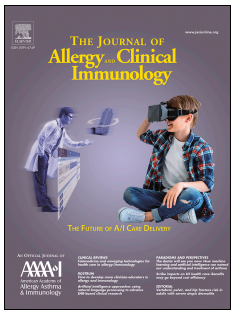
# Journal Pre-proof




Neuroimaging and biomarker evidence of neurodegeneration in asthma

Melissa A. Rosenkranz, Ph.D., Douglas C. Dean, III, Ph.D., Barbara B. Bendlin, Ph.D., Nizar N. Jarjour, M.D.., Stephane Esnault, Ph.D., Henrik Zetterberg, M.D., Ph.D., Amanda Heslegrave, Ph.D., Michael D. Evans, M.S., Richard J. Davidson, Ph.D., William W. Busse, M.D.

PII: S0091-6749(21)01396-8

DOI: https://doi.org/10.1016/j.jaci.2021.09.010

Reference: YMAI 15269

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 16 June 2021

Revised Date: 19 August 2021

Accepted Date: 7 September 2021

Please cite this article as: Rosenkranz MA, Dean III DC, Bendlin BB, Jarjour NN, Esnault S, Zetterberg H, Heslegrave A, Evans MD, Davidson RJ, Busse WW, Neuroimaging and biomarker evidence of neurodegeneration in asthma, *Journal of Allergy and Clinical Immunology* (2021), doi: https://doi.org/10.1016/j.jaci.2021.09.010.

# Neuroimaging and biomarker evidence of neurodegeneration in asthma

Melissa A. Rosenkranz, Ph.D.[a,b*], Douglas C. Dean III, Ph.D.[c,d,e], Barbara B. Bendlin, Ph.D.[f,g], Nizar N. Jarjour, M.D..[f], Stephane Esnault, Ph.D.[f], Henrik Zetterberg, M.D., Ph.D.[h,i,j,k,], Amanda Heslegrave, Ph.D.[k], Michael D. Evans, M.S.[l,], Richard J. Davidson, Ph.D. [a,b,m], and William W. Busse, M.D.[f]

[a]*Department of Psychiatry, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI 53719, USA*

[b]*Center for Heatlhy Minds, University of Wisconsin-Madison, 625 W. Washington Ave., Madison, Wisconsin 53703, USA*

[c]*Department of Pediatrics, University of Wisconsin-Madison, 600 Highland Ave, Madison, Wisconsin 53792, USA*

[d]*Department of Medical Physics, University of Wisconsin-Madison, 600 Highland Ave, Madison, Wisconsin 53792, USA*

[e]*Waisman Center, University of Wisconsin-Madison, 1500 Highland Ave, Madison, Wisconsin 53792, USA*

[f]*Department of Medicine, University of Wisconsin-Madison, 600 Highland Ave, Madison, Wisconsin 53792, USA*

[g]*Wisconsin Alzheimer's Disease Research Center, University School of Medicine and Public Health, Wisconsin 53792, USA*

[h]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*

[i]*Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden*

[j]*Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK*

[k]*UK Dementia Research Institute at UCL, London, UK*

[l] *Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, 717 Delaware St SE, Minneapolis, MN 55414, USA*

[m]*Department of Psychology, University of Wisconsin-Madison, 1202 W. Johnson St. Madison, Wisconsin 53706, USA*

*Address Correspondence to:
Melissa A. Rosenkranz
Center for Healthy Minds
University of Wisconsin-Madison
625 W. Washington Ave.
Madison, WI 53703
email: melissa.rosenkranz@wisc.edu
Phone: 608-262-5050

**Author Contributions**

MAR and DCD conceived and designed the study. MAR, DCD, HZ, BBB, SE, AH, and WWB acquired, analyzed, and/or interpreted the data. MAR, DCD, SE, and MDE performed statistical analyses. MAR, WWB, and RJD obtained funding for the study. All authors contributed meaningfully to the writing and revision of the manuscript. MAR had full access to all the data in the study and assumes final responsibility for the decision to submit this manuscript for publication

**Conflicts of Interest**

Dr. Nizar N. Jarjour has a consulting relationship with Glaxo Smith Kline, Astra Zeneca, and Boehringer Ingelheim.

Dr. Henrik Zetterberg has served at scientific advisory boards for Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies and CogRx, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

Dr. William W. Busse has a consulting relationship with Glaxo Smith Kline, Novartis, Astra Zeneca, Regeneron, and Sanofi.

Dr. Richard J. Davidson is the founder, president, and serves on the board of directors for the non-profit organization, Healthy Minds Innovations, Inc.

All other authors have nothing to disclose.

**Funding.** This work was supported by funding from National Heart, Lung, and Blood Institute (NHLBI) R01 HL123284 to WWB and U10HL109168 to NNJ, National Center for Complementary and Integrative Health (NCCIH) P01 AT004952 to RJD and by a core grant to the Waisman Center from the National Institute of Child Health and Human

Development (NICHD) U54 HD090256. HZ and AH acknowledge funding from the UK DRI. HZ is a Wallenberg Scholar.

Running title: Glial activation and neurodegeneration in asthma

Word Count: 3976

**Abstract**

**Background.** Epidemiological studies have shown that Alzheimer's disease and related dementias (ADRD) are seen more frequently with asthma, especially with greater asthma severity or exacerbation frequency.

**Objective.** To examine the changes in brain structure that may underlie this phenomenon, we examined diffusion-weighted magnetic resonance imaging (dMRI) and blood-based biomarkers of AD (p-Tau181), neurodegeneration (NfL) and glial activation (GFAP).

**Methods.** dMRI data were obtained in 111 individuals with asthma, ranging in disease severity from mild to severe, and 135 healthy controls. Regression analyses were used to test the relationships between asthma severity and neuroimaging measures, as well as AD pathology, neurodegeneration and glial activation, indexed by plasma p-Tau181, NfL and GFAP respectively. Additional relationships were tested with cognitive function.

**Results.** Asthma participants had widespread and large magnitude differences in several dMRI metrics, which were indicative of neuroinflammation and neurodegeneration, and robustly associated with GFAP and to a lesser extent, with NfL. The AD biomarker p-Tau181 was only minimally associated with neuroimaging outcomes. Further, asthma severity was associated with deleterious changes in neuroimaging outcomes, which in turn, were associated with slower processing speed, a test of cognitive performance.

**Conclusion.** These data suggest that asthma, particularly when severe, is associated with characteristics of neuroinflammation and neurodegeneration and may be a potential risk factor for neural injury and cognitive dysfunction. The results suggest a

need to determine how asthma may affect brain health and whether treatment directed toward characteristics of asthma associated with these risks can mitigate these effects.

Abstract word count: 246

**Key Messages**

- Brain white matter showed evidence of structural deterioration in individuals with asthma, relative to an age and sex-matched group of healthy controls, which was more pronounced with more severe disease.
- Relationships with blood-based biomarkers suggest that brain white matter changes observed in participants with asthma are neuroinflammatory and/or neurodegenerative in nature.
- While this sample was cognitively normal, a relationship with cognitive processing speed suggests that changes to brain white matter may confer greater functional consequences for individuals with asthma.

**Capsule Summary:** Neuroinflammation and neurodegeneration contribute to impaired brain health and cognitive decline. Here, we present evidence that these processes are observed in asthma, which may represent a modifiable risk factor.

**Keywords**: asthma, dementia, diffusion-weighted imaging, neurodegeneration, inflammation, GFAP, NfL

**Abbreviations:** ADRD (Alzheimer's and related dementias); AD (Alzheimer's disease); dMRI (diffusion-weighted magnetic resonance imaging); GFAP (glial fibrillary astrocytic protein); NfL (neurofilament light-chain); p-Tau 181 (phosphorylated-tau 181); IL-6

(interleukin-6); IL-17 (interleukin-17); TNF--$\alpha$ (tumor necrosis factor alpha); eosinophils (EOS); FeNO (fraction of exhaled nitric oxide); $FEV_1$ (forced expiratory volume in 1 second); T2 (type 2); ATS (American Thoracic Society); ICS (inhaled corticosteroids); ACQ-6 (6-item Asthma Control Questionnaire); DTI (diffusion-tensor imaging); NODDI (neurite orientation and dispersion density imaging); FA (fractional anisotropy); RT (reaction time); PALM (Permutation Analysis of Linear Models); CNS (central nervous system); RA (Rheumatoid Arthritis);

## Introduction

Airway inflammation is a pathogenic characteristic of asthma and contributes to its symptoms, susceptibility to exacerbations, airway remodeling, and serves as a primary target for effective therapy. Moreover, the effects of airway inflammation may not be restricted to the airways and systemic manifestations can occur. Peters *et al*. found metabolic dysfunction and increased serum concentrations of IL-6, primarily in a subgroup with severe asthma(1). Our understanding of the systemic effects of asthma are currently limited and their scope is likely under-appreciated; for example, the possibility that airway inflammation may contribute to impaired brain health, beyond the widely recognized and clinically important associations with depression, has generated interest but limited study. However, the potential importance and impact of asthma on brain health is emphasized by population-based studies which, though limited, found an increased risk for dementia in asthma(2–4) that was amplified in patients with frequent or severe exacerbations(5). These associations are further supported by animal studies showing that neuroinflammatory and neurodegenerative processes result from airway inflammation(6,7).

Although systemic effects associated with asthma suggest inflammatory injury to peripheral tissue, evidence of inflammatory injury in non-pulmonary target organs, such as the brain, is currently lacking. We previously demonstrated that an allergen-provoked eosinophilic airway inflammatory response was associated with changes in brain function(8,9). However, studies to assess whether asthma may also be associated with more fundamental changes in brain health have not been reported. To explore relationships between asthma and brain health, new developments in both neuroimaging and blood-based biomarker measurements make it feasible to identify

neuroinflammatory and neurodegenerative processes with high degrees of sensitivity. Using these neuroimaging and biofluid analytic approaches, we conducted a retrospective, cross-sectional, case-control analysis, to determine whether brain white matter microstructural changes exist in asthma and are associated with serological determinants of altered brain health. Our exploratory analyses represent an initial effort to evaluate the novel hypothesis that asthma is a risk factor for neuroinflammation and neurodegeneration, which may exist despite an absence of concurrent cognitive deficits. Longitudinal studies will be essential in establishing whether asthma confers an increase in risk for progression to clinically important manifestations of white matter deterioration and result in functional impairment. Nevertheless, our initial findings are a necessary first step in demonstrating that altered brain microstructure is found in asthma. Further, these data will be directive in clarifying phenotype(s) of disease that may confer the greatest risk, and in identifying potential therapeutic targets to prevent deleterious impacts of asthma on brain health.

## Methods

*Participants.*

Our analyses included 111 (57% female) participants with asthma and 135 (59% female) non-asthmatic healthy controls, ranging in age from 18-73 years. All asthma patients had a physician's diagnosis of asthma and stable disease control for at least 4 weeks prior to study in order to ensure safety in the conduct of the enrolled protocols (see below) and to avoid recent use of interventions which may affect baseline airway inflammation and concurrent neuroimaging measures. Neuroimaging data were analyzed retrospectively from participants who took part in previous University of

Wisconsin Asthma Research studies, for which MRI scans had been acquired. At enrollment measurements of lung function, peripheral blood eosinophils (EOS), and fraction of exhaled nitric oxide (FeNO) were made, along with a review of current medications and an assessment of disease control.

The asthma population evaluated represents a diverse group of participants with disease severity ranging from mild to severe. Twenty-five participants were recruited based on their participation in the University of Wisconsin Severe Asthma Research Project and met European Respiratory Society and American Thoracic Society (ATS) Workshop(10) criteria for severe asthma at the time of enrollment. Sixty-seven participants were recruited for a behavioral intervention study (reported elsewhere) and had evidence of persistent airway inflammation, as defined by FeNO $\geq$ 30 ppb, blood eosinophil count $\geq$ 150, or sputum eosinophils $\geq$ 2%, and had a minimum pre-albuterol baseline $FEV_1$ of 60% at enrollment. Finally, nineteen participants were recruited for a protocol to investigate neuroimmune interactions in asthma (reported elsewhere); these participants had a baseline $FEV_1$ of 70% or greater, with a 12% reversibility or $PC_{20}$ response to methacholine < 16.0 mg/ml and were not using inhaled corticosteroid medications.

Non-asthma healthy controls were recruited from the Madison, WI area as part of the behavioral intervention study (mentioned above) and were required to be free of an asthma diagnosis, symptoms compatible with asthma, and medications used to treat asthma. While none had assessment of pulmonary function or bronchial hyperresponsiveness to methacholine, all control participants were in good health and had no history of lung disease.

Across groups, participants were excluded for incompatibility with the MRI environment, current smoking, pregnancy, history of neurological disorder, traumatic brain injury, psychotic disorders, and all were cognitively normal. Recruitment information and complete inclusion and exclusion criteria are described in supplementary materials. Though the data reported here were acquired in the context of 3 separate studies, all data were collected contemporaneously, using the same equipment, scan protocols, processing pipelines, and personnel.

*Lung function assessment and measures of inflammation*

Lung function was measured according to ATS standards(11). As biomarkers for airway inflammation(12), FeNO was measured following ATS guidelines(13) (NIOX System; Aerocrine, Solna, Sweden) and a peripheral blood eosinophil (EOS) count (cells/uL) was obtained. In addition, participants completed the Asthma Control Questionnaire (ACQ-6) at enrollment(14).

Principal components analysis was used to create a composite score of asthma burden from five separate measures: $FEV_1$ percent predicted, ACQ-6 (ACQ score excluding $FEV_1$), FeNO, EOS, and a medication score (see supplemental information). This resulted in two orthogonal components: an asthma severity score comprised of ACQ-6, $FEV_1$, and medication score, and a Type (T)2 inflammation score comprised of FeNO and EOS. Details of this analysis and the relationships among the five measures and two derived scores are described in supplementary material.

*Brain imaging*

Diffusion-weighted magnetic resonance imaging (dMRI) data, a validated, non-invasive tool to examine regional microstructural alterations in the brain(15), were

acquired on a 3 Tesla General Electric MR750 Discovery scanner. Acquisition parameters are detailed in supplementary material. Each scan was reviewed by a neuroradiologist and participants with anatomical abnormalities were excluded (5 asthma, 5 control). Images underwent standard pre-processing procedures. Motion artifacts were visually assessed using in-house processing pipelines. Diffusion tensors (DTI) were estimated at each voxel and quantitative maps of fractional anisotropy (FA), and mean, radial and axial diffusivity were derived(16). DMRI data were also fit to the three-compartment *neurite orientation dispersion and density imaging* (NODDI) tissue model(17), using the AMICO-NODDI algorithm(18), to provide estimates of neurite density index, orientation dispersion index, and free water volume fractions. In white matter, these DTI and NODDI metrics inform the density, organization, and integrity of myelinated axons, which are critical for efficient brain network connectivity and when sufficiently compromised, gives rise to a wide variety of neurological disorders. DTI and NODDI parameter maps were aligned with a population-specific template and smoothed using a 4mm full-width-at-half-max Gaussian filter. See supplementary material for full processing methods.

*Glial activation, Neurodegeneration, and AD Biomarker Measures*

Blood samples for measurement of plasma biomarkers were acquired from asthma patients only, under baseline conditions, and stored at -80ºC until analysis. Glial fibrillary acidic protein (GFAP) was measured to assess neuroinflammation, neurofilament light chain (NfL) was measured to assess neurodegeneration, and p-Tau181 was measured to assess AD-specific pathology. Biomarker concentrations were measured using ultra-sensitive Single molecule array (Simoa) technology on an HD-X

instrument (Quanterix, Billerica, MA). Plasma GFAP concentration was measured using the GFAP Discovery Kit, plasma NfL concentration was measured using the NF-light Advantage Kit, and p-Tau181 concentration was measured using the pTau-181 Advantage Kit, according to manufacturer instructions (Quanterix, Billerica, MA). All measurements were performed in one round of experiments, using one batch of reagents by laboratory technicians who were blinded to clinical data. Mean intra-assay coefficients of variation (SD) were 6.63% (5.57%) for GFAP, 4.72% (3.45%) for NfL, and 5.13% (4.70%) for p-Tau181.

*Processing speed as an index of cognitive function*

Reaction time (RT) in an asthma variant of the Stroop Task(19) was used to assess processing speed. Processing speed, as indexed by mean RT, is a widely accepted indicator of global cognitive function and has been previously applied in dementia and AD research(20,21), but is not an indicator of dementia *per se*. Here, processing speed was used to assess the functional consequences associated with dMRI alterations. Briefly, participants were asked to identify the color of letters spelling asthma-specific, negative, and neutral words with a button press during the collection of neuroimaging data (for details see (9)). RT was averaged for trials with correct responses only, within-subject, across valence conditions.

*Data analysis*

Whole-brain voxel-wise group differences (Asthma vs. Control) in the neuroimaging metrics were tested with Permutation Analysis of Linear Models(22,23) (PALM) using tail acceleration and 500 permutations(24). PALM enables joint inference over multiple dMRI metrics, known as Non-Parametric Combination (NPC), while also

providing inference on the separate contribution of each metric(22). Joint inference of group differences was assessed with NPC and Fisher's combining function across seven dMRI metrics: FA, mean, radial, and axial diffusivity, neurite density index, orientation dispersion index, and free water volume fractions, while differences in individual metrics were also evaluated. Within the asthma group only, a similar whole-brain approach was used to investigate the association between dMRI metrics and asthma severity, T2 inflammation, and plasma biomarkers. The relationships among asthma severity, T2 inflammation, and plasma biomarkers were assessed using linear regression, with age as a covariate. Group differences in processing speed were tested using linear regression with group and age regressed on mean RT. Group differences in the relationship between processing speed and dMRI were examined using a voxel-wise approach in PALM, as described above.

Voxel-wise analyses were restricted to white matter using a tissue-specific mask, and age, sex, and total head motion were included as nuisance covariates. Voxels showing significant group differences in dMRI metrics, or significant associations with regressors of interest were identified in the omnibus test, using threshold-free cluster enhancement and family-wise error correction to control inflation of type I error. Significance was defined as $p<0.05$, corrected for multiple comparisons.

## Results

### *Participants*

Asthma and control groups did not differ in their distribution of sex, but the control group was significantly older ($M$ = 43.9 [25-66] years) than the asthma group ($M$ = 39.8 [18-73] years; $t$ = 2.2, $p$ = .03).

*Neuroimaging results*

Widespread and large magnitude differences in white matter microstructure were present between asthma and controls (corrected $p < .05$; Fig 1). After controlling for age, sex, and motion during collection of neuroimaging data, significant differences were observed in nearly every individual dMRI metric. When dMRI metrics were evaluated in relationship to asthma severity, deterioration in myelinated axons (mean and radial diffusivity) was more profound in the presence of severe disease (corrected $p < .05$; Fig 2). This deterioration was observed in multiple brain regions that include fiber bundles of the corticospinal tract, external capsule, inferior longitudinal fasciculi, superior longitudinal fasciculi, and inferior fronto-occipital fasciculi — tracts previously implicated in cognitive decline(25,26). In contrast, markers for T2 inflammation (FeNO and EOS) showed no significant associations with any of the dMRI metrics.

*Relationship of dMRI metrics to plasma biomarkers*

The association between deterioration in myelinated axons and GFAP was widespread and observed across dMRI metrics (Fig 3A). In comparison, the association between NfL and white matter microstructure (Fig 3B) was relatively circumscribed, localized primarily in the corona radiata and internal capsule, a fiber bundle that connects the cerebral cortex to mid-brain and brainstem. The relationship between white matter microstructure and p-Tau181 was limited to a very small region of cerebellar white matter, where a higher p-Tau181 concentration was associated with lower mean diffusivity. There were no regions in the cerebral cortex where p-Tau181 was associated with dMRI.

*Relationships of plasma biomarkers to phenotypic aspects of asthma*

Plasma GFAP concentration was positively associated with asthma severity ($t$ = 2.7, $p$ = .008; Fig 4), controlling for age, such that a one unit increase in asthma severity is associated with a 7.9 unit increase in GFAP. GFAP was not associated with T2 inflammation ($t$ = -.33, $p$ = .74). Plasma NfL concentration was not associated with asthma severity or T2 inflammation ($p$s > .05). Similarly, plasma p-tau181 concentration was unrelated to asthma severity and T2 score ($p$s > .1), respectively).

*Relationship of dMRI metrics to processing speed*

While a robust group difference in processing speed was not found ($t$ = 1.8, $p$ = .07) a marginal difference was present. In addition, significant group differences were observed in the slope of the relationship between processing speed and white matter microstructure, in tracts that mirrored those showing an association with asthma severity. This group difference in slopes was such that the deleterious effect of white matter microstructural change on processing speed was greater for participants with asthma (Fig. 5) and was present in multiple dMRI metrics.

## Discussion

Using newly developed blood-based biomarkers of glial activation and neurodegeneration, in addition to sensitive neuroimaging measures, we found that asthma was associated with significant deleterious alterations in white matter, resembling in extent and magnitude, those observed in neurodegenerative diseases. The striking differences in dMRI metrics were greater among participants with more severe asthma. Moreover, the deleterious nature of the white matter alterations was corroborated by their association with plasma concentrations of GFAP and to a lesser degree, NfL, suggesting that asthma is associated with glial activation and

neurodegenerative processes, independent of normal aging, with potentially important, but subtle, consequences for cognitive function.

Asthma severity was also an important factor in relationship to brain imaging findings. A relationship between asthma severity and altered brain microstructure was present in the same white matter regions that differed between asthma and controls. Given that these regions appear to be vulnerable to glial activation, we speculate that asthma-associated inflammation provokes central nervous system (CNS) inflammation, contributing to the vulnerability of these brain regions and eventual cognitive impairment. Prior work has shown that AD-associated glial activation influences large-scale brain network connectivity, which in turn is associated with cognitive deficits(27). The superior longitudinal fasciculus and inferior fronto-occipital fasciculus, in particular, connect cortical brain regions that are adversely affected by AD and subserve memory netoworks(28–30). Alterations in these pathways have also been shown to *precede* the development of dementia symptoms and to correlate with cerebrospinal fluid markers of microglia activation and AD pathology(31).

Increased expression of GFAP is a characteristic that defines reactive astrocytes(32). Indeed, together with NfL – a marker of axonal damage, GFAP has been used as an indicator of disease severity and progression in several neurodegenerative diseases(33–37). The presence of reactive astrocytes is an important indicator of neuroinflammation. Though astrocytes are essential in supporting brain health, they can lose their supportive functions, as well as cause the degeneration of neurons, an increase in microvascular permeability, and an amplification of the inflammatory state directly, and via their interactions with microglia when they become

reactive during CNS injury(38–40). Though neuroinflammation and neural injury have been identified in animal models of asthma(7,41), we report for the first time that these processes are also observed with asthma.

While the relationship between brain microstructure and GFAP was evident throughout the brain, the relationship with NfL was largely confined to the internal capsule. The internal capsule has been shown to be vulnerable to microvascular injury and increased arterial stiffness(42), which are apparent in asthma, even in children(43–45). Alterations in internal capsule integrity are found across numerous disorders of cognition and emotion, including depression(46,47) and ADRD(48,49), and correlate with symptom expression and degree of functional impairment. While cerebrovascular measures were not considered in our study, they deserve further research in the context of asthma, particularly given prior findings that altered subcortical white matter tracts contribute to cognitive impairment in vascular dementia(50).

To assess, in part, whether airway inflammation may instigate or exacerbate neural injury, we examined FeNO and EOS as surrogate markers of T2 inflammation in asthma. We did not observe a significant association between these proxies for T2 inflammation and white matter microstructure or plasma biomarkers of neural injury. However, determinations of T2 inflammation were obtained with 44% of participants on medications to reduce airway inflammation, which could obscure fluctuations in airway inflammation that might have cumulatively impacted the brain over time. Futhermore, in an exploratory analysis, we assessed the relationship between markers of T2 inflammation and dMRI in participants using only rescue medication (N = 62). Though insufficiently powered to reach significance, several regions of the brain showed

associations in the expected direction at an uncorrected threshold of $p < .01$. Nonetheless, our analysis captured a truncated range of airway inflammation. Therefore, a more accurate assessment of the impact of underlying airway inflammation on neural injury will require further study and an expanded assessment of the expression of inflammatory pathways, including Th17 activation and IL-17 generation, particularly among asthma patients with more pronounced and persistent airway inflammation or in proximity to an exacerbation.

The importance of peripheral inflammation to altered brain health is underscored by findings in Rheumatoid Arthritis (RA), which is also associated with increased prevalence of dementia that has been found to be abrogated by the recent introduction of anti-tumor necrosis factor alpha (TNF-$\alpha$) treatment(51), This suggests that chronic systemic inflammation contributes to neuropathology and dementia and can be attenuated by inhibiting the actions of a key inflammatory mediator, TNF-$\alpha$. TNF-$\alpha$ expression is increased in asthma, and further increased following an experimental allergen challenge(52) and during naturally occurring exacerbations(53). Similarly, the T17 immune response has a synergistic relationship with the T2 response in the pathogenicity of asthma(54,55). Moreover, TH17 cells traffic to the brain(56,57) and have been shown to play a role in neurodegeneration(58,59). Thus, a more expansive examination of inflammatory pathways and their interactions will be necessary to more fully and precisely establish the pathogenic pathways of inflammation associated with altered brain health in asthma.

The diagnosis of dementia is uncommon before 65 years of age, but the pathological processes that underlie its development and clinical expression are set in

motion long before cognitive decline occurs – perhaps even early in life(60–64). To put our findings into a clinical perspective, neuroinflammation and neurodegeneration are commonly observed processes in neurodegenerative diseases, and are closely associated with the clinical phenotype of dementia(65). Further, neuroinflammation likely accelerates the onset of dementia symptoms(66,67). Yet, the contribution of the white matter microstructural changes reported here to the eventual development of dementia remains speculative. In contrast to GFAP and NfL, p-Tau181, which is a specific marker of AD, was not associated with cortical neuroimaging metrics in asthma, suggesting either that asthma may not be associated with AD pathology specifically, or that AD pathology was not measurable in our cohort, which was cognitively unimpaired and relatively young (median age = 37.5 y), compared to typical studies of dementia.

The functional relevance of the brain alterations reported here is supported by an association with processing speed, a widely used index of cognitive function that correlates highly with performance on a broad range of more targeted cognitive tasks(20). Slower processing speed in asthma participants was associated with poorer white matter integrity in the tracts discussed above, in addition to the corticospinal tract, the inferior longitudinal fasciculus, and forceps major, indicative perhaps, of an accelerated decline in cognitive function in asthma when white matter microstructure is compromised. These observations corroborate prior research that demonstrates the importance of these tracts in processing speed(68–70) and deterioration in processing speed in neurodegenerative diseases(71,72). Nonetheless, processing speed represents only a single functional outcome and limits the conclusions we can draw regarding the implications of the white matter microstructural changes reported here for

functional impairment. A more comprehensive assessment of cognitive function and longitudinal evaluation will ultimately be required to determine whether these changes lead to increased risk of dementia.

A number of other factors may contribute to the observed brain changes, including effects of inflammation on the vasculature. Asthma exacerbations increase airway inflammation and airflow obstruction, sometimes resulting in hypoxia. The availability of historical data on the frequency and severity of asthma exacerbations in our participants was too sparse to support meaningful inference of these outcomes as contributors to neurodegeneration. Sleep deficit is also associated with neural injury, and often coexists with asthma(73). We examined group differences in self-reported sleep quality and relationships between sleep quality and white matter microstructure (see supplemental material Fig. 2); in those with sleep quality data, we found no evidence that sleep disruption accounted for our observed effects.

The influence of treatment must also be considered. The mitigating effects of anti-TNF-α in RA(51) suggest that treatment to suppress underlying peripheral inflammation may be neuroprotective. Inhaled and systemic corticosteroids diminish airway and peripheral markers of T2 inflammation(74). Our observations suggest that, despite ongoing treatment with ICS, brain microstructural changes were present raising the possibility that inflammatory factors not susceptible to corticosteroid regulation contribute to alteration in brain health. Although adverse effects of asthma medications may contribute to changes in brain structure, these associations are variable and infrequent(7,75–79). There is some evidence that Montelukast – a leukotriene receptor antagonist – is neuroprotective(76,80,81) and can slow age-related cognitive

decline(80,82). Prolonged oral corticosteroid use, on the other hand, has been associated with reduced grey matter volume of the amygdala and hippocampus, a global reduction in white matter volume, and reduced cognitive performance in cross-sectional studies(83–85). Nonetheless, the only prospective study found equivocal effects on cognitive performance and no change in hippocampal volume(86).

A few limitations of the study deserve mention. First, the analyses were retrospective, though the number of participants studied was large (n=111) and represented a broad spectrum of disease severity. Given the case-controlled nature of our analyses, these results will need to be replicated in an independent sample. Second, the scope of the functional consequences and clinical import of the white matter deterioration that we observed has not yet been established. Plasma p-tau181 concentration was unrelated to cortical white matter microstructure, suggesting that at least at the time of assessment, there was no evidence to indicate pathology specific to AD. Indeed, at recruitment, all participants were cognitively normal. Moreover, plasma for biomarker analysis was only acquired from participants with asthma, limiting the support that these measures can provide in interpreting group differences. Thus, additional research, including longitudinal study, is needed to definitively determine if the brain microstructural changes we observed contribute meaningfully to cognitive deficits and, in the long-term, to the development of dementia. Finally, our findings are descriptive and cannot yet establish the underlying mechanisms or inflammatory profile associated with these white matter structural changes. This need is a critical focus for future research; for therapeutic mitigation to be effective, a more precise understanding of the pathways involved will be required. Nonetheless, we believe our findings are of

potential clinical significance and reveal another important consequence of systemic inflammation in asthma.

The potential public health impact of our findings is considerable. More than 5 million people in the U.S currently live with ADRD, a prevalence that nearly doubles every two decades(87). The current lack of effective treatments for neurodegenerative disease makes identification of early risk factors a promising approach for potential interventions to delay onset, slow progression, or prevent these neural injuries and the risk for dementia that they confer, and is a major research priority(88). With increasing incidences of both chronic inflammatory diseases(89,90) and dementia(87), it will be critical to determine if persistent or poorly controlled airway inflammation in asthma is capable of provoking an inflammatory response in the brain, to either initiate or exacerbate neurodegenerative processes and eventually lead to impairment in cognitive function. Consequently, our findings invite the possibility that efforts designed to improve disease control by more effectively controlling airway inflammation will decrease or delay risks for neurodegeneration and dementia. Addressing this possibility is important and highly relevant to the large population of asthma patients who may be at risk for neurodegeneration and cognitive impairment and will be a focus for future research.

**Acknowledgements**

The authors wish to gratefully acknowledge Danika Klaus, Lori Wollet, Julia Bach, Evelyn Falibene, Corrina Frye, Michele Wolff, Ashlee Lindsay, Andrew Maddox, Heather Floerke, Michael Anderle, Ron Fisher, Jane Sachs, Ted Imhoff-Smith, Jeanne Harris, Elizabeth Nord, Kaley Ellis, Gina Bednarek, Kara Chung, and Pema Lhamo for their indispensable work in participant recruitment, data collection, and data analysis.

**Statement of Ethics**

All participants included in this manuscript provided written, informed consent before participating. All methods and procedures were reviewed and approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board.

## References Cited

1. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir Med [Internet]. 2016;4(7):574–84. Available from: http://dx.doi.org/10.1016/S2213-2600(16)30048-0
2. Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic obstructive pulmonary disease and asthma and the risk of mild cognitive impairment and dementia: a population based CAIDE study. Curr Alzheimer Res. 2013 Jun;10(5):549–55.
3. Chen M-H, Li C-T, Tsai C-F, Lin W-C, Chang W-H, Chen T-J, et al. Risk of dementia among patients with asthma: a nationwide longitudinal study. J Am Med Dir Assoc [Internet]. 2014 Oct [cited 2015 Jun 18];15(10):763–7. Available from: http://www.sciencedirect.com/science/article/pii/S1525861014003442
4. Lutsey PL, Chen N, Mirabelli MC, Lakshminarayan K, Knopman DS, Vossel KA, et al. Impaired lung function, lung disease, and risk of incident dementia. Am J Respir Crit Care Med. 2019;199(11):1385–96.
5. Peng Y-H, Wu B-R, Su C-H, Liao W-C, Muo C-H, Hsia T-C, et al. Adult asthma increases dementia risk: a nationwide cohort study. J Epidemiol Community Heal [Internet]. 2015;69(2):123–8. Available from: http://jech.bmj.com/cgi/doi/10.1136/jech-2014-204445
6. Zhuang TT, Pan C, Chen JJ, Han F, Zhu XL, Xu H, et al. Chronic asthma-induced behavioral and hippocampal neuronal morphological changes are concurrent with BDNF, cofilin1 and Cdc42/RhoA alterations in immature mice. Brain Res Bull [Internet]. 2018;143(September):194–206. Available from: https://doi.org/10.1016/j.brainresbull.2018.09.006
7. Xia M-X, Ding X, Qi J, Gu J, Hu G, Sun X-L. Inhaled budesonide protects against chronic asthma-induced neuroinflammation in mouse brain. J Neuroimmunol [Internet]. 2014 Aug 15 [cited 2016 Jan 25];273(1–2):53–7. Available from: http://www.sciencedirect.com/science/article/pii/S0165572814001763
8. Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci U S A. 2005;102:13319–24.
9. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS One [Internet]. 2012 Jan [cited 2012 Oct 25];7(8):e40921. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3411610&tool=pmcentrez&rendertype=abstract
10. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–73.
11. Anonymous. Standardization of spirometry. Am J Respir Crit Care Med [Internet]. 1995 Feb;152(3):1107–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18500705
12. Hoffmeyer F, Raulf-Heimsoth M, Brüning T. Exhaled breath condensate and

airway inflammation. Curr Opin Allergy Clin Immunol [Internet]. 2009 Feb [cited 2014 Sep 25];9(1):16–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19532089

13. Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, Szefler SJ. The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. J Allergy Clin Immunol [Internet]. 2004 Nov [cited 2014 Sep 20];114(5):1241–56. Available from: http://www.sciencedirect.com/science/article/pii/S0091674904022985
14. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest [Internet]. 1999 May;115(5):1265–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10334138
15. Johnson R, Wells JA, Schwarz AJ, Alexander DC, Zhang H, Holmes HE, et al. Application of neurite orientation dispersion and density imaging (NODDI) to a tau pathology model of Alzheimer's disease. Neuroimage [Internet]. 2016;125:739–44. Available from: http://dx.doi.org/10.1016/j.neuroimage.2015.10.043
16. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B [Internet]. 1996/06/01. 1996;111(3):209–19. Available from: internal-pdf://228.60.152.105/Basser - 1996 - Journal of magnetic resonance.pdf
17. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012 Jul;61(4):1000–16.
18. Daducci A, Canales-Rodriguez EJ, Zhang H, Dyrby TB, Alexander DC, Thiran JP. Accelerated Microstructure Imaging via Convex Optimization (AMICO) from diffusion MRI data. Neuroimage [Internet]. 2014/12/03. 2015;105:32–44. Available from: internal-pdf://189.27.88.186/Daducci-2015-Accelerated Microstructure Imagin.pdf
19. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18(6):643–62.
20. Lu H, Chan SSM, Lam LCW. ' Two-level ' measurements of processing speed as cognitive markers in the differential diagnosis of DSM-5 mild neurocognitive disorders ( NCD ). Sci Rep [Internet]. 2017;(April 2016):1–8. Available from: http://dx.doi.org/10.1038/s41598-017-00624-8
21. Gorus E, Raedt R De, Lambert M, Lemper J, Mets T. Reaction Times and Performance Variability in Normal Aging, Mild Cognitive Impairment, and Alzheimer ' s Disease. J Geriatr Psychiatry Neurol. 2008;21(3):204–18.
22. Winkler AM, Webster MA, Brooks JC, Tracey I, Smith SM, Nichols TE. Non-parametric combination and related permutation tests for neuroimaging. Hum Brain Mapp [Internet]. 2016/02/06. 2016;37(4):1486–511. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26848101
23. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. Neuroimage [Internet]. 2014 May 15 [cited 2014 Dec 7];92:381–97. Available from: http://www.sciencedirect.com/science/article/pii/S1053811914000913
24. Winkler AM, Ridgway GR, Douaud G, Nichols TE, Smith SM. Faster permutation

inference in brain imaging. Neuroimage [Internet]. 2016/06/12. 2016;141:502–16. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27288322
25. Mayo CD, Mazerolle EL, Ritchie L, Fisk JD, Gawryluk JR. Longitudinal changes in microstructural white matter metrics in Alzheimer's disease. NeuroImage Clin [Internet]. 2017;13:330–8. Available from: http://dx.doi.org/10.1016/j.nicl.2016.12.012
26. Tu MC, Lo CP, Huang CF, Hsu YH, Huang WH, Deng JF, et al. Effectiveness of diffusion tensor imaging in differentiating early-stage subcortical ischemic vascular disease, Alzheimer's disease and normal ageing. PLoS One. 2017;12(4):1–19.
27. Passamonti L, Tsvetanov KA, Jones PS, Bevan-Jones WR, Arnold R, Borchert RJ, et al. Neuroinflammation and Functional Connectivity in Alzheimer's Disease: Interactive Influences on Cognitive Performance. J Neurosci. 2019;39(36):7218–26.
28. Palmqvist S, Schöll M, Strandberg O, Mattsson N, Stomrud E, Zetterberg H, et al. Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nat Commun [Internet]. 2017;8(1). Available from: http://dx.doi.org/10.1038/s41467-017-01150-x
29. Brown CA, Jiang Y, Smith CD, Gold BT. Age and Alzheimer's pathology disrupt default mode network functioning via alterations in white matter microstructure but not hyperintensities. Cortex [Internet]. 2018;104:58–74. Available from: https://doi.org/10.1016/j.cortex.2018.04.006
30. Lee ES, Yoo K, Lee YB, Chung J, Lim JE, Yoon B, et al. Default Mode Network Functional Connectivity in Early and Late Mild Cognitive Impairment: Results from the Alzheimer's Disease Neuroimaging Initiative. Alzheimer Dis Assoc Disord. 2016;30(4):289–96.
31. Caballero MÁA, Suárez-Calvet M, Duering M, Franzmeier N, Benzinger T, Fagan AM, et al. White matter diffusion alterations precede symptom onset in autosomal dominant Alzheimer's disease. Brain. 2018;141(10):3065–80.
32. Escartin C, Guillemaud O, Carrillo-de Sauvage MA. Questions and (some) answers on reactive astrocytes. Glia. 2019;67(12):2221–47.
33. Abdelhak A, Huss A, Kassubek J, Tumani H, Otto M. Serum GFAP as a biomarker for disease severity in multiple sclerosis. Sci Rep. 2018;8(1):1–7.
34. Watanabe M, Nakamura Y, Michalak Z, Isobe N, Barro C, Leppert D, et al. Serum GFAP and neurofilament light as biomarkers of disease activity and disability in NMOSD. Neurology. 2019;93(13):E1299–311.
35. Benussi A, Ashton NJ, Karikari TK, Gazzina S, Premi E, Benussi L, et al. Serum Glial Fibrillary Acidic Protein (GFAP) Is a Marker of Disease Severity in Frontotemporal Lobar Degeneration. J Alzheimer's Dis. 2020;77:1129–41.
36. Su W, Chen HB, Li SH, Wu DY. Correlational study of the serum levels of the glial fibrillary acidic protein and neurofilament proteins in Parkinson's disease patients. Clin Neurol Neurosurg [Internet]. 2012;114(4):372–5. Available from: http://dx.doi.org/10.1016/j.clineuro.2011.11.002
37. Preische O, Schultz SA, Apel A, Kuhle J, Kaeser SA, Barro C, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med. 2019;25(2):277–83.

38. Xing LY, Yang T, Cui S Sen, Chen G. Connexin hemichannels in astrocytes: Role in CNS disorders. Front Mol Neurosci. 2019;12(February):1–10.
39. Sofroniew M V. Astrocyte Reactivity: Subtypes, States, and Functions in CNS Innate Immunity. Trends Immunol [Internet]. 2020;41(9):758–70. Available from: https://doi.org/10.1016/j.it.2020.07.004
40. Khakh BS, Deneen B. The Emerging Nature of Astrocyte Diversity. Annu Rev Neurosci. 2019;42:187–207.
41. Guo RB, Sun PL, Zhao AP, Gu J, Ding X, Qi J, et al. Chronic asthma results in cognitive dysfunction in immature mice. Exp Neurol [Internet]. 2013;247:209–17. Available from: http://dx.doi.org/10.1016/j.expneurol.2013.04.008
42. Badji A, Sabra D, Bherer L, Cohen-Adad J, Girouard H, Gauthier CJ. Arterial stiffness and brain integrity: A review of MRI findings. Ageing Res Rev. 2019;53(March).
43. Tattersall MC, Evans MD, Korcarz CE, Mitchell C, Anderson E, DaSilva DF, et al. Asthma is associated with carotid arterial injury in children: The Childhood Origins of Asthma (COAST) Cohort. PLoS One. 2018;13(9):1–12.
44. Steinmann M, Abbas C, Singer F, Casaulta C, Regamey N, Haffner D, et al. Arterial stiffness is increased in asthmatic children. Eur J Pediatr. 2015;174(4):519–23.
45. Tuleta I, Skowasch D, Aurich F, Eckstein N, Schueler R, Pizarro C, et al. Asthma is associated with atherosclerotic artery changes. PLoS One. 2017;12(10):1–11.
46. Silver M, Moore CM, Villamarin V, Jaitly N, Hall JE, Rothschild AJ, et al. White matter integrity in medication-free women with peripartum depression: A tract-based spatial statistics study. Neuropsychopharmacology [Internet]. 2018;43(7):1573–80. Available from: http://dx.doi.org/10.1038/s41386-018-0023-y
47. Chen G, Hu X, Li L, Huang X, Lui S, Kuang W, et al. Disorganization of white matter architecture in major depressive disorder: A meta-analysis of diffusion tensor imaging with tract-based spatial statistics. Sci Rep [Internet]. 2016;6(September 2015):1–11. Available from: http://dx.doi.org/10.1038/srep21825
48. Jiskoot LC, Bocchetta M, Nicholas JM, Cash DM, Thomas D, Modat M, et al. Presymptomatic white matter integrity loss in familial frontotemporal dementia in the GENFI cohort: A cross-sectional diffusion tensor imaging study. Ann Clin Transl Neurol. 2018;5(9):1025–36.
49. Yin R-H, Tan L, Liu Y, Wang W-Y, Wang H-F, Jiang T, et al. Multimodal Voxel-Based Meta-Analysis of White Matter Abnormalities in Alzheimer's Disease. J Alzheimers Dis. 2015;47(2):495–507.
50. Duering M, Zieren N, Hervé D, Jouvent E, Reyes S, Peters N, et al. Strategic role of frontal white matter tracts in vascular cognitive impairment: A voxel-based lesion-symptom mapping study in CADASIL. Brain. 2011;134(8):2366–75.
51. Chou RC, Kane M, Ghimire S, Gautam S, Gui J. Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis. CNS Drugs. 2016;30(11):1111–20.
52. Keatings VM, O'Connor BJ, Wright LG, Huston DP, Corrigan CJ, Barnes PJ. Late response to allergen is associated with increased concentrations of tumor necrosis factor-α and IL-5 in induced sputum. J Allergy Clin Immunol.

1997;99(5):693–8.
53. Koizumi A, Hashimoto S, Kobayashi T, Imai K, Yachi A, Horie T. Elevatian of serum soluble vascular cell adhesion molecule-1 (sVCAM-1) levels in bronchial asthma. Clin Exp Immunol. 1995;101(3):468–73.
54. Naji N, Smith SG, Gauvreau GM, O'Byrne PM. T helper 17 cells and related cytokines after allergen inhalation challenge in allergic asthmatics. Int Arch Allergy Immunol [Internet]. 2014;165(1):27–34. Available from: https://pubmed.ncbi.nlm.nih.gov/25301201/
55. Ramakrishnan RK, Al Heialy S, Hamid Q. Role of IL-17 in asthma pathogenesis and its implications for the clinic. Expert Rev Respir Med [Internet]. 2019;13(11):1057–68. Available from: https://doi.org/10.1080/17476348.2019.1666002
56. Cipollini V, Anrather J, Orzi F, Iadecola C. Th17 and cognitive impairment: Possible mechanisms of action. Front Neuroanat [Internet]. 2019;13:95. Available from: https://pubmed.ncbi.nlm.nih.gov/31803028/
57. Beurel E, Harrington LE, Jope RS. Inflammatory T helper 17 cells promote depression-like behavior in mice. Biol Psychiatry [Internet]. 2013 Apr [cited 2015 Feb 2];73(7):622–30. Available from: http://www.sciencedirect.com/science/article/pii/S0006322312008475
58. Liu Z, Qiu AW, Huang Y, Yang Y, Chen JN, Gu TT, et al. IL-17A exacerbates neuroinflammation and neurodegeneration by activating microglia in rodent models of Parkinson's disease. Brain Behav Immun [Internet]. 2019;81(May):630–45. Available from: https://doi.org/10.1016/j.bbi.2019.07.026
59. Chen J, Liu X, Zhong Y. Interleukin-17A: The Key Cytokine in Neurodegenerative Diseases. Front Aging Neurosci. 2020;12(September):1–13.
60. Calderón-Garcidueñas L, Franco-Lira M, Mora-Tiscareño A, Medina-Cortina H, Torres-Jardón R, Kavanaugh M. Early Alzheimer's and Parkinson's disease pathology in urban children: Friend versus Foe responses--it is time to face the evidence. Biomed Res Int [Internet]. 2013;2013:161687. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3581281&tool=pmcentrez&rendertype=abstract
61. Borenstein A, Copenhaver C, Mortimer J. Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord [Internet]. 2006;20(1):63–72. Available from: http://journals.lww.com/alzheimerjournal/fulltext/2006/01000/early_life_risk_factors_for_alzheimer_disease.12.aspx
62. Seifan A, Schelke M, Obeng-Aduasare Y, Isaacson R. Early Life Epidemiology of Alzheimer's Disease - A Critical Review. Neuroepidemiology [Internet]. 2015;237–54. Available from: http://www.karger.com/?doi=10.1159/000439568
63. Luciano R, Barraco GM, Muraca M, Ottino S, Spreghini MR, Sforza RW, et al. Biomarkers of Alzheimer Disease, Insulin Resistance, and Obesity in Childhood. Pediatrics [Internet]. 2015;135(6):1074–81. Available from: http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2014-2391
64. Lahiri DK, Maloney B. The "LEARn" (Latent Early-life Associated Regulation) model integrates environmental risk factors and the developmental basis of Alzheimer's disease, and proposes remedial steps. Exp Gerontol [Internet]. 2010 Apr [cited 2016 Jan 18];45(4):291–6. Available from:

http://www.sciencedirect.com/science/article/pii/S0531556510000331
65. Perez-Nievas BG, Stein TD, Tai HC, Dols-Icardo O, Scotton TC, Barroeta-Espar I, et al. Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. Brain. 2013;136(8):2510–26.
66. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci [Internet]. 2015;16(6):358–72. Available from: http://dx.doi.org/10.1038/nrn3880
67. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol [Internet]. 2014;14(7):463–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24962261
68. Karahan E, Costigan AG, Graham KS, Lawrence AD, Zhang J. Cognitive and White-Matter Compartment Models Reveal Selective Relations between Corticospinal Tract Microstructure and Simple Reaction Time. J Neurosci. 2019;39(30):5910–21.
69. Budisavljevic S, Dell'Acqua F, Zanatto D, Begliomini C, Miotto D, Motta R, et al. Asymmetry and Structure of the Fronto-Parietal Networks Underlie Visuomotor Processing in Humans. Cereb Cortex. 2017;27(2):1532–44.
70. Tu MC, Lo CP, Huang CF, Huang WH, Deng JF, Hsu YH. Visual attention performances and related cerebral microstructural integrity among subjects with subjective cognitive decline and mild cognitive impairment. Front Aging Neurosci. 2018;10(SEP):1–13.
71. Sisco S, Slonena E, Okun MS, Bowers D, Price C. Parkinson's Disease and the Stroop Color Word Test: Processing Speed and Interference Algorithms. Clin Neuropsychol. 2016;30(7):1104–17.
72. Phillips M, Rogers P, Haworth J, Bayer A, Tales A. Intra-Individual Reaction Time Variability in Mild Cognitive Impairment and Alzheimer's Disease: Gender, Processing Load and Speed Factors. PLoS One. 2013;8(6).
73. Janson C, De Backer W, Gislason T, Plaschke P, Björnsson E, Hetta J, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: A population study of young adults in three European countries. Eur Respir J. 1996;9(10):2132–8.
74. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: A randomised controlled trial. Lancet. 2002;360(9347):1715–21.
75. Lai J, Hu M, Wang H, Hu M, Long Y, Miao M, et al. Montelukast targeting the cysteinyl leukotriene receptor 1 ameliorates Aβ1-42-induced memory impairment and neuroinflammatory and apoptotic responses in mice. Neuropharmacology [Internet]. 2014 [cited 2017 Mar 28];79:707–14. Available from: http://www.sciencedirect.com.ezproxy.library.wisc.edu/science/article/pii/S0028390814000185
76. Lai J, Mei ZL, Wang H, Hu M, Long Y, Miao MX, et al. Montelukast rescues primary neurons against Aβ1–42-induced toxicity through inhibiting CysLT1R-mediated NF-κB signaling. Neurochem Int [Internet]. 2014 [cited 2017 Mar 28];75:26–31. Available from: http://www.sciencedirect.com.ezproxy.library.wisc.edu/science/article/pii/S0197018614001284

77. Kroll JL, Steele AM, Pinkham AE, Choi C, Khan DA, Patel S V., et al. Hippocampal metabolites in asthma and their implications for cognitive function. NeuroImage Clin [Internet]. 2018;19(April):213–21. Available from: https://doi.org/10.1016/j.nicl.2018.04.012
78. Halliday G. Pathology and hippocampal atrophy in Alzheimer's disease. Lancet Neurol [Internet]. 2017;16(11):862–4. Available from: http://dx.doi.org/10.1016/S1474-4422(17)30343-5
79. Woods CP, Argese N, Chapman M, Boot C, Webster R, Dabhi V, et al. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. Eur J Endocrinol. 2015;173(5):633–42.
80. Marschallinger J, Schäffner I, Klein B, Gelfert R, Rivera FJ, Illes S, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat Commun. 2015;6.
81. Jang H, Kim S, Lee JM, Oh YS, Park SM, Kim SR. Montelukast treatment protects nigral dopaminergic neurons against microglial activation in the 6-hydroxydopamine mouse model of Parkinson's disease. Neuroreport. 2017;28(5):242–9.
82. Grinde B, Schirmer H, Eggen AE, Aigner L, Engdahl B. A possible effect of montelukast on neurological aging examined by the use of register data. Int J Clin Pharm [Internet]. 2021;43(3):541–8. Available from: https://doi.org/10.1007/s11096-020-01160-8
83. Brown ES, Woolston DJ, Frol AB. Amygdala Volume in Patients Receiving Chronic Corticosteroid Therapy. Biol Psychiatry. 2008;63(7):705–9.
84. Brown ES, Woolston DJ, Frol A, Bobadilla L, Khan DA, Hanczyc M, et al. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol Psychiatry. 2004;55(5):538–45.
85. Gitelman DR, Klein-Gitelman MS, Ying J, Sagcal-Gironella ACP, Zelko F, Beebe DW, et al. Brain morphometric changes associated with childhood-onset systemic lupus erythematosus and neurocognitive deficit. Arthritis Rheum. 2013;65(8):2190–200.
86. Hájek T, Kopeček M, Preiss M, Alda M, Höschl C. Prospective study of hippocampal volume and function in human subjects treated with corticosteroids. Eur Psychiatry. 2006;21(2):123–8.
87. 2014-2015 Alzheimer's Disease Progress Report: Advancing Research Toward a Cure [Internet]. 2015. Available from: https://www.nia.nih.gov/alzheimers/publication/2014-2015-alzheimers-disease-progress-report/introduction#crisis
88. United States Department of Health & Human Services. National Plan to Address Alzheimer's Disease: 2015 Update.
89. Rook GAW. The hygiene hypothesis and the increasing prevalence of chronic inflammatory disorders. Trans R Soc Trop Med Hyg [Internet]. 2007;101(11):1072–4. Available from: http://trstmh.oxfordjournals.org/cgi/doi/10.1016/j.trstmh.2007.05.014
90. Raison C, Lowry C, Rook G. Inflammation, sanitation, and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and

842 treatment of major. Arch Gen Psychiatry [Internet]. 2010 [cited 2014 Oct
843 2];67(12):1211–24. Available from:
844 http://archpsyc.jamanetwork.com/article.aspx?articleid=210955
845
846

## Figure Captions

Figure 1: Group difference in white matter microstructure between Asthma (n = 111) and Control (n = 135) groups displayed on a standard white matter template. Representative sagittal (A) and axial (B) slices displaying the overall test (across diffusion-weighted imaging (DWI) metrics) of the group difference. Areas of yellow/orange represent regions where there is a significant group difference. Images were thresholded at a corrected $p < .05$. (C) Distribution of individual mean diffusivity (MD) means for each group, averaged over all voxels where MD was significantly greater in the asthma group, relative to the control group, in the whole-brain analysis displayed in (A) and (B). MD was chosen as a representative DWI metric for plotting purposes, but this effect was observed across most of the DWI metrics examined.

Figure 2: Greater asthma severity is associated with less white matter integrity. Representative sagittal (left) and axial (right) slices of a standard white matter template displaying voxels where asthma severity is significantly associated with overall white matter microstructure, across all diffusion-weighted imaging metrics (red) and greater mean diffusivity (MD; blue). The region shown in (A) includes fibers in the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and uncinate fasciculus. The region shown in (B) includes fibers in the superior longitudinal fasciculus, anterior thalamic radiation, and uncinate fasciculus. All images were thresholded at a corrected $p < .05$. (C) Scatter plot displaying the relationship between mean MD, averaged across all voxels in the blue cluster shown in (A) & (B) and asthma severity, with variance accounted for by age and sex removed from both variables.

Figure 3: Higher plasma biomarker concentrations are associated with less white matter integrity. Representative sagittal slices of a standard white matter template displaying voxels where plasma biomarker concentration is significantly associated with neurite density index (NDI). (A) Voxels where glial fibrillary astrocytic protein (GFAP) concentration showed a significant negative relationship with NDI. (B) Voxels where neurofilament light (NfL) concentration showed a significant negative relationship with NDI. This cluster is primarily composed of corona radiata and internal capsule fibers (including corticospinal tract and thalamic radiations). All images were thresholded at a corrected $p < .05$. (C & D) Scatter plots displaying the relationship between mean NDI, averaged across all voxels in the clusters shown in (A) & (B) and GFAP (C) and NfL (D), with variance accounted for by age and sex removed from both variables.

Figure 4: Relationship between plasma GFAP and asthma severity
Scatter plot displaying the relationship between plasma glial fibrillary astrocytic protein (GFAP) concentration and asthma severity, with variance accounted for by age removed from both variables ($B = 7.9$; $t = 2.7$, $p = .008$).

Figure 5: Reduced white matter integrity is associated with a deficit in processing speed in participants with asthma, but not in non-asthma healthy controls.
(A) Representative sagittal slice of a standard white matter template displaying voxels where the relationship between reaction time (RT) in the Stroop task and neurite density is significantly more negative for the asthma group compared to the control group.

Image thresholded at a corrected $p < .05$ (B) Scatter plot displaying the relationship between individual neurite density, averaged over the whole-brain analysis cluster shown in (A) and individual mean RT for each group, with variance accounted for by age and sex removed from both variables. Participants with asthma are shown in blue; non-asthma participants are shown in violet. Neurite density showed the strongest interaction between group and RT and was thus chosen as a representative diffusion-weighted imaging (DWI) metric for plotting purposes, but this effect was observed across multiple DWI metrics.

Figure 1



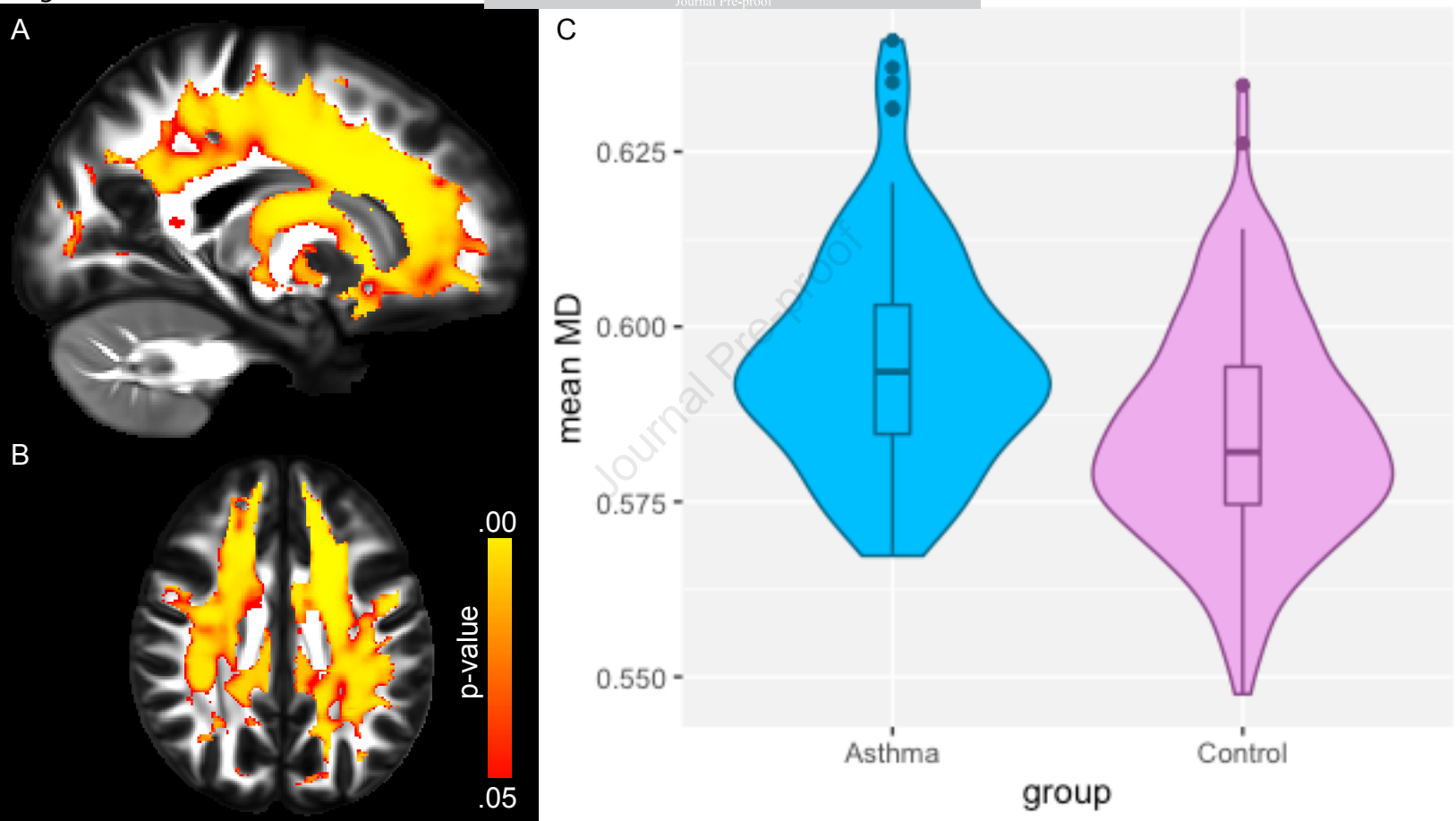
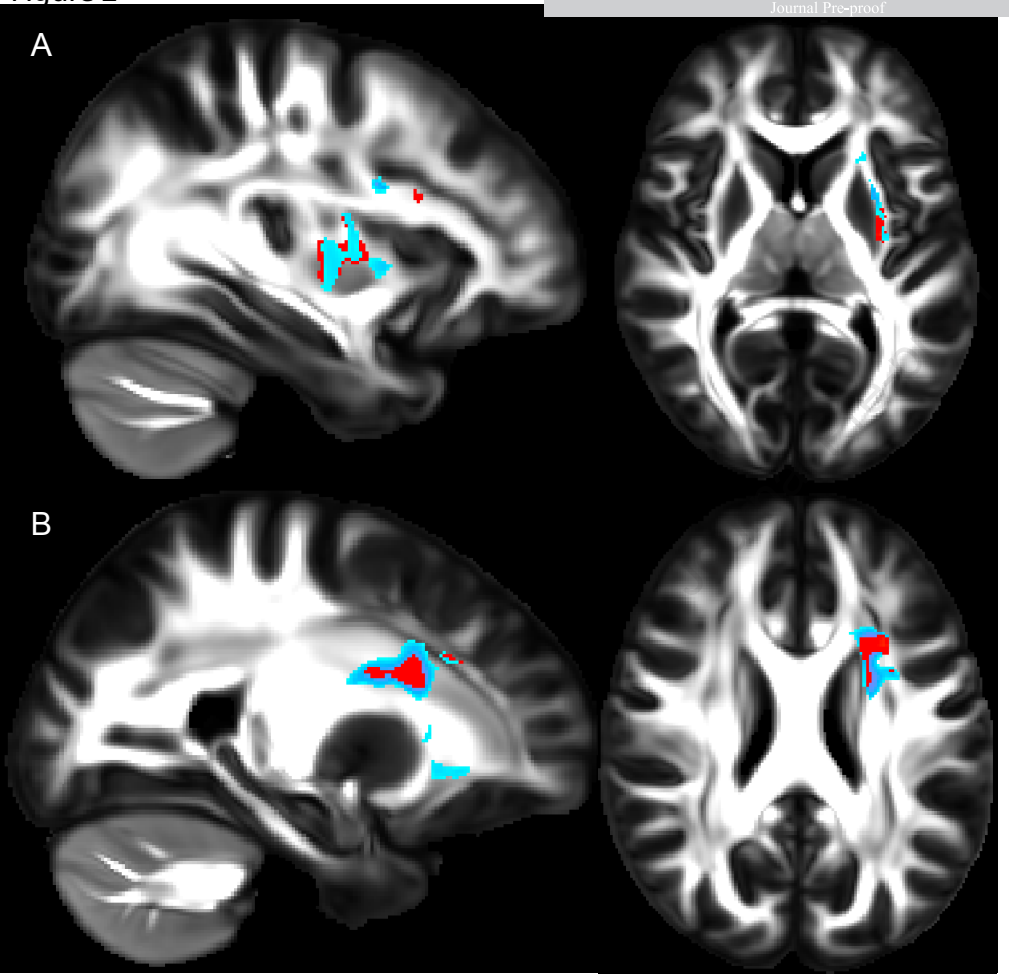


Figure 2





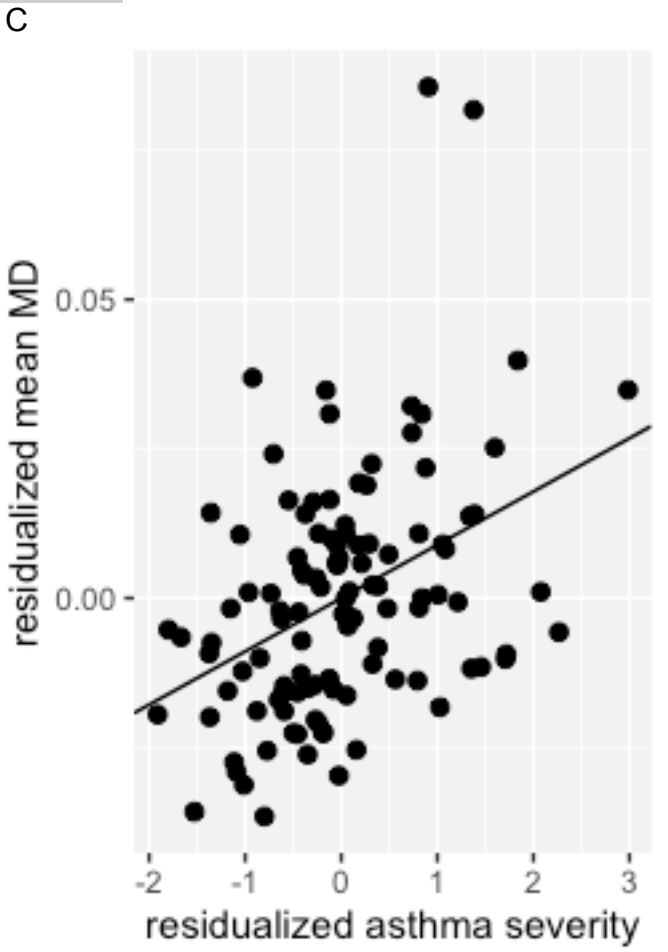
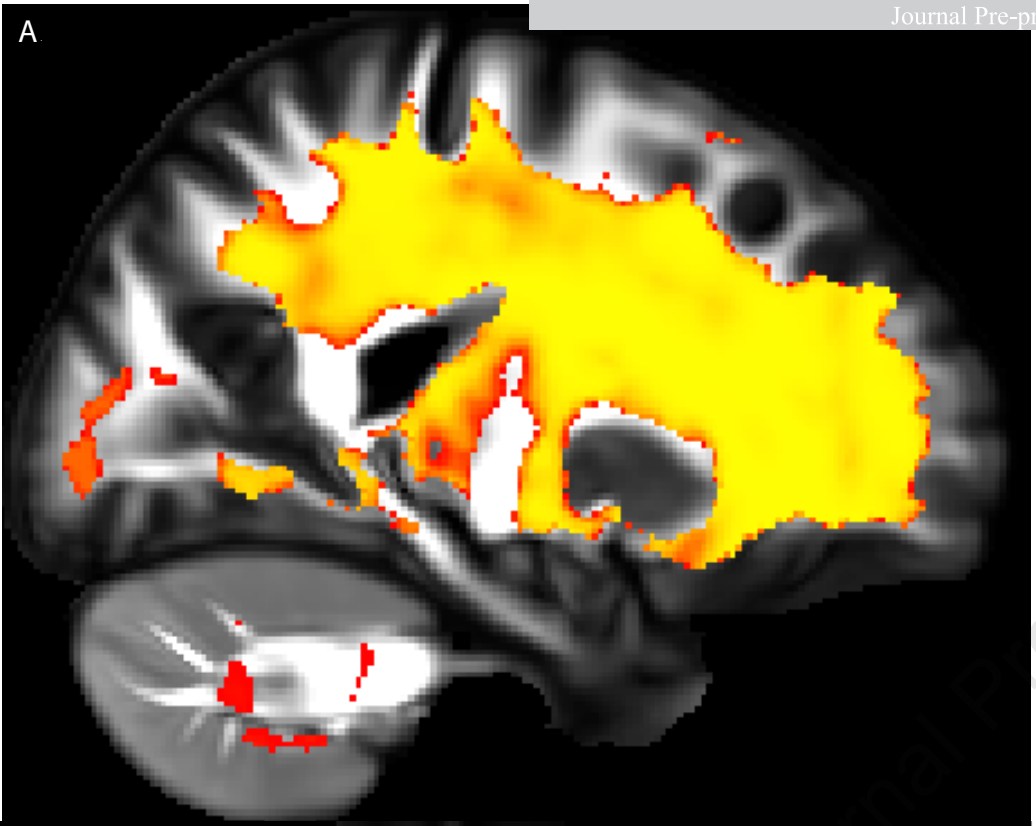
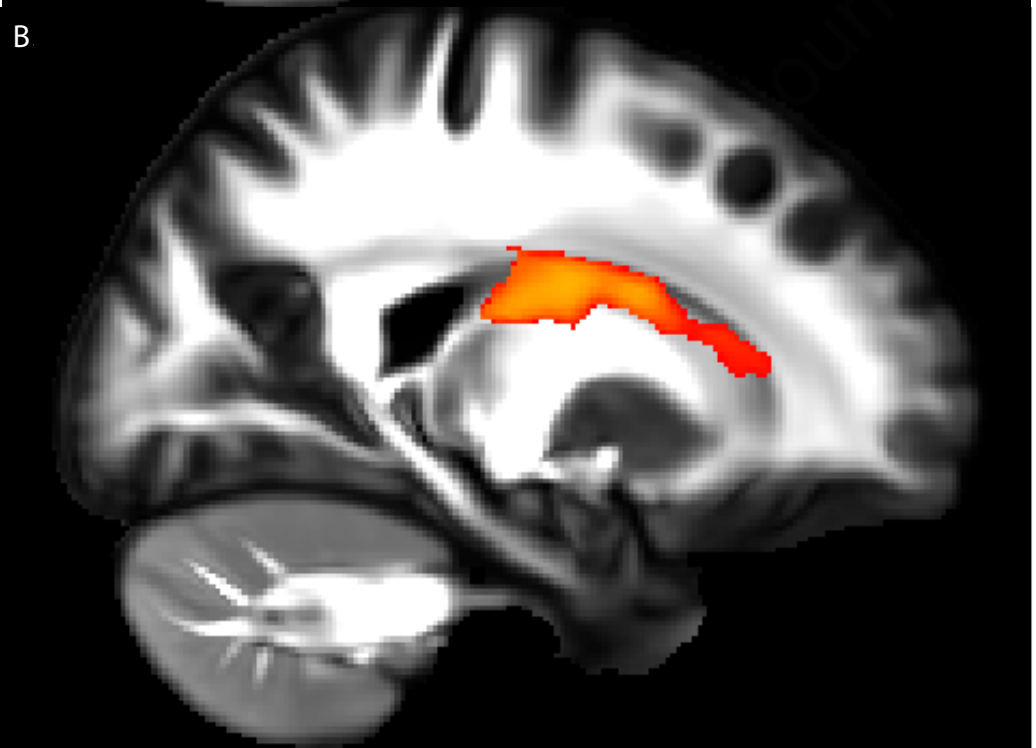
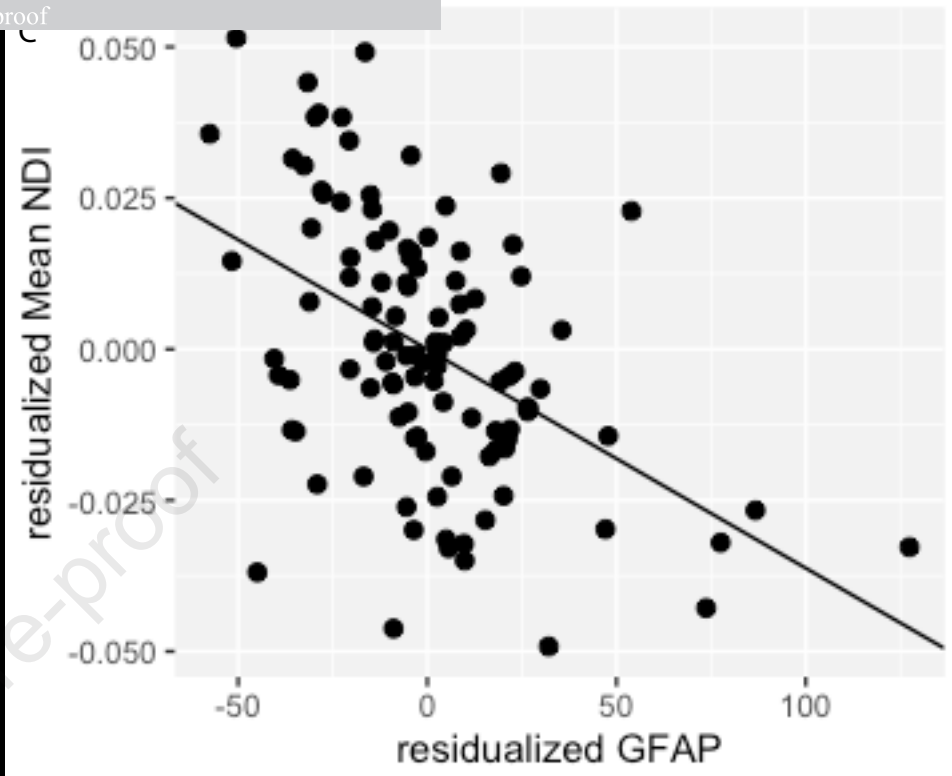



Figure 3





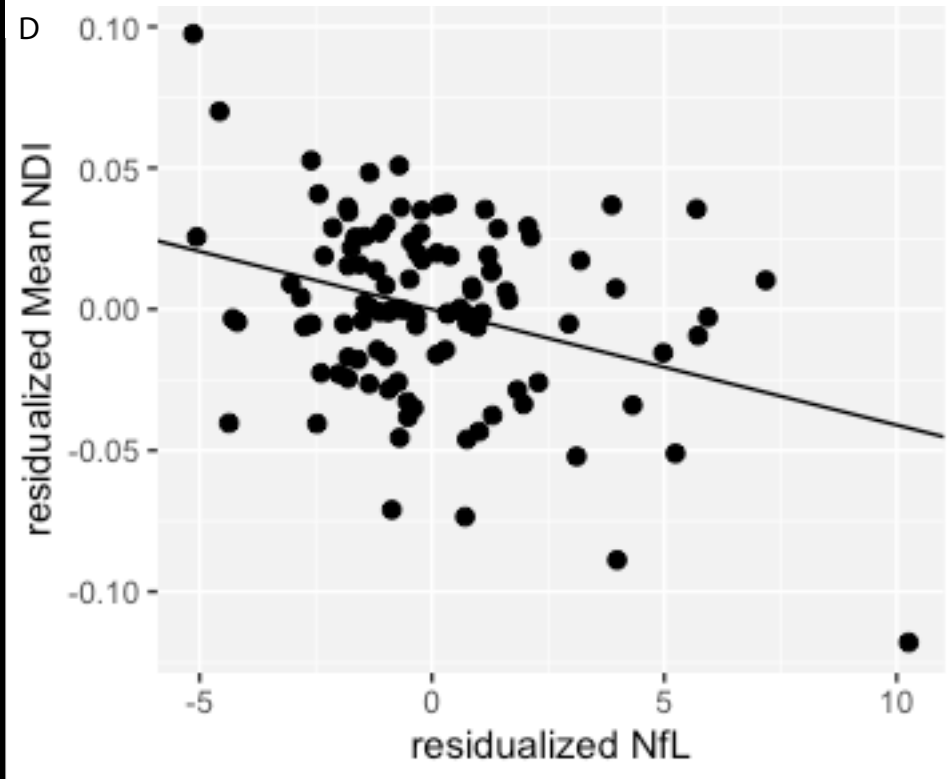



Figure 4



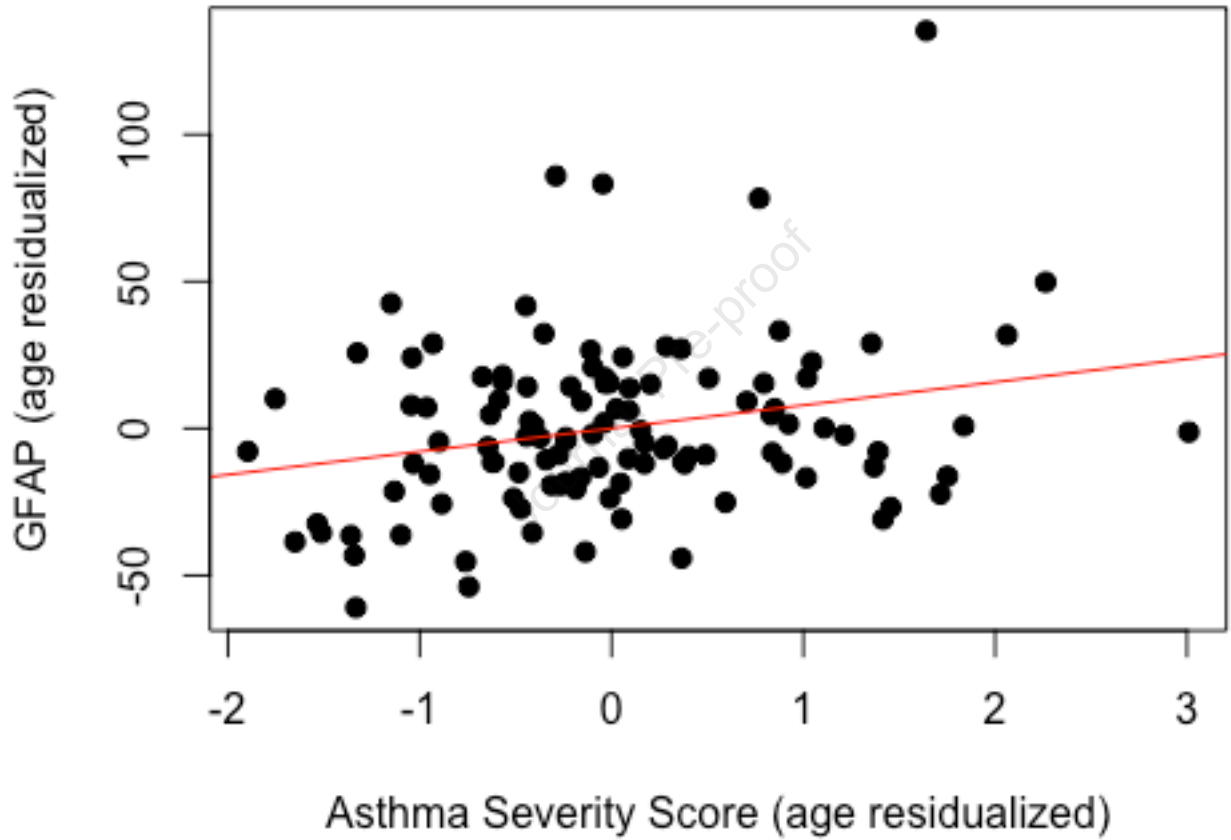
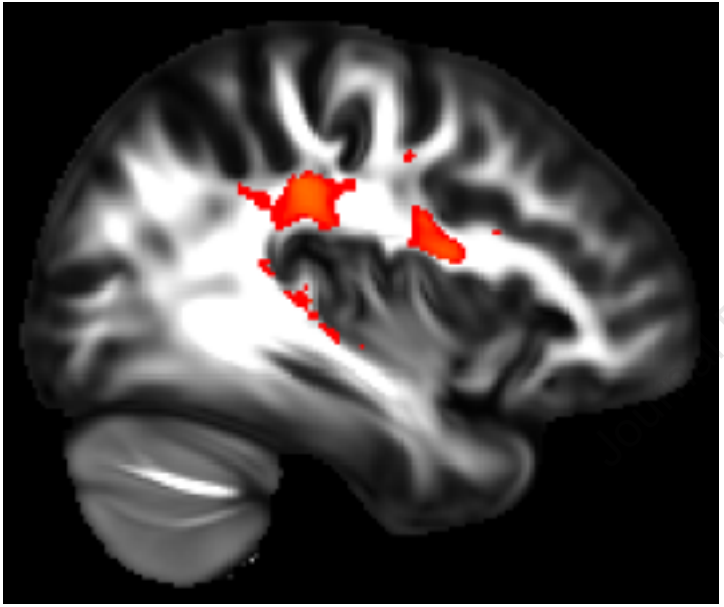


Figure 5



A



B