


## RESEARCH ARTICLE

# Association of latent factors of neuroinflammation with Alzheimer's disease pathology and longitudinal cognitive decline

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<sup>†</sup> Part of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of DELCODE investigators can be found in Appendix 1, of ADNI investigators at [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf) and in Appendix 2.

## Abstract

**INTRODUCTION:** We investigated the association of inflammatory mechanisms with markers of Alzheimer's disease (AD) pathology and rates of cognitive decline in the AD spectrum.

**METHODS:** We studied 296 cases from the Deutsches Zentrum für Neurodegenerative Erkrankungen Longitudinal Cognitive Impairment and Dementia Study (DELCODE) cohort, and an extension cohort of 276 cases of the Alzheimer's Disease Neuroimaging Initiative study. Using Bayesian confirmatory factor analysis, we constructed latent factors for synaptic integrity, microglia, cerebrovascular endothelial function, cytokine/chemokine, and complement components of the inflammatory response using a set of inflammatory markers in cerebrospinal fluid.

**RESULTS:** We found strong evidence for an association of synaptic integrity, microglia response, and cerebrovascular endothelial function with a latent factor of AD pathology and with rates of cognitive decline. We found evidence against an association of complement and cytokine/chemokine factors with AD pathology and rates of cognitive decline.

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**DISCUSSION:** Latent factors provided access to directly unobservable components of the neuroinflammatory response and their association with AD pathology and cognitive decline.

**KEYWORDS**

amyloid, chemokine factors, complement, endothelial function, microglia, structural equation models, tau

## 1 | INTRODUCTION

Inflammation is a central component of Alzheimer's disease (AD) pathophysiology, downstream of amyloid beta ( $A\beta$ ) and tau pathology.<sup>1–3</sup> At the same time, inflammatory mechanisms influence  $A\beta$  and tau pathology in the brain.<sup>4,5</sup> Several studies associated single inflammatory cerebrospinal fluid (CSF) markers with  $A\beta$  pathology, tau pathology, or both in the AD spectrum.<sup>6,7</sup> Results become heterogeneous when one concentrates on single inflammatory markers. For the well-established microglia marker soluble triggering receptor expressed on myeloid cells 2 (sTREM2) some studies found higher CSF sTREM2 levels associated with less  $A\beta$  pathology in the sporadic AD spectrum.<sup>8,9</sup> In contrast, several studies showed associations of sTREM2 levels mainly with phosphorylated tau (p-tau) pathology. They found decreased or unchanged levels of CSF sTREM2 in  $A\beta$ -positive but p-tau negative cases, and increased levels in p-tau positive cases, irrespective of  $A\beta$  status.<sup>7,9–11</sup>

These variations may reflect different inflammatory mechanisms in different disease stages. However, a more parsimonious interpretation should take into account that CSF markers are only surrogate measures for an underlying construct, that is, inflammation, which cannot be directly observed in clinical studies. Mathematically, one can express this epistemological reservation in the framework of structural equation models (SEM).<sup>12</sup> We can construct the inflammatory response in the brain as a latent factor that eludes direct observation but can be assessed by observable proxy markers in the CSF. Confirmatory factor analysis is a readily available tool to form such latent factors.

Here, we constructed latent factors for a priori defined inflammatory domains, including synaptic integrity, microglia, complement factors, adhesion, and cytokines/chemokines. We had two goals: First, to determine latent factors of neuroinflammation based on an a priori assignment of single inflammatory markers to certain inflammatory domains. Second, to characterize these neuroinflammation factors in relation to AD pathology markers from CSF and longitudinal rates of cognitive decline. We tested latent factors in two independent cohorts that included individuals from the AD spectrum and cognitively healthy controls, the Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) Longitudinal Cognitive Impairment and Dementia Study (DELCODE)<sup>13</sup> and the Alzheimer's Disease Neuroimaging Initiative (ADNI)<sup>14</sup> cohorts, respectively. Because of the small overlap of markers measured in both cohorts, we could not replicate the results across cohorts as originally planned, but used the ADNI data to

extend the neuroinflammation domains from DELCODE. This provided us with access to the additional domain of endothelial adhesion function that may be related to blood–brain barrier dysfunction. We used a Bayesian analysis framework for statistical inference that allowed us to directly quantify both evidence for and against an effect.<sup>15</sup> This is different from the *P* value, which tells us the probability that a similar or even more extreme effect will occur in future experiments if the null hypothesis were true.<sup>16,17</sup> Additionally, the 95% credible interval of the posterior distribution of the parameter estimates is directly interpretable as the range in which the parameter lies with 95% probability given the data. This is different from the interpretation of the frequentist 95% confidence interval: the parameter estimate will lie in this interval in 95% of future repeated experiments.<sup>15,17,18</sup>

## 2 | MATERIAL AND METHODS

### 2.1 | Data sources

Part of the data came from the DELCODE cohort, conducted by the DZNE. Another part of the data came from the ADNI cohorts, accessed via the ADNI database (<http://adni.loni.usc.edu/>). For a more detailed description of both cohorts see the supporting information.

### 2.2 | Consent statement

For both studies, DELCODE and ADNI, written informed consent was obtained from all participants and/or authorized representatives. The study protocols for both studies had been approved by the local institutional review boards and ethical committees of the centers participating in the respective study. DELCODE and ADNI are being conducted in accord with the Declaration of Helsinki of 1975 and its later amendments.

### 2.3 | Participants

For DELCODE, the baseline sample included  $n = 1079$  participants. After excluding cases without an available CSF sample, we were left with  $n = 309$  cases. After removing all cases without complete neuroinflammatory measures in the CSF, our baseline sample comprised  $n = 296$  cases. We included the following diagnoses: older healthy

controls, first-degree relatives, subjective cognitive decline (SCD), mild cognitive impairment (MCI), and AD dementia.

From the ADNI cohort, we retrieved  $n = 279$  cases who had complete measures on a previously reported inflammatory marker panel in CSF.<sup>19</sup> We included the following diagnoses: older healthy controls, MCI, and AD dementia.

Detailed diagnostic criteria for both cohorts are reported in the supporting information.

## 2.4 | Neuropsychological assessment

We aimed to cover similar cognitive domains across both cohorts. For the DELCODE and the ADNI cohort we used the Mini-Mental State Examination (MMSE) score<sup>20</sup> as a measure of global cognition. For DELCODE we chose the Preclinical Alzheimer Cognitive Composite score plus verbal fluency (PACC5 score)<sup>21</sup> as a composite measure of memory and executive function, the Free and Cued Selective Reminding Test (FCSRT)<sup>22</sup> immediate free recall as measure of memory, and the ratio of the Trail Making Test B to A (TMTB/A) as measure of executive function.<sup>23</sup>

For the ADNI cohort, we used the ADNI composite scores for memory<sup>24</sup> and executive function.<sup>25</sup>

## 2.5 | CSF sampling

For the DELCODE study details on standard operating procedures (SOP) for sampling and measurements of CSF can be found in Jessen et al.<sup>13</sup>

For the ADNI cohorts, details on SOPs for sampling and measurements of CSF can be found in the ADNI procedure manual (<http://adni.loni.usc.edu/methods/>).

For both DELCODE and ADNI, CSF samples were aliquoted after centrifugation and stored at  $-80^{\circ}\text{C}$  before measurements were conducted.

## 2.6 | CSF AD biomarker assessment

DELCODE features a centralized data management that provides access to the biomarker data. We used data for A $\beta$ 42, A $\beta$ 40, p-tau 181, and total tau that were determined with the following commercially available kits: V-PLEX A $\beta$  Peptide Panel 1 (6E10) Kit (K15200E) and V-PLEX Human Total Tau Kit (K151LAE; Mesoscale Diagnostics LLC), and Innostest Phospho-Tau(181P) (81581; Fujirebio Germany GmbH). The measurements were conducted in accordance with the vendor specifications.

The Biomarker Core of ADNI at the Translational Research Laboratory, Department of Pathology & Laboratory Medicine at the University of Pennsylvania Medical School is in charge of processing CSF samples. We used data for A $\beta$ 42, p-tau 181, and total tau measured by the Luminex multiplex immunoassay platform. A detailed descrip-

## RESEARCH IN CONTEXT

- 1. Systematic Review:** We reviewed the literature using PubMed. Studies suggest an association of cerebrospinal fluid (CSF) inflammatory markers with CSF markers of Alzheimer's disease (AD) pathology and measures of brain integrity, but results were heterogeneous.
- 2. Interpretation:** Heterogeneity of findings for individual inflammatory markers may be due to the fact that CSF markers are only surrogate measures for an underlying construct, that is, inflammation, which cannot be directly observed.
- 3. Future Directions:** We have constructed latent factors for a priori defined domains of inflammation to determine the association of these factors with AD pathology and rates of cognitive change. This approach can integrate other domains of inflammation as well as other markers of inflammatory domains, such as molecular imaging modalities. This approach is also useful to determine the reproducibility of results across different cohorts that are harmonized at the level of inflammatory domains but not at the level of individual markers.

tion of the ADNI CSF Biomarker Core procedures can be found in the data primer, "An Overview of the first 8 ADNI CSF Batch Analyses" (<http://adni.loni.usc.edu/methods/documents>).

## 2.7 | CSF inflammatory marker panel assessment

For the DELCODE cohort, a panel of markers had been defined that had been detected in previous studies with acceptable reliability<sup>7,26,27</sup> in CSF and serum, and is related to inflammation mechanisms. This panel includes the following markers: Ferritin, apolipoprotein E (apoE), sTrem2, serum-soluble AXL, sTyro3, interleukin 6 (IL-6), Interleukin 18 (IL-18), monocyte chemoattractant protein 1, interferon gamma inducible protein 10, macrophage migration inhibitory factor, YKL-40, C-reactive protein, complement C1q, C3, C3b, C4, factor B, and factor H. In addition, it includes neurogranin and FABP-3 as non-tau neurodegeneration markers.<sup>7,26,27</sup>

Detailed measurement procedures can be found in Brosseron et al.<sup>7,26,27</sup> Commercially available enzyme-linked immunosorbent assays (ELISA) were used to measure all markers of the panel in CSF and serum. The DELCODE biomarker group used internal control samples and measured marker levels in duplicate. Measures were accepted only if the coefficient of variance (CV) was  $< 20\%$ . We combined the CSF inflammatory markers into four categories: synaptic integrity markers, microglia markers, complement markers, and cytokine/chemokine markers, based on a literature review reported in Table S1 in supporting information.

In the ADNI cohort, we identified a marker panel in the ADNI database that had been reported before.<sup>19</sup> The Biomarker Core of ADNI measured CSF levels of the following inflammatory markers using multiplex immunoassays: interleukin 12 subunit p40 (IL-12-P40), interleukin 10 (IL-10), IL-6, tumor necrosis factor alpha (TNF $\alpha$ ), tumor necrosis factor receptor 1 (TNFR1), transforming growth factor beta 1 (TGF $\beta$ 1), vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1). We used one cluster of markers to create an adhesion factor (including TNF $\alpha$ , TNFR1, TGF $\beta$ 1, ICAM-1, and VCAM-1), and another cluster of markers to create a cytokine/chemokine factor (IL-6, IL-10, IL-12-P40).

## 2.8 | Statistical analysis

We compared demographic characteristics between diagnostic groups using Bayesian analysis of variance and contingency tables as required. For these calculations, we used Jeffreys's Amazing Statistics Program (JASP Version 0.11), available at jasp-stats.org. We report the Bayes factor (BF<sub>10</sub>) quantifying evidence against the null hypotheses.

We used Bayesian confirmatory factor analysis as implemented in the library "blavaan" in R version 4.2.1 (2022-06-23), accessed through R Studio, to construct latent factors for the classes of neuroinflammatory response. Model fit was assessed using posterior predictive *P* values. Factor scores for each individual were derived for the latent factors using least square regression with the "predict" function of R library "lavaan."

We compared the levels of latent factors across diagnostic groups, controlling for age and sex using Bayesian analysis of covariance (ANCOVA) in JASP. Furthermore, we analyzed the association of the latent factors with a latent factor of AD pathology constructed from CSF markers of A $\beta$ 42, A $\beta$ 40, total tau, and p-tau, controlling for diagnosis, age, sex, and APOE  $\epsilon$ 4 genotype (none vs. at least one allele).

Subsequently, we estimated generalized mixed effects models in a Bayesian framework with time nested within individuals with random intercept and slope terms, and longitudinal cognitive scores as outcomes. The models contained the main effect of the inflammation factor and the interaction of the inflammation factor with time as well as the main effects of p-tau, A $\beta$ 42, and diagnosis, and their interaction effects with time, and the main effects of age and sex. We compared fit of non-Gaussian versus Gaussian models for the dependent variables using posterior predictive checks. We determined the posterior estimates of the inflammation factor by time interaction and its 90% and 95% credible intervals as primary outcomes of this analysis. These analyses were conducted using library "brms" in R version 4.2.1 (2022-06-23), accessed through R Studio.

Finally, we determined if neuroinflammation factors mediated the effects of AD pathology on rates of cognitive change, using library "blavaan" in R version 4.2.1 (2022-06-23). We report the median and 95% credible intervals of the posterior distribution of the indirect (mediating) effect.

Adherence to Bayesian Analysis Reporting Guidelines<sup>28</sup> is illustrated in Table S2 in supporting information.

## 3 | RESULTS

### 3.1 | Demographics

As shown in Table 1, participants from the DELCODE cohort were highly likely to differ in age and sex, but not in years of education across diagnostic groups. In the ADNI cohort, diagnostic groups were highly likely to differ in age, but not in years of education and sex. In the DELCODE cohort sample, 272 of the 296 baseline cases had at least one clinical follow up with a median follow-up time of 4.0 years (range 0.9 to 6.3 years). From the 279 baseline cases of the ADNI sample, 213 had at least one clinical follow-up examination with a median follow-up time of 3.2 years (range 0.6 to 16.4 years). Number of cases per time points are shown in Figure S1 in supporting information.

### 3.2 | Inflammation latent factors and diagnoses

Fit indices of the SEM models for deriving the latent factors were high to very high (Table S3 in supporting information). The loading diagrams are plotted in Figure S2A in supporting information and the correlation matrices for the latent factors in Figure S3 in supporting information. In ANCOVA models, we compared the levels of latent factors across diagnoses, controlling for age and sex. We found strong to extremely strong evidence (BF<sub>10</sub> between 49 and  $1.8 \times 10^6$ ) for a difference of the synaptic integrity factor between AD patients and all other diagnostic groups (controls, MCI, SCD), but there was evidence against pairwise differences between the other diagnostic groups (BF<sub>10</sub> < 2.2). For the microglia, complement, and cytokine/chemokine factors, we found evidence against diagnostic group differences (Figure 1).

### 3.3 | Inflammation latent factors and AD pathology

For DELCODE, we constructed a latent factor of AD pathology based on CSF A $\beta$ 42, A $\beta$ 40, tau, and p-tau181 levels. P-tau, tau, and A $\beta$ 40 contributed positively and A $\beta$ 42 contributed negatively to the latent factor of AD pathology (Figure 2). We found extreme evidence for a positive association of the AD pathology factor with the synaptic (BF<sub>10</sub> =  $2.6 \times 10^{48}$ ) and the microglia factor (BF<sub>10</sub> =  $3.7 \times 10^{34}$ ). For the complement and cytokine/chemokine factors, we found inconclusive evidence (BF<sub>10</sub> = 0.536 and 0.562, respectively). Parameter estimates are shown in Table 2.

### 3.4 | Longitudinal analysis

Posterior predictive checks and testing the normality of the distribution of the residuals suggested that the dependent variables PACC5 score, free recall from the FCSRT, and MMSE score were fit very well by a Gaussian distribution, the TMTB/A ratio by a skewed normal distribution. Rates of cognitive change by diagnosis are shown in Figure S4A in supporting information; correlations between rates of change in Table S4A in supporting information.

**TABLE 1** Demographics.

DELCODE (N = 296)	N(f/m) [%] <sup>a</sup>	Age (years) <sup>b</sup> mean (95% CI)	MMSE <sup>c</sup> mean (95% CI)	Education (years) <sup>d</sup> mean (95% CI)
Controls	39/31 [56/44]	68.8 (67.6–69.9)	29.4 (29.2–29.7)	14.5 (13.9–15.2)
Relatives	16/6 [73/27]	64.9 (63.2–66.6)	29.0 (28.5–29.5)	13.5 (12.4–14.7)
SCD	43/55 [44/56]	71.1 (70.0–72.2)	29.2 (29.0–29.4)	15.1 (14.4–15.7)
MCI	22/47 [32/68]	72.3 (71.1–73.6)	27.9 (27.5–28.4)	14.0 (13.3–14.8)
AD	23/14 [62/38]	73.9 (71.8–76.0)	24.0 (22.9–25.2)	13.8 (12.9–14.8)
ADNI (N = 279)	N(f/m) [%] <sup>e</sup>	Age (years) <sup>f</sup> mean (95% CI)	MMSE <sup>g</sup> mean (95% CI)	Education (years) <sup>h</sup> mean (95% CI)
Controls	37/46 [45/55]	78.5 (77.2–79.8)	29 (28.8–29.2)	15.4 (14.5–16.3)
MCI	45/79 [36/64]	75.9 (74.5–77.3)	26.9 (26.6–27.2)	14.1 (13.1–15.2)
AD	31/41 [43/57]	74.4 (72.5–76.4)	23.6 (23.2–24)	13.8 (12.4–15.1)

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CI, credibility intervals; DELCODE, Deutsches Zentrum für Neurodegenerative Erkrankungen Longitudinal Cognitive Impairment and Dementia Study; MCI, mild cognitive impairment; MMSE Mini-Mental State Examination; SCD, subjective cognitive decline.

<sup>a</sup>Bayes factor in favor of a group effect ( $BF_{10}$ ) = 37.2; i.e., a group effect is 37.2 times more likely than the absence of such effect.

<sup>b</sup>Bayes factor in favor of a group effect ( $BF_{10}$ ) =  $2.2 \times 10^7$ .

<sup>c</sup>Bayes factor in favor of a group effect ( $BF_{10}$ ) =  $2.6 \times 10^{38}$ .

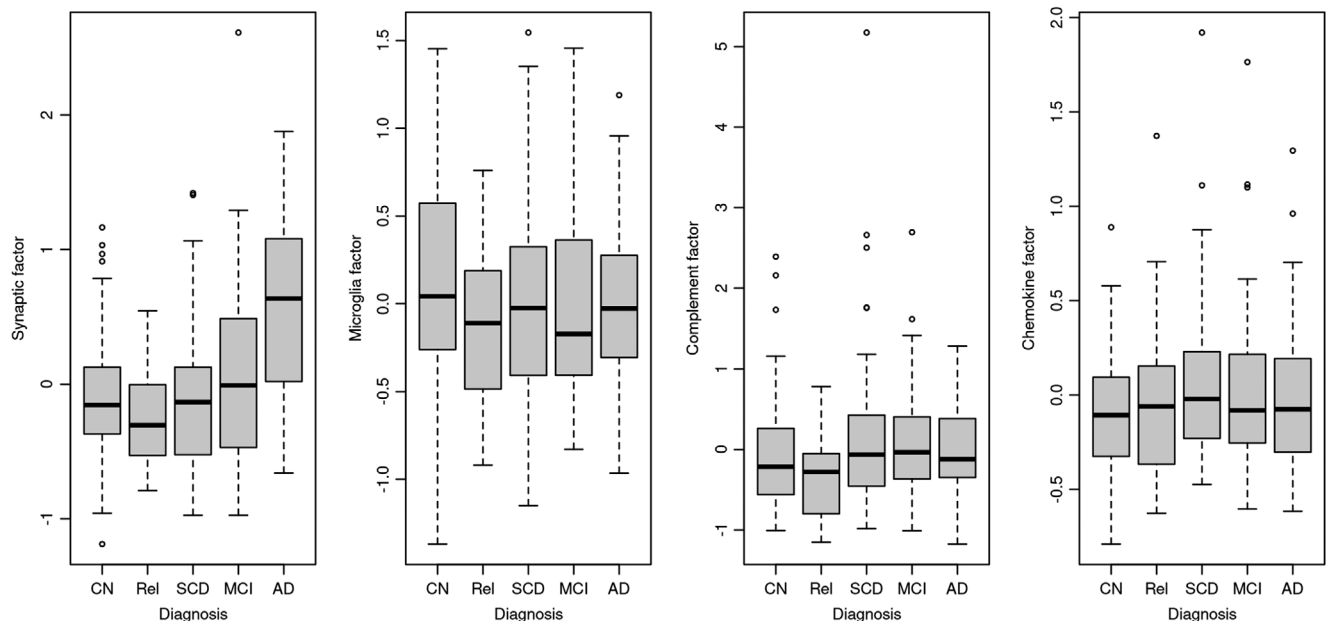
<sup>d</sup>Bayes factor in favor of the absence of a group effect ( $BF_{10}$ ) = 0.48.

<sup>e</sup>Bayes factor in favor of the absence of a group effect ( $BF_{10}$ ) = 0.26.

<sup>f</sup>Bayes factor in favor of a group effect ( $BF_{10}$ ) = 8.6.

<sup>g</sup>Bayes factor in favor of a group effect ( $BF_{10}$ ) =  $2.6 \times 10^{56}$ .

<sup>h</sup>Bayes factor in favor of the absence of a group effect ( $BF_{10}$ ) = 0.08.



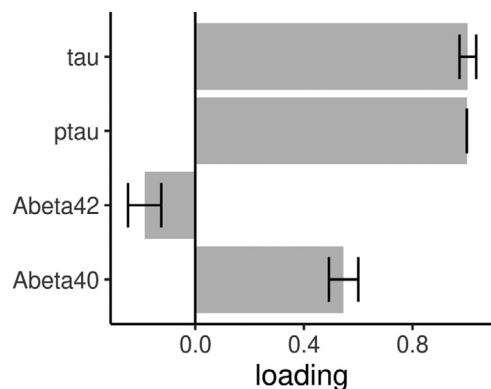
**FIGURE 1** Levels of inflammatory latent factors across groups in the DELCODE data. Boxplots of factor scores of the inflammation factors in the healthy controls (CN), the cognitively normal relatives of people with dementia (Rel), the individuals with subjective cognitive decline (SCD), and the mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia cases

We found an association of the synaptic factor with rates of change in FCSRT free recall, PACC5 score, MMSE, and TMTB/A, with higher synaptic factor being associated with more pronounced cognitive decline. For PACC5 and MMSE, the 95% credible interval excluded

zero, for FCSRT free recall and TMTB/A, it included zero (Figures 3A and 4).

Lower levels of the microglia factor were associated with more pronounced cognitive decline in FCSRT free recall, PACC5, and MMSE. For





**FIGURE 2** Latent factor Alzheimer's disease (AD) pathology and cerebrospinal fluid (CSF) pathology markers in the DELCODE data. Association of the CSF pathology markers with the latent factor AD pathology (bars are standard deviations of the estimates) in the DELCODE data

MMSE and PACC5 scores the 90% credible intervals of the posterior distribution excluded zero (Figures 3B and 5).

For cytokine/chemokine and complement factors, the 90% credibility intervals excluded zero for the associations with all cognitive scores (Figure 3C and D).

### 3.5 | ADNI sample

The factor loading diagrams are plotted in Figure 2. We found evidence against an association of diagnosis with the adhesion and the cytokine/chemokine factors (Figure S5 in supporting information). P-tau and tau contributed positively and  $A\beta_{42}$  contributed negatively to a latent factor of AD pathology constructed from the ADNI data (Figure S6 in supporting information). We found very strong evidence for a positive association of the AD pathology factor with the adhesion factor ( $BF_{10} = 202.4$ ), and moderate evidence against an association with the cytokine/chemokine factor ( $BF_{10} = 0.25$ ). Parameter estimates are shown in Table S5 in supporting information.

In the longitudinal data, the dependent variables ADNI memory and executive function as well as MMSE scores were fit very well by a Gaussian distribution. Rates of cognitive change by diagnosis are shown in Figure S4B; correlations between rates of change in Table S4B.

Lower levels of the adhesion factor were associated with more pronounced cognitive decline in ADNI memory and executive function and MMSE scores. For ADNI memory and executive function scores the 90% credible interval excluded zero; for MMSE score, it included zero (Figures S7A and S8 in supporting information).

For the cytokine/chemokine factor, the posterior distribution suggested no association with change in ADNI memory and executive function and MMSE scores (Figure S7B).

### 3.6 | Mediation analysis

In the DELCODE data, we found a consistent mediation effect of the microglia factor for the effect of AD pathology on rates of cognitive

**TABLE 2** Inflammatory and AD pathology factors in the DELCODE data.

(A) Association of synaptic and AD pathology factors					
Variable	Level	Mean	SD	95% credible interval	
				Lower	Upper
AD pathology		0.492	0.026	0.439	0.544
Sex	f	−0.046	0.020	−0.087	−0.007
	m	0.046	0.020	0.005	0.086
Age		0.027	0.022	−0.019	0.070
Diagnosis	AD	−0.048	0.049	−0.150	0.048
	CN	0.075	0.038	$-4.618 \times 10^{-4}$	0.151
	MCI	−0.035	0.037	−0.109	0.037
	Rel	0.005	0.053	−0.102	0.111
	SCD	0.003	0.034	−0.066	0.069
APOE $\epsilon 4$	0	−0.109	0.023	−0.154	−0.065
	1	0.109	0.023	0.063	0.153
(B) Association of microglia and AD pathology factors					
AD pathology		0.492	0.033	0.425	0.559
Sex	f	−0.006	0.025	−0.056	0.044
	m	0.006	0.025	−0.045	0.055
Age		0.062	0.027	0.005	0.115
Diagnosis	AD	−0.453	0.072	−0.598	−0.309
	CN	0.262	0.050	0.159	0.361
	MCI	−0.131	0.050	−0.229	−0.033
	Rel	0.196	0.078	0.041	0.353
	SCD	0.126	0.045	0.034	0.216
APOE $\epsilon 4$	0	0.082	0.028	0.027	0.136
	1	−0.082	0.028	−0.136	−0.027

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CN, cognitively normal; f, female; m, male; MCI, mild cognitive impairment; SCD, subjective cognitive decline; SD, standard deviation.

AD—dummy variable for AD patient (1/0 – yes/no).

CN—dummy variable for normal control (1/0 – yes/no).

MCI—dummy variable for MCI (1/0 – yes/no).

Rel—dummy variable for relative of person with dementia (1/0 – yes/no).

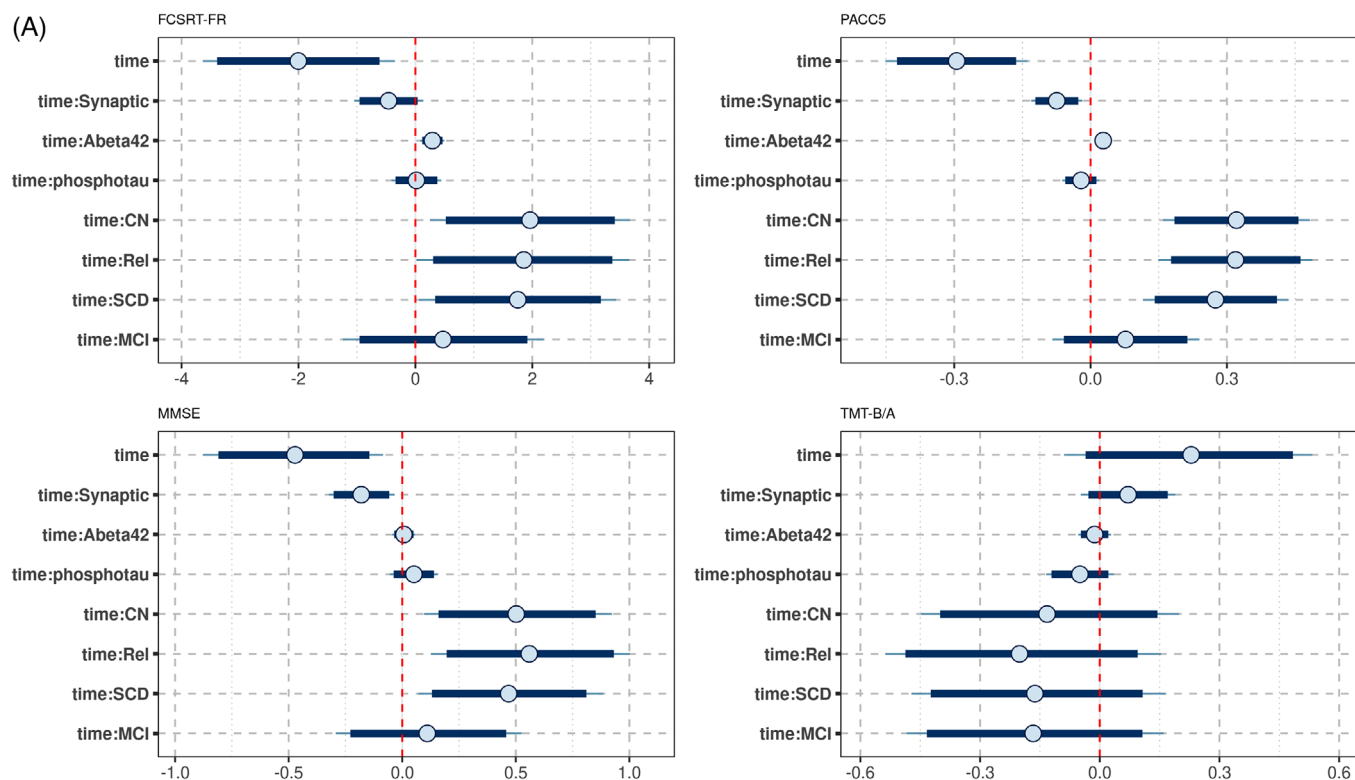
SCD—dummy variable for subjective cognitive decline (1/0 – yes/no).

APOE  $\epsilon 4$ —APOE  $\epsilon 4$  alleles; 0 = none, 1 = at least 1.

change for FCSRT free recall, PACC5, MMSE, and TMTB/A (Table S6 in supporting information). One example is shown in Figure S9 in supporting information. For all other factors and cognitive scores in the DELCODE and ADNI samples, there was no mediation effect of the neuroinflammation factors on the effect of AD pathology on rates of cognitive change (Table S6).

## 4 | DISCUSSION

We have determined latent factors of neuroinflammation based on an a priori assignment of individual inflammatory markers and characterized them in relation to AD pathology and longitudinal cognitive



**FIGURE 3** Posterior distribution of predictors of cognitive decline in the DELCODE data. Plots of the posterior distribution of the parameter estimates for the cognitive outcomes (FCSRT-FR, PACC5, MMSE, and TMTB/A, respectively), including effects of time and time by predictor interactions. The circle indicates the mean value, the thick segments the 90% credible intervals, and the thinner outer lines the 95% credible intervals of the posterior distribution. Of note, the time by diagnosis interactions (time:CN, controls; time:Rel, first-degree relatives; time:SCD, subjective cognitive decline; time:MCI, mild cognitive impairment) are plotted against the reference of the AD group. So positive values for time:CN indicate that rates of cognitive decline were less pronounced in the controls than the AD group. A, Synaptic factor. B, Microglia factor. C, Cytokine/chemokine factor. D, Complement factor. AD, Alzheimer's disease; CN, cognitively normal; FCSRT-FR, Free and Cued Selective Reminding Test Free Recall; MMSE, Mini-Mental State Examination; PACC5, Preclinical Alzheimer Cognitive Composite score plus verbal fluency; TMTB/A, Trail Making Test Parts B to A

decline. We found high to very high fit of the factor models. This suggests that the derived models are consistent with the a priori assumptions about the assignments of the individual markers, but of course does not prove their correctness.

We found very strong to extreme evidence for an association of the synaptic integrity, microglia, and adhesion factors with AD pathology. In contrast, evidence was against an association of complement and cytokine/chemokine factors with AD pathology. In addition, the posterior distributions of the parameter estimates suggested that the synaptic, microglia, and adhesion factors, but not the complement and cytokine/chemokine factors, were associated with rates of cognitive change.

The association of the microglia factor with AD pathology parallels our previous observation that early innate immune responses of microglia seemed to be associated with tau pathology markers.<sup>7</sup> Of note, the microglia factor was mainly associated with AD pathology but not with clinical diagnosis, that is, stage of disease. This is also reflected in the association of the microglia factor with rates of cognitive decline but not with baseline cognitive performance. However, the association was in an a priori unexpected direction, that is, higher

levels of microglia factor were associated with less cognitive decline. Studies suggest a negative impact of aberrant microglia activation on cognitive performance.<sup>29</sup> At the same time, a neuropathological study demonstrated higher microglial activation and TREM2 expression in brains of non-demented people than demented people with AD neuropathology<sup>30</sup> suggesting that microglia activation may contribute to synaptic integrity and resilience. In a mediation model, microglia factor mediated the effect of AD pathology on rates of change. The mediation effect had the same direction as the bilateral associations, that is, higher AD pathology was associated with higher microglia factor, which in turn was associated with less cognitive decline. This would suggest that in the presence of higher pathology, microglia response serves as a protective factor. However, such a model would require independent replication as it implies an a priori unexpected direction of the effects.

Associations of the synaptic factor with disease stage, AD pathology, and rates of cognitive decline are consistent with previous single-marker studies.<sup>31,32</sup> With an entirely different approach, fluorodeoxyglucose positron emission tomography (PET) as marker of neuronal metabolism and synaptic integrity showed strong

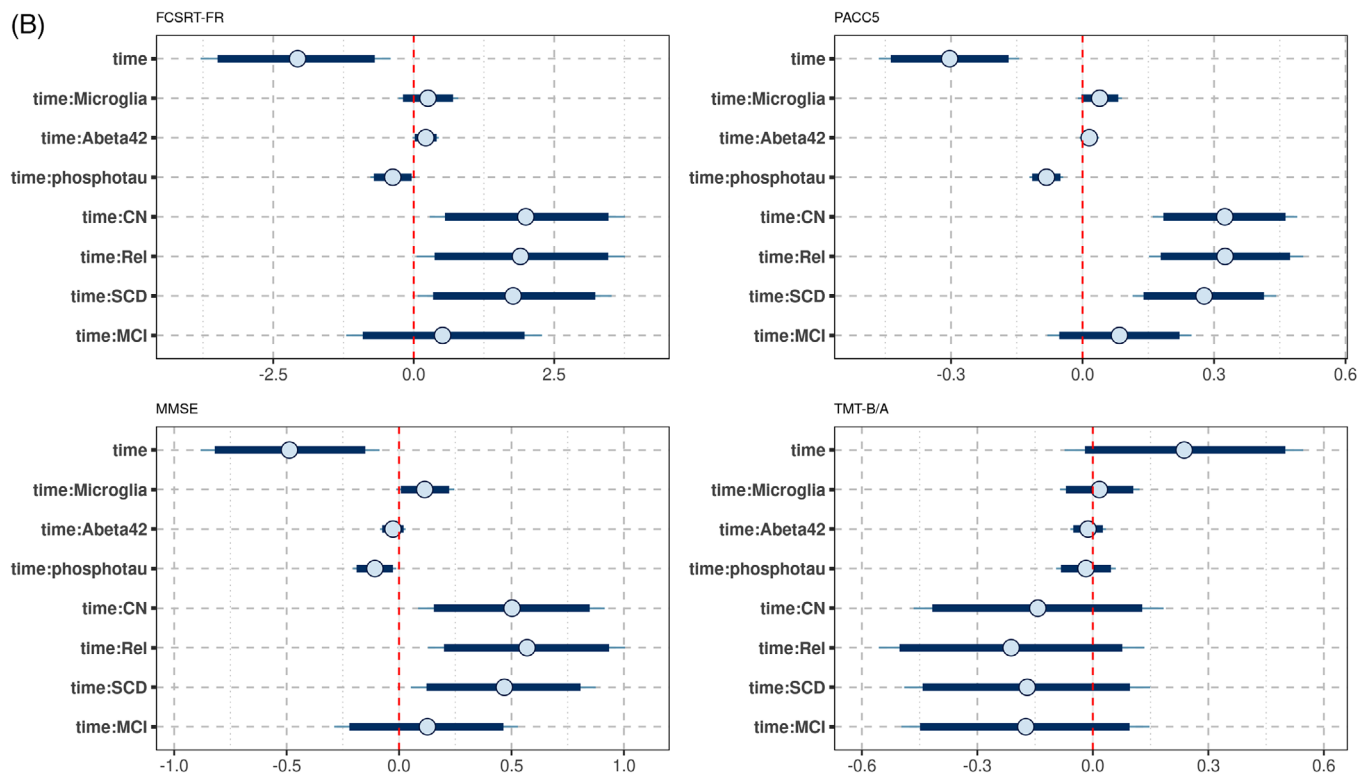


FIGURE 3 Continued

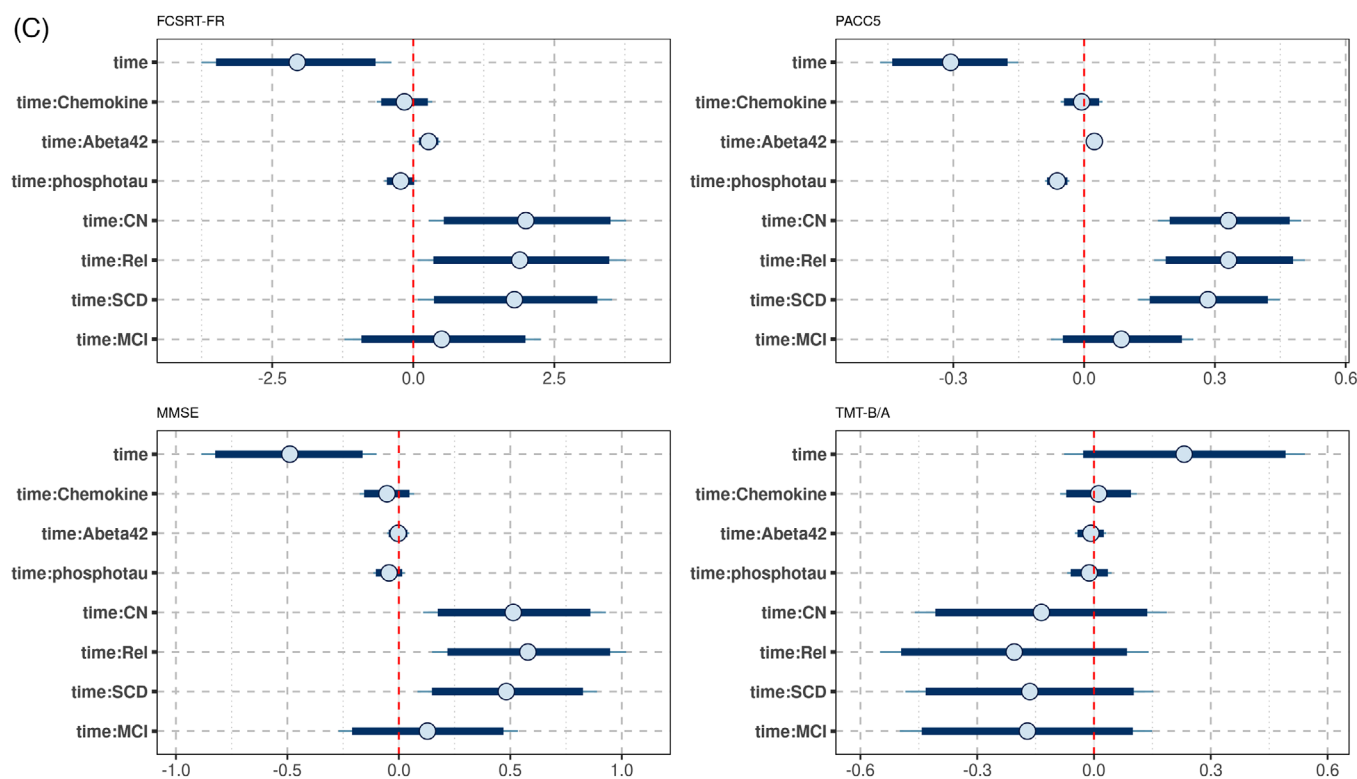


FIGURE 3 Continued



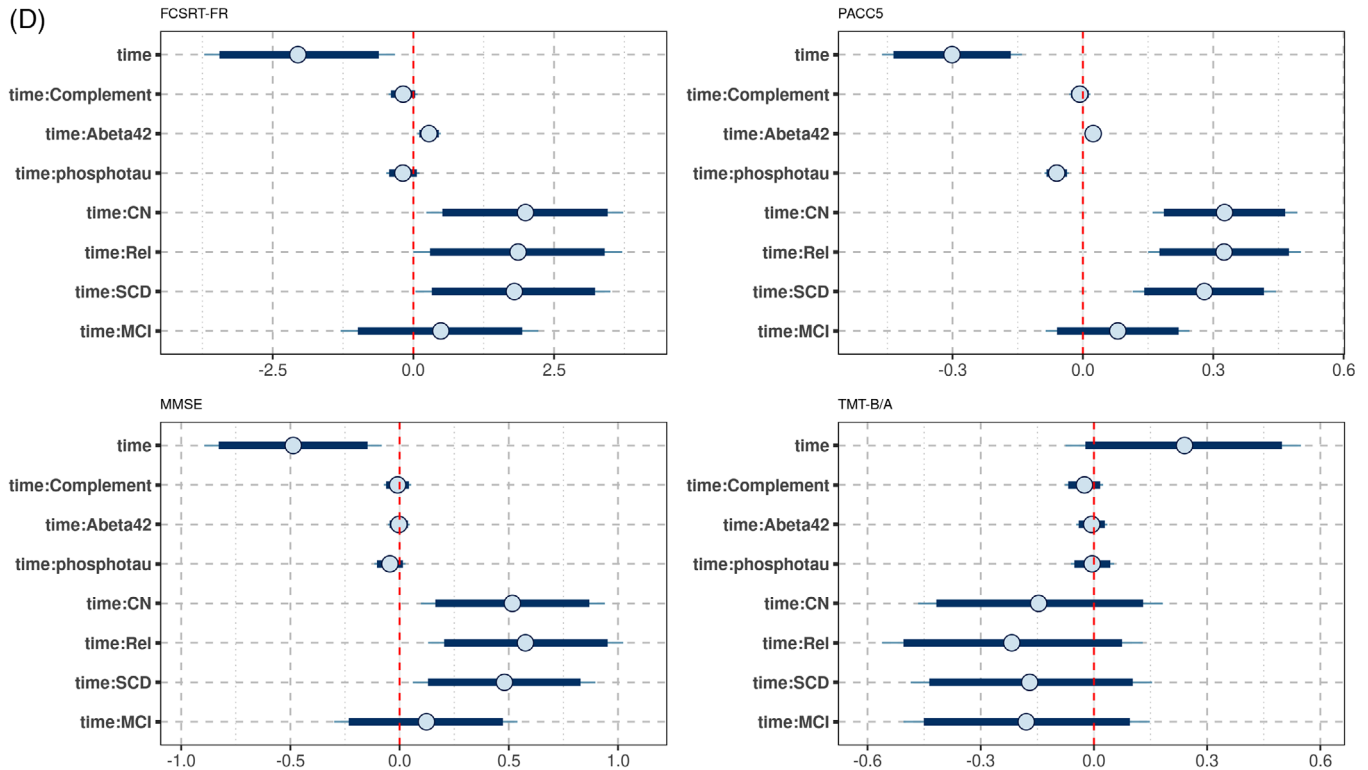
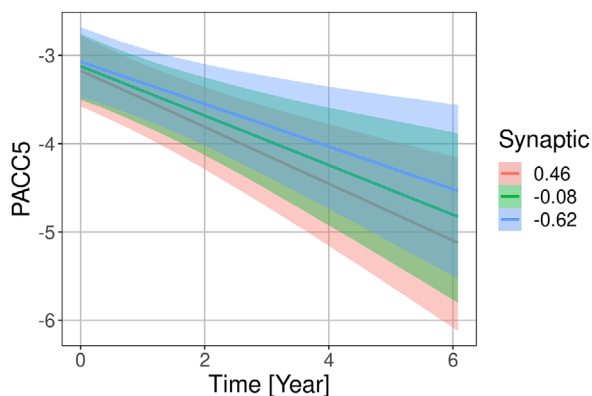
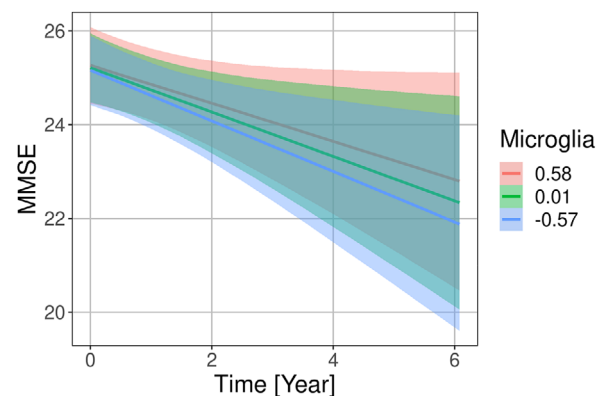


FIGURE 3 Continued



**FIGURE 4** Associations of synaptic factor with rates of Preclinical Alzheimer Cognitive Composite score plus verbal fluency (PACC5) change in the DELCODE cohort. Marginal interaction effect of time with synaptic factor for PACC5 change as dependent variable in linear mixed effect models predicting cognitive scores by diagnosis, amyloid beta 42 levels, phosphorylated tau levels, synaptic factor, and their interaction with time with a random intercept term, nested within individuals. The depicted values for the synaptic factor were chosen as the mean, and the mean plus and minus one standard deviation. This is used to illustrate the effect of the continuous synaptic variable on the rates of change



**FIGURE 5** Associations of microglia factor with rates of Mini-Mental State Examination (MMSE) score change in the DELCODE cohort. Marginal interaction effect of time with microglia factor for MMSE score as dependent variable in a generalized mixed effect model predicting MMSE score by diagnosis, amyloid beta 42 levels, phosphorylated tau levels, microglia factor, and their interaction with time with a random intercept term, nested within individuals. The depicted values for the microglia factor were chosen as the mean, and the mean plus and minus one standard deviation. This is used to illustrate the effect of the continuous microglia variable on the rates of change

association with AD pathology and rates of cognitive decline as well.<sup>33</sup> The absence of a mediation effect would suggest that the contributions of AD pathology and synaptic integrity to rates of cognitive decline are independent from each other. Because we lack previous

evidence, however, the finding of absence of a mediation effect needs independent replication.

Adhesion as marker of cerebrovascular integrity has not yet widely been studied. One previous study reported an association of plasma

markers of adhesion with AD pathology and cross-sectional measures of cognition in MCI and AD cases.<sup>34</sup> Our study extends these findings toward a strong association of the adhesion factor in CSF with AD pathology. In addition, the adhesion factor had a strong contribution to rates of memory and executive function change on top of p-tau and A $\beta$ 42 effects. These data encourage the further study of cerebrovascular endothelial dysfunction as potential driver of AD-related cognitive decline and may also highlight a role of extravasation of peripheral immune cells and systemic inflammation that has been suggested in experimental preclinical AD models.<sup>35,36</sup> Indeed, a range of previous studies reported blood–brain barrier dysfunction in AD, reviewed in Kurz et al.,<sup>37</sup> which may contribute to AD pathology through two related mechanisms: impaired clearance of A $\beta$  and other toxic proteins and reduced protection against peripheral and central inflammatory response.

Interestingly, we found evidence for no association of the cytokine/chemokine and complement factors with AD pathology, and associations with rates of cognitive decline were not detectable in the DELCODE and the ADNI data. Chemokine levels were increased in AD and were related to the level of A $\beta$ 42 pathology in a previous study.<sup>38</sup> However, in these previous results, just one among several selected chemokine markers showed such an association with the majority of markers showing no effect. These heterogeneous findings may be related to the short half-life of chemokines so that CSF levels may not always reflect tissue concentration. This underscores that the latent factor approach may lead to a more robust assessment with less propensity to false positive findings.

For a detailed discussion of the Bayesian framework of the analysis, we refer to the supporting information (pages 2 to 4).

A limitation and at the same time a strength of our study is the use of a priori assignment of markers to specific latent factors, such as synaptic integrity or microglial response. This was based on a review of the literature for each CSF marker. At the same time, a single marker typically is not only related to one single mechanism but contributes to several mechanisms of inflammation. Therefore, this a priori separation was to some extent arbitrary. At the same time the fit of the confirmatory factor models (including multiple factor models) was very high, supporting the a priori assignment of markers. In an alternative approach one could have used an unsupervised approach for creating composites of markers, for example with principal component analysis. If this approach is heuristically blind, that is, no specific domain of inflammation is being assigned to the resulting factors, such as in Clark et al.,<sup>19</sup> one cannot draw conclusions on the differential involvement of various domains of the inflammatory response. Alternatively, one may assign specific inflammatory mechanisms to the resulting factors post hoc based on the loadings of the original variables on the new composites. However, this approach is at least as arbitrary as the a priori clustering and less likely to be reproducible across different cohorts because of the post hoc assignment. The data-driven approach has the advantage that it can uncover unexpected clusters. However, these are difficult to interpret, and their validity depends heavily on replication in an independent cohort. Both cohorts, DELCODE and ADNI, include selected cases from memory clinic and research center contexts so that

our results cannot be generalized to the general population of older people.

In summary, confirmatory factor analysis revealed strong associations of synaptic integrity, microglia response, and cerebrovascular endothelial dysfunction with AD pathology. Even when AD pathology and stage of disease were accounted for, these three inflammation-related mechanisms contributed at least moderately to rates of cognitive decline on top of the effects of A $\beta$  and p-tau. The direction of effect for microglia, however, requires independent confirmation. Cytokine/chemokine and complement factors were robustly unrelated to AD pathology and rates of cognitive decline, suggesting a less important role of these particular innate components of the inflammatory response to AD pathology and course of disease. Future extensions of this approach can easily incorporate other inflammatory markers, such as translocator protein (TSPO) PET<sup>39</sup> imaging findings as microglia marker, or other domains of inflammatory response. Despite having > 250 cases in both cohorts, the number of cases did not allow for a meaningful substratification, for example, according to APOE genotype or amyloid positivity versus negativity, because a reliable estimate of latent factors requires a high enough number of cases. In the future, larger samples per cohort and better harmonized assessments of inflammation markers across cohorts may become available, allowing a more differentiated analysis of inflammatory domains. In addition, the associations of the adhesion factor, if replicated in another cohort, may point to an important link between inflammation and protein clearance from the brain. This indicates a promising research line that will deserve more in-depth study once in vivo measures of brain clearance, less invasive than current methods,<sup>40</sup> become available.

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## CONFLICT OF INTEREST STATEMENT

S.J.T. participated in scientific advisory boards of Roche Pharma AG, Biogen, Grifols, and MSD, and received lecture fees from Roche and MSD. M.T.H. serves as a scientific board member of IFM Therapeutics, Novo Nordisk, and Alector and has received lecture honoraria from NovoNordisk. The other authors state no competing interests. Author disclosures are available in the [supporting information](#).

## DATA AVAILABILITY STATEMENT

Anonymized data used in this article will be made available by request from any qualified investigator through the DELCODE Steering Board for purposes of replicating procedures and results.

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## SUPPORTING INFORMATION

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

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