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Soluble TREM2 and Biomarkers of Central and Peripheral Inflammation in Neurodegenerative Disease

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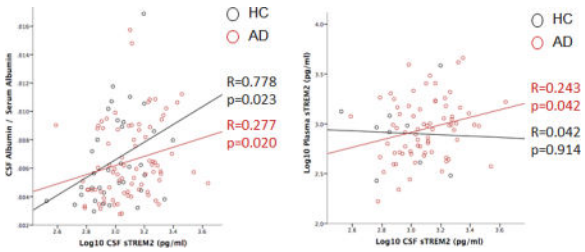
Abstract

Alzheimer's disease (AD) has been genetically and pathologically associated with neuroinflammation. Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglial receptor involved in innate immunity. TREM2 rare protein coding genetic variants have been linked to AD. A soluble TREM2 (sTREM2) cleavage product is elevated in AD. It is unclear whether there is a relationship between elevated sTREM2 and markers of inflammation. The hypothesis of this investigation was that central and peripheral inflammation play a role in sTREM2 levels in AD. A consistent association of peripheral or central markers of inflammation and CSF sTREM2 levels was not found, suggesting a limited impact of general inflammation on sTREM2 levels. An association between peripheral sTREM2 levels and CSF sTREM2, as well as an association between CSF sTREM2 and a marker of blood brain barrier integrity, was observed in AD, suggesting a potential role of peripheral TREM2 in central TREM2 biology.

Graphical abstract



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A correlation between CSF sTREM2 and blood brain barrier integrity was observed. Furthermore, CSF sTREM2 correlated with plasma sTREM2 in AD. Taken together, these results implicate a potential role of peripheral TREM2 in central TREM2 biology in AD.

Introduction

Triggering receptor expressed on myeloid cells 2 (TREM2) is part of the immunoglobulin-lectin-like receptor superfamily. The *TREM2* gene is part of a family of receptors that are clustered together on human chromosome 6. These receptors participate in various cellular processes such as inflammation, phagocytosis, bone homeostasis, and neural development (1–3). Genetic mutations in TREM2 cause the autosomal recessive disorder Nasu-Hakola disease (also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy), (4, 5). Carriers of the TREM2 R47H genetic variant have an increased risk for developing Alzheimer's disease (AD) (6, 7) and have a possible, but inconsistent increased risk for Parkinson's disease (PD) (8, 9).

TREM2 is expressed on the cell surface of microglia, macrophages, osteoclasts, and dendritic cells, as well as bronchial epithelial cells, fibroblasts, and lung adenocarcinoma cells (10). TREM2 is involved in the activation of monocyte-derived dendritic cells, osteoclast development, enhancement of chemotaxis, and reduction of pro-inflammatory cytokine release while promoting anti-inflammatory cytokine expression (11, 12). In the brain, TREM2 is expressed mainly in microglial cells and has been linked to phagocytosis, cell growth, regulation of actin cytoskeleton, migration towards chemokines, and cytokine release (13, 14). Ligands for TREM2 have not been verified to date; however, there is evidence that TREM2 interacts with apolipoproteins such as apoE and apoJ, Aβ, various anions, lipids, and hsp60 (15–18).

TREM2 transcripts and protein levels in blood and brain are elevated in AD patients compared to cognitively normal controls. (19, 20) TREM2 isoforms have been described including alternatively spliced isoforms and an isoform that is the result of cleavage at the membrane-spanning domain by ADAM10 or ADAM17 to produce a soluble TREM2 (sTREM2) protein fragment (20–25). These isoforms have been described in various human biofluids, tissues and cell types, such as cerebrospinal fluid (CSF), plasma, monocytes, microglia and brain (20–25). Some reports describe sTREM2 as increased in the CSF of AD patients, (26–28) while others report sTREM2 as decreased or unchanged in AD (29, 30). To our knowledge, sTREM2 levels in PD have not been reported previously. It has been suggested that sTREM2 promotes microglial survival and stimulates the production of innate immunity factors (17). However, the function of sTREM2 is still unclear.

Given that TREM2 is associated with neurodegenerative disease and is involved in innate immunity, we evaluated the relationship between CSF and plasma sTREM2 levels and biomarkers of inflammation and integrity of the blood brain barrier (BBB) in normal controls and patients with mild cognitive impairment (MCI), AD and PD. Our hypothesis was that central and peripheral inflammation influence CSF sTREM2 levels in neurodegenerative disorders.

Materials and Methods

Cerebrospinal fluid and Plasma Samples

Cerebrospinal fluid (CSF), plasma and DNA were collected from the institutional review board approved Lou Ruvo Center for Brain Health Aging and Neurodegeneration Biobank (CBH-Biobank). CSF, plasma and DNA samples from the CBH-Biobank included healthy cognitively normal healthy controls (HC), and patients with mild cognitive impairment (MCI), Alzheimer's disease (AD), and Parkinson's disease (PD; Table 1). All individuals entered into the CBH-Biobank undergo clinical evaluation, including neurological examination and neuropsychological testing, and collection of blood including plasma, serum, whole blood, DNA, and RNA. A subset of these individuals (approximately 40%) undergo coincident lumbar puncture with CSF undergoing measurments of Aβ42, total-tau, and phosphorylated tau (Figure 1).

Cerebrospinal fluid and Plasma Analyte Measurement

CSF and plasma soluble TREM2 (sTREM2) levels were measured using a Luminex 200 3.1 xPONENT System (EMD Millipore, Chicago, IL, USA) and a custom designed detection method designed to capture the soluble portion of TREM2 protein (sTREM2). A capture antibody bound to MagPlex bead binds sTREM2 (R&D #MAB1828 human TREM2 antibody monoclonal mouse IgG_{2B} Clone #263602; Immunogen His19-Ser174). A biotinylated antibody with a SAPE conjugate was used for detection (R&D: #BAF1828; human TREM2 biotinylated antibody; antigen affinity-purified polyclonal goat IgG; Immunogen His19-Ser174). Inflammation biomarkers were measured using Cleveland Clinic Clinical Chemistry services and included markers for blood brain barrier disruption CSF Albumin / Serum Albumin (31–33), central nervous system inflammation (Tortellotte Test including CNS IgG synthesis and IgG Index), and markers of peripheral inflammation including high-sensitivity C-reactive protein (CRP), erythrocyte sedimentation rate (sedimentation rate) and white blood cell count (WBC). CSF AD biomarkers were measured using the Luminex 200 xMap technology and the MILLIPLEX MAP® multiplex kit (Luminex xMAP technology; EMD Millipore, Chicago, IL, USA) following the manufacturer's instructions for $Aβ_{42}$, Total-tau (T-Tau) and phosphorylated-tau 181 (P-Tau) detection.

Genetic Analysis

Three genetic variants were selected based on their close proximity or location within the TREM2 gene and their reported significance in previous genetic studies. Given the small sample size, two of these variants were selected because of a high frequency in the general population. One variant, rs75932628 (R47H), was selected because of its strong association with AD, even though it is rare. The strongly AD associated rs75932628 (R47H) variant is located in exon 2 (risk allele T frequency is 0.0063) (6, 7). The two other genetic variants included were rs7748513 within TREM2 intron 2, that has been previously described as associated with CRP levels (risk allele G frequency is 0.432), (34) and the rs9381040 variant located in an intergenic region upstream from TREM2 that was identified in an AD meta-analysis (risk allele C frequency is 0.703) (35). The TaqMan genotyping method was used as previously described (36).

Statistical Analyses

Statistical analyses included one-way ANOVA with post-hoc Fisher's LSD to compare protein level means between patient groups. Linear regression analyses were used to demonstrate a correlation between proteins. Prism (GraphPad Software Inc. Version 6) and SPSS software were used for these analyses.

Results

Cohort and CSF AD Biomarkers

To demonstrate that the cohort (Table 1) had typical patterns of AD biomarkers, CSF $A\beta_{42}$ T-Tau and P-Tau levels, were compared between all patient groups (HC, MCI, AD, PD) using ANOVA both with and without post-hoc correction for multiple comparisons (Fig1, Supplemental Table 1). As expected, CSF $A\beta_{42}$ levels were significantly lower in MCI and AD compared to HC and PD (Fig1A). CSF T-Tau levels were significantly higher in MCI and AD compared to HC and PD respectively, as well as in AD compared to MCI (Fig1B). CSF P-Tau levels were significantly higher in MCI and AD compared to HC and PD respectively, as well as in AD compared to MCI (Fig1C).

CSF and Plasma Soluble TREM2 Levels, Age and Disease State

To determine if CSF or plasma sTREM2 levels differed by disease status all patient groups (NC, MCI and AD) were compared (Supplemental Table 1). CSF sTREM2 levels in MCI and AD were significantly elevated compared to HC (Fig2A). Plasma sTREM2 Levels were not significantly different between disease groups (Fig2B: Supplemental Table 2). CSF sTREM2 was associated with age in the group as a whole, but not upon stratification by disease group (Fig2C: Table 2G). Plasma sTREM2 and CSF sTREM2 were significantly correlated in AD and for the group as a whole (Fig2D: Table 2G).

CSF sTREM2 and CSF AD Biomarkers

To evaluate the relationship between CSF sTREM2 levels and central AD pathobiobiology, CSF sTREM2 was correlated with AD biomarkers; CSF Aβ42, CSF total tau (t-tau), and CSF phosphorylated tau (p-tau) (Fig3: Table 2A). CSF sTREM2 levels significantly positively correlate with CSF Aβ42 in HC and AD (Fig3A). CSF sTREM2 levels significantly positively correlated with CSF T-tau levels in AD as well as in the group as a whole (Fig3B). CSF sTREM2 levels did not significantly correlate with CSF P-tau levels (Fig3C). Plasma sTREM2 did not significantly correlate with CSF AD-related biomarkers (Table 2B).

CSF sTREM2 and Biomarkers of Central Nervous System Inflammation

To evaluate the relationship between CSF sTREM2 levels and central Inflammation, CSF sTREM2 was correlated with CSF Albumin/Serum Albumin ratio, CSF IgG synthesis and IgG index in individuals that had a CSF and a blood draw on the same day (Fig4: Table 2C). CSF sTREM2 levels significantly correlated with the blood brain barrier (BBB) integrity biomarker CSF Albumin/Serum Albumin ratio in HC and in AD as well as in the groups as a whole (Fig4A) but not CNS IgG synthesis (Fig4B) or IgG Index in any of the groups tested

or in the group as a whole (Fig4C). There was a significant correlation between CSF albumin / serum albumin level and Abeta42 (p= 0.005), p-tau (p=0.005), but not t-tau (p=0.283) in the group as a whole (data not shown). Plasma sTREM2 levels were not correlated with the CSF Albumin/Serum Albumin ratio, CNS IgG Synthesis, or IgG Index (Table 2D). Alone CSF Albumin/Serum Albumin ratio or CNS IgG synthesis were not significantly different between groups. PD IgG Index was significantly lower compared to MCI (p=0.0245) and AD (p=0.0321) after outlier removal and without correction for multiple comparison (Supplemental Table 3).

CSF sTREM2 and Biomarkers of Peripheral Inflammation

To evaluate the relationship between CSF sTREM2 levels and peripheral inflammation, CSF sTREM2 was correlated with biomarkers of peripheral inflammation including high-sensitivity C-reactive protein (CRP), sedimentation rate, and white blood cell count (WBC) (Fig5: Table 2E). CSF sTREM2 levels did not significantly correlate with CRP in any group (Fig5A) and were not different between groups (Supplemental Table 2). CSF sTREM2 levels significantly correlated with sedimentation rate in MCI (Fig5B) and with WBC in HC (Fig5C), but not in any other group (Table 2E). Only subjects that had a blood draw on the same day as CSF were included in the correlation analyses.

Plasma sTREM2 and Peripheral Biomarkers of Inflammation

To evaluate the relationship between plasma sTREM2 levels and peripheral inflammation, plasma sTREM2 was correlated with biomarkers of peripheral inflammation including CRP, sedimentation rate, and WBC. Plasma sTREM2 levels were significantly correlated with CRP in MCI and PD (Fig6A), sedimentation rate in AD (Fig6B), but not with white blood cell count (WBC) in any group (Fig6C) (Table 2F). Biomarkers of peripheral inflammation were also compared between disease groups (Supplemental Table 2). Sed rate was higher in AD compared to PD (p=0.0190) and WBC MCI was higher than HC (p=0.0108) and lower compared to AD (p=0.0012) (ANOVA uncorrected Fisher's LSD: Supplemental Table 2).

sTREM2 Levels and *TREM2* Genotype

The relationship between CSF or plasma sTREM2 levels and three GWAS genetic variants was evaluated (see Methods Section). Only rs7748513 was associated with increased CSF sTREM2 levels. None of the three variants tested were associated with plasma sTREM2 levels. Genetic variants were collapsed into carriers positive for the minor allele and compared to the most common genotype for individuals with CSF sTREM2; rs7748513 (allele G+: HC n=2, MCI n=6, AD n=10, PD n=2), rs75932628 (R47H allele T+: HC n=2, MCI n=1, AD n=1, PD n=0) and rs9381040 (allele T+: HC n=16, MCI n=18, AD n=45, PD n=14). CSF sTREM2 levels (Supplemental Table 4), but not plasma sTREM2 (Supplemental Table 5), were elevated in carriers of rs7748513 risk allele (G allele) compared non-carriers, in the group as a whole with (p=0.026) and without taking into account covariates (disease status, sex, age and *APOE* ε4: p=0.053) (Fig7A). This significant elevation remains after exculsion of rs75932628 R47H T allele carriers (data not shown; without taking into account covariates p=0.048). In addition, since our cohort has a different frequency of *APOE* ε4 compared to previous reports evaluating sTREM2 levels in AD, (26, 28) CSF and plasma sTREM2 levels were compared between *APOE* ε4 carriers and non-carriers. No significant

differences related to *APOE* ε4 were identified within each patient group or in the group as a whole (data not shown).

The other inflammatory markers were also evaluated for differences between rs7748513 genotypes. CRP levels were marginally different where rs7748513 G+ carriers had higher levels with (p=0.060) and without taking into account covariates (p=0.078) (Supplemental Table 5). IgG Index was significantly higher in G+ carriers both with (p=0.004) and without taking into account covariates (p=0.002) (Fig7B: Supplemental Table 6).

Discussion

It is increasingly recognized that the inflammatory system plays a role in the pathobiology of AD and other neurodegenerative diseases. How the inflammatory system interacts both peripherally and centrally to influence neurodegeneration is, as yet, unclear. The overall aim of this investigation was to examine one aspect of the inflammatory system strongly linked to AD, TREM2, and it's relationship to central and peripheral biomarkers of inflammation and BBB integrity.

We found that CSF sTREM2 levels were significantly elevated in both MCI and AD compared to cognitively normal controls (HC), but plasma sTREM2 levels were not significantly different between disease groups. These results are consistent with a number of previous reports (26–28). There has also been a suggestion of a relationship between PD and TREM2 (8, 9). We did not observe an altered level of CSF or plasma sTREM2 in our PD sample. However, we did observe a significant correlation between CRP levels and plasma sTREM2 levels in PD.

Elevated CSF sTREM2 in MCI and AD continues to support the increasingly recognized role for TREM2 in the pathobiology in AD, which is consistent with the genetic link of TREM2 variants and increased risk for AD. CSF sTREM2 was positively correlated with Aβ42 and t-tau, but not p-tau in AD. This result is supported by another report where a positive correlation between CSF Aβ42 and CSF sTREM2 was described (30). However, it differs from other reports that describe a significant positive correlation between CSF sTREM2 and CSF t-tau and p-tau, but no correlation with CSF Aβ42 (26, 28, 37). The reason for the differences between our study and these previous studies is unknown but may include cohort differences in frequency of *APOE* ε4 or other factors. Notably, a relationship between *APOE* ε4 status and sTREM2 levels was not found in our cohort. In addition, no significant differences in inflammatory markers in *APOE* ε4 carriers, compared to non-carriers, were identified either within each patient group or in the group as a whole (data not shown). Taken together, this discrepancy between our results and results by others may be related to small sample size of our cohort, *APOE* ε4 frequency or the age of our cohort..

We observed, when all groups were combined, an age-associated modest increase in CSF sTREM2, which has been reported by others. (26–28, 30, 37, 38) This could be driven by the increasing risk of AD pathology across groups with increased age, or there may be a link between the aging process and changes in the TREM2 linked inflammatory system.

CSF sTREM2 was positively correlated with plasma sTREM2 across all groups, but only for AD in the subgroup analysis. Others have showed an increasing positive correlation between CSF sTREM2 and plasma sTREM2 that was not significant which may reflect differences between study cohorts. (28) It is unknown what might drive this positive correlation. However, the positive correlation between CSF sTREM2 and plasma sTREM2 in our AD group, but not the other groups, may suggest that AD pathobiology drives this correlation. In this context, it is interesting that we also found that CSF sTREM2 was significantly correlated with a marker of BBB disruption (CSF Albumin / Serum Albumin ratio) in both HC and AD. These results raise the possibility that disruption of the BBB may account for the relationship observed between peripheral and central sTREM2 levels. In support of this concept, other reports suggest that the peripheral TREM2 system (2, 3, 39) as well as the BBB (40, 41) play a role in AD pathobiology.

The mechanism underlying a relationship between TREM2 and BBB integrity in both HC and AD is difficult to interpret. While others have described a difference in BBB integrity between AD and healthy controls (42) in our cohort BBB integrity was not significantly different between HC and AD. However, there was a significant association between CSF albumin / serum albumin level and Abeta42 as well as p-tau in the group as a whole suggesting that there is a relationship between BBB integrity and AD pathobiology. The lack of a significant difference between AD and HC in our cohort may reflect small sample size. A relationship between CSF Abeta42 and CSF sTREM2 in both AD and HC suggests that CSF sTREM2 levels are related to underlying AD pathology prior to AD clinical symptoms. Interestingly, since CSF sTrem2, but not plasma sTREM2, significantly correlates with BBB disruption in both HC and AD and there is a significant association between CSF sTREM2 and plasma sTREM2 in AD, but not HC, it is possible that sTREM2 passes the BBB by either clearance from the CNS into periphery, or passage from the periphery into the CNS. However, either way, it appears that this may occur differently in AD compared to HC and suggests that sTREM2 passage across the BBB might be a later event in AD progression.

A loss of BBB integrity relationship with AD and AD-related traits has been described by some (41–44) but not all (40, 45) and has been associated with accumulation of blood-derived proteins in the brain (e.g., immunoglobulins, fibrinogen, and thrombin). (46–48) In addition, peripheral monocytes have been described surrounding amyloid plaques in the brain. (45) It is still unclear whether changes in BBB permeability influence AD progression.

Overall, CSF sTREM2 levels had only a few significant correlations with biomarkers of central and peripheral inflammation suggesting a limited relationship between more generalized inflammation and sTREM2 biology in the brain. Even though there was an inconsistent association between sTrem2 and markers of peripheral inflammation, there were several interesting pieces of data that suggest a possible association between sTREM2 and peripheral inflammation. For example, in MCI there was an association between CSF sTrem2 and sedimentation rate as well as an association with white blood cell count (WBC) in HC. In addition, while not significant, there were trends toward an association between CSF sTrem2 and CRP as well as sedimentation rate in all groups combined. Furthermore, there was a correlation between plasma sTrem2 and CRP within the MCI and PD groups,

but not HC or AD emphasizing the importance of continuing investigation into the relationship between peripheral and central inflammatory factors in MCI and PD. These results are supported by a previous report that describes no significant differences in plasma CRP between AD and control groups and no correlation between plasma CRP levels and CSF sTREM2 levels in AD or controls. (27)

Previous studies support the notion that peripheral inflammatory factors might play a role in central nervous system inflammatory response. Studies in AD mouse models suggest that the TREM2-dependent activation of microglia is required to limit Aβ pathology depending on the age of the animals. (2, 3, 49–52) Emerging evidence suggests that TREM2+ cells sense Aβ accumulation and neuronal degeneration, which then triggers signals that activate microglia. (52) A microglial repopulation model revealed a robust homeostatic process for replacing central myeloid cells. (53) However, an opposing unclear impact of TREM2 on resident microglia by peripherally derived macrophages in AD mouse models appears to be complicated by a relationship with age. (3, 54) Others have reported that replacing resident microglia with peripherally derived myeloid cells does not impact pathology in AD mouse models. (55) Microglial and astrocyte chemokine regulation of monocyte migration through the BBB has been reported in other diseases, such as in human immunodeficiency virus-1 encephalitis. (56) However, in AD, how peripheral TREM2+ cells might play a role in the brain remains a critical question.

The AD GWAS risk allele for rs7748513 (G allele), but not the other SNPs tested, was associated with higher CSF sTREM2 levels, but not plasma sTREM2, as well as a marginal association with CRP levels and a significant association with IgG index. A relationship between CRP levels and rs7748513 has been previously reported. (34) The rs7748513 is located in intron 2 and may not be a functional variant but instead a surrogate marker for another TREM2 genetic variant not evaluated here. Of note, rs7748513 is located within a CTCF zinc finger transcription factor site identified in both K562 and GM12878 cells via a functional digital analysis of noncoding elements and chromatin structure. (57) CTCF is a sequence specific DNA binding protein that can function as an insulator, blocking enhancer activity. CTCF has also been suggested to block the spreading of chromatin structure in certain instances. (57) In addition, the rs7748513 variant is within a described DNase hypersensitive area (58) and a SINE of the MRIc type (59) suggesting that this region may play a role in gene regulation. How this *TREM2* genetic variant impacts TREM2 expression or levels of other proteins such as CRP or the IgG index remains to be determined. A limitation of this exploratory part of our study was the small sample size for TREM2 genetic variant carriers. Therefore, further replication in other cohorts is needed to verify these results.

Taken together, our results continue to support an important role of TREM2 in the pathobiology of AD. The results also implicate a potential role for peripheral TREM2 signalling and breakdown of the BBB in AD suggesting that modifying the TREM2-linked inflammatory system both in the CNS and periphery has the potential to impact the pathobiology and clinical course of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- We confirmed previous findings of elevated CSF sTREM2 in Mild Cognitive Impairment and Alzheimer's disease.
- Overall, CSF sTREM2 levels had only a few significant correlations with biomarkers of central and peripheral inflammation suggesting a limited relationship between more generalized inflammation and sTREM2 biology in the brain.
- There were significantly positive correlations between CSF sTREM2 and plasma sTREM2 and between CSF sTREM2 and a marker for blood brain barrier integrity.
- Taken together, these results suggest there is a potential role of peripheral TREM2 in central TREM2 biology that is unrelated to general inflammation in the periphery.

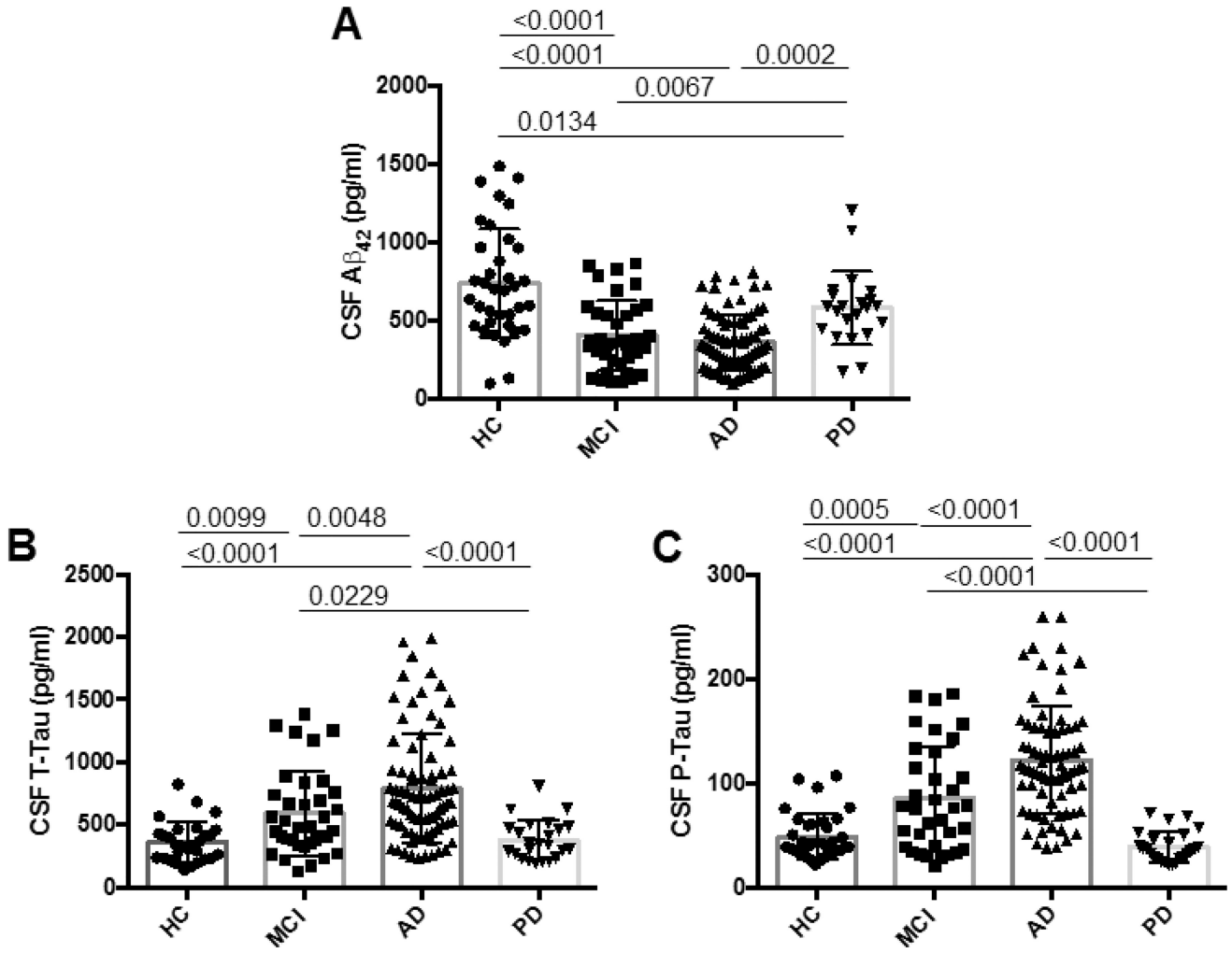

Figure 1. CSF AD Biomarkers

CSF $A\beta_{42}$ levels are significantly lower in MCI ($p<0.0001$; $p=0.0067$) and AD ($p<0.0001$; $p=0.002$) compared to HC and PD respectively. PD is lower than HC ($p=0.0134$) **(A).** CSF T-Tau levels are significantly higher in MCI ($p=0.048$) and AD ($p<0.0001$; $p<0.0001$) compared to HC and PD respectively, as well as in AD ($p=0.0245$) compared to MCI **(B).** CSF P-Tau levels are significantly higher in MCI ($p=0.0027$; $p=0.0003$) and AD ($p<0.0001$; $p<0.0001$) compared to HC and PD respectively, as well as in AD ($p=0.0003$) compared to MCI **(C).** Graphs and p-values are one-way ANOVA uncorrected Fisher's LSD derived after removal of outliers.

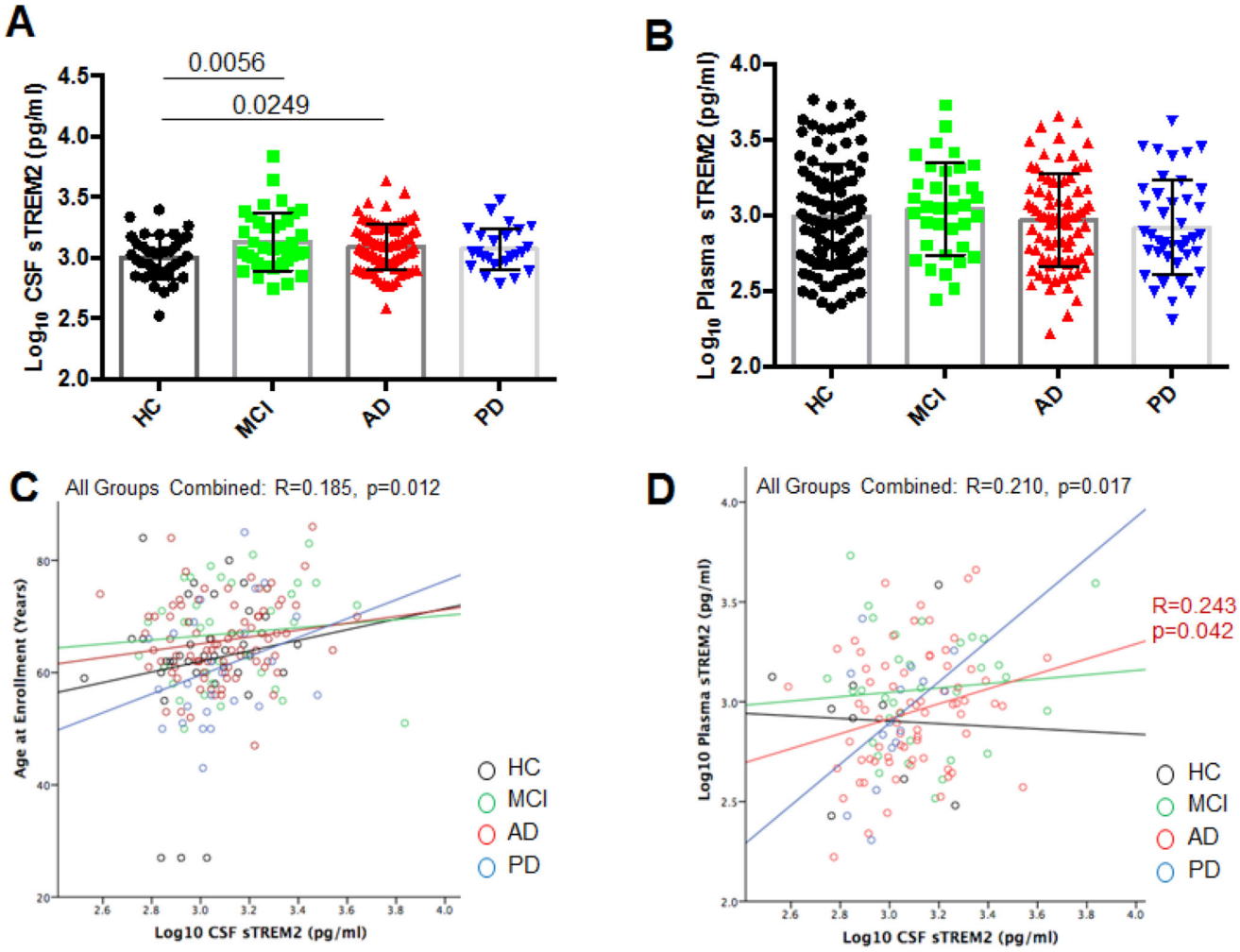

Figure 2. CSF and Plasma Soluble TREM2 levels

Soluble TREM2 (sTREM2) levels in healthy controls (HC), mild cognitive impairment (MCI), Alzheimer's disease (AD) and Parkinson disease (PD) in the CSF cohort are significantly different between HC and MCI (p=0.0056) and between HC and AD (p=0.0249) **(A).** Plasma sTREM2 Levels were not significantly different between disease groups in the plasma cohort. ANOVA Fisher's LSD test p-values are shown **(B).** CSF sTREM2 is associated with age (p=0.012) in the group as a whole but not upon stratification by disease group **(C).** Plasma and CSF sTREM2 levels were significantly correlated in AD (p=0.042) and for the groups as a whole (when not stratified by disease group: p=0.017) **(D).**

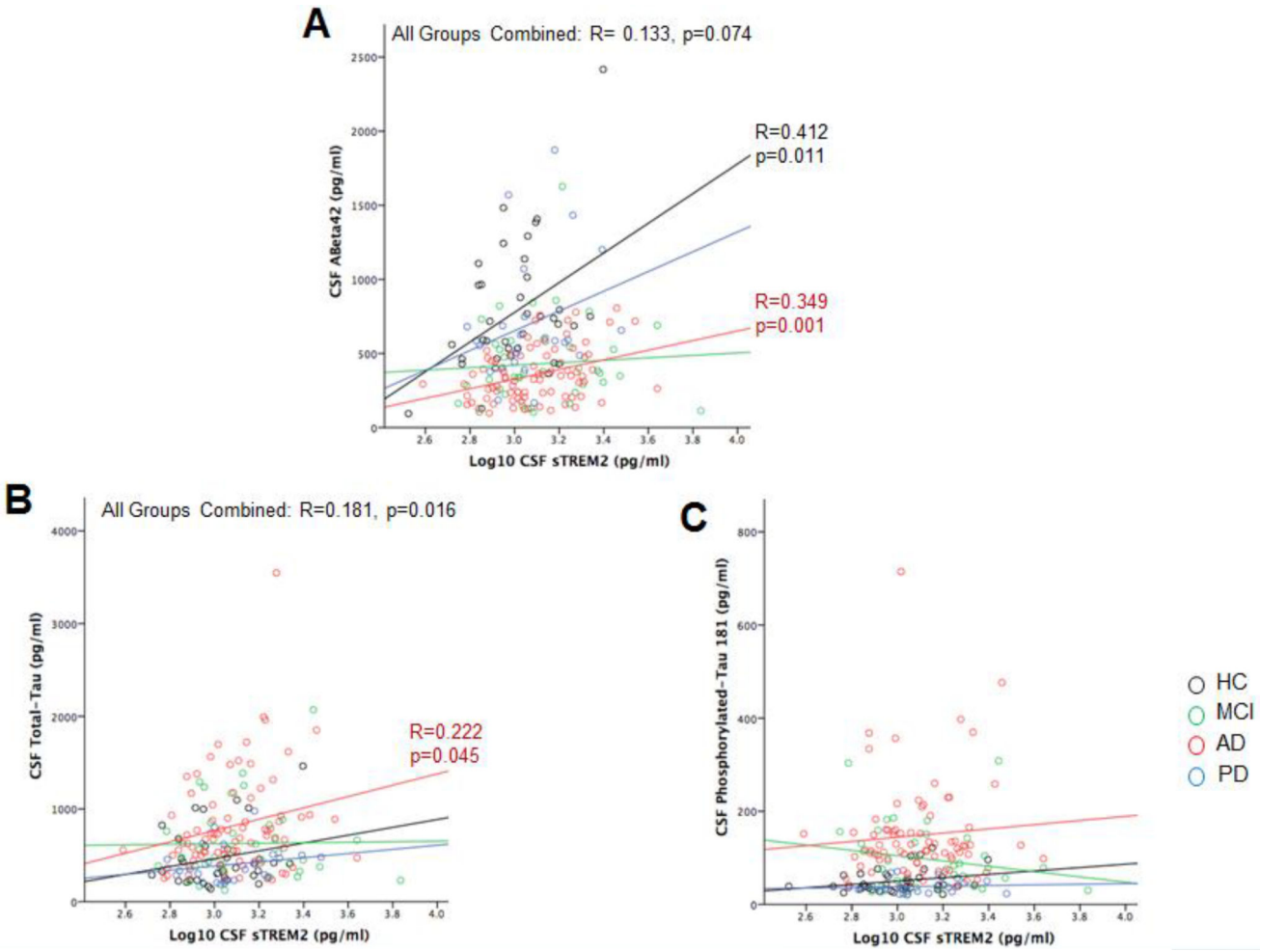

Figure 3. CSF sTREM2 Correlation with CSF AD Biomarkers

CSF sTREM2 levels significantly positively correlate with CSF Aβ42 in HC (p=0.011) and AD (p=0.001) **(A).** CSF sTREM2 levels significantly positively correlate with CSF Total-tau levels in AD (p=0.045) as well as the group as a whole (p=0.016) **(B).** CSF sTREM2 levels do not significantly correlate with CSF phosphorylated-tau levels **(C).**

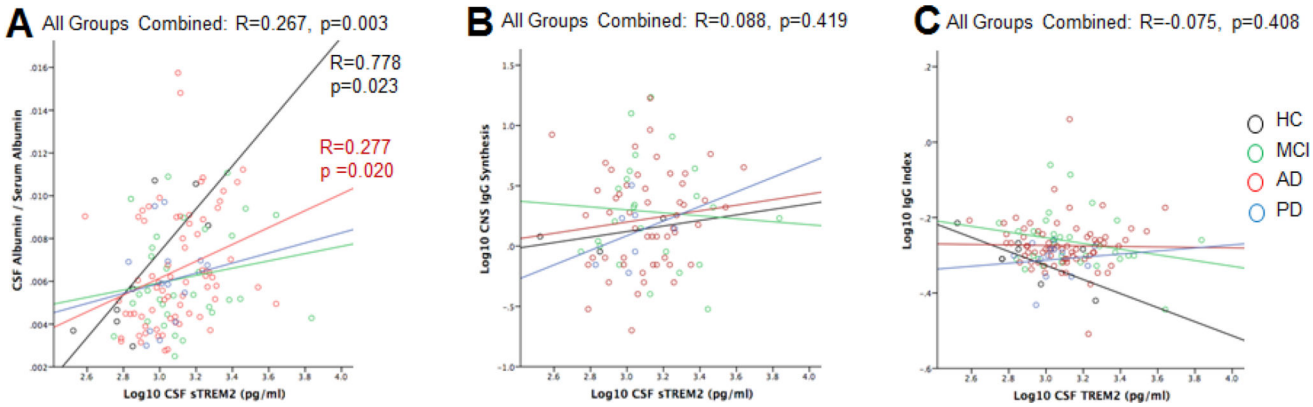

Figure 4. CSF sTREM2 Correlation with Central Nervous System (CNS) Biomarkers of Inflammation

CSF sTREM2 levels significantly correlate with the CSF Albumin / Serum Albumin ratio in HC (p=0.023) and in AD (p=0.020) as well as the groups as a whole (p=0.003) **(A).** CSF sTREM2 levels did not significantly correlate with CNS IgG Synthesis **(B).** CSF sTREM2 levels do not significantly correlate with IgG Index **(C).** Only subjects that had a blood draw on the same day as the CSF were included.

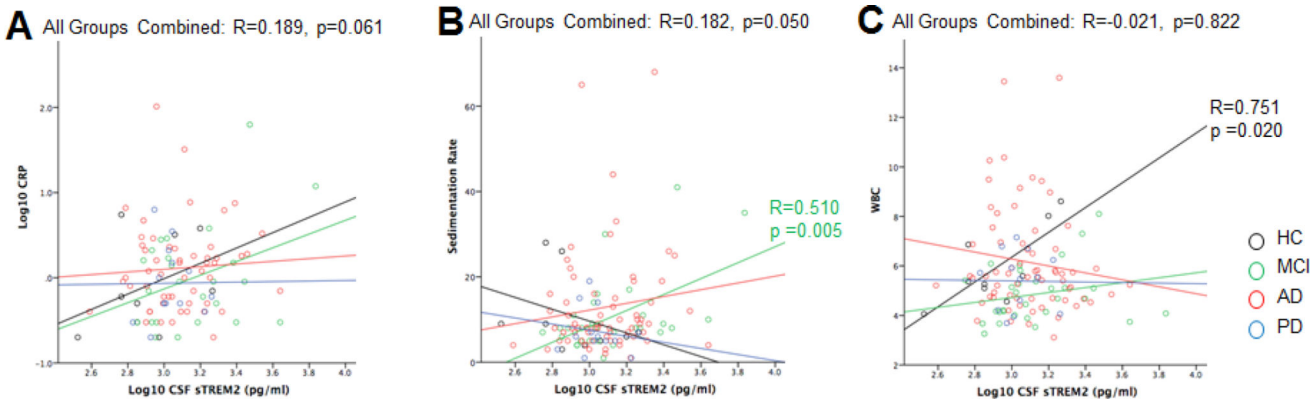

Figure 5. CSF sTREM2 Correlation with Peripheral Biomarkers of Inflammation

CSF sTREM2 levels do not significantly correlate with high-sensitivity C-reactive protein (CRP) **(A),** CSF sTREM2 levels significantly correlate with sedimentation rate in MCI (p=0.005) **(B).** CSF sTREM2 levels significantly correlate with white blood cell count (WBC) in HC (p=0.020) **(C).** Only subjects that had a blood draw on the same day as the CSF were included (CSF and Plasma from the same visit).

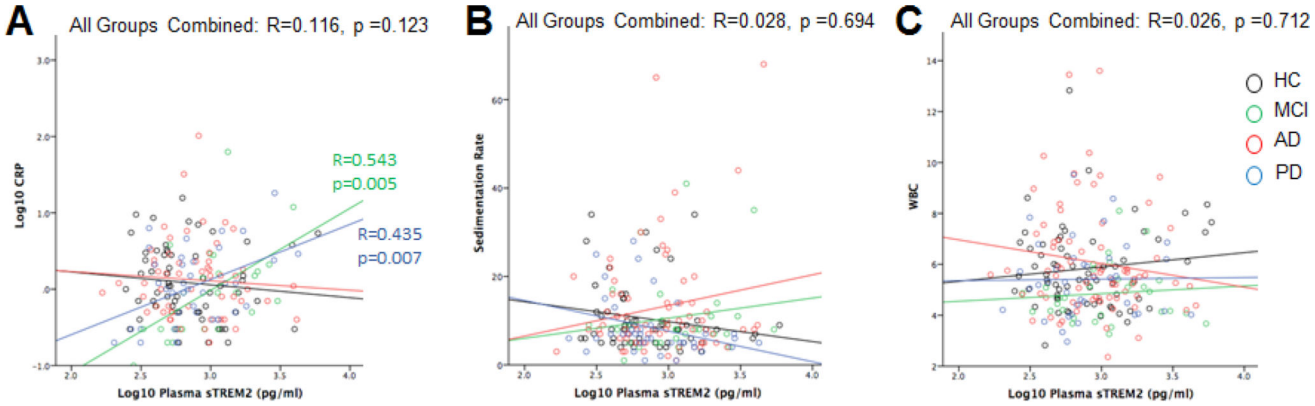

Figure 6. Plasma sTREM2 Correlation with Peripheral Biomarkers of Inflammation

Plasma sTREM2 levels are significantly correlated with C-reactive protein (CRP-ultra) in MCI (p=0.005) and PD (p=0.007) **(A),** not sedimentation rate **(B),** and not with white blood cell count (WBC) **(C).**

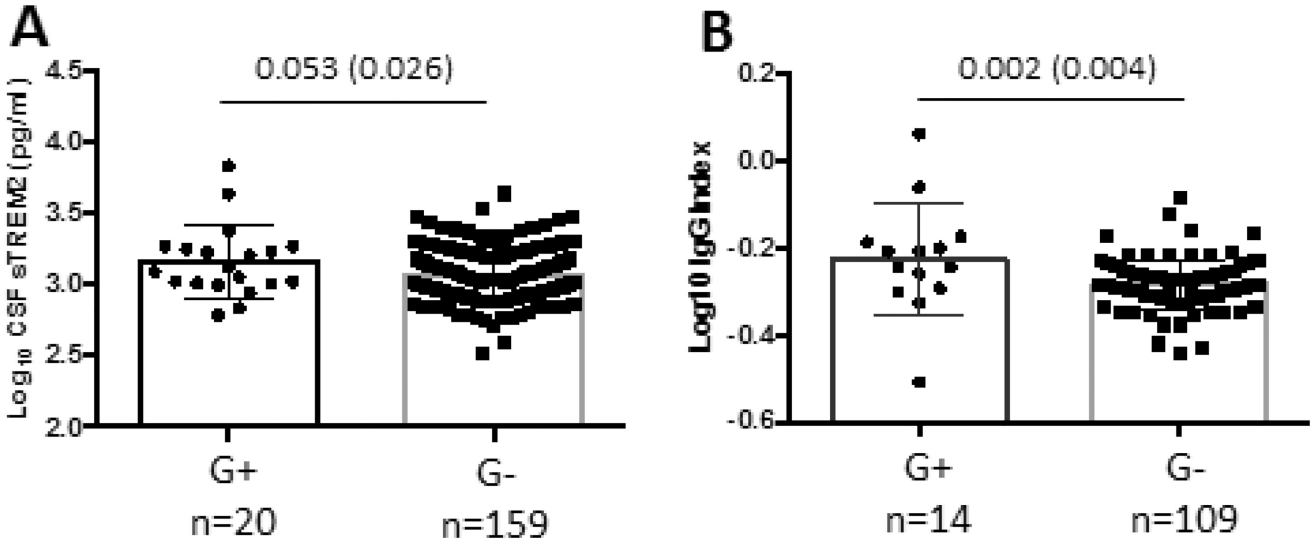

Figure 7. Protein levels associated with rs7748513 genotype

CSF sTREM2 levels are marginally higher in carriers of the AD GWAS risk allele for rs7748513 (G+; GG or AG) in the group as a whole (p=0.053) and after taking into account disease status, age, sex and *APOE* ε4 status (p=0.026) **(A).** The IgG Index is higher in carriers of the AD GWAS risk allele for rs7748513 (G+; GG or AG) in the group as a whole (p=0.002) and after taking into account disease status, age, sex and *APOE* ε4 status (p=0.004) **(B).** Linear regression models were used to analyze the difference between protein markers both with and without covariates. Graphs are without taking into account covariates.

Table 1

Sample Description

Biofluid samples were collected from the Center for Brain Health Aging and Neurodegeneration Biobank (CBH-biobank): Some individuals donated cerebrospinal fluid (CSF cohort) **(A).** Most individuals donated plasma (Plasma cohort) **(B).** P-values represent results from ANOVA LSD post-hoc correction for multiple comparisons.

A CSF Cohort	**HC**	**MCI**	**AD**	**PD**	**HC vs MCI**	**HC vs AD**	**HC vs PD**	**MCI vs AD**	**MCI vs PD**	**AD vs PD**
	n = 37	n = 38	n = 83	n = 25						
% Female	43%	45%	51%	40%	0.917	0.64	0.649	0.553	0.715	0.357
% APOE ε4 +	41%	63%	64%	28%	0.056	0.012	0.277	0.745	0.005	0.001
Age Mean (St. Dev.)	62 (12)	67 (9)	66 (7)	61 (10)	0.019	0.044	0.595	0.461	0.009	0.019
B Plasma Cohort	**HC**	**MCI**	**AD**	**PD**	**HC vs MCI**	**HC vs AD**	**HC vs PD**	**MCI vs AD**	**MCI vs PD**	**AD vs PD**
	n = 104	n = 35	n = 83	n = 42						
% Female	48%	43%	48%	38%	0.594	0.987	0.276	0.597	0.678	0.288
% APOE ε4 +	38%	63%	69%	26%	0.002	<0.0001	0.871	0.410	0.012	<0.0001
Age Mean (St. Dev.)	62 (13)	67 (9)	66 (7)	63 (10)	0.008	0.007	0.359	0.528	0.121	0.227

Table 2

Biomarker Result Summary. Biofluid samples were collected from the Center for Brain Health Aging and Neurodegeneration Biobank (CBH-biobank): There is a significant relationship between Log10 CSF sTREM2 and CSF Aβ42 in healthy controls (HC) and Alzheimer's disease patients (AD) as well as CSF T-Tau but not P-Tau (also shown in Fig. 3). (A). There is not a significant relationship between Log10 plasma sTREM2 and CSF Aβ42, T-Tau or P-Tau (B). There is not a significant relationship between Log10 CSF sTREM2 and general central inflammatory markers, but there is with CSF Albumin/Serum Albumin (marker of blood brain barrier (BBB) integrity) in HC and AD patients (AD) as well as in the group as a whole (also shown in Fig. 4) (C). There is not a significant relationship between Log10 plasma sTREM2 and general central inflammatory markers (D). There is a significant relationship between Log10 CSF sTREM2 and (Sed Rate in Table 2) in MCI and white blood cell count (WBC) in HC (also shown in Fig. 5) (E). There is a significant relationship between Log10 plasma sTREM2 and Log10 C-reactive protein (CRP) in MCI and PD (also shown in Fig. 6) (F). There is a significant relationship between Log10 CSF sTREM2 (Fig. 2C), but not Log10 plasma sTREM2, and age in the group as whole and between Log10 CSF sTREM2 and Log10 plasma sTREM2 in AD as well as the group as a whole (Fig. 2D) (G). R-values and p-values represent results from linear regression analyses where either CSF or plasma sTREM2 was the dependent variable.

		All		HC		MCI		AD		PD	
		R	**p-Value**	**R**	**p-Value**	**R**	**p-Value**	**R**	**p-Value**	**R**	**p-Value**
A	AD-related CSF biomarker	Log10 CSF sTREM2									
	Aβ42	0.133	0.074	0.412	0.011	0.067	0.690	0.349	0.001	0.280	0.175
	T-Tau	0.181	0.016	0.221	0.210	0.016	0.924	0.222	0.045	0.200	0.337
	P-Tau	0.071	0.341	0.265	0.118	0.196	0.245	0.081	0.469	0.080	0.704
B	AD-related CSF biomarker	Log10 plasma sTREM2									
	Aβ42	0.111	0.212	0.431	0.246	0.294	0.091	0.091	0.904	0.158	0.575
	T-Tau	0.064	0.476	0.337	0.414	0.060	0.738	0.150	0.213	0.038	0.892
	P-Tau	0.083	0.348	0.360	0.342	0.073	0.683	0.135	0.261	0.173	0.538
C	Central inflammatory marker	Log10 CSF sTREM2									
	CSF Albumin/Serum Albumin	0.267	0.003	0.777	0.023	0.178	0.331	0.277	0.020	0.130	0.671
	Log10 CNS IgG synthesis Log10	0.088	0.419	0.560	0.622	0.068	0.753	0.119	0.401	0.302	0.510
	IgG index	0.075	0.408	0.704	0.051	0.250	0.167	0.019	0.878	0.102	0.741
D	Central inflammatory marker	Log10 plasma sTREM2									
	CSF Albumin/Serum Albumin	0.142	0.116	0.304	0.464	0.002	0.993	0.174	0.151	0.173	0.571
	Log10 CNS IgG synthesis Log10	0.133	0.224	0.925	0.248	0.091	0.671	0.128	0.365	0.248	0.592
	IgG index	0.128	0.158	0.513	0.194	0.238	0.190	0.008	0.949	0.089	0.771
E	Peripheral inflammatory marker	Log10 CSF sTREM2									

		All		HC		MCI		AD		PD	
		R	p-Value	R	p-Value	R	p-Value	R	p-Value	R	p-Value
	Log10 CRP	0.189	0.061	0.376	0.318	0.348	0.096	0.064	0.651	0.009	0.977
	Sed Rate	0.182	0.050	0.342	0.367	0.510	0.005	0.126	0.312	0.155	0.613
	WBC	0.021	0.822	0.751	0.020	0.220	0.243	0.132	0.289	0.011	0.971
F	Peripheral inflammatory marker	Log10 plasma sTREM2									
	Log10 CRP	0.116	0.123	0.107	0.420	0.543	0.005	0.067	0.623	0.435	0.007
	Sed Rate	0.028	0.694	0.181	0.174	0.156	0.411	0.169	0.160	0.318	0.052
	WBC	0.026	0.712	0.117	0.349	0.087	0.644	0.131	0.264	0.013	0.940
G	Other										
	Age and Log10 plasma sTREM2	0.071	0.250	0.152	0.123	0.263	0.123	0.117	0.292	0.291	0.061
	Age and Log10 CSF sTREM2	0.185	0.012	0.138	0.417	0.098	0.558	0.163	0.140	0.291	0.158
	Log10 CSF sTREM2 and Log10 plasma sTREM2	0.210	0.017	0.042	0.914	0.090	0.612	0.243	0.042	0.419	0.120