectivity between the hippocampus and the cortical regions reported above (Ranganath and Ritchey, 2012). It is not clear, however, whether pathophysiological mechanisms of asthma exert direct influence on these other cortical regions, or if they exhibit asthma-related changes as a consequence of altered hippocampal integrity.

In addition to brain regions associated with memory and high-order cognition, other neuroimaging studies have reported associations between asthma and functional responses in regions subserving sensory processing and perception (Huang et al., 2021; Li et al., 2018; von Leupoldt et al., 2009b; Xiong et al., 2016; Zhang et al., 2021). For example, individuals with asthma showed reduced neural responses in somatosensory regions as well as reduced volume in the brainstem which significantly correlated with both asthma duration and perception of dyspnea (Davenport et al., 2000; Fauroux et al., 2007; von Leupoldt et al., 2011, 2009a). Moreover, other studies reported altered neural processing in regions known to subserve valence and appraisal. For example, one study found reduced deactivation in ventromedial PFC to emotional film stimuli and reduced activation during a post-stimulus recovery period (Ritz et al., 2024); others have reported associations between levels of inflammatory markers and activation patterns in the anterior cingulate and insula in response to emotional stimuli (Rosenkranz et al., 2012, 2005; Rosenkranz and Davidson, 2009). These responses may not be unique to interactions with emotional stimuli, but could also reflect hypersensitivity in these regions due to a bidirectional relation between asthma-related changes and psychological symptoms (e.g., depression), such that assessment of well-being or lack-thereof may mediate the association between asthma and altered neural responses (Rosenkranz et al., 2012; Rosenkranz and Davidson, 2009). Together, these findings highlight that neural risk in asthma may involve hippocampal integrity, converging with evidence from non-human studies, but also multiple cortical regions.

3.1.2.2. Behavioral indices. An ongoing line of research in humans has established that adults with asthma are at greater risk of developing mild cognitive impairments and dementia in comparison to the general population (Caldera-Alvarado et al., 2013; Kroll and Ritz, 2023; Nair et al., 2023, 2022; Rosenkranz et al., 2022; Rusanen et al., 2013). The mechanisms linking asthma with risk for dementia are not well understood, though research in this area has just begun (Nair et al., 2023, 2022). One possibility is that early asthma-related alterations to neural development may increase the susceptibility for developing dementia later in life. Therefore, research in youth populations suffering from the disease may inform asthma-related cognitive changes in older adults.

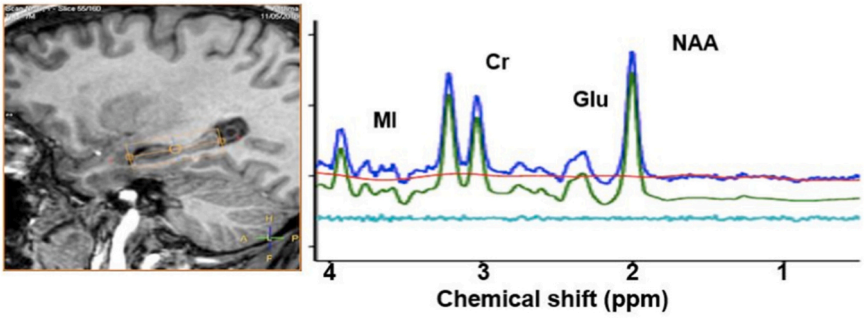

Fig. 3. MRI voxel placement and 1H-MRS spectra from the hippocampus of a participant with asthma. Sagittal view demonstrates placement of the volume of interest in the left hippocampus. The area under the spectra represents the concentration of each metabolite in the identified tissue. Red line, baseline; blue line, in vivo data; green line, fit; light blue line, residual. Abbreviations: Cr, creatine; NAA, N-acetylaspartate; MI, myo-inositol; Glu, glutamate. Adapted from Kroll, J.L., Steele, A.M., Pinkham, A.E., Choi, C., Khan, D.A., Patel, S.V., Chen, J.R., Aslan, S., Sherwood Brown, E., Ritz, T., 2018. Hippocampal metabolites in asthma and their implications for cognitive function. NeuroImage: Clinical 19, 213–221. https://doi.org/10.1016/j.nicl.2018.04.012.

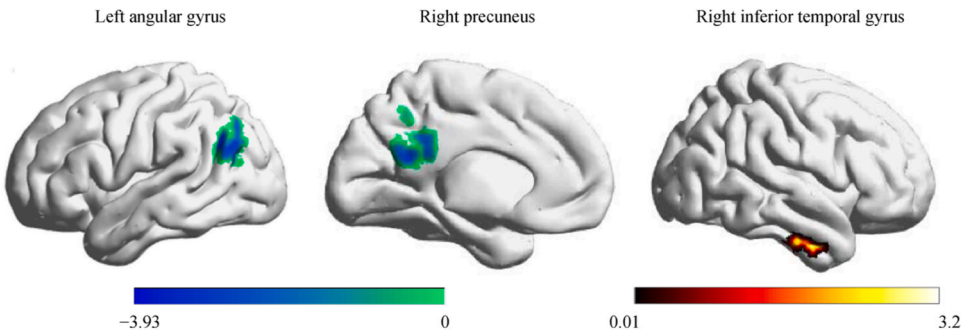

Fig. 4. Patients with asthma showed decreased amplitude of low-frequency fluctuation (ALFF) values in the left angular gyrus and right precuneus (green and blue) and increased ALFF values in the right inferior temporal gyrus (red and yellow). Adapted from Li, S., Lv, P., He, M., Zhang, W., Liu, J., Gong, Y., Wang, T., Gong, Q., Ji, Y., Lui, S., 2020. Cerebral regional and network characteristics in asthma patients: a resting-state fMRI study. Front. Med. 14, 792–801. https://doi.org/10.1007/s11684-020–0745-1.

In one study with older adults, participants in the asthma group exhibited reduced delayed recall relative to a comparison group of healthy older adults (Moss et al., 2005). The authors found that the asthma group also exhibited reduced blood oxygen saturation levels, possibly suggesting a link between memory difficulties and disease-related difficulties with oxygen absorption and subsequent delivery to the brain (Moss et al., 2005). However, oxygen saturation level was not correlated with measures of delayed recall, but only short-term memory, consistent with asthma effects that may not be selective to long-term memory. Bian and colleagues (2018) reported significant group differences, such that participants with asthma performed significantly worse than a comparison group in measures of executive function and visual-spatial processing, a pattern of results also demonstrated in a different study with a substantially larger sample but using a single measure of general cognitive status (Caldera-Alvarado et al., 2013). The study by Bian et al. (2018) also examined associations between these neuropsychological measures and clinical indicators of asthma control and duration, however, no such association was found (Bian et al., 2018). Other research has found that systemic inflammation mediated associations between asthma and reduced cognitive function on a digit symbol substitution test which relies on processing speed and working memory (Hu et al., 2024). One meta-analytic report substantiated such cognitive effects, showing significant group differences for academic achievement, attention, executive functioning, processing speed, learning and memory, language, and visual-spatial functioning (Fig. 5)(Irani et al., 2017). Interestingly, they also reported that more severe asthma was associated with larger effects sizes across these domains, suggesting that some, but not all, clinically-relevant indicators of asthma may show dose-dependent associations to cognitive outcomes (Becker et al., 2020).

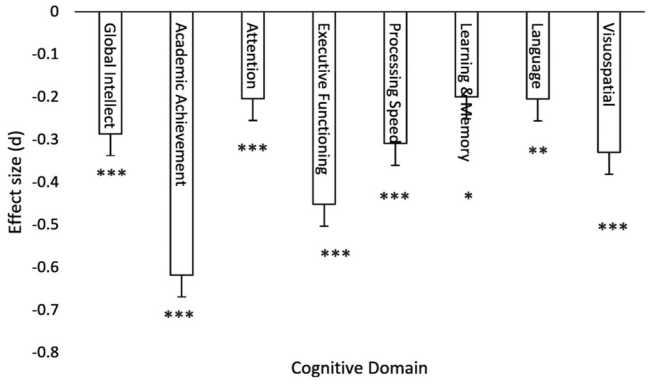

Fig. 5. Cognitive deficits in asthma. *p < .05. **p < .01. ***p < .001. Adapted from Irani, F., Barbone, J.M., Beausoleil, J., Gerald, L., 2017. Is asthma associated with cognitive impairments? A meta-analytic review. Journal of Clinical and Experimental Neuropsychology 39, 965–978. https://doi.org/10.1080/13803395.2017.1288802.

It is not surprising that the documented dementia risk and coincidence, in combination with animal literature on asthma, has guided human studies of asthma toward older adults. However, asthma is a prevalent pediatric disease with a peak incidence in early childhood (Nunes et al., 2017a; Stanescu et al., 2019). One of the earliest developmental studies assessed twenty children ages 9–14 years with severe asthma and found that those children exhibited significantly lower scores of memory and executive function as compared to a group of children with no history of asthma matched on sex, age, race, and socioeconomic status (Dunleavy and Baade, 1980). However, due to issues with the study design relating to selection bias, it is difficult to generalize these findings to the population, which led some to conclude that there is little evidence supporting an association between pediatric asthma and neuropsychological dysfunction (Annett and Bender, 1994). Other studies in children have confirmed difficulties in short term verbal memory, attention, executive function, and working memory (Hajek et al., 2014; Taha, 2017; Taha and Khalil, 2019; Zhu et al., 2023); however, these studies did not account for confounding effects of common demographic variables that might affect both the probability of developing asthma and cognitive difficulties. A recent study by our group examined associations between asthma and neurocognitive functioning in a large sample of 2062 9–10 year-old children (Christopher-Hayes et al., 2024). We found that children with asthma had lower scores in measures of episodic memory, processing speed, and inhibition and attention relative to a comparison group of children without asthma who were matched on several demographic and health variables (Fig. 6) (Christopher-Hayes et al., 2024). These results highlight the importance of considering asthma as a potential source of cognitive difficulty in children. Still, many questions remain about the extent to which children diagnosed with asthma are affected.

3.1.3. *Summary*

There is now a small, but growing literature on the pathophysiology of asthma, and how the disease may lead to neural injury and cognitive consequences. Across each of the proposed mechanisms, results suggest that asthma may lead to perturbations in hippocampal structure and function due to prolonged exposure to systemic proinflammatory mechanisms or to repeated hypoxic events, and that these injuries may result in learning and memory difficulties (Busse, 2012; Chen and Miller, 2007; Christopher-Hayes et al., 2024; Kroll and Ritz, 2023; Rosenkranz et al., 2022; Xia et al., 2014; Zhu et al., 2023).

The extent to which these effects are present in children might depend on: 1) the degree of systemic inflammation and/or the frequency of hypoxic events; and 2) the timing in development in which these mechanisms emerge. For example, regarding the first point, though the few rodent models of asthma did include a sample of young pups, the

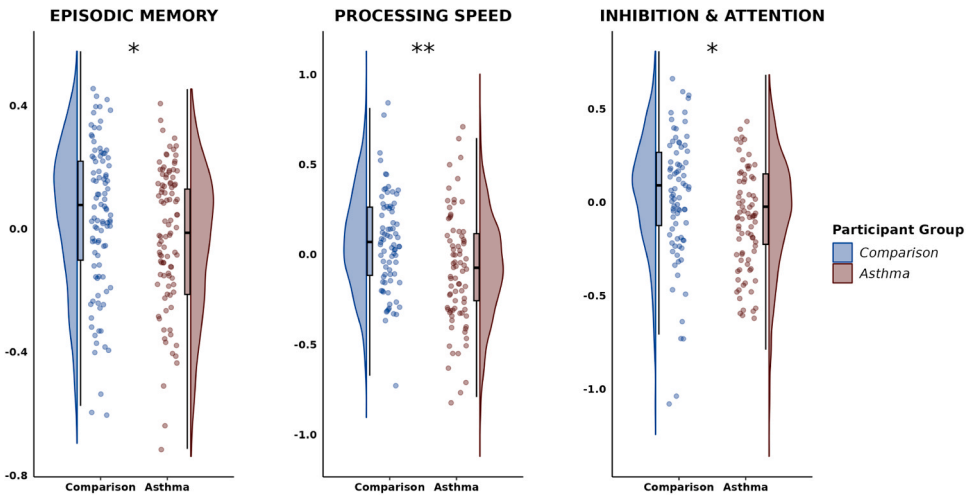

Fig. 6. Episodic Memory, Processing Speed, and Inhibition and Attention in Children With and Without a History of Asthma. Participant group is denoted on the x-axis, and scaled predicted scores for each cognitive measure (Episodic Memory, Processing Speed, Inhibition and Attention) are shown on the y-axis. Colors indicate different participant groups (Red = Asthma, Blue = Comparison). *p < .05. **p < .01. Adapted from Christopher-Hayes, N.J., Haynes, S.C., Kenyon, N.J., Merchant, V.D., Schweitzer, J.B., Ghetti, S., 2024. Asthma and Memory Function in Children. JAMA Network Open 7, e2442803. https://doi.org/10.1001/jamanetworkopen.2024.42803.

degree of experimentally manipulated inflammation or hypoxia may be different than what is expected with early-onset asthma in young children. In the study by Guo and colleagues (2013), mice were exposed to the asthma-inducing allergen 3 days per week, which would be roughly equivalent to 3–4 events per year at a human timescale. As just one comparable measure, prior research indicates that half of individuals with asthma experience 1 or more asthma attacks per year (Pate et al., 2021). Unfortunately, there is very little research that distinguishes the frequency of asthma attacks per year at higher numbers. However, it is reasonable to speculate many individuals with asthma experience several attacks per year, with exposure to allergens or other exacerbating factors at an even higher rate. In longitudinal analyses from our study, children who experienced more asthma attacks during the course of a 2-year period showed slower development of episodic memory than children who experienced fewer or no asthma attacks during the same period, consistent with the idea that asthma severity as measured by the frequency of potentially hypoxic events may be a moderating factor of the developmental trajectory of episodic memory (Fig. 7) (Christopher-Hayes et al., 2024; Ghetti and Fandakova, 2020).

Regarding the second point, there is evidence that certain developmental periods are associated with increased vulnerability to neurocognitive difficulties (Ghetti et al., 2023, 2020; Larsen and Luna, 2018). Research in children with Type 1 diabetes has shown that children who experience complications (e.g., incidents of diabetic ketoacidosis) at a younger age were more likely to exhibit subsequent cognitive difficulties (Ghetti et al., 2023, 2020; Schwartz et al., 2014). These studies suggest that effects of asthma may be more adverse when exposure begins at a young age. More specifically, children with earlier-onset asthma may show attenuated developmental improvements in cognitive abilities supported by brain regions, such as the hippocampus, which undergo

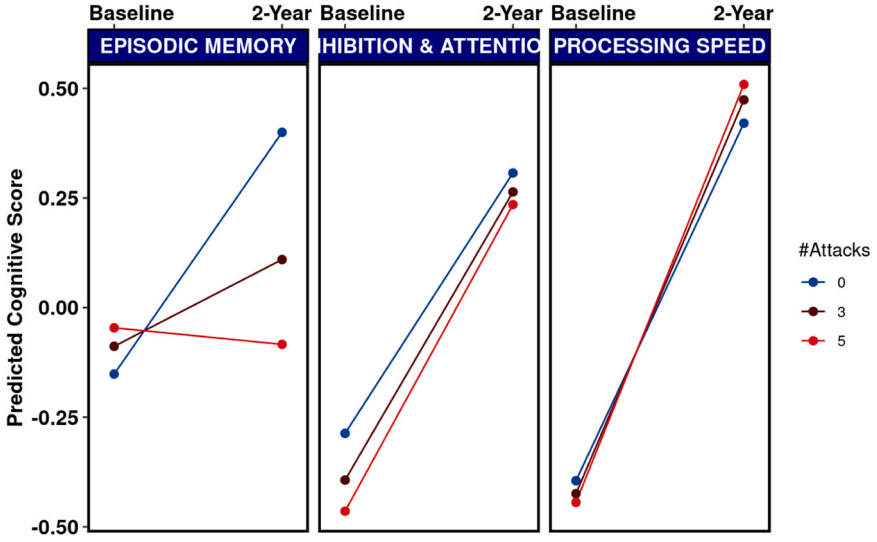

Fig. 7. Longitudinal Sample Sensitivity Analyses Examining Developmental Trajectories of Cognitive Outcomes as a Function of Asthma Attacks. Interaction between number of asthma attacks (0, 3, 5) and time with lines-of-best-fit for fixed effects and 95 % confidence interval around prediction lines (Light Red = Earlier Onset Asthma, Maroon = Later Onset Asthma, Blue = Comparison). Change in age (years) from the baseline timepoint is denoted on the x-axis, and scaled predicted scores for episodic memory are shown on the y-axis.*p-Episodic Memory < .05. Adapted from Christopher-Hayes, N.J., Haynes, S.C., Kenyon, N.J., Merchant, V.D., Schweitzer, J.B., Ghetti, S., 2024. Asthma and Memory Function in Children. JAMA Network Open 7, e2442803. https://doi.org/10.1001/jamanetworkopen.2024.42803.

robust development during childhood (Ghetti and Fandakova, 2020). Consistent with this hypothesis, a longitudinal analysis from our recent study including 474 children showed that those with earlier onset of asthma exhibited lower rates of memory improvements over time relative to a comparison group of children without asthma (Fig. 8) (Christopher-Hayes et al., 2024); children with later onset of asthma exhibited a developmental trajectory that was statistically comparable to that of the comparison group. This study provides further evidence that neurocognitive risks of asthma should be assessed using a developmental lens.

3.2. Consequences of medications

Asthma-related mechanisms might not be the only source of neurocognitive difficulties; the medications used to treat asthma may also be a contributing factor. Prescription corticosteroids are routinely used to treat asthma symptoms because of their anti-inflammatory properties (Naudé and Pretorius, 2003; Ramamoorthy and Cidlowski, 2016). Glucocorticoids are a class of corticosteroids in humans. The body naturally produces endogenous glucocorticoids (cortisol), a process that is regulated by the hypothalamic-pituitary-adrenal axis (HPAA). To do this, signaling between hypothalamic nuclei triggers the release of hormones which act on the pituitary. In turn, the pituitary gland secretes adrenocorticotrophin hormone (ACTH) into the general circulation, eventually reaching the adrenal cortex where glucocorticoids are synthesized (Ramamoorthy and Cidlowski, 2016; Vafaee et al., 2022). Endogenous glucocorticoids are critical to how the body meets environmental and stress challenges, and are involved in numerous physiologic processes, namely they act to suppress the immune system and decrease inflammation (Ramamoorthy and Cidlowski, 2016; Vafaee et al., 2022). Additionally, endogenous glucocorticoids are necessary to promote brain development, providing protection against neuroinflammation, regulating hippocampal neurogenesis, and more (Malaeb and Stonestreet, 2014; Manuela et al., 2021).

International guidelines for asthma management describe inhaled corticosteroids (ICS) as the first line of treatment (Bleecker et al., 2020; Bloom et al., 2019; Brown, 2009; de Benedictis and Bush, 2017; Vafaee et al., 2022). For example, a study reported that the percent of asthma cases managed with ICS has recently risen to 80 % (up from 65 % in 2006) (Bloom et al., 2019; Bloomfield et al., 2019). Several studies have examined the efficacy of treatment with ICS, concluding that the benefits outweigh rare adverse effects (Kurahashi et al., 2006) and common side effects such as hypertension and water retention (Bleecker et al., 2020; Ciriaco et al., 2013; Ramadan et al., 2019; Smith et al., 2003). These benefits are notable. For example, in cases where hospital admission was necessary, children were discharged earlier and less likely to show symptom relapse (Smith et al., 2003). Yet, there is evidence that corticosteroids may have adverse effects on cardiovascular and neurophysiological systems (Bleecker et al., 2020; Brown, 2009; Brown et al., 2004; Lunine, 1997; Meulen et al., 2022; Ren et al., 2021; Sapolsky et al., 1985; Uno et al., 1994) and cognition (Brown and Chandler, 2001; Prado and Crowe, 2019; Ren et al., 2021; Savas et al., 2020). The degree of adverse effects of corticosteroids on the brain may vary as a function of route of administration (i.e., oral vs inhaled)

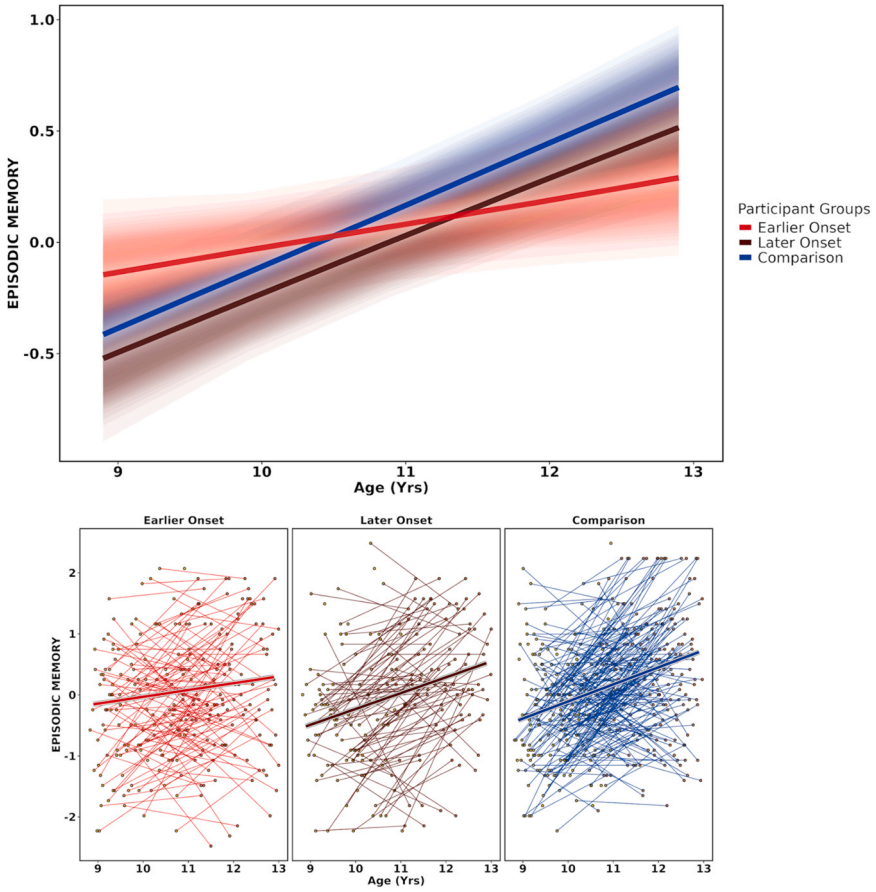

Fig. 8. Developmental trajectories of memory abilities as a function of participant group. A) Interactions between participant group and time with lines-of-best-fit for fixed effects B) Subject-level trajectories for each participant group from which estimates shown in panel A are obtained. Color denotes participant group (Light Red = Earlier Childhood Onset, Maroon = Later Childhood Onset, Blue = Healthy Comparison). Age (years) is denoted on the x-axis, and scaled scores for Episodic Memory are shown on the y-axis. Adapted from Christopher-Hayes, N.J., Haynes, S.C., Kenyon, N.J., Merchant, V.D., Schweitzer, J.B., Ghetti, S., 2024. Asthma and Memory Function in Children. JAMA Network Open 7, e2442803. https://doi.org/10.1001/jamanetworkopen.2024.42803.

(Brown et al., 2004; Kroll et al., 2018b; Meulen et al., 2022; Savas et al., 2020). However, the reviewed literature does not present any firm conclusions about this possibility. Nevertheless, given the evidence on adverse effects of corticosteroids and the frequency by which these medications are prescribed (Bloomfield et al., 2019), there has been a growing body of research to examine the neurocognitive effects of these medications.

3.2.1. *Non-human animal studies*

Past studies examining the effects of corticosteroids in animals have reported results that largely point to corticosteroids as being detrimental to hippocampal physiology and hippocampal-dependent cognitive processes. Here, we review evidence of mechanisms by which corticosteroids may affect hippocampal integrity.

3.2.1.1. Neural indices. One mechanism of action of glucocorticoids is via low-affinity glucocorticoid receptors, with high concentrations of these receptors found in the pituitary and hippocampus (de Kloet et al., 1998; Lunine, 1997; Ramamoorthy and Cidlowski, 2016). Several studies have found deleterious effects of corticosteroids to the hippocampus in otherwise healthy mice, including a reduced number of corticosterone receptors in pyramidal neurons of the CA1 and CA3 subfields (Sapolsky et al., 1985; Sorrells et al., 2014), reduced cells and synapses in the CA3 (Hu et al., 2016; Sapolsky et al., 1985), and reduced apical dendritic branch points in the CA3 (Conrad et al., 2007). Moreover, studies reported increased apoptotic cells – indicative of cell death – in the CA3, and decreased MAP2 expression – indicative of structural integrity – in both CA1 and CA3 (Hu et al., 2016), suggesting global consequences for cell health. Finally, morphological changes in the CA1 and CA3 subfields appear to depend on the degree of corticosteroid exposure (Hu et al., 2016; Sapolsky et al., 1985).

However, when the effects of corticosteroid exposure were examined specifically in rodent models of asthma, the results have been mixed. For example, one study replicated a significant reduction of synapse densities in the CA3 in mice exposed to corticosteroids compared to controls regardless of whether or not they had asthma (Fig. 9)(Guo et al., 2013; Sorrells et al., 2014), underscoring that negative effects of corticosteroids may not depend on the presence of clinical features in the population and therefore may generalize outside of the context of asthma. Other deleterious effects of corticosteroids found in rodent models of asthma include increased upregulation of inflammatory cytokines (i.e., TGFβ and IL-10) (Xia et al., 2014) and disrupted LTP (Guo et al., 2013). In contrast, another study showed that a group of mice with asthma treated with corticosteroids showed similar levels of neuroinflammatory markers as non-asthmatic animals; both groups exhibited significantly lower levels of activated microglia compared to a group with asthma that did not receive corticosteroids, suggesting protection against, rather than risk of, further neural injury (Xia et al., 2014). In another experiment, the untreated asthma group exhibited reduced synaptic zones and greater vessel swelling as compared to all other groups (Ren et al., 2021). However, corticosteroid treatment sufficiently reduced inflammatory markers and limited asthma-related morphological changes. More research is necessary to fully elucidate the effects of corticosteroids in rodents because each study assessed the effects of a different corticosteroid medication, making it difficult to draw direct comparisons. Moreover, no study involving rodent models of asthma used a chronic treatment group, and therefore it remains unknown whether the same benefits to neuroinflammatory mechanisms observed under acute treatment conditions would be observed under chronic exposure conditions. Finally, it is possible that the discrepancy in the reported effect depends on age differences. Specifically, the rodent models examining the effects of corticosteroids without asthma tended to include adult animals, whereas those with asthma included adolescent animals. Therefore, there may be some additional factors present during development that give rise to individual differences and serve to protect against negative effects of corticosteroids.

3.2.1.2. Behavioral indices. Several studies we have reviewed that investigated the neural effects of corticosteroids in rodents included experimental designs that also assessed behavior. In one study, the corticosteroid-treated group was significantly slower than controls in latency to escape the Morris Water Maze Task, indicating deficits in learning, as well as reduced memory as measured by time spent in the target quadrant during a probe test (Guo et al., 2013). Of note, the corticosteroid-treated group was an asthma model group and not a healthy group treated with corticosteroids. Yet, they performed worse in

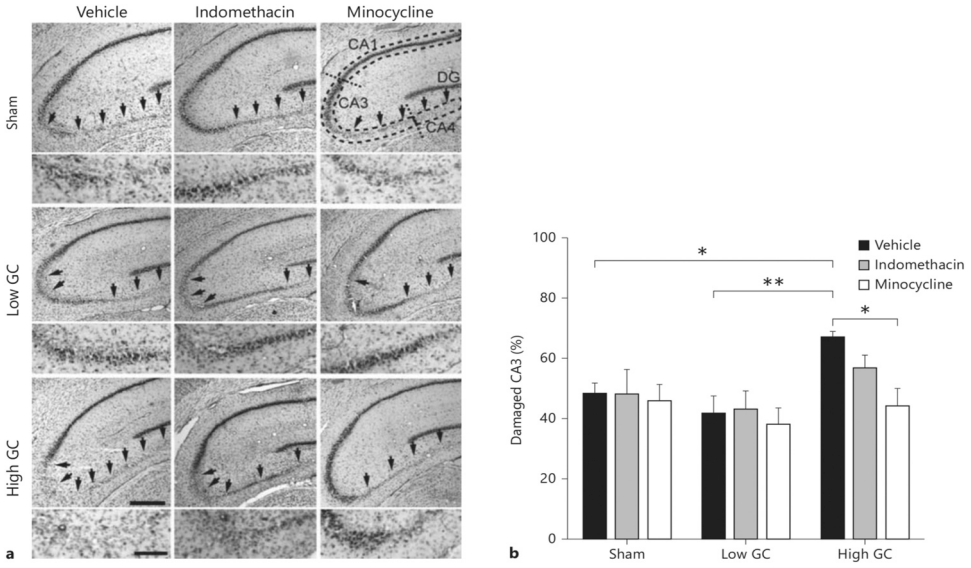

Fig. 9. High GCs increase excitotoxic injury which is reversed by minocycline. a) Representative images of Nissl-stained sections following each treatment combination 72 h after KA. Damage was quantified in the CA3 region (magnified below each image). Hippocampal subregions are indicated with dashed lines. Arrows point to areas of neuron loss. Scale bars = 500 μm (200 μm, magnification). b Quantification of the CA3-lesioned area 72 h after injury. High GCs significantly increased CA3 damage relative to low GCs and sham rats. This was reversed by minocycline, but not indomethacin treatment. * $p < 0.05$ and ** $p < 0.01$. Adapted from Sorrells, S.F., Munhoz, C.D., Manley, N.C., Yen, S., Sapolsky, R.M., 2014. Glucocorticoids Increase Excitotoxic Injury and Inflammation in the Hippocampus of Adult Male Rats. Neuroendocrinology 100, 129–140. https://doi.org/10.1159/000367849.

the delayed memory probe test in comparison to the untreated asthma group (Guo et al., 2013). One interpretation is that the treatment was unable to rescue memory deficits related to asthma, and instead, added to these deficits in a unique way. Another is that the consequential effect of corticosteroids depended on the presence of pathophysiological mechanisms of asthma. This pattern of results, akin to statistical suppression, suggests that the association between corticosteroids and cognition is weak or unreliable, but when asthma is present and modeled simultaneously, the magnitude of the effect of corticosteroids is increased. Such a perspective lends itself well given that prior work has shown that corticosteroids exacerbated neurotoxin-induced CA3 damage (Conrad et al., 2007), meaning that if asthma-related neural injury in the CA3 preceded corticosteroid exposure, it may increase the susceptibility to any negative effects of corticosteroids. However, this is a speculative consideration which requires empirical testing. Future research should also seek to include a healthy group treated with corticosteroids as an additional control group. One limitation is that the study by Guo and colleagues (2013) did not control for baseline abilities in memory and so we cannot exclude pre-existing differences among groups. In contrast, results from a different study with a corticosteroid-treated group did not exhibit any deficits on learning or memory, controlling for baseline memory performance (Ren et al., 2021). As was the case with previously outlined neural findings, because the intervention corticosteroid was not consistent across studies, it is difficult to draw a first conclusion about the effects of corticosteroids in rodent models.

3.2.2. Human studies

Research studies with human subjects have examined how different treatment regimens (i.e., acute vs chronic) with corticosteroids affect neural processing and cognitive functions. Below we discuss the literature examining neurocognitive effects of corticosteroids in humans.

3.2.2.1. Neural indices. To our knowledge, one study has assessed the effects of corticosteroids on neural indices among individuals with asthma (Kroll et al., 2018b). Kroll and colleagues (2018b) found asthma-related reductions in cellular energy and metabolism in the hippocampus as measured by Cr (creatine+phosphocreatine). Moreover, Cr was positively correlated with corticosteroid intake, suggesting that corticosteroids may help remediate asthma-related reductions in Cr. However, Cr was not associated with cognitive functioning, raising questions about the functional significance of these findings. We can also infer possible neural effects of corticosteroids on the brain in asthma by interpreting across findings described in both rodent models and human neuroimaging studies of subjects without asthma. Studies of acute exposure to corticosteroids have reported altered PET-based regional cerebral activity (de Leon et al., 1997; de Quervain et al., 2003; Ganguli et al., 2002) and reduced brain glucose utilization (de Leon et al., 1997) in the hippocampus, as well as reduced cerebral blood flow in medial temporal regions neighboring the hippocampus (e.g., parahippocampal gyrus) (de Quervain et al., 2003). Research on chronic exposure has revealed that patients undergoing long-term corticosteroid therapy showed significant bilateral hippocampal volume reductions, as well as significantly reduced hippocampal neuronal density and viability as measured with N-acetyl aspartate (NAA) ratios (Brown et al., 2004; Nguyen et al., 2019). Moreover, such corticosteroid-related hippocampal volume reductions have been localized to the CA3 subfield, a finding consistent with research in rodent models (Nguyen et al., 2019). Finally, a recent study found glucocorticoid use to be associated with white matter abnormalities in several tracts, including a section of the cingulum tract within the hippocampus (Meulen et al., 2022). These findings indicate that corticosteroids affect the hippocampus and its projections. Specifically, functional or chemical neuroimaging measures are sensitive to altered physiological processes under conditions of acute corticosteroid exposure, with structural alterations manifesting under conditions of chronic exposure. As such, we expect functional or chemical neuroimaging measures to be more sensitive to medication-related neural injury in children given the effects likely manifest early in the disease process when treatment with corticosteroids begins. This is, however, highly speculative because it is not clear what timescale (i.e., weeks, months, years) or frequency of dosage would qualify as chronic exposure – as it pertains to neural injury – for children. Additionally, such effects will likely depend on individual differences in glucocorticoid receptor sensitivity. Though there is no current method to directly assess glucocorticoid receptor sensitivity in vivo, future research should seek to characterize receptor sensitivity through alternative approaches, such as through review of medical history and assessment of trialed medication regimens.

3.2.2.2. Behavioral indices. The majority of studies in humans have demonstrated consistently deleterious effects of corticosteroid treatment on cognition. Studies in adults have shown reductions in various forms of declarative memory (e.g., verbal, visuo-spatial) (Bermond et al., 2005; Brown et al., 2007, 2004; Keenan et al., 1996; Newcomer et al., 1999, 1994; Wolkowitz et al., 1990; Young et al., 1999), and working memory (Lupien et al., 1999; Young et al., 1999) in response to exposure at both acute (Lupien et al., 1999; Newcomer et al., 1999, 1994; Wolkowitz et al., 1990; Young et al., 1999) and chronic levels (Bermond et al., 2005; Brown et al., 2007; Keenan et al., 1996), which is also consistent with past reviews on memory impairments reported with treatment of corticosteroids (Brown and Chandler, 2001). However, more recent research has demonstrated in cases of short term or acute treatment that the effects of corticosteroids include, in addition to memory, other cognitive domains such as executive functions and language (Ciriaco et al., 2013; Meulen et al., 2022; Prado and Crowe, 2019; Savas et al., 2020).

Suess and colleagues (1986) conducted one of the earliest developmental studies examining the effects of corticosteroid medications on cognitive functioning in children with asthma. In this study, two groups of children with asthma ages 9–18 years treated with only an anticholinergic bronchodilator (asthma-theophylline) or treated with both corticosteroids and an anticholinergic bronchodilator (asthma-theophylline-corticosteroids) were assessed on paired-associate verbal memory to determine systemic effects of steroids (Suess et al., 1986). Differences were found 6–8 hours after steroid administration, but not 24 hours after, and no differences were observed between the asthma-theophylline group and a control group. To determine if the effects of memory depended on transient medication-related effects on attention, Bender and colleagues (1988) conducted a within-subjects design consisting of 27 8–16 year-old children with asthma history and history of receiving corticosteroids. The study found that children exhibited reduced verbal memory, but not attention, following treatment with higher doses of corticosteroids compared to treatment at lower doses with a 25 day delay between testing occasions, and controlling for time passed, treatment progress, and repeat testing (Bender et al., 1988). In one other study, parents and teachers completed questionnaires regarding the children's cognitive functioning and academic achievement of approximately 600 children (Naudé and Pretorius, 2003). Among them were 59 children whose parents reported asthma. Teachers' reports indicated that ~50 % exhibited lower levels of academic achievement and learning difficulties, in line with the findings from Bender and colleagues (1988). However, the authors also point out that academic achievement was strongly correlated with school absences, making it difficult to determine the extent to which these results may be attributed to the disease itself or one consequence of the disease. Additionally, the authors identified a single case study participant (a 9-year-old) within the sample that had a long history of corticosteroid treatment. Similar to prior research (Bender et al., 1988; Suess et al., 1986), this child subject demonstrated reduced attention and memory performance on subscales of an intelligence test (Naudé and Pretorius,

2003). Our study found that parents of children with asthma history reported that they used corticosteroids more frequently than children without asthma (Christopher-Hayes et al., 2024). Although in that study we also found reduced memory in the former compared to the latter group, we could not precisely assess whether and to what extent these neurocognitive effects were explained by medication use. This question should be examined in future research. Taken together, these findings indicate that treatment with corticosteroid may affect memory abilities in children.

3.2.3. Summary

The evidence from animal and human studies strongly implicate treatment with corticosteroids in altered neurobiological processes (Annett and Bender, 1994; Brown, 2009; Guo et al., 2013; Nguyen et al., 2019; Sapolsky et al., 1985; Xia et al., 2014) and deficits in a variety of cognitive functions (Prado and Crowe, 2019). Neural substrates of memory and associated behavioral outcomes seem particularly vulnerable under conditions of chronic corticosteroid exposure (Brown, 2009; Brown and Chandler, 2001; Guo et al., 2013; Lunine, 1997; Prado and Crowe, 2019). In addition, and however limited, there is some evidence that these effects may be detected even in children (Annett and Bender, 1994; Bender et al., 1988; Naudé and Pretorius, 2003). Future research should examine the documented benefits of corticosteroid-based medication regimens relative to the neurocognitive risks at different points in development characterized by potentially different levels of vulnerability to neural injury.

4. Elements of additional risk: environmental factors

The effects of asthma may be exacerbated by the co-occurrence of several factors associated with disease morbidity and greater societal impacts (Fig. 10) (Chatkin et al., 2022; Chen and Miller, 2007; Holst et al., 2020; Lu et al., 2010; Miller et al., 2009; Palumbo et al., 2020; Vafaee et al., 2022).

4.1. Stress

In our review of the effects of corticosteroids, we discussed two types of glucocorticoids, those that are exogenous (e.g., medications) and those that are endogenous (i.e., cortisol). Of note, cortisol plays an important role in how our bodies physiologically manage stress (Busse, 2012; Chen and Miller, 2007; Ramamoorthy and Cidlowski, 2016; Vafaee et al., 2022). The common model for involvement of cortisol in suppressing the immune system and decreasing inflammation may be notably ill-suited in the case of asthma. Much research has been done to understand how mechanisms underlying psychological stress often exacerbate asthma (Buske-Kirschbaum et al., 2003; Busse, 2012; Chen and Miller, 2007; Rosa et al., 2018; Sandberg et al., 2000), with some models demonstrating relevant pathways by which psychological stress may affect airway inflammation more directly. It has been proposed that such a model for the role of cortisol in mediating stress-induced inflammation works well under acute exposure, where transient stressors – here stressors are referring to environmental challenges to one's adaptive capacity such as a school change, or family death or conflict – may help to ameliorate asthma symptoms. However, in chronic exposure, reduced sensitivity (e.g., resistance) to cortisol – possibly via downregulation of glucocorticoid receptor expression and functioning - is established and inflammatory processes may persist (Busse, 2012; Chen and Miller, 2007; Cohen et al., 2012; Sandberg et al., 2000; Vafaee et al., 2022). This is in line with other research suggesting that timing is critical; if corticosteroid transmission occurs acutely prior to an immune challenge, it may facilitate the inflammatory response to the challenge, whereas if transmission occurs after an immune challenge, it may suppress the inflammatory response (Barrientos et al., 2015; Li et al., 2013a).

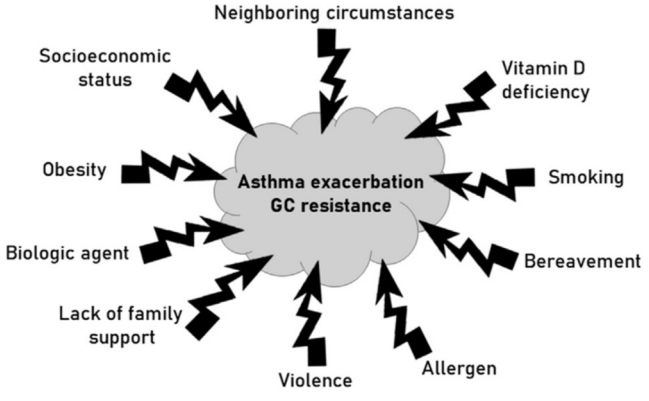

Fig. 10. External factors that could alter the biology of the receptor inducing glucocorticoid receptor (GR) resistance. Among them are environmental factors such as exposure to allergen or biological agents and cigarette smoking, nutritional factors of diseases such as obesity and vitamin D deficiency and psychological stress such as family and neighboring circumstances. Adapted from Palumbo, M.L., Prochnik, A., Wald, M.R., Genaro, A.M., 2020. Chronic Stress and Glucocorticoid Receptor Resistance in Asthma. Clinical Therapeutics 42, 993–1006. https://doi.org/10.1016/j.clinthera.2020.03.002.

It has also been posited that chronic stress enhances airway inflammation to an immune challenge, and these effects are associated with the development of corticosteroid unresponsiveness (Busse, 2012; Miller et al., 2009; Palumbo et al., 2020). This idea has been supported in both rodent and human literature. In a rodent model study by Li and colleagues (2013), it was found that circulating corticosterone was increased for asthma-stress and stress only groups (indicating successful activation of the HPAA). However, the inhibitory effects of corticosterone did not function in decreasing inflammatory cytokines, as levels were simultaneously elevated in these groups. Miller and colleagues (2009) examined perceived parental support as a stress marker in children with asthma to determine whether this was associated to stress-induced corticosteroid desensitization. Interestingly, children who felt less supported by their parents showed lower sensitivity (e.g., more resistance) to anti-inflammatory properties of corticosteroids on peripheral inflammatory markers, suggesting that stress is associated with a greater likelihood to exacerbate asthma pasthophysiology (Miller et al., 2009). Yet, there is some debate as to whether individuals with asthma exhibit normal HPAA function as it pertains to the regulation of endogenous cortisol to manage stress. For example, some research has reported lower levels of cortisol in asthma (Kroll et al., 2019; Landstra et al., 2002), whereas others have not (Buske-Kirschbaum et al., 2003; Li et al., 2013a). These findings are important because if glucocorticoid receptors become desensitized, this could lead to unbound corticosteroid messengers. It is not clear, however, if they would remain in circulation in the bloodstream or trigger the HPAA to produce more cortisol given the tissue unresponsiveness (resulting in elevated levels), or if they would be subsequently broken down/deactivated or decrease production through negative feedback to the HPAA (resulting in a recovery-to-baseline), making it difficult to fully assess interactions between endogenously produced and exogenously administered glucocorticoids (Lockett et al., 2024). Additionally, altered HPAA functioning could affect stress reactivity. In response to stressors, the rodent study of asthma reported an expected elevation of corticosterone associated with stress indicating normal HPAA function (Li et al., 2013b), whereas a study in children with asthma showed a dampened cortisol response to a stress test (Buske-Kirschbaum et al., 2003). These results highlight that cortisol-signaling in asthma may be altered in stressful contexts, and this may be further modified by asthma characteristics. Future studies are needed to better elucidate how interactions between exogenous and endogenous corticosteroids relate to glucocorticoid receptor sensitivity and asthma symptom exacerbation.

Prior work with rodent models investigating stress-induced effects

on the brain have been informative in understanding where stress-induced exacerbation in asthma might be expected. Previous research has shown that subfields of the hippocampus are stress-sensitive (Barrientos et al., 2015; Bergström et al., 2008; Green and McCormick, 2013; Lunine, 1997; Vouimba et al., 2007), and processes in these subfields are modulated by baso-lateral-amygdala stress-related activation (Lunine, 1997; Vouimba et al., 2007). Others have found asthma had acute effects on HPA function but without acute alterations to stress-related gene expression in the hippocampus of two-month-old mice, possibly indicating that stress-induced changes in the hippocampus may occur over a longer timescale (Caulfield et al., 2021). Indeed, Green and McCormick (2013) concluded in their review that adolescent stressors are particularly likely to alter the developmental trajectory of the hippocampus. Together, this research brings attention to the possibility that psychological stressors may alter hippocampal development, as well as destabilize corticosteroid-mediated mechanisms that support anti-inflammatory responses.

4.2. Pollution

We previously noted that rates of asthma have markedly increased in recent years likely due to increased exposure to environmental risk factors such as pollution (Nunes et al., 2017a; Zanobetti et al., 2024). One example of an environmental polluting agent is particulate matter. These agents, which can be solid or liquid, can be released from a host of sources including vehicle emissions, household cooking devices, and dust (Chatkin et al., 2022). Moreover, particulate matter pollutants can range in size, and these differences are largely determinant for where they can be retained; larger agents may be retained in the upper airway, smaller particles may reach the bronchiolar (airway branches of the lungs) and alveolar (air sacs for exchange of oxygen and carbon dioxide between lungs and blood) regions, or they may pass through these regions en route to the bloodstream (Chatkin et al., 2022). Once entered into the body, these agents can result in the development of persistent oxidative stress and inflammation, which can lead to induction or exacerbation of asthma (Chatkin et al., 2022; Zanobetti et al., 2024). For example, several studies revealed that children exposed to higher concentrations of particulate matter pollutants throughout their childhood were at a greater risk for asthma and/or persistent wheezing (which could represent undiagnosed asthma) (Holst et al., 2020; Zanobetti et al., 2024).

The effects of environmental pollution and asthma on neurocognitive development have not been directly examined together. Recent studies in children that do not suffer from asthma have shown altered structural and functional brain connectivity and white matter microstructure associated with various markers of environmental pollutants (Cotter et al., 2023, 2024; Herting et al., 2019; Parenteau et al., 2024; Pérez-Crespo et al., 2022; Pujol et al., 2016; Szwed et al., 2025). Using data from the large ABCD Study, Cotter and colleagues (2023) found that higher concentrations of particulate matter were associated with increasing hippocampal connectivity with the default mode, salience, and frontoparietal networks. This pattern of integrative change in connectivity was in opposition to the general developmental trajectory across the sample, which demonstrated segregation, or decreasing connectivity between hippocampus and cortical networks (Cotter et al., 2023). In a follow up study, they also reported that higher concentrations of particulate matter were associated with white-matter abnormalities in several regions, including in the uncinate fasciculus and frontal tracts (Cotter et al., 2024). Interestingly, effects of pollutants on these neural measures were not consistent. For example, higher NO2 levels had the opposite effect on cortico-hippocampal connectivity, resulting in decreasing connectivity over time. One explanation for this contrast is that particulate matter agents may lead to perturbations to functional network reorganization during development, whereas NO2 may result in more accelerated change (Cotter et al., 2023). The implication of these neural alterations on cognitive development, or their interaction with asthma remains unclear.

4.3. Summary

These additional risks are pertinent to research revolving neurodevelopment of children with asthma. Both the exposure to varied concentrations and categories of pollutants (Chatkin et al., 2022; Cotter et al., 2023; Holst et al., 2020; Nunes et al., 2017a) and the degree of exposure to stress (Busse, 2012; Miller et al., 2009; Palumbo et al., 2020) offer considerable evidence consistent with the hypothesis that children with asthma are susceptible to further disease complexity, exacerbation, and altered neurocognitive development.

5. Potential avenues for future research

We have reviewed a wide range of disparate research. First, we discussed the prevalence, pathogenesis, and pathophysiology of asthma to highlight the potential societal impact for investigating neurodevelopment in this population. Second, we reviewed putative mechanisms of neural inflammation and hypoxia in the context of asthma, along with neural and behavioral evidence from animal and human studies. Similarly, we discussed mechanisms of corticosteroid action and sensitivity, given the frequency of which these medication classes are used for the treatment of asthma symptoms. Finally, we reviewed models of stress and environmental polluting agents, and the potential for these factors to induce or exacerbate asthma. Overall, this review spans theories, methods, and population models. Together, advances in these fields have blossomed into a new and interconnected avenue of research, spurring many unresolved questions concerning asthma and neurodevelopment (see Table 1). These questions are organized around three key elements: mechanisms, risk and protective factors, and medications. For example, is the pathophysiology of asthma itself associated with neurocognitive outcomes? Recent results indicate that the development of memory in children with asthma is associated with asthma severity (number of asthma attacks) (Christopher-Hayes et al., 2024). Yet, it is currently unknown whether this association may depend on the degree of underlying inflammatory processes, the experience of hypoxic events, or some other factor (e.g., pollutants). Additionally, whether such cognitive difficulties are associated with signatures of underlying neural injury is largely unexplored.

Here, we have proposed a framework in which children with asthma may be at risk for altered neurocognitive development. We are encouraged that this framework will drive future research. The key points we have discussed include differences in incidence along the age continuum with early peaks in childhood, pathophysiological mechanisms such as prolonged inflammation or repeated hypoxic events, exposure to medication regimens involving the chemical class of steroids, and life experience with environmental factors like stress and pollutants.

There is some indication that standards of asthma management including treatment with inhaled corticosteroids for brief periods of time may serve to limit the degree of neural injury. However, cognitive effects of asthma remain common regardless of treatment regimens, indicating the possibility that neural injury persists but current practices and methods of measurement may lack in sensitivity. In complex cases where asthma is either uncontrolled, exacerbated by environmental factors, or managed with temporally chronic treatment regimens, a set of features which are common in this population, we hypothesize a small but critical burden on neurocognitive development in children. Thus, it is paramount that we seek to understand the impact of asthma on cognitive functioning during development.

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Table 1
Questions for future research.

Mechanisms
Is the pathophysiology of asthma itself associated with neurocognitive outcomes?
How does reduced oxygen intake during an asthma attack affect blood flow in the brain?
How does asthma severity, as in number of asthma attacks, modify neurodevelopmental change?
Are children with a TH2 immune profile of asthma more likely to experience cognitive difficulties compared to other profiles of asthma?
Are difficulties particularly pronounced in the domain of episodic memory or are other cognitive domains equally affected? Does this depend on separable mechanisms of injury?
Does the timing of disease onset best explain neurodevelopmental changes? Does the timing change which cognitive faculties are affected?
Risk and Protective Factors
Are there factors that protect against neural injury or cognitive difficulties?
How might environmental factors exacerbate asthma?
Is the degree of access to healthcare associated with neurocognitive outcomes in children with asthma?
Do physically active children with asthma show any evidence for "recovery" of hippocampal integrity or related cognition?
Does acute versus chronic stress differentially relate to neurocognitive outcomes in children with asthma?
Can specific pollutants increase the risk for individuals with asthma to exhibit reduced hippocampal integrity?
How does maternal exposure to risk factors as a route for indirect effects on the child modify neurocognitive outcomes in children with asthma?
Medications
What role do medications play in the relationship between asthma and neurocognitive outcomes?
Is the level of corticosteroid use associated with neurocognitive development?
What medication regimen features are most likely to modify associations with neurocognitive outcomes? Features may include dose, method of administration, type of medication.
How does stress interact with corticosteroid treatment?
To what extent does the temporal chronicity – long-term doses – of therapeutic corticosteroid regimens augment neurocognitive difficulties?

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CRediT authorship contribution statement

Christopher-Hayes Nicholas J.: Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Ghetti Simona:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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