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RESEARCH ARTICLE

Asthma amplifies dementia risk: Evidence from CSF biomarkers and cognitive decline

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Abstract

Introduction: Evidence from epidemiology, neuroimaging, and animal models indicates that asthma adversely affects the brain, but the nature and extent of neuropathophysiological impact remain unclear.

Methods: We tested the hypothesis that asthma is a risk factor for dementia by comparing cognitive performance and cerebrospinal fluid biomarkers of glial activation/neuroinflammation, neurodegeneration, and Alzheimer's disease (AD) pathology in 60 participants with asthma to 315 non-asthma age-matched control participants (45–93 years), in a sample enriched for AD risk.

Results: Participants with severe asthma had higher neurogranin concentrations compared to controls and those with mild asthma. Positive relationships between cardiovascular risk and concentrations of neurogranin and α-synuclein were amplified in severe asthma. Severe asthma also amplified the deleterious associations

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that apolipoprotein E ε4 carrier status, cardiovascular risk, and phosphorylated tau_{181}/amyloid $beta_{42}$ have with rate of cognitive decline.

Discussion: Our data suggest that severe asthma is associated with synaptic degeneration and may compound risk for dementia posed by cardiovascular disease and genetic predisposition.

KEYWORDS

Alzheimer's disease, asthma, cerebrospinal fluid biomarkers, cognition, comorbidities, dementia, glial activation, neurodegeneration, neuroinflammation, synaptic dysfunction cognition

Highlights

Those with severe asthma showed evidence of higher dementia risk than controls evidenced by:

- higher levels of the synaptic degeneration biomarker neurogranin regardless of cognitive status, cardiovascular or genetic risk, and controlling for demographics.
- steeper increase in levels of synaptic degeneration biomarkers neurogranin and α-synuclein with increasing cardiovascular risk.
- accelerated cognitive decline with higher cardiovascular risk, genetic predisposition, or pathological tau.

1 | BACKGROUND

Dementia is a major public health challenge with rapidly increasing prevalence and no effective disease-modifying treatments presently available, although progress is being made.[1–3] A number of possible risk factors for dementia have been identified, including genetic (apolipoprotein E [*APOE*] ε4 carriers and parental history), environmental (pollutants), socio-demographic, and lifestyle (diet, sleep, and physical, mental, and social activity) factors, as well as presence of comorbid conditions.[1,4–6] The co-expression of these risk factors amplifies the overall risk for dementia. Efforts to identify and address these modifiable risk factors could substantially reduce the prevalence and/or delay the onset of dementia.[6–8]

Accumulating evidence from several lines of inquiry suggests that asthma, a chronic inflammatory disease of the airways, may be a highly prevalent and modifiable risk factor. Asthma is a complex heterogeneous disorder with multiple etiologies and molecular phenotypes (eosinophilic, neutrophilic, paucigranulocytic, based on the nature of airway inflammation).[9–11] A growing body of research suggests that the adverse effects of asthma on the brain[12,13] are mediated by neuroinflammatory processes, potentially via the interleukin-17 pathway,[14] though hypoxia and changes to the neurovasculature[15] are additional possible mechanisms. Allergen exposure in mouse models of asthma, for example, activates microglial cells and evokes pro-inflammatory cytokine expression, as well as deleterious structural brain changes, in regions relevant to dementia and Alzheimer's disease (AD).[16,17] With data from a large human sample, we recently demonstrated that widespread subcortical white matter alterations occur in asthma and show significant associations with blood-based biomarkers of glial activation and axonal injury.[13] Further, findings from several epidemiological studies indicate that asthma is associated with increased risk of mild cognitive impairment (MCI) and dementia.[18–20] More generally, patients with chronic peripheral inflammation, who also carry the *APOE* ε4 allele, are at greater risk of AD dementia, relative to those with only chronic inflammation or *APOE* ε4.[21] Taken together, these complementary threads of evidence point toward the adverse effects of asthma on the brain and its potential promise as a modifiable risk factor for dementia. Because onset of asthma typically begins in the first decade of life and affects more than 10% of the US population,[22] its potential impact as a risk factor for dementia and target for modification is of great interest and public health importance.

Here, we investigated asthma as a risk factor for dementia in participants recruited to the Wisconsin Alzheimer's Disease Research Center (ADRC). Our objectives were to determine whether asthma patients have (1) higher cerebrospinal fluid (CSF) biomarker concentrations indicative of neuropathology and (2) lower cognitive scores, compared to controls. Further, we sought to evaluate whether these differences were related to asthma severity.

2 | METHODS

Participants (n = 404) aged 45 to 93 years with a diagnosis of MCI, AD dementia, or cognitively unimpaired (CU), were recruited to the Wisconsin ADRC from several sources including memory clinics, community lectures, radio and newspaper advertisements, and word of mouth. Participants were included in the current analysis based on

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using Google Scholar and PubMed. Epidemiological studies have examined the association of asthma with dementia. Studies in animal models of asthma have demonstrated neuroinflammation and poorer performance on behavioral tasks. Our study examines the adverse impact of asthma on brain health using cerebrospinal fluid (CSF) biomarkers and a composite cognitive measure.
2. **Interpretation**: Severe asthma is associated with synaptic degeneration and contributes to dementia risk independently, as well as synergistically, with cardiovascular and genetic risk factors.
3. **Future directions**: Our findings generate several testable hypotheses. We expect that a prospective longitudinal study including asthma clinical history will reveal lower concentrations of CSF neurogranin and α-synuclein, and slower cognitive decline in those with well-controlled asthma, than those with more exacerbations. Mechanistic studies with rodent models of asthma can examine blood brain barrier compromise and abnormal synaptic protein expression, in addition to behavior indicative of cognitive deterioration.

provision of at least one lumbar puncture for CSF collection, and available CSF assay results. Exclusion criteria included major medical, neurological, or psychiatric conditions other than MCI or dementia. For the present study, participants with any history of major central nervous system comorbidities or other systemic inflammatory conditions (see supporting information) were excluded from analyses, resulting in a final sample size of $n = 375$. All participants provided written informed consent.

The presence of asthma ($n = 60$) was determined based on detailed information of physician prescribed medication use to control asthma and was confirmed by self-reported diagnosis where available. The presence of asthma was based on the prescription of the following medications: short-acting bronchodilators (SABA), inhaled corticosteroids (ICS), long-acting bronchodilators (LABA), theophylline, systemic corticosteroids, and/or biologics specific for asthma. Based on medication prescription, asthma severity was estimated from criteria advanced in the National Institutes of Health Guidelines for Asthma Diagnosis and Management.[23] Three severity subgroups were identified (see supporting information). The mild asthma group (Sev1, $n = 18$) was composed of patients who used only rescue medications (SABA). Those categorized as moderate asthma (Sev2, $n = 22$) additionally used ICS; and those categorized as severe asthma (Sev3, $n = 20$) used a combination of LABA and ICS or systemic corticosteroids, in addition to SABA. The control group in these analyses comprised non-asthmatic participants ($n = 315$) who had no record of asthma diagnosis or prescription of medications for asthma.

The CSF sample collection and assay details have been described previously;[24] see supporting information for specific details. All CSF samples were assayed at the Clinical Neurochemistry Laboratory, University of Gothenburg, with strict quality control procedures, using the prototype NeuroToolKit (NTK; Roche Diagnostics International Ltd.) panel of CSF biomarkers, which show promise for early detection of AD dementia.[25,26] Biomarkers for AD-specific pathology included amyloid beta (1-42) ($A\beta_{42}$), phosphorylated tau (181P; p-tau$_{181}$), $A\beta$ (1-40) ($A\beta_{40}$), and their ratios ($A\beta_{42}/A\beta_{40}$ and p-tau$_{181}/A\beta_{42}$).[27] Biomarkers for glial activation and inflammation included glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), chitinase-3-like protein 1 (YKL-40), soluble triggering receptor expressed on myeloid cells 2 (sTREM2) and interleukin-6 (IL-6). Other biomarkers included those indicative of synaptic damage (neurogranin, α-synuclein) and neuronal degeneration (neurofilament light protein, NfL). The coefficient of variation for all assays ranged between 1% and 3%, except for S100B, which was 9%. All CSF biomarker values were z-transformed based on the distribution of corresponding data from controls.

Positivity thresholds for $A\beta_{42/40}$ and p-tau$_{181}/A\beta_{42}$ were derived as previously reported[24] using receiver operating characteristic analyses with positivity on [C-11]Pittsburgh compound B positron emission tomography (PET) imaging as the standard of comparison. Accordingly, participants with $A\beta_{42/40} < 0.046$ (96% negative agreement, 92% positive agreement) were considered $A\beta+$ and those with p-tau$_{181}/A\beta_{42} > 0.038$ (98% negative agreement, 83% positive agreement) were considered p-tau+. *APOE* genotype information (available in $n = 349$) was dichotomized for *APOE* $\varepsilon4$ status, such that carriers of at least one *APOE* $\varepsilon4$ allele were considered to have a higher genetic predisposition for AD.

To assess cognitive function, we used a preclinical cognitive composite measure that is reliable and sensitive to detection of early changes in cognitive performance among CU individuals.[28,29] Cognitive testing was performed annually for those with cognitive impairment and for CU participants > = 65 years of age, and biennially for CU participants <65 years of age. Participants completed up to 10 visits (mean [m] = 4.91, standard deviation [SD] = 2.24). There were no systematic differences between the number of follow up visits for asthma and controls ($P = .46$) or by severity groups ($P = .476$). Preclinical Alzheimer Cognitive Composite (PACC)[28,29] scores were computed as previously described[24] and z-transformed based on the distribution of data from a larger pool of all ADRC participants ($n = 922$).

Atherosclerotic cardiovascular disease (ASCVD) 10-year risk at study entry was calculated ($n = 317$) using the 2013 American College of Cardiology/American Heart Association algorithm.[24,30] The algorithm includes age, treated or untreated systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, history of diabetes, and smoker status as covariates to predict sex- and race-specific (Black or non-Hispanic White) risk of developing an ASCVD event.

Statistical analyses were carried out using R software (version 3.6.1).[31] Linear regression was used to evaluate the association of CSF biomarkers with asthma status, including demographic (age, sex, and

race) covariates. To examine the potential influence of education, we also re-ran all analyses including education as an additional covariate. Analyses were carried out both comparing asthma (collapsed across severity groups) and control groups, as well as comparing controls and all asthma severity levels (separating the asthma group into severity subgroups). See supporting information for additional details.

As several of the CSF analytes predict cognitive decline,[26] we hypothesized that asthma status would interact with CSF biomarker concentration and lead to poorer cognitive outcomes. Consequently, we determined the association between cognitive function and asthma status cross-sectionally, using baseline PACC scores, and included the interaction of asthma status and each CSF biomarker as a term in the models. To evaluate changes in cognition over time, we used PACC slopes derived from a linear mixed effects model[24] as the outcome measure, additionally adjusting for baseline PACC scores.

We also evaluated possible compounding effects of other risk factors such as cardiovascular risk and *APOE* ε4 genotype. Thus, models with CSF biomarkers and cognitive function as outcomes included an interaction of group with ASCVD, and all analyses were run with and without interaction of group with *APOE* ε4 status. Further, we re-ran all analyses with only CU participants to determine the impact of asthma prior to symptom onset.

Influential model outliers were identified as those values exceeding a threshold of 10% of the F-distribution of Cook's distance, and were dropped from analyses. Statistical significance was set at $P < .05$. To control for inflation of type I error due to multiple testing, Bonferroni correction thresholds were set for each comparison category based on number of outcome variables per category for models in which CSF was the outcome (glial activation/inflammation: $P < .01$; neurodegeneration: $P < .016$; AD pathology: $P < .025$) and models with CSF covariates in which cognitive function was the outcome ($P < .005$).

3 | RESULTS

3.1 | Participant characteristics

Characteristics of the participants by asthma status and asthma severity subcategories are presented in Table 1. Participants were aged 45 to 93 years ($m = 63.7$, SD = 9.59), and predominantly non-Hispanic Whites (92.5%). Although the majority had a parental history of dementia (68.5%), most were CU (76.5%). The asthma prevalence in this sample was high (16%) but the asthma and control groups did not differ in terms of demographic variables (all $P > .05$). Descriptive statistics of PACC scores (baseline and slopes across time) and CSF analyte concentrations are presented in Table 2.

3.2 | Relationship between asthma and CSF biomarkers of dementia risk

Regression analyses assessing concentrations of CSF analytes related to neurodegeneration revealed that, compared to controls, Sev3 had significantly higher concentrations of neurogranin (Figure 1). Further, interactions (one outlier removed) were present between asthma status and ASCVD in models with neurogranin and α-synuclein concentrations as outcomes. ASCVD was positively associated with neurogranin and α-synuclein concentrations, and this relationship was

TABLE 1 Sample characteristics

Measure	Total	Control	Asthma	Sev1	Sev2	Sev3
n	375	315	60	18	22	20
Age LP, *m* (SD)	63.66 (9.59)	63.47 (9.83)	64.65 (8.23)	65.4 (6.8)	64.5 (9.12)	64.14 (8.74)
ASCVD, *m* (SD)	10.25 (10.23)	9.89 (10.11)	11.92 (10.73)	12.59 (9.98)	13.56 (10.89)	9.64 (11.42)
Education, *m* (SD)	16.02 (2.48)	15.92 (2.46)	16.52 (2.55)	16.56 (2.09)	17.14 (2.83)	15.8 (2.53)
Female, *n* (%)	229 (61.1%)	196 (62.2%)	33 (55.0%)	11 (61.1%)	8 (36.4%)	14 (70.0%)
Non-Hispanic White, *n* (%)	347 (92.5%)	294 (93.3%)	53 (88.3%)	16 (88.9%)	19 (86.4%)	18 (90.0%)
Parental AD+, *n* (%)	257 (68.5%)	219 (69.5%)	38 (63.3%)	12 (66.7%)	13 (59.1%)	13 (65.0%)
Dementia, *n* (%)	57 (15.2%)	49 (15.6%)	8 (13.3%)	0 (0.0%)	4 (18.2%)	4 (20.0%)
MCI, *n* (%)	29 (7.7%)	25 (7.9%)	4 (6.7%)	1 (5.6%)	2 (9.1%)	1 (5.0%)
CU, *n* (%)	287 (76.5%)	240 (76.2%)	47 (78.3%)	16 (88.9%)	16 (72.7%)	15 (75.0%)
Aβ+, *n* (%)	33 (11.7%)	27 (11.3%)	6 (14.0%)	3 (20.0%)	2 (13.3%)	1 (7.7%)
p-tau+, *n* (%)	21 (7.4%)	16 (6.7%)	5 (11.4%)	2 (13.3%)	3 (18.8%)	0 (0.0%)
ASCVD+, *n* (%)	87 (33.9%)	68 (32.2%)	19 (41.3%)	7 (43.8%)	6 (40.0%)	6 (40.0%)
APOE ε4+, *n* (%)	99 (37.5%)	85 (39.0%)	14 (30.4%)	3 (20.0%)	7 (43.8%)	4 (26.7%)

Abbreviations: Aβ, amyloid beta; Aβ+, $A\beta_{42/40} < 0.046$; AD, Alzheimer's disease; *APOE* ε4+, apolipoprotein E ε4 carrier; ASCVD, atherosclerotic cardiovascular disease 10-year risk; ASCVD+, ASCVD > 7.5; Asthma, all asthma participants; CU, cognitively unimpaired; Dementia, dementia due to suspected AD or other causes; LP, lumbar puncture; MCI, mild cognitive impairment due to suspected AD or other causes; *m*, mean; *n*, number of observations; p-tau, phosphorylated tau; p-tau+, $pTau_{181}/A\beta_{42} > 0.038$; SD, standard deviation; Sev1, mild asthma; Sev2, moderate asthma; Sev3, severe asthma.

TABLE 2 Descriptive statistics of cognitive scores and CSF biomarker concentrations

Outcome	Control	Asthma	Sev1	Sev2	Sev3	*P*	*PSev*
Cognitive scores							
PACC baseline, *m* (SD)	0.211 (0.76)	0.214 (0.666)	0.46 (0.307)	0.131 (0.692)	0.096 (0.817)	.976	.453
PACC slopes, *m* (SD)	−0.027 (0.028)	−0.026 (0.029)	−0.016 (0.011)	−0.031 (0.03)	−0.029 (0.037)	.745	.350
Glial activation/neuroinflammation markers							
YKL-40 ng/mL, *m* (SD)	158.56 (75.31)	164.33 (64.84)	151.62 (50.96)	162.65 (66.75)	177.63 (73.91)	.540	.682
sTREM2 ng/mL, *m* (SD)	8.3 (2.6)	7.79 (2.49)	7.37 (2.63)	7.88 (2.42)	8.08 (2.51)	.151	.437
GFAP ng/mL, *m* (SD)	10.43 (4.87)	9.56 (3.7)	10 (5.13)	9.28 (2.87)	9.47 (3.11)	.118	.581
S100B ng/mL, *m* (SD)	1.19 (0.29)	1.14 (0.21)	1.19 (0.22)	1.11 (0.22)	1.12 (0.18)	.081	.379
IL-6 pg/mL, *m* (SD)	4.8 (3.21)	5.28 (4.59)	5.81 (6.66)	4.87 (3.1)	5.26 (3.76)	.459	.659
Neurodegeneration markers							
Neurogranin pg/mL, *m* (SD)	821 (403.49)	821.68 (374.68)	686.46 (290.61)	758.4 (350.56)	1013 (405.04)	.990	.064
NfL pg/mL, *m* (SD)	118.97 (105.5)	105.08 (52.1)	114.89 (61.86)	102.47 (49.04)	99.11 (47)	.124	.741
α-Synuclein pg/mL, *m* (SD)	172.57 (87.77)	161.63 (75.27)	147.54 (61.24)	146.1 (50.71)	191.39 (99.97)	.318	.219
AD pathology markers							
p-tau$_{181}$ pg/mL, *m* (SD)	21 (13.89)	20.1 (10.44)	17.69 (10.85)	18.69 (7.76)	24.32 (12.25)	.572	.442
p-tau$_{181}$/Aβ_{42}, *m* (SD)	0.033 (0.035)	0.034 (0.035)	0.03 (0.031)	0.032 (0.027)	0.041 (0.047)	.818	.825
A$\beta_{42/40}$, *m* (SD)	0.06 (0.019)	0.059 (0.018)	0.06 (0.016)	0.059 (0.019)	0.058 (0.019)	.624	.949

Abbreviations: Aβ, amyloid beta; Asthma, all asthma participants; GFAP, glial fibrillary acidic protein; IL-6, interleukin 6; *m*, mean; NfL, neurofilament light protein; PACC, Preclinical Alzheimer Cognitive Composite; *P*, *P*-values for controls vs. asthma (overall); *PSev*, *P*-values for controls vs. asthma severity subgroups; p-tau, phosphorylated tau; S100B, S100 calcium-binding protein B; SD, standard deviation; Sev1, mild asthma; Sev2, moderate asthma; Sev3, severe asthma; sTREM2, soluble triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1.

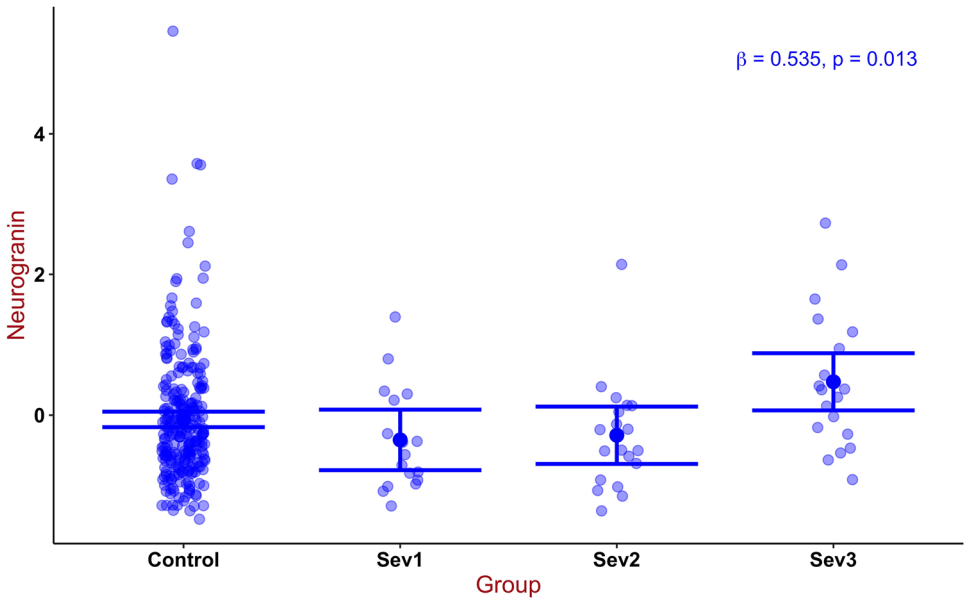

FIGURE 1 Sev3 had higher concentrations of CSF neurogranin compared to control and Sev1 groups. Neurogranin values are z-scored with respect to controls. The results were similar when controlling for demographics, cardiovascular risk, and genetic predisposition. CSF, cerebrospinal fluid; Sev1, mild asthma; Sev2, moderate asthma; Sev3, severe asthma.

significantly more positive for those with Sev3 compared to controls (Figure 2A,B). These findings were consistent for Sev3 versus Sev1 and when restricting analyses to CU participants (Table 3). There were no other group differences between controls and asthma by severity or asthma overall for CSF biomarkers of neurodegeneration. Assessments of group differences in CSF analytes related to glial activation, neuroinflammation, and AD yielded several significant findings that were limited to subgroup analyses (e.g., males or *APOE* ε4 carriers) or did not survive Bonferroni correction (see supporting information results 2.2 and 2.3).

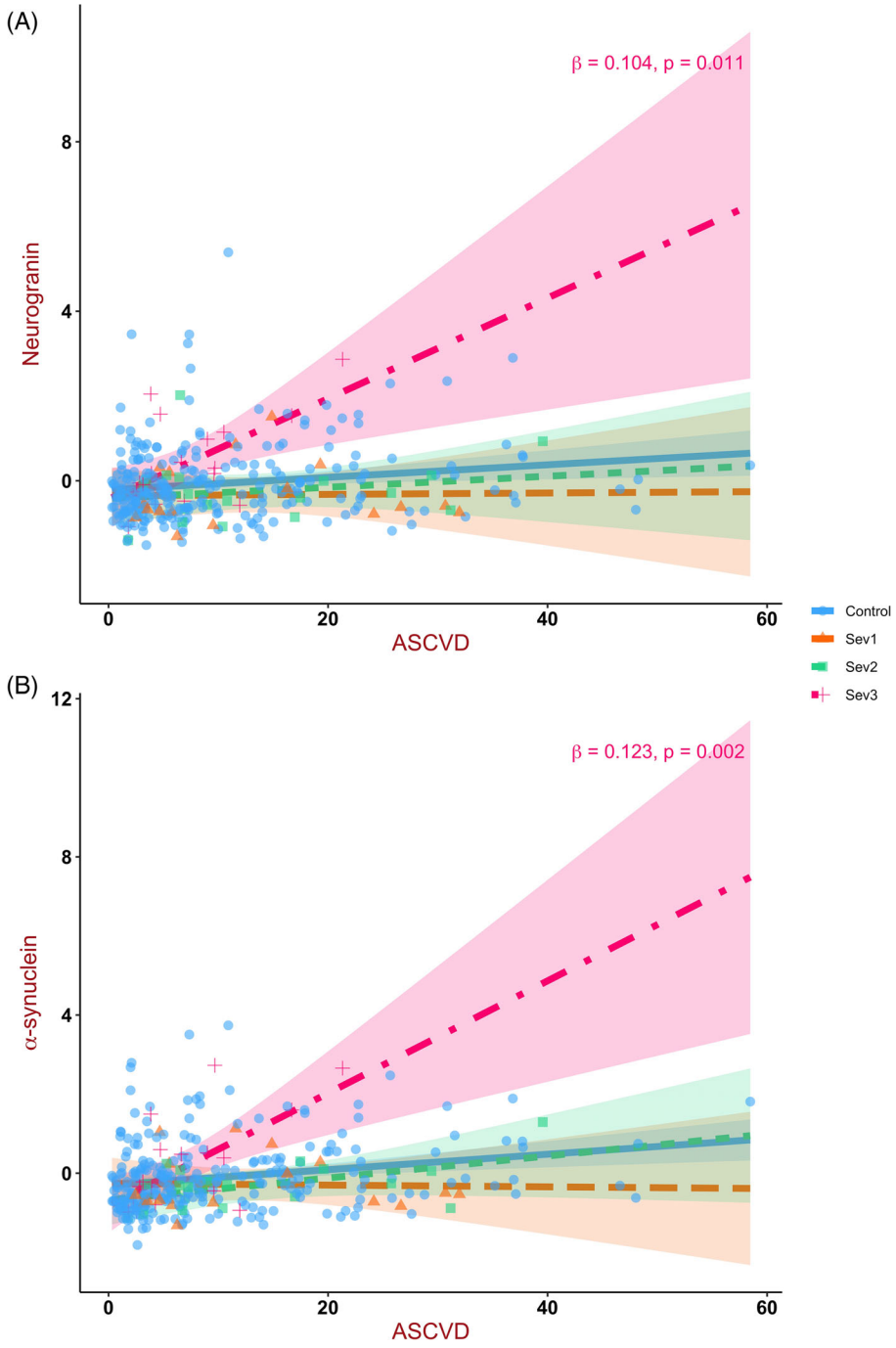

FIGURE 2 The positive relationships between ASCVD and concentrations of CSF neurogranin (A) and α-synuclein (B) were significantly greater for Sev3 compared to controls and Sev1. Values of neurogranin and α-synuclein are z-scored with respect to controls. The results were similar when controlling for genetic predisposition. ASCVD, atherosclerotic cardiovascular disease 10-year risk; CSF, cerebrospinal fluid; Sev1, mild asthma; Sev2, moderate asthma; Sev3, severe asthma.

3.3 | Relationship between asthma and measures of cognition

Analyses examining longitudinal changes in PACC scores (slope) as the outcome variable, controlling for baseline PACC scores, revealed significant interactions (one outlier removed) between group and other risk factors, such that the adverse effect of ASCVD ($\beta = -0.0019$, $P = .0467$; Figure 3A) and *APOE* ε4 status ($\beta = -0.0227$, $P = .0367$) on change in PACC score over time was more pronounced for Sev3 than for controls. There were no main or interaction effects with group comparing asthma, as a single group, to controls.

Examination of the moderating influence of asthma on the relationship between CSF biomarkers and change in PACC slopes over time revealed a significant interaction (one outlier removed) between

TABLE 3 Results of regression analyses assessing CSF biomarkers of neurodegeneration

			All participants				Cognitively unimpaired			
			Sev3 vs. Controls		Sev3 vs. Sev1		Sev3 vs. Controls		Sev3 vs. Sev1	
Outcome	Term	Covariates	β	P	β	P	β	P	β	P
Neurogranin	Sev3	Demographics	0.456	.038[a]	0.827	.0077	0.557	.035[a]	0.922	.0097
		Demographics + *APOE* ε4	0.529	.0156	0.819	.0084	0.616	.0149	0.934	.0068
		ASCVD	0.536	.0122	0.843	.0046	0.635	.0138	0.909	.0087
		ASCVD + *APOE* ε4	0.582	.0064	0.802	.0075	0.652	.0124	0.879	.0132
α-Synuclein	Sev3	ASCVD			0.579	.045[a]				
Neurogranin	Sev3:ASCVD	ASCVD	0.104	.0113	0.117	.0112	0.138	.0073	0.158	.0053
		ASCVD + *APOE* ε4	0.101	.0152	0.111	.018[a]	0.133	.016[a]	0.150	.0137
α-Synuclein	Sev3:ASCVD	ASCVD	0.122	.0021	0.144	.0013	0.155	.0033	0.182	.0017
		ASCVD + *APOE* ε4	0.119	.0033	0.140	.0022	0.144	.0114	0.174	.0054

Abbreviations: *APOE* ε4, apolipoprotein E ε4 carrier; ASCVD, atherosclerotic cardiovascular disease 10-year risk; Sev1, mild asthma; Sev2, moderate asthma; Sev3, severe asthma.

Notes: The columns labeled Outcome, Term, and Covariates pertain to the constituents of regression models with significant results, and the remaining columns comprise beta estimates and *P*-values resulting from the evaluation of each term, with separate estimates and *P*-values for the comparison of Sev3 to each reference group (control, Sev1), for analyses that include all participants and analyses restricted to cognitively unimpaired participants. See supporting information methods for details on the regression analyses.

[a]Did not survive Bonferroni correction.

asthma severity group and p-tau$_{181}$/Aβ_{42} concentration, such that p-tau$_{181}$/Aβ_{42} concentration was associated with a steeper decline in cognitive function for Sev3 compared to controls ($\beta = -0.0167$, $P = .0019$) and Sev1 ($\beta = -0.0283$, $P = .0008$), controlling for demographic variables (Figure 3B). There were no other significant interactions. Including education as a covariate did not alter our findings (see supporting information 2.4). See supporting information 2.5 for results of analyses examining baseline PACC scores as the outcome.

4 | DISCUSSION

We examined CSF biomarkers of glial activation, neuroinflammation, neurodegeneration, and AD pathology in relation to asthma, and report for the first time, consistent indications of synaptic degeneration in patients with severe asthma, compared to mild asthma and non-asthma controls. Further, concentrations of biomarkers of synaptic degeneration were more strongly associated with cardiovascular risk in severe asthma. Finally, cardiovascular risk, genetic predisposition for AD, and/or phosphorylated tau pathology accelerated the decline in cognitive function over time in those with severe asthma.

4.1 | Asthma and CSF biomarkers of synaptic degeneration

Although the precise etiopathogenesis of dementia is unclear, the expression of a number of CSF biomarkers changes prior to the onset of dementia. In AD, the core pathology markers (amyloid and tau) appear first, followed by markers of glial activation (such as sTREM2), synaptic degeneration (neurogranin), and axonal degeneration (NfL), even before clinical symptoms are apparent.[32] Vascular dysfunction and neuroinflammatory conditions, as well as several lifestyle and environmental factors, are putative contributors to the neuropathology that gives rise to dementia.[8,33]

Participants with severe asthma had higher concentrations of neurogranin compared to those with mild asthma (147%) and non-asthma controls (123%). Neurogranin is a post-synaptic protein expressed predominantly in dendritic spines. It regulates calmodulin availability and plays a crucial role in synaptic plasticity and memory consolidation.[34] CSF neurogranin concentrations have been found to be elevated in MCI and early-stage AD, compared to controls, and predict future cognitive decline in CU individuals.[34,35] Further, CSF neurogranin concentrations have been found to be elevated in AD, compared to other neurodegenerative disorders, and provide specificity and additional diagnostic support for AD dementia.[36] As such, CSF neurogranin is considered a marker of synaptic dysfunction and a candidate biomarker for AD.[26] It is noteworthy that we found neurogranin concentrations to be elevated in severe asthma, even when analyses were restricted to CU individuals. Controlling for *APOE* ε4 status and ASCVD risk did not alter this result, suggesting that the influence of asthma on neurogranin is independent of cardiovascular risk and genetic predisposition.

While this is the first human study to show a relationship between asthma and synaptic degeneration, prior animal work may shed light on the mechanisms. Studies in animal models of chronic asthma have demonstrated that peripheral inflammation can lead to microglial activation, elevated levels of inflammatory cytokines in the hippocampus and pre-frontal cortex, and altered dendritic morphology including reduced spine density characteristic of synaptic pathology.[16,37] Accumulating evidence suggests that signaling pathways important in asthmatic airway inflammation, such as the leukotriene pathway, also

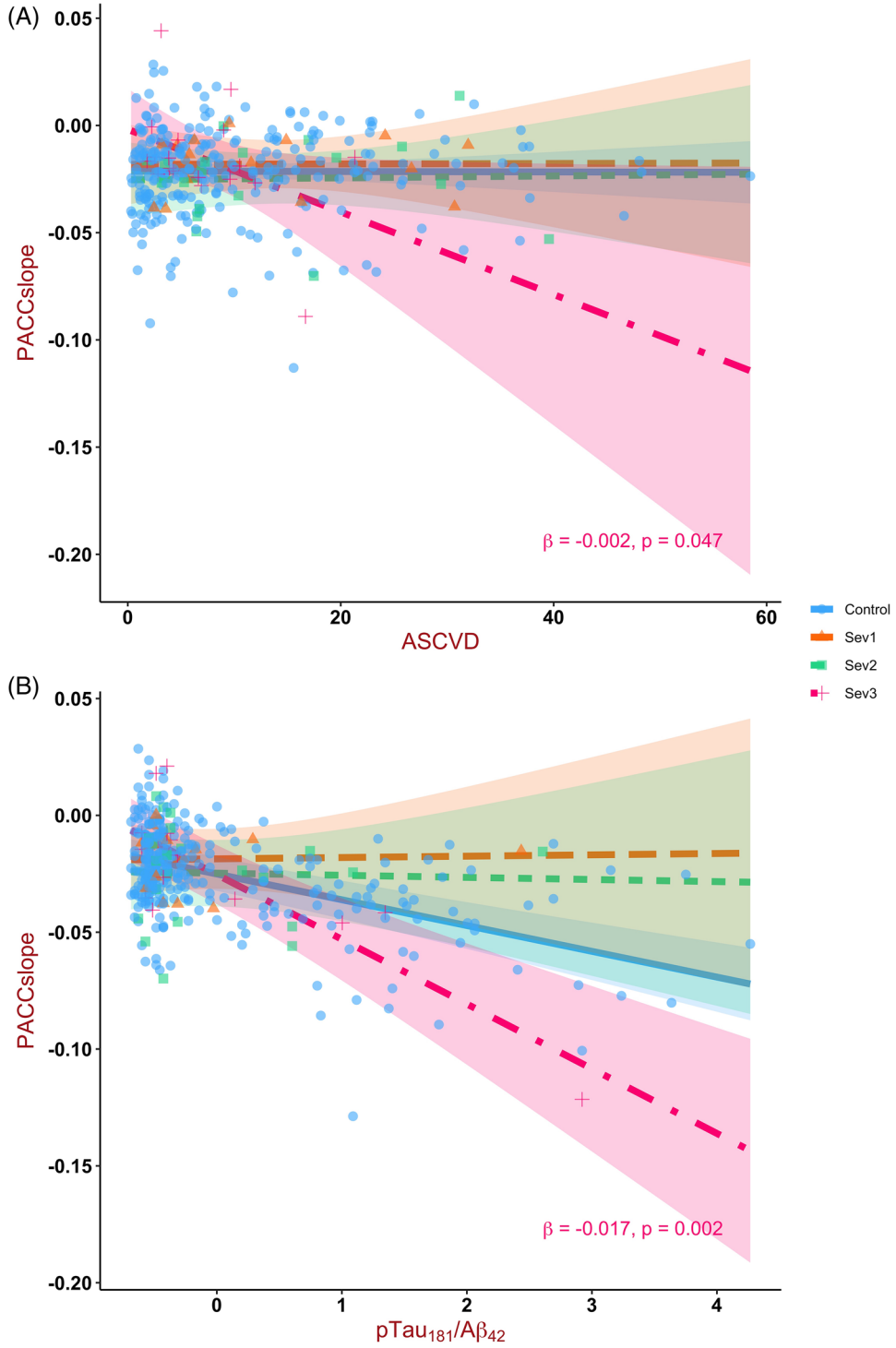

FIGURE 3 The acceleration in cognitive decline (adjusting for baseline cognition and genetic predisposition) over time associated with elevated ASCVD, was exaggerated in Sev3 compared to controls (A). The acceleration in cognitive decline (adjusting for baseline cognition and demographics) over time associated with increasing concentrations of CSF phosphorylated tau was also exaggerated in Sev3, compared to both controls and Sev1 (B). Values of p-tau$_{181}$/Aβ_{42} are z-scored with respect to controls. PACCslope values were z-scored with respect to data from all participants at the Wisconsin Alzheimer's Disease Research Center (ADRC). Aβ, amyloid beta; ASCVD, atherosclerotic cardiovascular disease 10-year risk; CSF, cerebrospinal fluid; PACCslope, change of Preclinical Alzheimer Cognitive Composite scores across assessment visits; p-tau$_{181}$, phosphorylated tau; Sev1, mild asthma; Sev2, moderate asthma; Sev3, severe asthma.

contribute to blood-brain barrier (BBB) compromise, microglial activation, and cognitive decline.[38] Thus, inflammatory signaling pathways that characterize asthma pathophysiology could represent a future therapeutic target in AD,[39] despite an incomplete understanding of the pathways that contribute specifically to synaptic degeneration in asthma.

Though there were no group differences in cardiovascular risk in our sample, there is growing evidence from prospective studies that asthma is a risk factor for cardiovascular disease[40] and stroke,[41] attributed in large part to Type 2 and mast cell-mediated inflammation[42] and the development of a hypercoagulable state.[43] It is likely, therefore, that the impact of asthma on brain health is mediated by the effects of airway inflammation on both neuroinflammatory and vascular dysfunction, as well as their interactions. The relationship between severe asthma and neurogranin in our data persisted when controlling for ASCVD. Nonetheless, we observed that the relationships between vascular risk and concentrations of neurogranin and α-synuclein were stronger in those with severe asthma than in those without asthma and in those with mild disease. These proteins are abundant in synapses[34,44] and their elevated presence in CSF indicates synaptic degeneration. Thus, individuals with more severe asthma may be at greater risk for cerebrovascular-mediated neural injury, or the presence of multiple co-morbidities may accelerate neurodegeneration. Given that vascular dysfunction with a compromised BBB is observed early in AD and may contribute to AD pathogenesis or exacerbate the AD clinical syndrome,[33,45] our findings suggest that severe asthma contributes to or amplifies the dementia risk associated with vascular dysfunction, in addition to its independent effects on synaptic degeneration. It is noteworthy that montelukast, a leukotriene receptor inhibitor widely used in asthma treatment, has been shown to reduce α-synuclein aggregation and restore cognitive functions, and to protect against the neurotoxic consequences of neuroinflammation and AD-related pathology in rodent models.[46,47]

4.2 | Asthma and impaired cognition

Evidence for the impact of asthma on cognitive function is variable and incomplete, but overall, suggests that asthma is associated with reduced cognitive performance. A meta-analysis identified a range of cognitive deficits in asthma, with greater impact on those with severe disease.[48] Prior studies in animal models of asthma have found that chronic airway inflammation leads to microglial activation, neuronal loss in the hippocampus, and behavior indicative of cognitive decline.[16,17] In addition to vascular dysfunction, *APOE* ε4 also accelerates age-related changes in the BBB, leading to cognitive decline and predisposition for AD dementia.[49] Similarly, hyperphosphorylation of tau and accumulation of neurofibrillary tangles is strongly correlated with cognitive decline and is a core feature of AD pathology.[44]

The results of analyses addressing decline in cognition over time revealed a consistent pattern that implicates severe asthma as an important risk factor. The presence of severe asthma amplified relationships between rate of cognitive decline and cardiovascular risk, genetic predisposition, and tau pathology, indicating that severe asthma compounds the risk posed by these factors, contributing to the increased prevalence of AD dementia in asthma reported in epidemiological studies.[18–20,50] Two aspects of our study suggest that the impact of severe asthma on cognitive decline and dementia risk may be specific to AD dementia. First, those with severe asthma had elevated neurogranin, a candidate biomarker with high specificity for AD.[27] Second, the cognitive decline associated with two AD proteinopathies, using the ratio of tau pathology to Aβ, was exaggerated in those with severe asthma, in line with previous reports that the ratio of these two biomarkers was more sensitive and specific in terms of amyloid PET agreement than the individual biomarkers.[51,52] The association of severe asthma with elevated α-synuclein is less specific to AD. Even though α-synuclein is considered useful for the differential diagnosis of AD when combined with other biomarkers[53] and may contribute to AD pathophysiology, it is also present in other forms of dementia.[54] Indeed, severe asthma may amplify the effect of risk factors of all-cause dementia as well. Overall, our findings imply a potential acceleration of the progression toward dementia when asthma is severe, a phenotype associated with the greatest degree of both systemic and airway inflammation and at greatest risk for exacerbation. In considering the possibility of reverse causality—that AD pathology may contribute to asthma severity—the very limited available data opposes this hypothesis, showing that compared to wild-type controls, induced asthma in a genetic mouse model of AD was associated with reduced severity of asthma symptoms such as airway hyper-responsiveness, via epigenetic mechanisms that increase the number of regulatory immune cells thereby decreasing airway inflammation.[55]

4.3 | Limitations and future directions

The effects of specific types of asthma medications on CSF biomarkers of neurodegeneration and rate of cognitive decline could not be ascertained in this study because severity groups were defined by classes of medications used in the management of different levels of asthma severity. For example, biologics and oral steroids are both classes of medications used in the treatment of severe asthma, but may differ in their impact on brain health,[12,43,56] independent of their efficacy in reducing airway inflammation. Future research should address the question of the impact of medication use[43] directly, an endeavor that has shown some merit in patients with rheumatoid arthritis.[57] In addition, history of asthma exacerbations and disease duration were not available in this dataset, but reflect the presence of greater airway inflammation and chronicity and thus are likely to add important nuance to the relationships reported here. Further, it will be important for future studies to examine the impact of asthma on neurodegeneration and risk for dementia in a racially and economically diverse sample. Asthma disproportionately impacts Black Americans and those living in poverty.[58] Yet, our sample was predominantly non-Hispanic White and college educated, which prevents further generalization of our findings to individuals potentially most impacted. Finally, our

sample had very few asthma participants who met positivity thresholds for AD biomarkers for amyloid and hyperphosphorylated tau, limiting our findings primarily to the pre-clinical stage preceding the AD continuum.[44]

To definitively address these important questions will require prospective studies that acquire CSF samples in well-characterized asthma patients, with comprehensive medical history, and track changes in asthma disease activity, brain health, and cognitive function over time. Future studies in animal models of asthma should examine mechanisms by which asthma contributes to synaptic degeneration and cognitive decline by measuring protein and messenger RNA expression of neurogranin and α-synuclein, while evaluating changes in dendritic morphology and spine density, together with behavioral indices of cognitive function in relation to both brain and pulmonary pathology.

5 | CONCLUSION

We report evidence of the impact of severe asthma on synaptic neurodegeneration. Patients with severe asthma had elevated concentrations of CSF neurogranin and amplification of synaptic degeneration associated with cardiovascular risk. Individuals with severe asthma also showed accelerated cognitive decline in the presence of increased cardiovascular risk and genetic risk for AD dementia, as well as with tau pathology, relative to controls. Our findings have clinical relevance, as asthma and cardiovascular comorbidity is high and asthma-related pathology may accelerate and/or exacerbate the neuropathological consequences of other risk factors, leading to a greater prevalence of adverse dementia-related outcomes. More importantly, the public health ramifications of identification of asthma as a risk factor for dementia are large and opportunistic. Currently, uncontrolled asthma is very common and is itself a large public health burden.[59] In light of the large number of asthma patients worldwide, and the life-long duration of this disease, there is substantial potential for benefit by aggressively reducing asthma-related inflammation and possibly diminishing the consequent neural injury and progression to dementia.

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CONFLICTS OF INTEREST

Dr. Barbara Bendlin has received precursor and compounds from Avid Radiopharmaceuticals. Dr. Henrik Zetterberg has served on scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, AZTherapies, CogRx, Denali, Eisai, Nervgen, Pinteon Therapeutics, Red Abbey Labs, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; 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. Kaj Blennow has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, 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 GlaxoSmithKline, Novartis, AstraZeneca, Regeneron, and Sanofi. Gwendlyn Kollmorgen and Norbert Wild are full-time employees of Roche Diagnostics GmbH. Ivonne Suridjan is a full-time employee and shareholder of Roche Diagnostics International Ltd. All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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REFERENCES

1. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimer's Res Ther*. 2017;9:1-9. https://doi.org/10.1186/s13195-017-0297-z
2. The Lancet Neurology. A contentious FDA ruling for Alzheimer's disease. *Lancet Neurol*. 2021;20:585. https://doi.org/10.1016/S1474-4422(21)00215-5
3. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. *Alzheimer's Dement Transl Res Clin Interv*. 2021;7:1-24. https://doi.org/10.1002/trc2.12179
4. Cunningham C, Hennessy E. Co-morbidity and systemic inflammation as drivers of cognitive decline: new experimental models adopting a broader paradigm in dementia research. *Alzheimer's Res Ther*. 2015;7:1-13. https://doi.org/10.1186/s13195-015-0117-2
5. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413-446. https://doi.org/10.1016/S0140-6736(20)30367-6
6. Licher S, Ahmad S, Karamujić-Čomić H, et al. Genetic predisposition, modifiable-risk-factor profile and long-term dementia risk in the general population. *Nat Med* 2019;25:1364-1369. https://doi.org/10.1038/s41591-019-0547-7
7. de Bruijn RFAG, Bos MJ, Portegies MLP, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med*. 2015;13:1-8. https://doi.org/10.1186/s12916-015-0377-5
8. Grande G, Marengoni A, Vetrano DL, et al. Multimorbidity burden and dementia risk in older adults: the role of inflammation and genetics. *Alzheimer's Dement*. 2021;17(5):768-776. https://doi.org/10.1002/alz.12237
9. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18:716-725. https://doi.org/10.1038/nm.2678
10. Borish L. The immunology of asthma: asthma phenotypes and their implications for personalized treatment. *Ann Allergy Asthma Immunol*. 2016;117:108-114. https://doi.org/10.1016/j.anai.2016.04.022
11. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386:157-171. https://doi.org/10.1056/nejmra2032506
12. Kroll JL, Steele AM, Pinkham AE, et al. Hippocampal metabolites in asthma and their implications for cognitive function. *NeuroImage Clin*. 2018;19:213-221. https://doi.org/10.1016/j.nicl.2018.04.012
13. Rosenkranz MA, Dean DC, Bendlin BB, et al. Neuroimaging and biomarker evidence of neurodegeneration in asthma. *J Allergy Clin Immunol*. 2021;149(2):589-598.e6. https://doi.org/10.1016/j.jaci.2021.09.010
14. Lewkowich I, Ahlbrand R, Johnson E, et al. Modulation of fear behavior and neuroimmune alterations in house dust mite exposed A/J mice, a model of severe asthma. *Brain Behav Immun*. 2020;88:688-698. https://doi.org/10.1016/j.bbi.2020.04.084
15. Ren M, Feng M, Long Z, Ma J, Peng X, He G. Allergic asthma-induced cognitive impairment is alleviated by dexamethasone. *Front Pharmacol*. 2021;12:1-12. https://doi.org/10.3389/fphar.2021.680815
16. 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*. 2014;273:53-57. https://doi.org/10.1016/j.jneuroim.2014.06.005
17. Zhuang TT, Pan C, Chen JJ, 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*. 2018;143:194-206. https://doi.org/10.1016/j.brainresbull.2018.09.006
18. Caldera-Alvarado G, Khan DA, Defina LF, Pieper A, Brown ES. Relationship between asthma and cognition: the cooper center longitudinal study. *Allergy Eur J Allergy Clin Immunol*. 2013;68:545-548. https://doi.org/10.1111/all.12125
19. Peng YH, Wu BR, Su CH, et al. Adult asthma increases dementia risk: a nationwide cohort study. *J Epidemiol Community Health*. 2015;69:123-128. https://doi.org/10.1136/jech-2014-204445
20. Chen, Mu-Hong, Cheng-Ta Li, Chia-Fen Tsai, et al. Risk of dementia among patients with asthma: a nationwide longitudinal study. *J Am Med Dir Assoc*. 2014;15:763-767.
21. Tao Q, Ang TFA, DeCarli C, et al. Association of Chronic low-grade inflammation with risk of Alzheimer disease in ApoE4 carriers. *JAMA Netw Open*. 2018;1:e183597. https://doi.org/10.1001/jamanetworkopen.2018.3597
22. Centers for Disease Control and Prevention. 2019 National Health Interview Survey (NHIS) data. Accessed December 7, 2021. https://www.cdc.gov/asthma/nhis/2019/table2-1.htm
23. National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma – full report 2007. Accessed November 20, 2021. https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf
24. Van Hulle C, Jonaitis EM, Betthauser TJ, et al. An examination of a novel multipanel of CSF biomarkers in the Alzheimer's disease clinical and pathological continuum. *Alzheimer's Dement*. 2021;17:431-445. https://doi.org/10.1002/alz.12204
25. Milà-Alomà M, Salvadó G, Gispert JD, et al. Amyloid beta, tau, synaptic, neurodegeneration, and glial biomarkers in the preclinical stage of the Alzheimer's continuum. *Alzheimer's Dement*. 2020;16:1358-1371. https://doi.org/10.1002/alz.12131
26. Molinuevo JL, Ayton S, Batrla R, et al. *Current State of Alzheimer's Fluid Biomarkers*. Vol. 136. Springer Berlin Heidelberg; 2018. https://doi.org/10.1007/s00401-018-1932-x
27. Blennow K, Zetterberg H. The past and the future of Alzheimer's disease fluid biomarkers. *J Alzheimer's Dis*. 2018;62:1125-1140. https://doi.org/10.3233/JAD-170773
28. Jonaitis EM, Koscik RL, Clark LR, et al. Measuring longitudinal cognition: individual tests versus composites. *Alzheimers Dement: Diagn Assess Dis Monit*. 2019;11(1):74-84. https://doi.org/10.1016/j.dadm.2018.11.006
29. Donohue MC, Sun CK, Raman R, Insel PS, Aisen PS. Cross-validation of optimized composites for preclinical Alzheimer's disease. Alzheimer's *Dement Transl Res Clin Interv*. 2017;3:123-129. https://doi.org/10.1016/j.trci.2016.12.001
30. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation*. 2014;129:49-73. https://doi.org/10.1161/01.cir.0000437741.48606.98
31. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2019. Available from: http://www.r-project.org
32. Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease – preparing for a new era of disease-modifying therapies. *Mol Psychiatry*. 2021;26:296-308. https://doi.org/10.1038/s41380-020-0721-9
33. Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction – the disregarded partner of Alzheimer's disease. *Alzheimer's Dement*. 2019;15:158-167. https://doi.org/10.1016/j.jalz.2018.07.222
34. Kester MI, Teunissen CE, Crimmins DL, et al. Neurogranin as a cerebrospinal fluid biomarker for synaptic loss in symptomatic Alzheimer disease. *JAMA Neurol*. 2015;72:1275-1280. https://doi.org/10.1001/jamaneurol.2015.1867
35. Tarawneh R, D'Angelo G, Crimmins D, et al. Diagnostic and prognostic utility of the synaptic marker neurogranin in Alzheimer disease. *JAMA Neurol*. 2016;73:561-571. https://doi.org/10.1001/jamaneurol.2016.0086
36. Portelius E, Olsson B, Höglund K, et al. Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes

and neuropathology. *Acta Neuropathol*. 2018;136:363-376. https://doi.org/10.1007/s00401-018-1851-x
37. Hoogland ICM, Houbolt C, van Westerloo DJ, van Gool WA, van de Beek D. Systemic inflammation and microglial activation: systematic review of animal experiments. *J Neuroinflammation*. 2015;12:1-13. https://doi.org/10.1186/s12974-015-0332-6
38. Marschallinger J, Schäffner I, Klein B, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat Commun*. 2015;6:8466. https://doi.org/10.1038/ncomms9466
39. Michael J, Marschallinger J, Aigner L. The leukotriene signaling pathway: a druggable target in Alzheimer's disease. *Drug Discov Today*. 2019;24:505-516. https://doi.org/10.1016/j.drudis.2018.09.008
40. Pollevick ME, Xu KY, Mhango G, et al. The relationship between asthma and cardiovascular disease: an examination of the framingham offspring study. *Chest*. 2021;159:1338-1345. https://doi.org/10.1016/j.chest.2020.11.053
41. Wen LY, Ni H, Li KS, et al. Asthma and risk of stroke: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2016;25:497-503. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.11.030
42. Tattersall MC, Evans MD, Korcarz CE, et al. Asthma is associated with carotid arterial injury in children: the Childhood Origins of Asthma (COAST) Cohort. *PLoS One*. 2018;13:1-12. https://doi.org/10.1371/journal.pone.0204708
43. Corlateanu A, Stratan I, Covantev S, Botnaru V, Corlateanu O, Siafakas N. Asthma and stroke: a narrative review. *Asthma Res Pract*. 2021;7:1-17. https://doi.org/10.1186/s40733-021-00069-x
44. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's Dement*. 2018;14:535-62. https://doi.org/10.1016/j.jalz.2018.02.018
45. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. *Alzheimer's Dement: Diagn Assess Dis Monit*. 2017;7(1):69-87. https://doi.org/10.1016/j.dadm.2017.01.005
46. Lai J, Hu M, Wang H, et al. Montelukast targeting the cysteinyl leukotriene receptor 1 ameliorates Aβ1-42-induced memory impairment and neuroinflammatory and apoptotic responses in mice. *Neuropharmacology*. 2014;79:707-714. https://doi.org/10.1016/j.neuropharm.2014.01.011
47. Marschallinger J, Altendorfer B, Rockenstein E, et al. The leukotriene receptor antagonist montelukast reduces alpha-synuclein load and restores memory in an animal model of dementia with lewy bodies. *Neurotherapeutics*. 2020;17:1061-1074. https://doi.org/10.1007/s13311-020-00836-3
48. Irani F, Barbone JM, Beausoleil J, Gerald L. Is asthma associated with cognitive impairments? A meta-analytic review. *J Clin Exp Neuropsychol*. 2017;39:965-978. https://doi.org/10.1080/13803395.2017.1288802
49. Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood – brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581:71-76. https://doi.org/10.1038/s41586-020-2247-3
50. 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;10:549-555.
51. Li QX, Villemagne VL, Doecke JD, et al. Alzheimer's disease normative cerebrospinal fluid biomarkers validated in pet amyloid-β characterized subjects from the australian imaging, biomarkers and lifestyle (AIBL) study. *J Alzheimer's Dis*. 2015;48:175-187. https://doi.org/10.3233/JAD-150247
52. Campbell MR, Ashrafzadeh-Kian S, Petersen RC, et al. P-tau/aβ42 and aβ42/40 ratios in csf are equally predictive of amyloid pet status. *Alzheimer's Dement*. 2021;13(1):1-9. https://doi.org/10.1002/dad2.12190
53. Shi M, Tang L, Toledo JB, et al. Cerebrospinal fluid α-synuclein contributes to the differential diagnosis of Alzheimer's disease. *Alzheimer's Dement*. 2018;14:1052-1062. https://doi.org/10.1016/j.jalz.2018.02.015
54. Twohig D, Nielsen HM. α-synuclein in the pathophysiology of Alzheimer's disease. *Mol Neurodegener*. 2019;14:23. https://doi.org/10.1186/s13024-019-0320-x
55. Wu Y, Zhao Y, Xu T, You LW, Zhang H, Liu F. Alzheimer's disease affects severity of asthma through methylation control of Foxp3 promoter. *J Alzheimer's Dis*. 2019;70:121-129. https://doi.org/10.3233/JAD-190315
56. Brown ES, Woolston DJ, Frol A, et al. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biol Psychiatry*. 2004;55:538-545. https://doi.org/10.1016/j.biopsych.2003.09.010
57. 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;30:1111-1120. https://doi.org/10.1007/s40263-016-0374-z
58. Grant T, Croce E, Matsui EC. Asthma and the social determinants of health. *Ann Allergy Asthma Immunol*. 2022;128:5-11. https://doi.org/10.1016/j.anai.2021.10.002
59. Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M. The projected economic and health burden of uncontrolled asthma in the United States. *Am J Respir Crit Care Med*. 2019;200:1102-1112. https://doi.org/10.1164/rccm.201901-0016OC

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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