Title

Elevated Inflammatory Markers and Arterial Stiffening Exacerbate Tau but Not Amyloid Pathology in Older Adults with Mild Cognitive Impairment.

Journal

Journal of Alzheimer's Disease, 80(4)

ISSN

1387-2877

Authors

Clark, Alexandra L
Weigand, Alexandra J
Thomas, Kelsey R
et al.

Publication Date

2021

DOI

10.3233/jad-201382

Peer reviewed

Published in final edited form as:

J Alzheimers Dis. 2021 ; 80(4): 1451–1463. doi:10.3233/JAD-201382.

Elevated Inflammatory Markers and Arterial Stiffening Exacerbate Tau but Not Amyloid Pathology in Older Adults with Mild Cognitive Impairment

Alexandra L. Clark[a,b,c], **Alexandra J. Weigand**[a,d], **Kelsey R. Thomas**[a,c], **Seraphina K. Solders**[e], **Lisa Delano-Wood**[a,b,c], **Mark W. Bondi**[a,b,c], **Rachel A. Bernier**[e], **Erin E. Sundermann**[c], **Sarah J. Banks**[e], **Katherine J. Bangen**[a,c,*], **Alzheimer's Disease Neuroimaging Initiative**[1]

[a] Research Services, VA San Diego Healthcare System, San Diego, CA, USA

[b] Psychology Service, VA San Diego Healthcare System, San Diego, CA, USA

[c] University of California San Diego, School of Medicine, Department of Psychiatry, La Jolla, CA, USA

[d] San Diego State University/University of California, San Diego (SDSU/UCSD), La Jolla, CA, USA

[e] Department of Neuroscience, University of California, San Diego, La Jolla, CA, USA

Abstract

Background: Age-related cerebrovascular and neuroinflammatory processes have been independently identified as key mechanisms of Alzheimer's disease (AD), although their interactive effects have yet to be fully examined.

Objective: The current study examined 1) the influence of pulse pressure (PP) and inflammatory markers on AD protein levels and 2) links between protein biomarkers and cognitive function in older adults with and without mild cognitive impairment (MCI).

Methods: This study included 218 ADNI (81 cognitively normal [CN], 137 MCI) participants who underwent lumbar punctures, apolipoprotein E (*APOE*) genotyping, and cognitive testing. Cerebrospinal (CSF) levels of eight pro-inflammatory markers were used to create an inflammation composite, and amyloid-beta 1−42 ($A\beta_{42}$), phosphorylated tau (p-tau), and total tau (t-tau) were quantified.

Results: Multiple regression analyses controlling for age, education, and *APOE* ε4 genotype revealed significant PP x inflammation interactions for t-tau (B = 0.88, $p = 0.01$) and p-tau

[1]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 ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledsement_List.pdf

*Correspondence to: Katherine J. Bangen, Ph.D., VA San Diego Healthcare System (151B), 3350 La Jolla Village Drive, San Diego, CA 92161, USA. Tel.: +1 858 552 8585 /Ex 5794; kbangen@health.uscd.edu.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-201382.

(B = 0.84, $p = 0.02$); higher inflammation was associated with higher levels of tau within the MCI group. However, within the CN group, analyses revealed a significant PP x inflammation interaction for $A\beta_{42}$ (B = −1.01, $P = 0.02$); greater inflammation was associated with higher levels of $A\beta_{42}$ (indicative of lower cerebral amyloid burden) in those with lower PP. Finally, higher levels of tau were associated with poorer memory performance within the MCI group only ($ps < 0.05$).

Conclusion: PP and inflammation exert differential effects on AD CSF proteins and provide evidence that vascular risk is associated with greater AD pathology across our sample of CN and MCI older adults.

Keywords

Cerebrospinal fluid; inflammation; mild cognitive impairment; tau; vascular dysfunction

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia among older adults, and significant efforts have been placed upon identifying factors that may ultimately prevent or halt disease progression [1]. AD pathology is characterized by the accumulation and aggregation of amyloid-β (Aβ) and pathological tau proteins, with consequential neuronal loss and cerebral atrophy [2]. Although genetic susceptibility (e.g., apolipoprotein E [*APOE*] *ε*4 genotype) plays a clear role in the risk for AD, other—potentially modifiable—environmental, lifestyle, and health factors (e.g., exposure to pollutants, diet, diabetes) have also been forwarded as propagators of AD-related pathology [3–6].

While not included in most AD pathological staging frameworks [7, 8], cerebrovascular dysfunction represent one such risk factor, or critical "hit", in the pathogenesis of AD [9–11], For example, research has shown that the increased presence of vascular risk factors (e.g., hypertension, obesity, hypercholesteremia) beginning in mid-life, coupled with age-related cerebrovascular changes (e.g., pericyte and microvascular loss, increased vascular permeability), is associated with cerebral blood flow alterations and blood-brain barrier breakdown in older adults [9, 12, 13]. These vascular changes have been linked to AD pathology in the form of increased Aβ production and accumulation as well as tau hyperphosphorylation and neurofibrillary tangle formation [14, 15]. Importantly, these vascular-mediated pathways have been posited to be some of the earliest drivers of neurodegeneration and cognitive decline in AD and other AD-related dementias [16, 17].

Inflammation has also been implicated as an important factor in the AD cascade in recent years. As a common consequence of both vascular dysfunction and amyloid accumulation, the brain's immune response is activated and uncontrolled neuroinflammatory processes contribute to neuronal damage and synaptic loss [18–20]. Although this immune response may initially be protective—activated microglia have been demonstrated to promote amyloid clearance and degradation—prolonged inflammation leads to the release of cytokines that have been directly linked to tau tangle formation [20–22]. The precise nature, temporal aspect, and pathological consequences associated with the activation of inflammatory pathways has yet to be fully characterized, but research from both animal and human

studies have highlighted that inflammation precedes and may exacerbate a primarily tau-mediated neurodegeneration that is associated with worse overall disease severity, cognitive impairment, and conversion to AD [23–27], Nevertheless, as detailed in a review by Golde [28], immunoproteiostasis, or the link between immune system activation and neurodegenerative proteinopathy, is incredibly complex, and the manipulation of either pro- and/or anti-inflammatory pathways may yield adverse neurological consequences [28, 29].

There is a complex interplay between vascular dysfunction and inflammation, as they both commonly co-occur and are associated with worsening levels of neuronal injury [30–32]. Currently, most studies of older adults have centered on exploring the independent contributions of vascular risk and inflammation on AD pathologic changes, and models incorporating both have found that each uniquely explains functional impairment and neuropsychiatric functioning of older adults at risk for AD [33]. However, they may in fact act in synergistic fashion to worsen AD pathology, and the extent to which both may differentially affect specific AD proteins across various stages of the disease remains understudied. Therefore, we investigated the interactive effects of vascular risk and inflammation on AD cerebrospinal fluid (CSF) biomarkers (i.e., Aβ and tau) and stratified by diagnostic group (i.e., cognitively normal versus mild cognitive impairment (MCI)) to examine whether the interactive effects of vascular risk and inflammation differed across the aging spectrum from normal cognition to MCI. We then explored the extent to which AD biomarkers were directly related to cognition within each cognitive group.

METHODS

Data availability

Data used for the present study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). ADNI is a public-private partnership that was launched in 2003 by Principal Investigator, Michael W. Weiner, MD. The primary goal of ADNI is to explore whether serial magnetic resonance imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and preclinical stages of AD. Information on ADNI can found at http://www.adni-info.org. The ADNI study was approved by the Institutional Review Boards of all participating sites and written informed consent was obtained for all study participants prior to engagement in the study.

Participants and inclusion/exclusion criteria

Enrollment criteria for the ADNI study are described in detail elsewhere [34], but briefly include: adults between the ages of 55–90 years with ≥ 6 years of education or work-history equivalent, that are fluent in English or Spanish, have adequate vision and hearing to perform neuropsychological tests and are in generally good health without significant neurologic disease or history of traumatic brain injury. Per the ADNI website's reported biofluid banking statistics (http://adni.loni.usc.edu/methods/), approximately 1,118 participants of the ADNI 1 cohort had CSF samples collected. However, only a small subsample of 386 participants had CSF data for nonamyloid/tau inflammatory biomarker baseline data (collected primary between 2005–2008) that was available for download from

the ADNI_HULAB.csv on August 1, 2020. The final study sample consisted of 218 ADNI participants that were not diagnosed with dementia at their initial study visit and had data available for: all CSF inflammatory protein markers of interest for creation of our composite; Elecys CSF AD protein markers; blood pressure measurements, other relevant medical/health background information (e.g., history of heart disease or diabetes); key demographic information, (e.g., age, education, sex); apolipoprotein E (*APOE*) genotyping; and Mini-Mental Status Exam (MMSE) and cognitive scores.

Assessment of cognitive functioning

Participants completed neuropsychological testing and variables of interest included performance on measures of general cognition (MMSE) and the cognitive subdomains of attention/executive functioning (Trail Making Test Parts A and B), verbal memory (Immediate and Delayed Recall and Recognition Total from Story A of the Weschler Memory ScaleRevised; Delayed Recall and Recognition Total of the Rey Auditory Verbal Learning Test), and language (Boston Naming Test or Multilingual Naming Test; animal fluency). Raw scores for each of the measures representing the cognitive subdomains were converted to z-scores that were based on predicted values from regression equations (adjusted for age, sex, and education) that had been derived from a robust normal control group that has remained cognitively normal (CN) throughout their duration of participation in ADNI [35–38]. Finally, z-scores across tests within each cognitive subdomain were then averaged to create attention/executive, language, and memory composites.

MCI diagnosis was based upon Jak/Bondi *actuarial* neuropsychological criteria, which has previously been shown to improve diagnostic precision, biomarker associations, and AD progression rates when compared with *conventional* ADNI MCI criteria (35–38). Jak/Bondi MCI criteria is based upon the above tests (with the exception of MMSE and the Wechsler Memory Scale Story A) and participants were characterized as MCI if they showed 1) impairment on at least two scores within one cognitive subdomain or 2) one impaired score across three separate cognitive subdomains [37, 38]. Importantly, Story A measures have traditionally been utilized for ADNI MCI conventional diagnostic criteria and were intentionally not been included within the Jak/Bondi actuarial criteria to ensure independence of the criteria for comparisons purposes in the original investigation. Please see [38], the original investigation, for a graphical representation of the cognitive measures utilized in the actuarial criteria employed here. Of the 218 participants, 81 were classified as CN, whereas 137 were classified as MCI.

AD CSF and genetic markers

Baseline levels of CSF $A\beta_{42}$, total tau (t-tau), and tau phosphorylated at the threonine 181 position (p-tau) were measured using Elecsys immunoassays on a fully automated cobas e601 platform. Higher levels of CSF t-tau and p-tau and lower levels of $A\beta_{42}$ are indicative of greater AD pathology within the central nervous system [39–42]. Positivity rates of CSF $A\beta_{42}$ (< 1,098 pg/mL), t-tau (> 242 pg/mL), and p-tau (>19.2pg/mL) were calculated based on Schindler (2018) criteria. *APOE ε*4 positivity was determined by the possession of at least one *APOE ε*4 allele.

Neuroinflammatory and physiological vascular markers

CSF levels of eight pro-inflammatory markers were quantified using multiplex immunoassays: Interleukin-7, Interleukin-6, Interleukin-9, Interferon Gamma-Induced Protein 10, Tumor Necrosis Factor Alpha, Tumor Necrosis Factor Receptor 1, Vascular Cell Adhesion Molecule-1, Intercellular Adhesion Molecule 1 (IL-7, IL-6, IL-9, IP-10, TNFα, TNFR1, VCAM1, ICAM1, respectively). We focused on markers that were not highly correlated with one another (to ensure appropriate statistical approaches), were repeatedly documented to have largely pro-inflammatory effects, were consistently implicated in the AD literature, and consistently had estimated values for use in analyses.

In an effort to preserve power and reduce the number of comparisons, a principal component analysis (PCA) was performed to reduce data into one fixed pro-inflammatory marker. An orthogonal (varimax) rotation was utilized to enhance interpretability and to obtain a set of independent loadings that are reflective of simple correlations between individual inflammatory markers and the overall composite. All loadings for individual inflammatory markers were required to be >0.4 in an effort to ensure meaningful contribution of each inflammatory marker to the larger pro-inflammatory composite [43, 44].

During the first PCA iteration, 35% of the variance in the data was explained by the eight component pro-inflammatory composite. However, the rotated component matrix revealed IL-6 and IL-7 factor loadings (0.19, 0.38, respectively) were below the acceptable loading range, although loading values for all other factors ranged from 0.51–0.76. PCA analyses were repeated with both factors removed one at a time until all loadings were determined to be in the acceptable range. Results revealed that 45% of the variance in the data was explained by a 6-component pro-inflammatory composite (IL-9, IP-10, TNFα, TNFR1, ICAM1, VCAM1) an all rotated factor loadings ranged from 0.49–0.82. Standardized principal component scores for this 6-component pro-inflammatory composite were calculated for each study participant and utilized in subsequent analyses.

Finally, pulse pressure (PP), an indirect index of arterial stiffening, was calculated as the difference between systolic and diastolic blood pressure measurements. Notably, a Pearson's correlation test was performed to demonstrate PP and inflammation were independent markers and revealed there was no significant association between PP and the pro-inflammatory composite across the entire sample ($r = 0.11$, $P = 0.11$).

Statistical analyses

All data were checked for outliers (defined as > 3 standard deviations from the mean) and to ensure no basic statistical assumptions were violated; for cognitive analyses, scores for 1 CN and 1 MCI subject on the language and attention/executive composites were deemed to be outliers and thus not included in the analyses. Multicollinearity statistics were performed prior to analyses and determined to be in the acceptable range for all regression models (variance inflation factor < 1.5, tolerance, < 1, all rs < 0.4). All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 26 and R version 3.5.0 (https://cran.r-project.org/).

Analyses of variance (ANOVAs) were used to determine whether the groups (CN versus MCI) differed on continuous demographic and clinical variables. Chi-squared analyses examined group differences on categorical demographic and clinical variables. Analyses of covariance (ANCOVAs) were used to explore whether the groups differed on AD CSF markers. Covariates (age, education, and *APOE ε*4 genotype) were included when there was a relationship between the potential covariate and dependent variables of interests; model parsimony was preferred and thus sex was not included as a covariate in our primary analyses given there were no sex differences in dependent variables of interest. Please note degrees of freedom slightly differ across CSF AD analyses as t-tau and p-tau data were degraded for four subjects (1 CN, 3 MCI) and, therefore, these individuals were not included in the tau analyses. Multiple regression analyses were used to explore 1) main effects of PP and inflammation, 2) PP x inflammation interactions, and 3) the association between AD CSF biomarkers and cognitive performance within the CN and MCI groups. The standardized beta estimates for continuous predictors are reported in the text.

RESULTS

Participant demographics and clinical characteristics are presented in Table 1. Although mean age and the proportion of women within each group were comparable, the MCI group had significantly fewer years of education ($p = 0.007$) and, as expected, lower MMSE scores ($p < 0.001$). Also as expected, relative to the CN group, the MCI group also had a greater proportion of individuals that were *APOE ε*4 positive, as well as CSF amyloid, t-tau, and p-tau positive (ps < 0.001). There were no group differences on markers of vascular risk or inflammation (ps < 0.05), but as expected, the MCI group performed significantly worse than the CN group on all cognitive composites (ps < 0.001).

Main effects of group (CN versus MCI) on AD CSF biomarkers

ANCOVAs adjusting for age, education, and *APOE ε*4 positivity revealed that the MCI group displayed significantly higher levels of t-tau ($F(1, 209) = 19.41$, $p < 0.001$, $\eta_p^2 = 0.085$) and p-tau ($F(1, 209) = 19.60$, $p < 0.001$, $\eta_p^2 = 0.086$), and lower levels of $A\beta_{42}$ (indicative of higher cerebral amyloid pathology in the brain; ($F(1, 213) = 31.74$, $p < 0.001$, $\eta_p^2 = 0.130$)) relative to the CN group. Given that the groups differed on AD CSF biomarkers, a series of parallel analyses were performed in an effort to better understand the associations between inflammation, pulse pressure, and AD CSF biomarkers within each cognitive group.

Pulse pressure x inflammation interactions on AD CSF biomarkers in CN and MCI groups

Multiple regression analyses adjusting for age, education, and *APOE ε*4 positivity, were used to explore PP x inflammation interactions on AD CSF biomarkers within the MCI group. Results revealed there were significant PP x inflammation interactions for t-tau (B = 0.88, t = 2.55, $p = 0.01$) and p-tau (B = 0.84, t = 2.39, $p = 0.02$) such that higher levels of inflammation were significantly associated with higher levels of tau in those with higher levels of PP. A median split for pulse pressure (60 mmHg) was conducted to aid in interpretation and to graphically depict the association between the three continuous variables, and MCI participants were divided into those with low ($n = 65$) versus high levels

of pulse pressure (n = 69). See Figs. 1 and 2. In contrast, there were no significant PP x inflammation interactions for amyloid (B = 0.02, t = 0.06, p = 0.96) in the MCI group. See the Supplementary Material for a depiction of this non-significant association in the MCI group.

With regard to the CN group, results revealed there was a significant PP x inflammation interaction for amyloid (B = −1.01, t = 2.43, p = 0.02) such that inflammation was associated with higher levels of $A\beta_{42}$ (indicative of lower cerebral amyloid burden) in those with lower PP. As with the MCI group, median split for pulse pressure (60 mmHg) was conducted in order to aid in interpretation and graphically depict the association between the three continuous variables and CN participants were divided into those with low (n = 39) versus high levels of pulse pressure (n = 42). See Fig. 3. In contrast, there were no significant PP x inflammation interactions for t-tau (B = 0.16, t = 0.45, p = 0.66) and p-tau (B = 0.25, t = 0.67, p = 0.51) within the CN group. See the Supplemental Material for depictions of these non-significant association in the CN group.

Main effects of pulse pressure and inflammation on AD CSF biomarkers in CN and MCI groups

Multiple regression analyses adjusting for age, education, and *APOE ε*4 positivity, were used to explore main effects of 1) pulse pressure and 2) inflammation on AD CSF biomarkers within each group. Results from the first set of regressions revealed no significant associations between PP and amyloid (B = 0.03, t = 0.42, p = 0.68), t-tau (B = 0.08, t = 0.94, p = 0.35), or p-tau (B = 0.08, t = 0.89, p = 0.37) within the MCI group. However, higher PP was significantly associated with higher levels of t-tau (B = 0.21, t = 2.09, p = 0.04) and p-tau (B = 0.24, t = 2.38, p = 0.02), but not amyloid (B = 0.04, t = 0.39, p = 0.70) within the CN group.

Results from the second set of regressions revealed that inflammation was significantly associated with higher levels of t-tau (B = 0.54, t = 6.26, p < 0.001) and p-tau (B = 0.49, t = 5.52, p < 0.001), but not amyloid (B = 0.14, t = 1.67, p = 0.10) within the MCI group. Pearson's correlations between individual inflammatory markers and AD CSF biomarkers are presented in Table 2A. Within the CN group, results revealed that higher inflammation was significantly associated with higher levels of $A\beta_{42}$ (indicative of lower cerebral amyloid burden) (B = 0.25, t = 2.29, p = 0.03), t-tau (B = 0.57, t = 5.84, p < 0.001), and p-tau (B = 0.48, t = 4.70, p < 0.001). Pearson's correlations between individual inflammatory markers and AD CSF biomarkers are presented in Table 2B.

AD CSF biomarkers and cognitive associations within CN and MCI groups

Regressions adjusting for age, education, and *APOE ε*4 positivity, were used to determine whether levels of AD CSF biomarkers were associated with cognitive performance within the groups.

Within the MCI group, results revealed there were significant associations between lower $A\beta_{42}$ (indicating higher cerebral amyloid burden; B = 0.26, t = 2.89, p = 0.005), higher t-tau (B = −0.26, t = −3.28, p = 0.001), and p-tau (B = −0.24, t = −2.96, p = 0.004), and poorer performance on the memory composite. In contrast, there were no significant

associations between amyloid (B = 0.18, t = 1.84, $p = 0.07$), t-tau (B = −0.16, t = −1.79, $p = 0.08$), or p-tau (B = −0.14, t = −1.59, $p = 0.11$) and performance on the attention/executive composite, nor were there any significant associations between amyloid (B = 0.10, t = 1.40, $p = 0.29$), t-tau (B = −0.14, t = 1.67, $p = 0.09$), or p-tau (B = −0.09, t = 0.99, $p = 0.32$) and performance on the language composite within the MCI group. Results revealed no significant associations between amyloid (Bs range = −0.09 to 0.17; ps range = 0.18 to 0.47), t-tau (Bs range = −0.06 to −0.18; ps range = 0.15 to 0.64), or p-tau (Bs range = −0.08 to −0.22; ps range = 0.09 to 0.53) and performance on any of the cognitive composites within the CN group.

DISCUSSION

We examined the independent and interactive effects of PP and inflammation on AD CSF protein markers, as well as associations between AD protein markers and cognition, within CN and MCI groups. Results showed no main effects of PP on CSF AD proteins markers within the MCI group, although higher PP was associated with higher levels of tau in CN older adults. Within each group, higher levels of inflammation were associated with higher tau burden. Interestingly, inflammation was positively related to higher levels of $A\beta_{42}$ (indicative of lower cerebral amyloid burden) within the CN group only, suggesting that inflammation was protective against cerebral amyloid burden among the cognitively unimpaired. Results also revealed that the combination of elevated PP and inflammation exacerbated tau levels within the MCI group. However, lower levels of PP and higher inflammation was associated with higher levels of $A\beta_{42}$ (indicative of lower cerebral amyloid burden) in the CN group, although the CN group had lower amyloid when compared to the MCI group. Finally, higher tau and lower levels of $A\beta_{42}$ (indicative of higher cerebral amyloid burden) were associated with poorer memory performance in the MCI group, but no such associations were observed within the CN group. Overall, findings suggest that increased PP and inflammation are independently associated with AD CSF protein markers, and they interact to produce unique effects on amyloid and tau that appear to differ amongst older adults with and without MCI.

Our results demonstrating that PP and inflammation interact on CSF levels of tau in older adults with MCI illustrate the importance of considering *both* factors when assessing AD risk and/or underlying pathology. Importantly, arterial stiffening in combination with inflammation confers a unique risk on tau, and interventions aimed at controlling both factors may ultimately delay disease progression. The importance of multiple targets in preventing neurological injury has been highlighted by Zlokovic and Griffin's (2011) "vasculo-neuronal-inflammatory" triad model. Importantly, they highlight that "multi-point" therapeutic targets aimed at reducing both inflammation and vascular dysfunction may more effectively modify complex disease mechanisms responsible for neurodegeneration. Although vascular dysfunction and inflammation are intertwined, it is important to note that our metrics of PP and inflammation were not significantly associated with another. In other words, we suspect that each may be capturing somewhat unique disease processes that are not merely the byproduct of each other, and thus further illustrate the point that *both* vascular and inflammatory driven pathophysiological processes represent critical points of intervention.

In contrast to what was observed within our MCI group, we found that at lower levels of PP and higher levels of inflammation were associated with higher levels of CSF amyloid—reflecting less amyloid in the brain and suggesting the possibility of successful amyloid clearance and lower plaque formation in our CN group. This relationship was somewhat surprising, as sustained inflammatory processes have consistently been demonstrated to promote AD pathology [24, 26, 45]. However, there is some evidence to suggest that inflammation may be helpful acutely and may lead to successful amyloid clearance in the early AD pathologic stages before inflammation becomes more chronic [24, 46]. Given there was no association between inflammation and amyloid accumulation in those with higher levels of PP, it is possible that any "helpful" inflammatory cascades are negated in the presence of vascular dysfunction. Indeed, vascular dysfunction itself has been independently linked to amyloid angiopathy and links between elevated PP and greater CSF amyloid have also been established in other samples of older adults, although this association was not significant in our CN sample [41, 42]. While we cannot fully speak to the temporal relationship between inflammation and AD pathology within this group, given this was a cross-sectional analysis of cognitively normal individuals with lower overall levels of amyloid and tau positivity, we suspect they may not have experienced detrimental effects of *prolonged* inflammation characteristic of more advanced disease states (MCI, AD).

Somewhat in line with the hypothesis that *phase* along the AD continuum may be relevant with regard to inflammation, an intact cholinergic system is essential for delicately balancing the antiand pro-inflammatory M1/M2 microglial pathways [47]. However, degradation of this system due to AD pathological changes has been linked to unchecked pro-inflammatory pathways. For example, in a recent ADNI study, CN older adults were subdivided into neurotypical versus preclinical subgroups based on CSF amyloid and tau cut-offs, and associations between inflammation and basal forebrain volume (a posited metric of cholinergic system integrity) were explored over time. The study demonstrated that the preclinical subgroup demonstrated higher levels of inflammation with greater levels of basal forebrain loss, although this relationship was not observed in the neurotypical group [48]. In our study, given the CN group is not yet experiencing significant AD pathologic changes (as evidenced by their relatively low levels of amyloid and tau positivity when compared to the MCI group), pro-inflammatory cascades (at least with regard to amyloid) may not yet be inflicting harmful neuronal damage and instead are being properly "regulated". However, additional studies that also model vascular dysfunction are needed to better understand the interactive nature of these findings and to ensure the validity of this finding within the CN group via replication given the numerous comparisons and weaker nature of this finding.

We also demonstrated a main effect of inflammation on tau accumulation within both the CN and MCI groups. Findings comport with several animal and human AD studies that have shown microglial activation is a critical component of tau accumulation, occurs independently of amyloid status, and is a main driver of neurodegeneration and disease progression over time [24–27]. Results align with the notion that inflammation is a critical part of the AD continuum and direct remediation may prevent tau hyperphosphorylation and tangle formation across the preclinical, early, and late AD disease states. This is especially important given we also demonstrated that tau, but not amyloid, had an adverse effect on

memory performance in the MCI group. While spatio-temporal patterns of tau pathology cannot be delineated with CSF biomarkers, tau-PET and neuropathological studies have revealed that brainstem and medial temporal cortices, which houses brain regions important in memory function, are some of the earliest regions affected by AD tau pathology [49–51]. As such, this may explain why only tau and memory correlations were observed in our MCI group, as additional cognitive domains such as language and attention may be more likely to be affected with disease progression and the spread of tau pathology to regions beyond the medial temporal lobe. However, it is important to note that the CN group had lower levels of amyloid and tau and a relatively restricted range of cognitive performance compared to the MCI group, and may therefore have made the detection of brain-behavior associations within the CN group more difficult.

Interestingly, a close inspection of our inflammatory composite (see Tables 2A and 2B) revealed that the individual markers of IL-9, TNFR1, ICAM1, and VCAM1 were most strongly associated with the AD CSF protein markers of interest. While these individual inflammatory markers have a diverse range of regulatory and functional pathways—many of which are still being characterized—there is some evidence to suggest that each of these markers are somewhat involved in immune reactions that target elements of the blood-brain barrier and/or vascular pathways [52, 53]. While we suspect that vascular health-related risk factors (e.g., diabetes, heart disease, hypertension, and stroke) are, again, intimately tied to vascular inflammatory processes, we believe this provides further evidence that 1) AD risk and development is also tied to vascular heath and maintenance, and 2) vascular pathways may be independent contributors of both amyloid and tau pathology within the central nervous system. Nevertheless, additional work centered on clarifying and the negative effects of each of these inflammatory markers is needed in order to better understand the precise role and consequences of these immune pathways. Finally, the relationship between innate immune activation and AD is incredibly complex, and there is a growing appreciation for challenges to the long-standing hypothesis that pro-inflammatory activation accelerates AD processes, whereas anti-inflammatory strategies are neuroprotective. For example, pleiotropic anti-inflammatory cytokines (e.g., interleukin-4 and 10) have been demonstrated to relate to increased amyloid plaque deposition and impaired cognition in mice [29, 54], and anti-inflammatory therapeutics in AD trials have revealed harmful effects on cognition and disease progression [55–57]. Although we focused on pro- inflammatory markers in the current investigation, additional research that encompasses anti-inflammatory markers is also needed, as anti-inflammatory cytokines may disrupt proteostasis underlying neurodegeneration in ways that may currently be underappreciated. Taken together, both suppression and/or activation of the immune response may yield negative and/or positive effects, and additional research is needed to clarify key functions of immune activation along the spectrum of normal to pathological aging trajectories.

As noted by Golde [28], it may be beneficial to move away from the somewhat oversimplified dichotomization of pro- and anti-inflammatory cascades into a lexical description of “immune response” that ultimately elevates the complex and variable function of the immune system in disease states.

In contrast, despite the fact that elevated PP has been linked to greater levels of amyloid and tau in other studies of adults [58, 59], we found that PP was associated with CSF tau in our CN, but not MCI, group. Importantly, there is some evidence to suggest that the negative effects of PP on AD protein accumulation are age-dependent, with the independent effects of PP being most evident in the fifth and sixth decade of life [58]. The mean age of both CN and MCI groups was in the mid-seventies and we may not be capturing what may be earlier effects of influences of vascular disease on AD processes. Alternatively, it is important to note that the groups display similarly low levels of vascular risk, and findings may differ among individuals with greater levels of vascular disease burden, especially given that the ADNI primarily excludes individuals with high vascular risk. Other vascular markers (e.g., cerebral blood flow) may alternatively be more strongly associated with AD biomarkers in individuals in the CN and MCI stage. Moreover, findings might vary with the use of other amyloid metrics such as CSF $A\beta_{40}$ or $A\beta_{40/42}$ concentrations, which are not currently publicly available for download and exploration from Elecsys immunoassay metrics of ADNI 1 cohort participants.

There are several limitations to our study that warrant careful consideration. First, this was a relatively healthy, homogenous sample of predominantly educated, older White adults, which is not reflective of the United States larger racial and ethnic demographics. While ADNI provides a unique opportunity to characterize AD pathological processes using sophisticated novel biomarkers, there is an ever-pressing and critical need to better understand how sociodemographic factors may influence AD and its risks (e.g., access to healthcare, quality of education, prolonged stress) in more representative samples, and thus the generalizability of these findings to diverse samples are likely limited. How vascular risk, inflammation, and AD risk differ across different racial groups in an effort to better understand factors driving these disparities is clearly needed (see [60]). Second, this sample was a relatively healthy sample with generally low levels of vascular risk and findings may differ in those with greater vascular disease risk burden. Third, only a small subsample of participants from the initial ADNI cohort had analyzed CSF inflammatory markers available for use and dataavailability or selection bias may be an important factor to consider. Although its currently difficult to explore potential factors, as information pertaining to the sub-selection of these participants is limited and not clearly delineated in the accompanying Hu laboratory methods document available within the ADNI data portal, more aggressive brain pathology as indexed by neuroimaging metrics (e.g., hippocampal volume loss) have been noted within ADNI when compared to another population-based sample [61]. In order to ensure generalizability of these results, future work within the larger ADNI cohort, as well as other non-ADNI samples is needed, and efforts to explore analytic changes in estimates of CSF metrics with additional data should be reported. Strengths of the study include the creation of data-driven composite measures of pro-inflammatory markers and cognition in an effort to reduce the likelihood of Type I errors; the exploration of both independent and interactive effects of pulse pressure and inflammation; as well as the inclusion of parallel statistical analyses in CN and MCI individuals in order to better understand how pathological mechanisms differ across various stages of disease.

CONCLUSIONS

Our findings suggest that PP and inflammation exert differential effects on AD protein markers in individuals with and without MCI. While inflammation is associated with higher levels of $A\beta_{42}$ (indicative of lower cerebral amyloid burden) in CN individuals with low levels of vascular risk, this benefit is not observed in those with elevated levels of arterial stiffening. Moreover, the combination of elevated vascular risk and inflammation appear to be associated with greater tau levels in older adults with MCI. Results highlight that vascular risk and inflammation may be beneficial intervention targets, particularly when both are elevated, to slow or prevent AD pathogenesis. Future studies should clarify these findings in more racially diverse samples, as well as explore the influence of potential protective factors (e.g., exercise, sleep) in reducing inflammation, arterial stiffening, and associated AD pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank all participants of the Alzheimer's Disease Neuroimaging Initiative for providing data for this manuscript, as well as the individuals who work to make these data available for public use.

This work was supported by the U.S. Department of Veterans Affairs Clinical Sciences Research and Development Service (Merit Award 1I01CX001842 to K.J.B. and Career Development Award-2 1IK2CX 001865 to K.R.T.), NIA/NIH grants (R01 AG063782 to K.J.B.; R01 AG049810 and R01 AG054049 to M.W.B.), and the Alzheimer's Association (AARF-17–528918 to K.R.T. and AARG-18–566254 to K. J.B.).

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12–2–0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; BristolMyers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Eurolmmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc,; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

This work was further supported by a Veterans Affairs Advanced Polytrauma and TBI Rehabilitation Research Fellowship awarded to Dr. Clark.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-1382rl).

REFERENCES

[1]. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's

Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7, 280–292. [PubMed: 21514248]

[2]. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Elliott C, Masliah E, Ryan L, Silverberg N (2018) NIAAA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14, 535–562. [PubMed: 29653606]

[3]. Dosunmu R, Wu J, Basha MR, Zawia NH (2007) Environmental and dietary risk factors in Alzheimer's disease. Expert Rev Neurother 7, 887–900. [PubMed: 17610395]

[4]. Eid A, Mhatre I, Richardson JR (2019) Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. Pharmacol Ther 199, 173–187. [PubMed: 30877021]

[5]. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA (2006) Mediterranean diet, Alzheimer disease, and vascular mediation. Arch Neurol 63, 1709–1717. [PubMed: 17030648]

[6]. Yaffe K, Falvey C, Harris TB, Newman A, Satterfield S, Koster A, Ayonayon H, Simonsick E (2013) Effect of socioeconomic disparities on incidence of dementia among biracial older adults: Prospective study. BMJ 347, f7051. [PubMed: 24355614]

[7]. Braak H, Braak E (1995) Staging of alzheimer's diseaserelated neurofibrillary changes. Neurobiol Aging 16, 271–278. [PubMed: 7566337]

[8]. Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, Hampel H, Jagust WJ, Johnson KA, Knopman DS, Petersen RC, Scheltens P, Sperling RA, Dubois B (2016) A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 87, 539–547. [PubMed: 27371494]

[9]. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, Sepehrband F, Nelson AR, Buennagel DP, Harrington MG (2019) Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med 25, 270–276. [PubMed: 30643288]

[10]. Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, Lamb BT, Montine TJ, Nedergaard M, Schaffer CB (2015) Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimers Dement 11, 710–717. [PubMed: 25510382]

[11]. Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, Harrington MG, Pa J, Law M, Wang DJ (2019) Vascular dysfunction—The disregarded partner of Alzheimer's disease. Alzheimers Dement 15, 158–167. [PubMed: 30642436]

[12]. Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 14, 133. [PubMed: 29377008]

[13]. Yew B, Nation DA, Alzheimer's Disease Neuroimaging Initiative (2017) Cerebrovascular resistance: Effects on cognitive decline, cortical atrophy, and progression to dementia. Brain 140, 1987–2001. [PubMed: 28575149]

[14]. Montagne A, Nation DA, Pa J, Sweeney MD, Toga AW, Zlokovic BV (2016) Brain imaging of neurovascular dysfunction in Alzheimer's disease. Acta Neuropathol (Berl) 131, 687–707. [PubMed: 27038189]

[15]. Zlokovic BV, Griffin JH (2011) Cytoprotective protein C pathways and implications for stroke and neurological disorders. Trends Neurosci 34, 198–209. [PubMed: 21353711]

[16]. Pimentel-Coelho PM, Rivest S (2012) The early contribution of cerebrovascular factors to the pathogenesis of Alzheimer's disease. Eur J Neurosci 35, 1917–1937. [PubMed: 22708603]

[17]. Raz L, Knoefel J, Bhaskar K (2016) The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab 36, 172–186. [PubMed: 26174330]

[18]. Agostinho P, Cunha AR, Oliveira C (2010) Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. Curr Pharm Des 16, 2766–2778. [PubMed: 20698820]

[19]. Gao H-M, Hong J-S (2008) Why neurodegenerative diseases are progressive: Uncontrolled inflammation drives disease progression. Trends Immunol 29, 357–365. [PubMed: 18599350]

[20]. Laurent C, Buée L, Blum D (2018) Tau and neuroinflammation: What impact for Alzheimer's disease and tauopathies? Biomed J 41, 21–33. [PubMed: 29673549]

[21]. Metcalfe MJ, Figueiredo-Pereira ME (2010) Relationship between tau pathology and neuroinflammation in Alzheimer's disease. Mt Sinai J Med 77, 50–58. [PubMed: 20101714]

[22]. Vogels T, Murgoci A-N, Hromádka T (2019) Intersection of pathological tau and microglia at the synapse. Acta Neuropathol Commun 7, 109. [PubMed: 31277708]

[23]. Dani M, Wood M, Mizoguchi R, Fan Z, Walker Z, Morgan R, Hinz R, Biju M, Kuruvilla T, Brooks DJ (2018) Microglial activation correlates in vivo with both tau and amyloid in Alzheimer's disease. Brain 141, 2740–2754. [PubMed: 30052812]

[24]. Ismail R, Parbo P, Madsen LS, Hansen AK, Hansen KV, Schaldemose JL, Kjeldsen PL, Stokholm MG, Gottrup H, Eskildsen SF (2020) The relationships between neuroinflammation, beta-amyloid and tau deposition in Alzheimer's disease: A longitudinal PET study. J Neuroinflammation 17, 151. [PubMed: 32375809]

[25]. Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, Lamb BT, Bhaskar K (2015) Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. Brain 138, 1738–1755. [PubMed: 25833819]

[26]. Parbo P, Ismail R, Sommerauer M, Stokholm MG, Hansen AK, Hansen KV, Amidi A, Schaldemose JL, Gottrup H, Braendgaard H, Eskildsen SF, Borghammer P, Hinz R, Aanerud J, Brooks DJ (2018) Does inflammation precede tau aggregation in early Alzheimer's disease? A PET study. Neurobiol Dis 117, 211–216. [PubMed: 29902557]

[27]. Yoshiyama Y, Higuchi M, Zhang B, Huang S-M, Iwata N, Saido TC, Maeda J, Suhara T, Trojanowski JQ, Lee VMY (2007) Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. Neuron 53, 337–351. [PubMed: 17270732]

[28]. Golde TE (2019) Harnessing immunoproteostasis to treat neurodegenerative disorders. Neuron 101, 1003–1015. [PubMed: 30897353]

[29]. Chakrabarty P, Li A, Ceballos-Diaz C, Eddy JA, Funk CC, Moore B, DiNunno N, Rosario AM, Cruz PE, Verbeeck C (2015) IL-10 alters immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. Neuron 85, 519–533. [PubMed: 25619653]

[30]. Donato AJ, Machin DR, Lesniewski LA (2018) Mechanisms of dysfunction in the aging vasculature and role in age-related disease. Circ Res 123, 825–848. [PubMed: 30355078]

[31]. Grammas P (2011) Neurovascular dysfunction, inflammation and endothelial activation: Implications for the pathogenesis of Alzheimer's disease. J Neuroinflammation 8, 1–12. [PubMed: 21208419]

[32]. Govindpani K, McNamara LG, Smith NR, Vinnakota C, Waldvogel HJ, Faull RL, Kwakowsky A (2019) Vascular dysfunction in Alzheimer's disease: A prelude to the pathological process or a consequence of it? J Clin Med 8, 651.

[33]. Hall JR, Wiechmann AR, Johnson LA, Edwards M, Barber RC, Winter AS, Singh M, O'Bryant SE (2013) Biomarkers of vascular risk, systemic inflammation, and microvascular pathology and neuropsychiatric symptoms in alzheimer's disease. J Alzheimers Dis 35, 363–371. [PubMed: 23403534]

[34]. Petersen RC, Aisen P, Beckett LA, Donohue M, Gamst A, Harvey DJ, Jack C, Jagust W, Shaw L, Toga A (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. Neurology 74, 201–209. [PubMed: 20042704]

[35]. Eppig JS, Edmonds EC, Campbell L, Sanderson M, Delano-Wood L, Bondi MW, Alzheimer's Disease Neuroimaging Initiative (2017) Statistically-derived subtypes and associations with cerebrospinal fluid and genetic biomarkers in mild cognitive impairment: A latent profile analysis. J Int Neuropsychol Soc 23, 564. [PubMed: 28578726]

[36]. Thomas KR, Edmonds EC, Eppig JS, Wong CG, Weigand AJ, Bangen KJ, Jak AJ, Delano-Wood L, Galasko DR, Salmon DP (2019) MCI-to-normal reversion using neuropsychological criteria in the Alzheimer's Disease Neuroimaging Initiative. Alzheimers Dement 15, 1322–1332. [PubMed: 31495605]

[37]. Bondi MW, Edmonds EC, Jak AJ, Clark LR, DelanoWood L, McDonald CR, Nation DA, Libon DJ, Au R, Galasko D (2014) Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. J Alzheimers Dis 42, 275–289. [PubMed: 24844687]

[38]. Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, CoreyBloom J, Salmon DP, Delis DC (2009) Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry 17, 368–375. [PubMed: 19390294]

[39]. Andreasen N, Vanmechelen E, Vanderstichele H, Davidsson P, Blennow K (2003) Cerebrospinal fluid levels of total-tau, phospho-tau and A(342 predicts development of Alzheimer's disease in patients with mild cognitive impairment. Acta Neurol Scand 107, 47–51.

[40]. Blennow K, Vanmechelen E, Hampel H (2001) CSF total tau, $A\beta_{42}$ and phosphorylated tau protein as biomarkers for Alzheimer's disease. Mol Neurobiol 24, 87. [PubMed: 11831556]

[41]. Diniz BS, Pinto JA Jr, Forlenza OV (2008) Do CSF total tau, phosphorylated tau, and β-amyloid 42 help to predict progression of mild cognitive impairment to Alzheimer's disease? A systematic review and meta-analysis of the literature. World J Biol Psychiatry 9, 172–182. [PubMed: 17886169]

[42]. Seppälä T, Nerg O, Koivisto A, Rummukainen J, Puli L, Zetterberg H, Pyykkö O, Helisalmi S, Alafuzoff I, Hiltunen M (2012) CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. Neurology 78, 1568–1575. [PubMed: 22517093]

[43]. Yong AG, Pearce S (2013) A beginner's guide to factor analysis: Focusing on exploratory factor analysis. Tutor Quant Methods Psychol 9, 79–94.

[44]. Hsu F-C, Kritchevsky SB, Liu Y, Kanaya A, Newman AB, Perry SE, Visser M, Pahor M, Harris TB, Nicklas BJ (2009) Association between inflammatory components and physical function in the health, aging, and body composition study: A principal component analysis approach. J Gerontol Ser Biomed Sci Med Sci 64, 581–589.

[45]. Fan Z, Aman Y, Ahmed I, Chetelat G, Landeau B, Ray Chaudhuri K, Brooks DJ, Edison P (2015) Influence of microglial activation on neuronal function in Alzheimer's and Parkinson's disease dementia. Alzheimers Dement 11, 608–621.e7. [PubMed: 25239737]

[46]. Fan Z, Brooks DJ, Okello A, Edison P (2017) An early and late peak in microglial activation in Alzheimer's disease trajectory. Brain 140, 792–803. [PubMed: 28122877]

[47]. Rosas-Ballina M, Tracey K (2009) Cholinergic control of inflammation. J Intern Med 265, 663–679. [PubMed: 19493060]

[48]. Schmitz TW, Soreq H, Poirier J, Spreng RN (2020) Longitudinal basal forebrain degeneration interacts with TREM2/C3 biomarkers of inflammation in presymptomatic Alzheimer's disease. J Neuro sci 40, 1931–1942.

[49]. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 82, 239–259. [PubMed: 1759558]

[50]. Braak H, Thai DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. J Neuropathol Exp Neurol 70, 960–969. [PubMed: 22002422]

[51]. Cho H, Choi JY, Hwang MS, Kim YJ, Lee HM, Lee HS, Lee JH, Ryu YH, Lee MS, Lyoo CH (2016) *In vivo* cortical spreading pattern of tau and amyloid in the Alzheimer disease spectrum. Ann Neurol 80, 247–258. [PubMed: 27323247]

[52]. Feng R-Y, Chen Q, Yang W-J, Tong X-G, Sun Z-M, Yan H (2018) Immune tolerance therapy: A new method for treatment of traumatic brain injury. Chin Med J (Engl) 131, 1990–1998. [PubMed: 30082532]

[53]. Ji H, Liu Y, Zhang Y, Shen X, Gao F, Busuttil RW, Kuchroo VK, Kupiec-Weglinski JW (2014) T-cell immunoglobulin and mucin domain 4 (TIM-4) signaling in innate immunemediated liver ischemia-reperfusion injury. Hepatology 60, 2052–2064. [PubMed: 25066922]

[54]. Chakrabarty P, Tianbai L, Herring A, Ceballos-Diaz C, Das P, Golde TE (2012) Hippocampal expression of murine IL-4 results in exacerbation of amyloid deposition. Mol Neurodegener 7, 36. [PubMed: 22838967]

[55]. ADAPT-FS Research Group (2015) Follow-up evaluation of cognitive function in the randomized Alzheimer's Disease Anti-Inflammatory Prevention Trial and its follow-up study. Alzheimers Dement 11, 216–225.e1. [PubMed: 25022541]

[56]. ADAPT Research Group, Lyketsos CG, Breitner JCS, Green RC, Martin BK, Meinert C, Piantadosi S, Sabbagh M (2007) Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 68, 1800–1808. [PubMed: 17460158]

[57]. Soininen H, West C, Robbins J, Niculescu L (2007) Longterm efficacy and safety of celecoxib in Alzheimer's disease. Dement Geriatr Cogn Disord 23, 8–21. [PubMed: 17068392]

[58]. Nation DA, Edland SD, Bondi MW, Salmon DP, DelanoWood L, Peskind ER, Quinn JF, Galasko DR (2013) Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults. Neurology 81, 2024–2027. [PubMed: 24225352]

[59]. Shi W-Y, Wang Z-T, Sun F-R, Ma Y-H, Xu W, Shen X-N, Dong Q, Tan L, Yu J-T, Yu Y (2020) High pulse pressure is a risk factor for prodromal Alzheimer's disease: A longitudinal study. Aging 12, 18221. [PubMed: 32960784]

[60]. Babulal GM, Quiroz YT, Albensi BC, Arenaza-Urquijo E, Astell AJ, Babiloni C, Bahar-Fuchs A, Bell J, Bowman GL, Brickman AM (2019) Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. Alzheimers Dement 15, 292–312. [PubMed: 30555031]

[61]. Whitwell JL (2012) Comparison of imaging biomarkers in the Alzheimer Disease Neuroimaging Initiative and the Mayo Clinic Study of Aging. Arch Neurol 69, 614. [PubMed: 22782510]

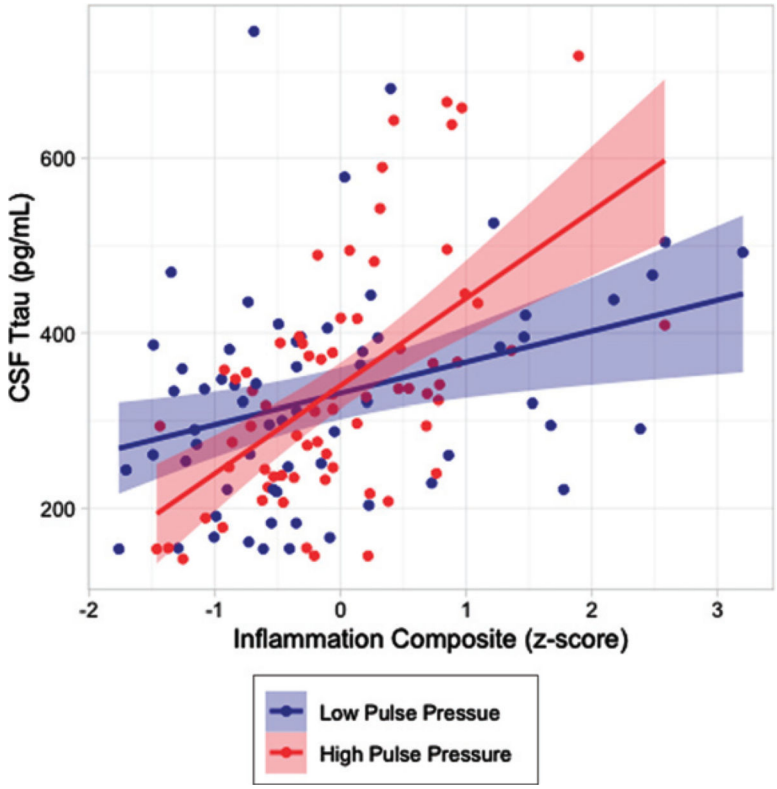

Fig. 1.

PP x inflammation on CSF T-tau within the MCI group. PP, pulse pressure; MCI, mild cognitive impairment; CSF, cerebrospinal fluid. CSF T-tau (pg/mL) is depicted on the y-axis. The inflammatory composite is on the x-axis (z-score). The red dots and line represent the association inflammation and t-tau within the high pulse pressure group for MCI participants. The blue dots and line represent the association inflammation and t-tau within the low pulse pressure group for MCI participants.

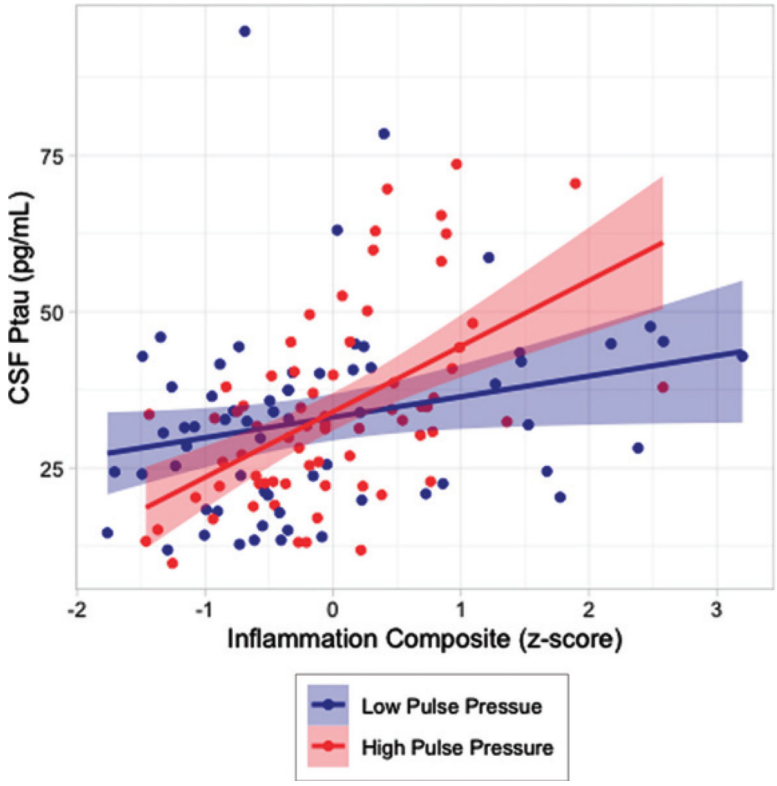

Fig. 2.

PP x inflammation on CSF P-tau within the MCI group. PP, pulse pressure; MCI, mild cognitive impairment; CSF, cerebrospinal fluid. CSF P-tau (pg/mL) is depicted on the y-axis. The inflammatory composite is on the x-axis (z-score). The red dots and line represent the association inflammation and p-tau within the high pulse pressure group for MCI participants. The blue dots and line represent the association inflammation and p-tau within the low pulse pressure group for MCI participants.

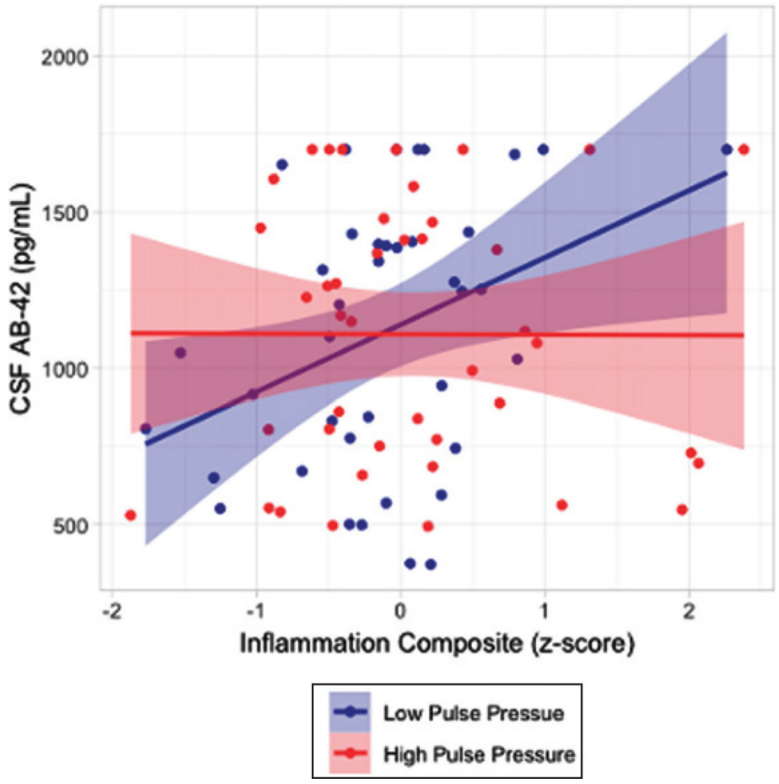

Fig. 3.

PP x inflammation on CSF AB-42 within the CN group. PP, pulse pressure; CN, cognitively normal; CSF, cerebrospinal fluid. CSF AB-42 (pg/mL) is depicted on the y-axis. The inflammatory composite is on the x-axis (z-score). The red dots and line represent the association inflammation and AB-42 within the high pulse pressure group for CN participants. The blue dots and line represent the association inflammation and AB-42 within the low pulse pressure group for CN participants.

J Alzheimers Dis. Author manuscript; available in PMC 2022 April 29.

Table 1

Participant demographics and clinical characteristics

	Total sample N = 218		**CN N = 81**		**MCI N = 137**		***F* or χ^2**	***p***
	Mean or %	**SD**	**Mean or %**	**SD**	**Mean or %**	**SD**		
Age, y	74.75	7.24	75.22	6.02	74.47	7.59	$F = 0.55$	0.46
Education, y	15.50	3.02	16.21	2.98	15.07	2.97	$F = 7.41$	**0.007**
Women, %	43	–	43	–	42	–	$\chi^2 = 0.01$	0.90
Race/ethnicity, %							$\chi^2 = 3.92^{\wedge}$	0.14
Black	4	–	6	–	2	–		
Asian	1	–	0	–	2	–		
White	95	–	94	–	96	–		
CSF $A\beta_{42}$ total, pg/mL	868.02	429.58	1110.46	424.76	724.64	364.15	*F = 50.40*	< **0.001**
CSF t-tau total, pg/mL	300.98	123.08	245.90	88.61	333.85	129.16	$F = 28.93$	< **0.001**
CSF p-tau total, pgmL	29.53	14.21	23.03	9.70	33.42	14.21	$F = 30.49$	< **0.001**
*APOE ε*4+, %	50	–	30	–	61	–	$\chi^2 = 20.44$	< **0.001**
CSF Aβ+, %	72	–	47	–	86	–	$\chi^2 = 38.47$	< **0.001**
CSF t-tau+, %	63	–	43	–	75	–	$\chi^2 = 20.09$	< **0.001**
CSF p-tau+, %	74	–	58	–	84	–	$\chi^2 = 17.63$	< **0.001**
MMSE total score	26.60	2.67	28.42	1.77	25.52	2.53	$F = 82.09$	< **0.001**
Vascular risk								
Pulse pressure, mmHg	58.54	15.66	56.90	15.11	59.59	15.96	$F = 1.42$	0.24
Diabetes history, %Y	6	–	5	–	7	–	$\chi^2 = 0.24$	0.62
Smoking history, %Y	45	–	44	–	45	–	$\chi^2 = 0.01$	0.91
Cardiac history, %Y	6	–	5	–	7	–	$\chi^2 = 0.24$	0.62
Hachinski score total	0.58	0.69	0.63	0.72	0.55	0.67	$F = 0.60$	0.44
Pro-inflammatory composite	−0.03	0.95	−0.01	0.83	−0.05	1.00	$F = 0.70$	0.79
Language composite, z-score	−0.97	1.27	−0.18	0.68	−1.45	1.31	$F = 65.81$	< **0.001**
Memory composite, z-score	−1.73	1.31	−0.40	0.79	−2.51	0.84	$F = 334.49$	< **0.001**
Attention/executive composite, z-score	−1.16	1.92	−0.01	0.70	−1.84	2.08	$F = 57.66$	< **0.001**

F statistic reported for one-way ANOVAs; χ^2 statistic report for chi-square tests

^ denotes utilization of the Likelihood Ratio.

CN, cognitively normal; MCI, mild cognitive impairment; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; Aβ, amyloid-beta. Please note 4 MCI subjects were missing t and p-tau data due to sample degradation. 1 CN subject and 1 MCI subject were considered outliers and excluded from analyses with the language and attention/executive composite. Please note the reported statistics for CSF levels of amyloid and tau within the table slightly differenced from within-text statistics which included covariates and utilized ANCOVAs.

Table 2A

Pearson's correlations between individual CSF inflammatory and AD markers within the MCI group

	IL-9	IP-10	TNFR1	TNFα	ICAM-1	VCAM-I
$A\beta_{42}$	r = 0.19	r = 0.13	r = 0.18	r = 0.04	r = 0.02	r = 0.17
	$p = 0.03^{*}$	$p = 0.12$	$p = 0.04^{*}$	$p = 0.64$	$p = 0.85$	$p = 0.05$
t-tau	r = 0.31	r = −0.04	r = 0.56	r = 0.05	r = 0.31	r = 0.38
	$p < 0.001^{**}$	$p = 0.69$	$p < 0.001^{**}$	$p = 0.58$	$p < 0.001^{**}$	$p < 0.001^{**}$
p-tau	r = 0.26	r = −0.07	r = 0.51	r = 0.04	r = 0.28	r = 0.31
	$p = 0.001^{**}$	$p = 0.42$	$p = 0.001^{**}$	$p = 0.62$	$p = 0.001^{**}$	$p = 0.001^{**}$

Please note that $n = 134$ for inflammation, t-tau, and p-tau data as samples degraded for 3 subjects; $n = 137$ for inflammation and amyloid comparisons

$^{*}p < 0.05$

$^{**}p < 0.005$.

Table 2B

Pearson's correlations between individual CSF inflammatory and AD markers within the CN group

	IL-9	IP-10	TNFR1	TNFα	ICAM-1	VCAM-I
$A\beta_{42}$	r = 0.23	r = 0.21	r = 0.25	r = −0.10	r = 0.12	r = 0.15
	$p = 0.03^{*}$	$p = 0.05$	$p = 0.02^{*}$	$p = 0.37$	$p = 0.29$	$p = 0.17$
t-tau	r = 0.31	r = 0.15	r = 0.70	r = 0.28	r = 0.31	r = 0.31
	$p < 0.005^{**}$	$p = 0.29$	$p < 0.001^{**}$	$p = 0.01^{*}$	$p < 0.005^{**}$	$p < 0.005^{**}$
p-tau	r = 0.26	r = 0.08	r = 0.60	r = 0.26	r = 0.28	r = 0.28
	$p = 0.02^{*}$	$p = 0.52$	$p < 0.001^{**}$	$p = 0.02^{*}$	$p = 0.01^{*}$	$p = 0.01^{*}$

Please note that $n = 80$ for inflammation, t-tau, and p-tau data as samples degraded for 1 subject; $n = 81$ for inflammation and amyloid comparisons

$^{*}p < 0.05$

$^{**}p < 0.005$.