

Neuroimaging and biomarker evidence of neurodegeneration in asthma

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Background: Epidemiologic studies have shown that Alzheimer's disease (AD) 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 (phosphorylated tau 181, p-Tau181), neurodegeneration (neurofilament light chain, NfL), and glial activation (glial fibrillary acidic protein, 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 which were robustly associated with GFAP and, to a lesser extent, 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.

Conclusions: 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. There is 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. (J Allergy Clin Immunol 2021;■■■■:■■■-■■■.)

Key words: Asthma, dementia, diffusion-weighted imaging, neurodegeneration, inflammation, GFAP, NfL

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This work was supported by funding from the National Heart, Lung, and Blood Institute R01 HL123284 to W.W.B. and U10HL109168 to N.N.J.; from the National Center for Complementary and Integrative Health P01 AT004952 to R.J.D.; and by a core grant to the Waisman Center from the National Institute of Child Health and Human Development U54 HD090256. H.Z. and A.H. acknowledge funding from the UK Dementia Research Institute. H.Z. is a Wallenberg Scholar.

Disclosure of potential conflict of interest: N. N. Jarjour has a consulting relationship with GlaxoSmithKline, AstraZeneca, and Boehringer Ingelheim. H. 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 cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. W. W. Busse has a consulting relationship with GlaxoSmithKline, Novartis, AstraZeneca, Regeneron, and Sanofi. R. J. Davidson is the founder and president, and serves on the board of directors for the nonprofit organization Healthy Minds Innovations Inc. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 16, 2021; revised August 19, 2021; accepted for publication September 7, 2021.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2021.09.010>

Airway inflammation is a pathogenic characteristic of asthma and contributes to its symptoms, susceptibility to exacerbations, and airway remodeling; it also serves as a primary target for effective therapy. Moreover, the effects of airway inflammation may not be restricted to the airways; systemic manifestations can occur. Peters et al¹ found metabolic dysfunction and increased serum concentrations of IL-6, primarily in a subgroup with severe asthma. Our understanding of the systemic effects of asthma are currently limited, and their scope is likely underappreciated; 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 that, although limited, found an increased risk for dementia in asthma²⁻⁴ 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 nonpulmonary 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

Abbreviations used

ACQ-6:	6-item Asthma Control Questionnaire
AD:	Alzheimer's disease
ATS:	American Thoracic Society
dmMRI:	Diffusion-weighted magnetic resonance imaging
DTI:	Diffusion-tensor imaging
EOS:	Eosinophil
FA:	Fractional anisotropy
FENO:	Fraction of exhaled nitric oxide
FEV ₁ :	Forced expiratory volume in 1 second
GFAP:	Glial fibrillary acidic protein
NfL:	Neurofilament light chain
NODDI:	Neurite orientation and dispersion density imaging
PALM:	permutation analysis of linear models
p-Tau181:	Phosphorylated tau 181
RT:	Reaction time
T2:	Type 2

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 serologic 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 the phenotype or phenotypes 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) healthy controls without asthma, ranging in age from 18 to 73 years. All asthma patients had a physician's diagnosis of asthma and stable disease control for at least 4 weeks before the study in order to ensure safety in the conduct of the enrolled protocols and to avoid recent use of interventions that 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 magnetic resonance imaging (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 on the basis of their participation in the University of Wisconsin severe asthma research project and met European Respiratory Society and American Thoracic Society (ATS) Workshop¹⁰ 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 EOS count \geq 150 cells/ μ L, or sputum EOS \geq 2%, and had a minimum prealbuterol baseline forced expiratory volume in 1 second (FEV₁) of 60% at enrollment. Finally, 19 participants were recruited for a protocol to investigate neuroimmune interactions in asthma (reported elsewhere); these participants had a baseline FEV₁ of 70% or greater, with a 12% reversibility or PC₂₀ response to methacholine $<$ 16.0 mg/mL and were not using inhaled corticosteroid medications.

Healthy controls without asthma were recruited from the Madison, Wisconsin, area as part of a behavioral intervention study and were required to be free of an asthma diagnosis, symptoms compatible with asthma, and medications used to treat asthma. Although none had undergone 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 neurologic disorder, traumatic brain injury, and psychotic disorders, and all were cognitively normal. Recruitment information and complete inclusion and exclusion criteria are described in the Online Repository at www.jacionline.org. Although 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.

All participants 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.

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 guidelines¹³ (NIOX System; Aerocrine, Solna, Sweden), and a peripheral blood EOS count (cells/ μ L) was obtained. In addition, participants completed the Asthma Control Questionnaire (ACQ-6) at enrollment.¹⁴

Principal components analysis (PCA) was used to create a composite score of asthma burden from 5 separate measures: FEV₁ percentage predicted, ACQ-6 (ACQ score excluding FEV₁), FENO, EOS, and a medication score (see the Online Repository). This resulted in 2 orthogonal components: an asthma severity score comprising ACQ-6, FEV₁, and medication score, and a type 2 (T2) inflammation score comprising FENO and EOS. Details of this analysis and the relationships among the 5 measures and 2 derived scores are described in the Online Repository.

Brain imaging

Diffusion-weighted MRI (dmMRI) data, a validated, noninvasive tool to examine regional microstructural alterations in the brain,¹⁵ were acquired on a 3 T General Electric MR750 Discovery scanner. Acquisition parameters are detailed in the Online Repository. Each scan was reviewed by a neuroradiologist and participants with anatomic abnormalities were excluded (5 asthma, 5 control). Images underwent standard preprocessing 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 dmMRI data were also fit to the 3-compartment neurite orientation dispersion and density imaging (NODDI) tissue model¹⁷ 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 which, when sufficiently compromised, give rise to a wide variety of neurologic disorders. DTI and NODDI parameter maps were aligned with a population-specific template and smoothed using a 4 mm full-width-at-half-max Gaussian filter. The full processing methods are presented in the Online Repository.

Glial activation, neurodegeneration, and Alzheimer disease biomarker measures

Blood samples for measurement of plasma biomarkers were acquired from asthma patients only, under baseline conditions, and were stored at -80°C until analysis. Glial fibrillary acidic protein (GFAP) was measured to assess neuroinflammation, neurofilament light chain (NfL) was measured to assess neurodegeneration, and phosphorylated tau 181 (p-Tau181) was measured to assess Alzheimer's disease (AD)-specific pathology. Biomarker concentrations were measured using ultrasensitive single-molecule array technology on an HD-X instrument (Quanterix, Billerica, Mass). 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 the manufacturer's instructions (Quanterix). All measurements were performed in 1 round of experiments, using 1 batch of reagents by laboratory technicians who were unaware of the 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 task¹⁹ 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 it 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, as described in detail elsewhere.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 nonparametric combination, while also providing inference on the separate contribution of each metric.²² Joint inference of group differences was assessed with nonparametric combination and the Fisher combining function across 7 dMRI metrics (FA, mean, radial, and axial diffusivity, neurite density index, orientation dispersion index, 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 $P < .05$, 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, including 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 3, A). In comparison, the association between NfL and white matter microstructure (Fig 3, B) was relatively circumscribed, localized primarily in the corona radiata and internal capsule, a fiber bundle that connects the cerebral cortex to midbrain and brain stem. 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 1-unit increase in asthma severity is associated with a 7.9-unit increase in GFAP. GFAP was not associated with T2 inflammation ($t = -0.33$, $P = .74$). Plasma NfL concentration was not associated with asthma severity or T2 inflammation (all $P > .05$). Similarly, plasma p-Tau181 concentration was unrelated to asthma severity and T2 score (all $P > .1$), respectively).

Relationship of dMRI metrics to processing speed

Although 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.

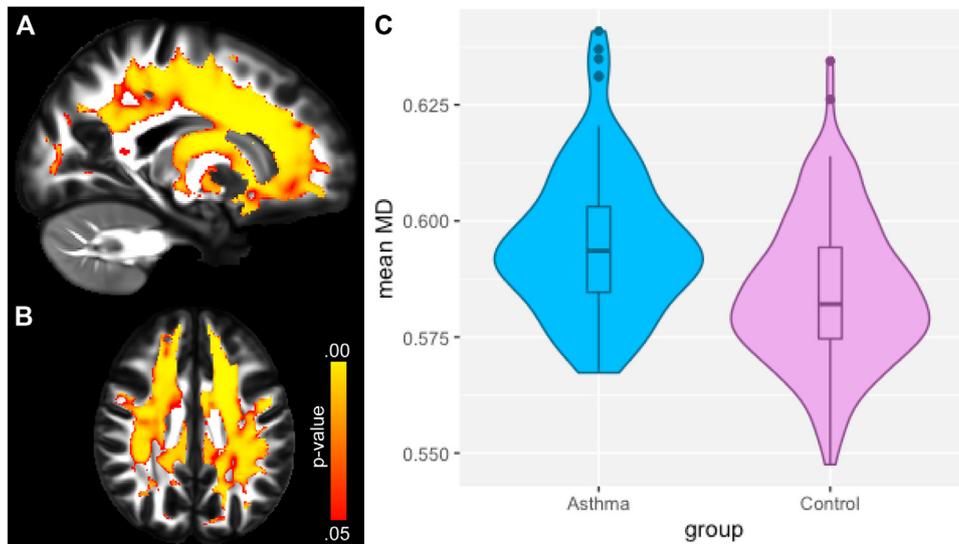


FIG 1. Group difference in white matter microstructure between asthma ($n = 111$) and control ($n = 135$) groups displayed on a standard white matter template. Representative sagittal (**A**) and axial (**B**) slices displaying the overall test (across diffusion-weighted imaging [DWI] metrics) of the group difference. Yellow-orange areas 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.

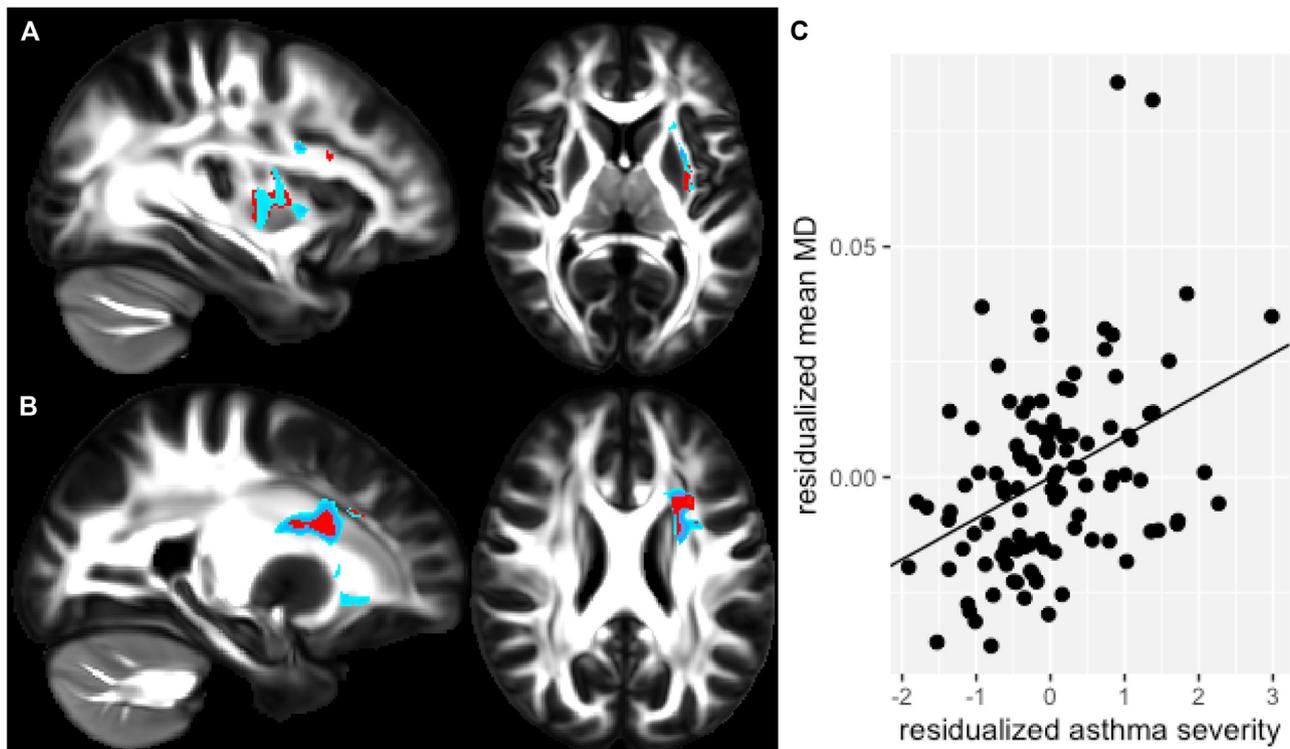


FIG 2. Greater asthma severity is associated with less white matter integrity. Representative sagittal (*left*) and axial (*right*) slices of a standard white matter template displaying voxels where asthma severity is significantly associated with overall white matter microstructure, across all diffusion-weighted 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**) Scatterplot displaying the relationship between mean MD, averaged across all voxels in the *blue cluster* shown in (**A**) and (**B**) and asthma severity, with variance accounted for by age and sex removed from both variables.

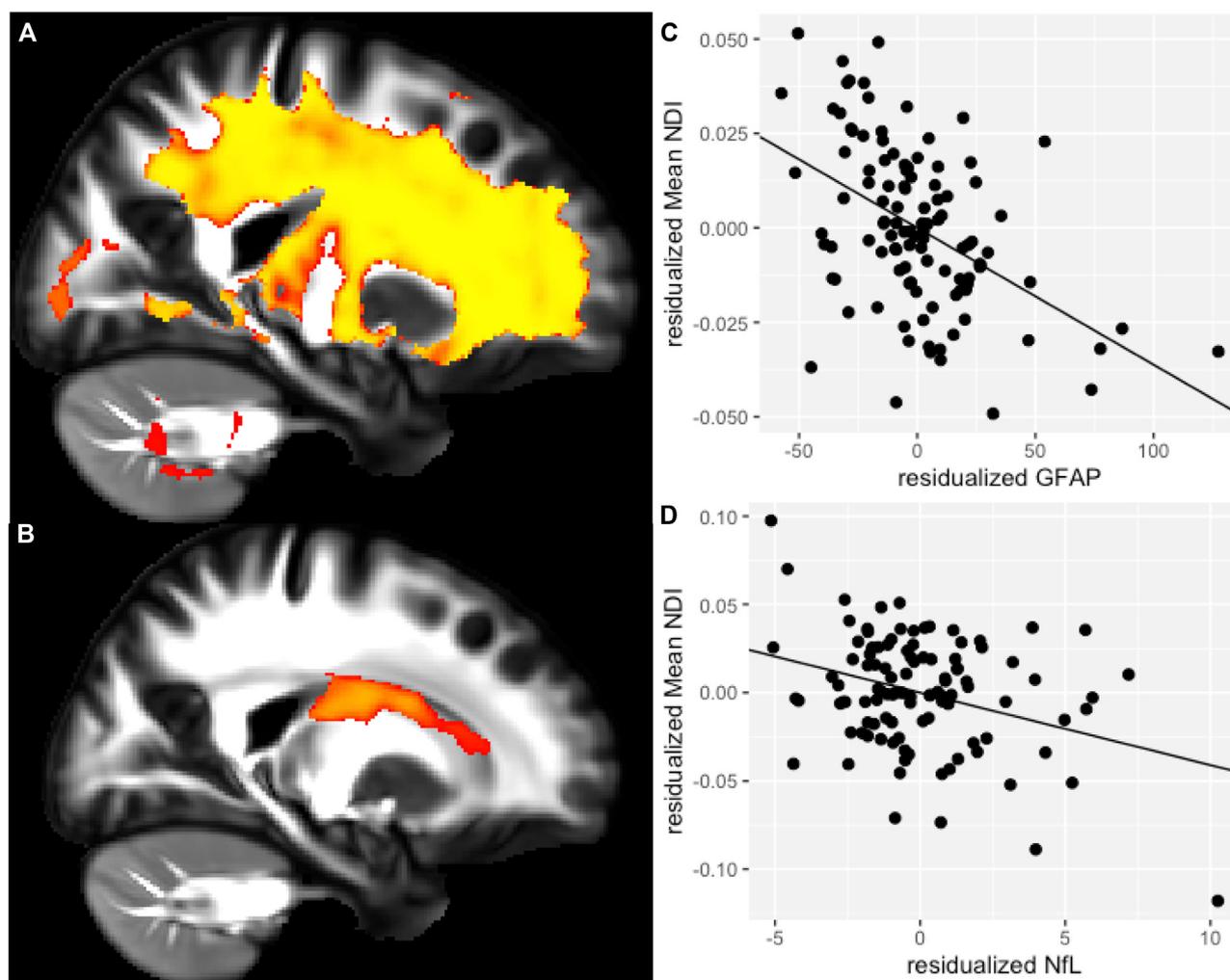


FIG 3. Higher plasma biomarker concentrations are associated with less white matter integrity. Representative sagittal slices of a standard white matter template displaying voxels where plasma biomarker concentration is significantly associated with neurite density index (NDI). (A) Voxels where glial fibrillary acidic 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 and D) Scatterplots displaying the relationship between mean NDI, averaged across all voxels in the clusters shown in (A) and (B) and GFAP (C) and NfL (D), with variance accounted for by age and sex removed from both variables.

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 of 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 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 networks.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

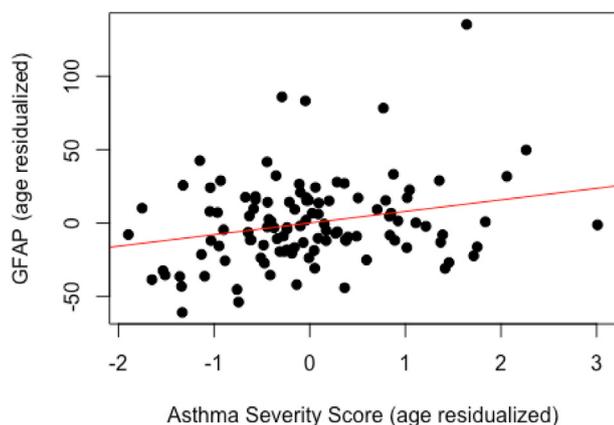


FIG 4. Relationship between plasma GFAP and asthma severity. Scatterplot displaying the relationship between plasma GFAP concentration and asthma severity, with variance accounted for by age removed from both variables ($b = 7.9$; $t = 2.7$, $P = .008$).

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. Although 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, as well as via their interactions with microglia, when they become reactive during central nervous system 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.

Although 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 AD and related dementias,^{48,49} and correlate with symptom expression and degree of functional impairment. Although 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 receiving medications to reduce airway inflammation, which could obscure fluctuations in airway inflammation that might have cumulatively affected the brain over time. Furthermore, in an exploratory analysis, we assessed the relationship between markers of T2 inflammation and dMRI in participants using only rescue medication ($n = 62$). Although 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 T_H17 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, which is also associated with increased prevalence of dementia that has been found to be abrogated by the recent introduction of anti-TNF- α 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- α . TNF- α expression is increased in asthma, and is further increased following an experimental allergen challenge⁵² and during naturally occurring exacerbations.⁵³ Similarly, the T_H17 immune response has a synergistic relationship with the T2 response in the pathogenicity of asthma.^{54,55} Moreover, T_H17 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 pathologic 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 years) 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

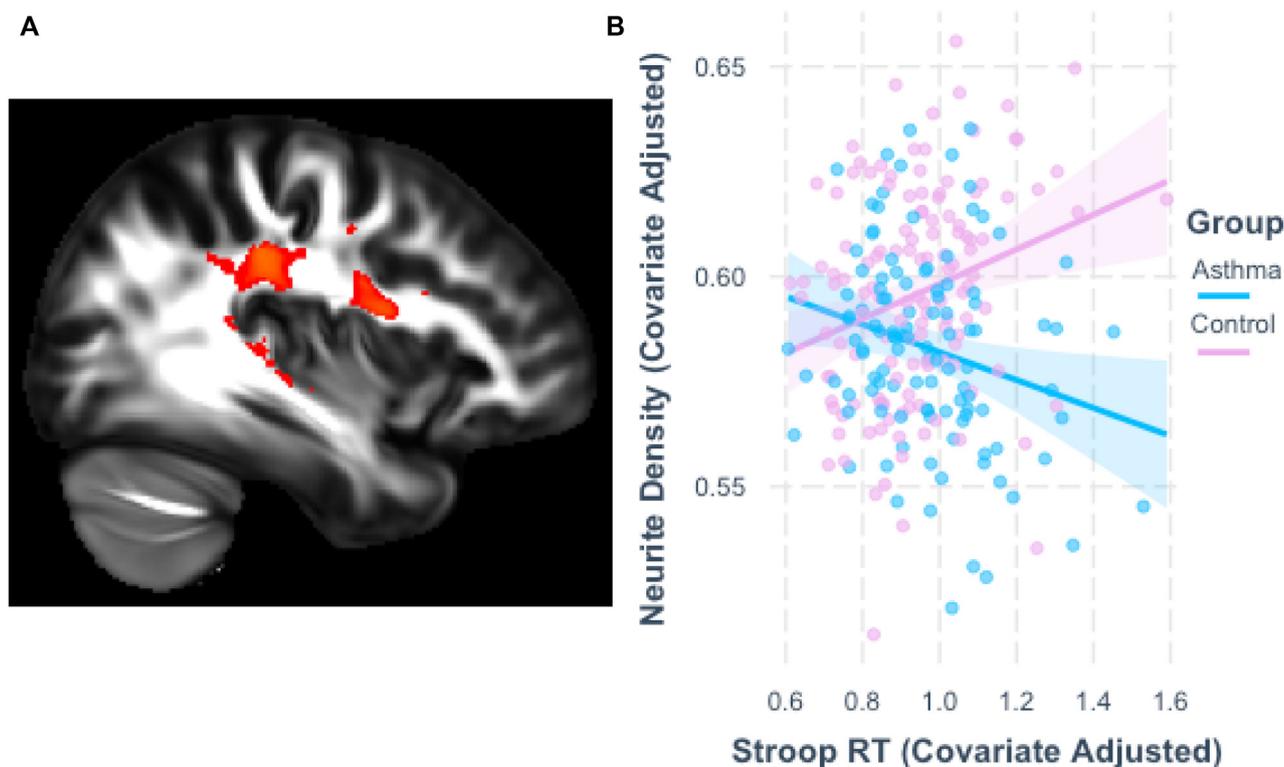


FIG 5. Reduced white matter integrity is associated with a deficit in processing speed in participants with asthma, but not in nonasthma healthy controls. (A) Representative sagittal slice of a standard white matter template displaying voxels where the relationship between RT in the Stroop task and neurite density is significantly more negative for the asthma group compared to the control group. Image thresholded at a corrected $P < .05$. (B) Scatterplot 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. Blue indicates participants with asthma; violet, nonasthma participants. 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.

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 as well as relationships between sleep quality and white matter microstructure in those with sleep quality data available (see Fig E2 in the Online Repository available at www.jacionline.org). 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 rheumatoid arthritis⁵¹ 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 inhaled corticosteroids, brain microstructural changes were present, thus 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 therapy with oral corticosteroids, on the other hand, has been associated with reduced gray 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, although the number of participants studied was large ($n = 111$) and represented a broad spectrum of disease severity. Given the case-control 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 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 United States currently live with AD and related dementias, a prevalence that nearly doubles every 2 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.

We 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.

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.
- Although 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.

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METHODS

Recruitment and enrollment criteria

Individuals with severe asthma were part of the University of Wisconsin Severe Asthma Research Project population (<http://www.severeasthma.org/home.html>) and met criteria for severe asthma established by the European Respiratory Society and ATS.^{E1}

Participants with moderate asthma severity were recruited as part of a study investigating the ability of mindfulness-based stress reduction training to improve asthma control and airway inflammation in asthma. Inclusion criteria for this sample included a physician's diagnosis of asthma with moderate levels of airway inflammation, defined as fraction of exhaled FENO ≥ 30 ppb, blood EOS count ≥ 150 cells/ μL , or sputum EOS $\geq 2\%$ of total lymphocytes, and a minimum prealbuterol FEV₁ of 60% while holding medication. In addition, participants were required to use an acceptable form of contraception during study participation. Exclusion criteria included regular receipt of oral steroids or >1000 μg fluticasone or equivalent inhaled corticosteroids per day, use of biologics, and smoking history exceeding 5 pack-years within the last 10 years.

Individuals with mild asthma were recruited as part of a study investigating the mechanisms of interaction between airway inflammation and function in emotion-related neural pathways. Inclusion criteria included a physician's diagnosis of asthma, a positive skin test to common allergens, a minimum baseline FEV₁ of 70% with 12% reversibility, or PC₂₀ response to methacholine <16.0 mg/mL. Individuals in this sample were excluded if they required inhaled corticosteroids to manage their asthma.

Individuals in the nonasthma control group were recruited as part of a study investigating the neural mechanisms and peripheral biological correlates of meditation practice. Individuals were excluded from this sample if they had a body mass index of >35 kg/m², disrupted sleep or regular sleep medication use, a diagnosis of asthma or a history of asthma or wheezing, or required corticosteroid-containing medication in the last 4 weeks.

Across groups, inclusion required US citizenship, green card, or an F-1 or J-1 visa; ability to speak and read English fluently; and ability to provide informed consent. Participants were excluded for incompatibility with the MRI environment (eg, claustrophobia; ferrous or magnetic field-sensitive implants), night shift work, current smoker status, pregnancy, history of neurologic disorder, traumatic brain injury, current prescribed psychotropic medication (included at the principal investigator's discretion), major medical illness, or bipolar or psychotic disorders. All participants with asthma were free from respiratory infection for at least 4 weeks before data collection.

Brain image acquisition

Diffusion-weighted images were acquired on a 3 T General Electric MR750 Discovery scanner equipped using a 32-channel receive-only head RF array coil (Nova Medical, Wakefield, Mass) and a single shot spin-echo echoplanar imaging pulse sequence. Sixty-three noncollinear diffusion encoding directions were acquired across 3 diffusion encoding strengths (ie, *b* values) of 500 s/mm² (9 directions), 800 s/mm² (18 directions), and 2000 s/mm² (36 directions), while 6 non-diffusion encoded images (ie, *b* = 0 s/mm²) were also acquired. Other imaging parameters included repetition time (TR), echo time (TE), flip angle, and bandwidth were, respectively, 8575 ms, 76.6 ms, 90°, and 3906.25 Hz per pixel. The imaging field of view was 25.6 cm \times 25.6 cm, with an acquisition matrix of 128 \times 128, providing a 2 mm \times 2 mm in-plane resolution. Whole brain coverage was achieved with seventy-five 2 mm sagittal-oriented slices. Total acquisition time was approximately 10 minutes. An additional field map was acquired for correction of susceptibility artifacts.^{E2} Each scan was reviewed by a neuroradiologist; participants with anatomic abnormalities were excluded from analyses.

Brain image preprocessing

DWIs underwent standard preprocessing procedures. Motion artifacts were visually assessed while preprocessing was performed using in-house processing pipelines. Briefly, Rician noise and Gibbs ringing artifacts were removed.^{E3,E4} Eddy current-induced distortions and subject movements,^{E5}

outlier detection and correction,^{E6} and susceptibility artifacts^{E2} were also accounted for using available tools from the FMRIB Software Library.^{E7} A measure of total head motion was calculated from the average displacement of each diffusion-weighted imaging (DWI), relative to the first image, and was used as a covariate in subsequent analyses.^{E8} Diffusion tensors were estimated at each voxel using a weighted-least squares algorithm as part of the diffusion imaging in the Python (DIPY) open source software package.^{E9} Quantitative maps of FA as well as mean, radial, and axial diffusivity (MD, RD, AD, respectively) were derived.^{E10} DWIs were also fit to the 3-compartment NODDI tissue model^{E11} using the AMICO-NODDI algorithm^{E12} to provide estimates of neurite density index, orientation dispersion index, and free water volume fractions (NDI, ODI, and FISO, respectively).

Symmetric diffeomorphic normalization, as implemented in the Advanced Normalization Tools (ANTs) software suite,^{E13} was used to construct a population-specific template from subject FA maps and bring the DTI and NODDI parameter maps into spatial alignment. DTI and NODDI parameter maps were brought into alignment of the population-specific template and subsequently smoothed using a 4 mm full-width-at-half-max Gaussian filter. The population-specific template was normalized to the Human Connectome 1065 (HCP1065) template in Montreal Neurological Institute space using the FLIRT^{E14} tool in the FMRIB Software Library.^{E7} The transformation matrix from the template normalization was then applied to the statistical output for visualization and localization purposes.

Medication score

The medication score used in the principal component analysis was computed on the basis of the scoring system developed according to GINA step-care guidelines. All asthma medications used within 1 month of study entry were assigned a score and summed for each individual.

Principal components analysis

In order to create a composite measure of asthma severity, we used PCA to explore the relationships among 5 separate measures representing different aspects of asthma severity: FEV₁ percentage predicted, ACQ-6 (ACQ score excluding FEV₁), FENO, EOS, and a medication score developed in house (Tables E1 and E2). Z scores were calculated for each measure (following log-transforming FENO and EOS) before entering the PCA. The resulting first principal component was oriented in the direction of higher (worse) ACQ-6, higher medication score, and lower FEV₁, with nearly equal loadings on each measure, and almost zero loading on FENO and EOS. The second principal component, orthogonal to the first, was oriented in the direction of higher EOS and higher FENO with equal weight, and minimal correlation with the other 3 measures. These first 2 components explained 61% of the total variance across the 5 measures, indicating that the creation of 2 composite variables, an asthma severity score comprising ACQ-6, FEV₁, and medication score, and a T2 inflammation score comprising FENO and EOS would provide an informative representation of overall asthma burden. Given the observed loadings, equal weights were assigned to each variable in this calculation. Thus, the asthma severity score was calculated as the sum ($Z_{ACQ-6} + Z_{med} - Z_{FEV1}$). The T2 score was calculated as ($Z_{EOS} + Z_{FENO}$). Each score was then Z transformed. The relationships among the 5 measures and 2 derived scores are shown in the correlation plot in Fig E1.

Sleep quality assessment

Sleep was assessed using 7 individual items from 2 different self-report assessments. The following items were drawn from the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form 4a:^{E15} "My sleep quality was . . ." (scale 1-5, from "very poor" to "very good;" reverse scored), "My sleep was refreshing" (reverse scored), "I had a problem with my sleep," and "I had difficulty falling asleep" (scale 1-5 from "not at all" to "very much"). All PROMIS questions asked participants to report on their sleep in the previous 7 days. The following items were drawn from the Symptom Checklist 90^{E16} (SCL-90) and were endorsed on a scale from 1 (not at all) to 5 (extremely) in response to the question, "How much

has this problem stressed or bothered you in the last 7 days”: “Trouble falling asleep,” “Awakening in the early morning,” and “Sleep that is restless or disturbed.” The value (or reverse-scored value) endorsed for each item was summed to create a composite sleep quality variable with a range from 7 to 23.

Sleep quality associations with white matter microstructure

Previous research has shown that sleep deficit is also associated with compromised white matter microstructure. Therefore, we examined group differences in self-reported sleep quality and relationships between sleep quality and white matter microstructure (Fig E2). Sleep quality data were available for all of the participants without asthma, but for only 67 participants with asthma (all in the moderate range). A *t* test was used to test for group differences in sleep quality. All DWI models described above were repeated in the subset of individuals in whom measures of sleep quality were available, both with and without sleep as a covariate.

There was no difference in sleep quality between groups ($t = 0.59, P > .1$; $M(\text{asthma}) = 12.78, M(\text{control}) = 12.53$). In the subset of 67 participants in whom sleep data and DWI data were available, the omnibus test of group showed a significant difference (corrected $P < .05$) that was limited to a cluster located in the cingulum. When sleep was included as a covariate in the omnibus test, the effect size in the cingulum was slightly stronger and nearly spatially identical (Fig E2). In the subsample restricted to participants with sleep quality data, there were no significant associations with either asthma severity or markers of T2 inflammation.

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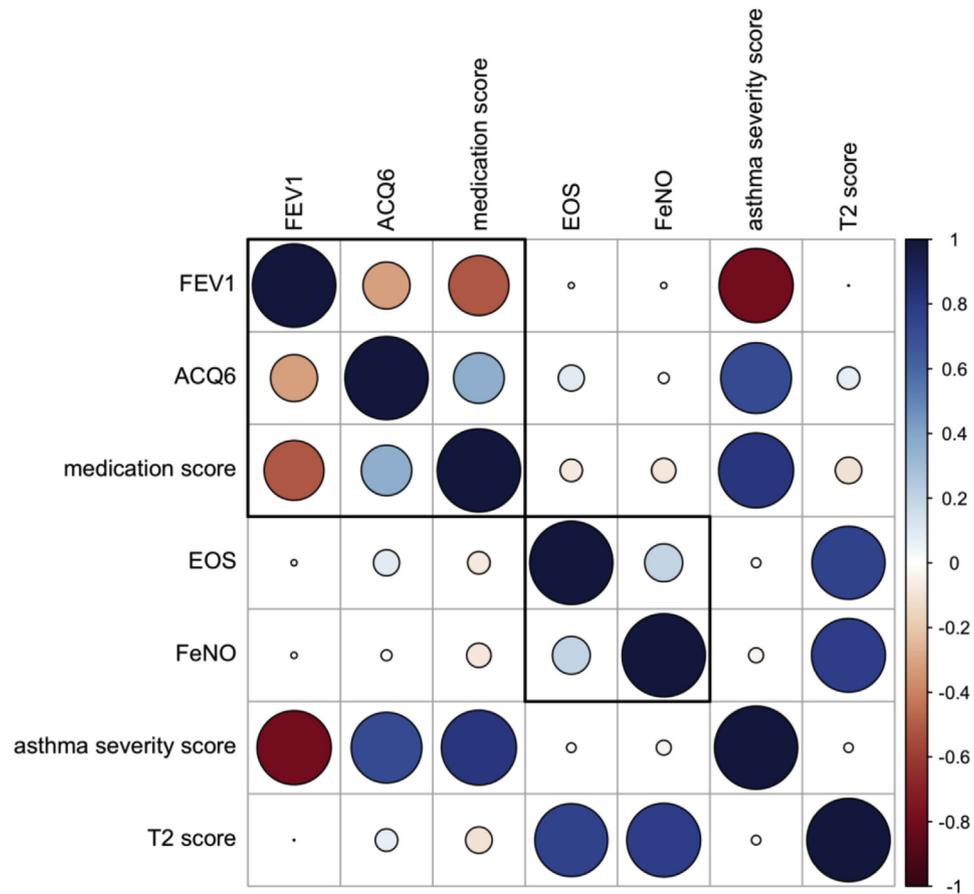


FIG E1. Correlation plot of asthma characteristics and scores. The correlation plot displays the matrix of Pearson correlation coefficients between each pair of asthma measures and derived scores. *Blue* and *red* indicate positive and negative correlation, respectively. *Larger circles/darker colors* indicate stronger correlations. Two boxes are drawn to emphasize groupings of correlated features: the asthma severity characteristics FEV₁, ACQ-6, and medication burden, and the T2 inflammation features EOS and FeNO.

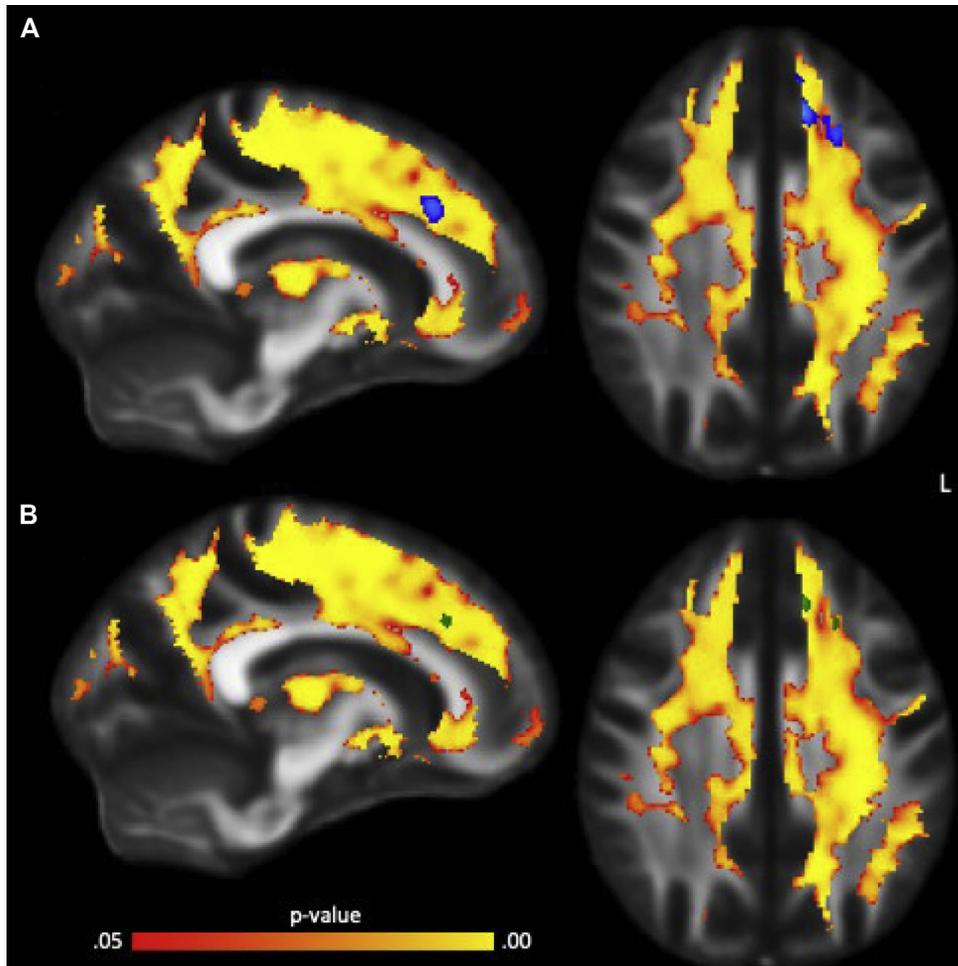


FIG E2. Group difference in white matter microstructure between asthma ($n = 111$) and control ($n = 135$) groups. Representative sagittal (*left*) and axial (*right*) slices displaying the omnibus test of the group difference. *Yellow-orange areas* show a significant difference, such that the integrity of white matter microstructure is lower in the asthma group. **(A)** *Blue clusters* reflect voxels in this slice that show a significant group difference in the subgroup of participants who have sleep data when sleep is included as a covariate in the model. **(B)** *Green clusters* reflect voxels in this slice that show a significant group difference in the subgroup of participants who have sleep data without sleep as a covariate. Nuisance covariates of motion, age, and sex were included in all models. All images were thresholded at a corrected $P < .05$.

TABLE E1. Scoring of asthma medications used within 1 month of study entry

Medication	Score
Albuterol/levalbuterol	1
Long-acting beta-agonist (LABA)	3
Long-acting muscarinic antagonists (LAMA)	3
Theophylline	1
Leukotriene receptor antagonists (LTRA)	1
Fluticasone propionate (see Table E2)	
44 µg/d	3
200 µg/d	3
500 µg/d	5
1000 µg/d	7
1500 µg/d	9
2000 µg/d	12
Biologics	10

TABLE E2. Fluticasone propionate equivalency

Therapy	Equivalency example
Beclomethasone and budesonide 1:2	500 μ g budesonide = 1000 μ g fluticasone propionate
Mometasone 1:1	200 μ g mometasone = 200 μ g fluticasone propionate
Fluticasone furoate 1:4	200 μ g fluticasone furoate = 800 μ g fluticasone propionate
Triamcinolone 120 mg	~1000 μ g fluticasone/d