

RESEARCH ARTICLE

Inflammatory protein associations with brain MRI measures: Framingham Offspring Cohort

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Abstract

INTRODUCTION: Brain magnetic resonance imaging (MRI) and inflammatory biomarkers are crucial for investigating preclinical neurocognitive disorders. Current investigations focus on a few inflammatory markers. The study aims to investigate the associations between inflammatory biomarkers and MRI measures and to examine sex differences among the associations in the Framingham Heart Study.

METHODS: Dementia and stroke-free participants underwent OLINK Proteomics profiling and MRI measurements within 5 years. Pairwise cross-sectional analysis assessed 68 biomarkers with 13 brain MRI volumes, adjusting for covariates and familial correlations.

RESULTS: Elevated CDCP1, IL6, OPG, and 4E.BP1 were related to smaller total cerebral brain volume (TCBV), whereas higher HGF, IL8, and MMP10 were associated with smaller TCBV, total and frontal white matter volumes. Higher SCF and TWEAK were associated with larger TCBV. In sex-stratified analyses, associations were observed exclusively among males.

Jiachen Chen and Ahmed A. Y. Ragab contributed equally to this study.

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DISCUSSION: We report several associations between inflammatory biomarkers and brain volumes, highlighting different associations within sex subgroups.

KEYWORDS

aging, Alzheimer's disease, biomarkers, cognitive aging, dementia, MRI

Highlights

- Higher CDCP1, IL6, OPG, and 4E.BP1 levels were associated with smaller TCBV.
- Higher levels of HGF, IL8 and MMP10 were associated with smaller TCBV, CWV and FWV.
- Higher levels of SCF and TWEAK, were associated with larger TCBV.
- Significance diminished in models adjusting for CVD risk factors.
- Associations were observed exclusively in males.

1 | INTRODUCTION

Alzheimer's disease (AD) and AD related dementias (ADRD) pose a significant public health challenge. It is estimated that by 2050, approximately 153 million people worldwide will be suffering from these diseases.¹ The escalating prevalence will exert immense strain on healthcare systems worldwide, resulting in substantial economic implications. It is estimated that by 2050, the cost of dementia care alone will exceed 17 trillion USD.² AD is the most common subtype of dementia, accounting for approximately 70%–80% of all dementia cases.

It is crucial to detect AD at an early stage to enhance the likelihood of more effective management strategies prior to substantial cognitive decline. Brain magnetic resonance imaging (MRI) measures of total cerebral brain volume (TCBV), white matter hyperintensity volume (WMH), hippocampal volume, and regional gray and white matter volumes, have been used as important endophenotypes of AD/ADRD, as they indicate abnormal changes before the onset of the disease.^{3–6} For example, higher TCBV is hypothesized to be a buffer, providing the brain with an increased ability to adapt in the presence of neurodegenerative processes, while diverse patterns of regional gray matter atrophy associate with dementia onset and cognitive function.⁷

Neuroinflammation as one of the major pillars of aging contributes to the pathogenesis of dementia and chronic peripheral inflammation has been related to an increased risk for AD.^{8,9} Inflammatory biomarkers are a promising candidate to detect patterns of neurodegeneration that can lead to higher risk for ADRD. Therefore, investigating the relationship between circulating inflammatory biomarkers and neuroimaging biomarkers using total and regional brain volume measures could provide a better understanding of the complex relationship between neuroinflammation and neurodegenerative pathophysiology, and potentially identify individuals earlier in the disease course.

Several population-based studies have observed associations between C-reactive protein (CRP) and/or interleukin 6 (IL6) with TCBV, WMH, hippocampal volume, and total gray and white matter

volumes. Research conducted in the population-based Rotterdam Study and the Framingham Heart Study (FHS) have reported an association between higher levels of CRP and smaller TCBV along with greater WMH volume.^{10–12} In contrast, a report from the Study of Health in Pomerania (SHIP) did not find an association between CRP and TCBV, but did observe an association with gray matter volume.¹³ Larger panels of inflammatory biomarkers have demonstrated associations of osteoprotegerin (OPG), IL6, and tumor necrosis factor alpha (TNF α) with smaller TCBV.¹⁴ In a recent report from our group, higher CD5L and CD14 levels were significantly associated with smaller TCBV, whereas higher levels of sRAGE were linked to larger TCBV.¹⁵ Most studies to date have focused on a select number of circulating biomarkers, focusing almost exclusively on pro-inflammatory biomarkers. Additionally, no potential sex differences have been investigated in these associations. Furthermore, the majority of studies have not investigated specific regional gray and white matter volume measurements. Exploring brain atrophy patterns at the regional level as outcomes can potentially unveil more granular information on the processes leading to neurodegenerative disorders. The exploration of a comprehensive panel of inflammatory markers has not been examined in relation to global and regional brain volumes in a carefully characterized community-based cohort. Therefore, the aim of this study is to investigate the association of multiple circulating inflammatory biomarkers, measured with the OLINK inflammatory panel, with various brain MRI markers of AD/ADRD in the FHS Offspring cohort, while also examining potential sex differences in these associations.

2 | METHODS

2.1 | Study sample

The Framingham Offspring Study recruited 5214 offspring of the FHS Original cohort and Offspring spouses in 1971.¹⁶ The FHS offspring cohort has been examined every 4–8 years since enrollment and has

had brain MRI assessed every 2–6 years beginning with Exam 7 in 1999.¹⁷ Sample selection for brain MRI outcomes is provided in the flow chart in Figure S1. Overall, 879 dementia-free Offspring participants at least 40 years old at Exam 7 had stored plasma for inflammatory biomarker profiling. We excluded participants with incomplete biomarker profiles that did not pass the quality control procedures ($n = 2$), without *apolipoprotein E* (APOE) genotypes ($n = 8$), missing a brain MRI within 5 years before or after Exam 7 ($n = 211$), and those with prevalent stroke ($n = 12$), leaving a final sample of 646 participants for analyses. Participants provided written informed consent before attending each examination. The Institutional Review Board at Boston University Medical Center reviewed and approved the study protocol and examinations.

2.2 | OLINK inflammatory panel

Stored EDTA plasma samples from Exam 7 were sent to OLINK (Waltham, MA, USA) for proteomics using their OLINK Target 96 inflammatory panel, which provides measurements of 92 protein biomarkers. The approach is based on high-throughput and multiplexing Proximity Extension Assay (PEA) technology. Protein expression levels were quantified using Normalized Protein eXpression (NPX) units, which is a relative measurement on \log_2 scale, where one NPX difference corresponds to a doubling of protein concentrations.¹⁸ Details can be found at: <https://olink.com/>. To assist in the quality control of plasma samples, phantoms and OLINK plate controls were included as part of the sample for calculations of the limit of detection (LOD) for OLINK panels.¹⁸ The samples were randomly distributed in 11 plates and then processed together in a single batch at OLINK. The coefficient of variation for all proteins across the plates was less than 5%, indicating the absence of any plate-related effects. A selection of 68 proteins with <50% of participant values below LOD were selected for downstream analyses as suggested by OLINK and other investigations.^{19,20} The full list of protein biomarkers in the OLINK inflammatory panel and the percentage of samples missing or with values below LOD for each of them are provided in Table S1, while the list of 68 proteins for analysis is shown in Table S2a. The actual data value below LOD was used in accordance with the OLINK guidelines for the subset of proteins that fell below LOD.²⁰ This approach was adopted due to the conservative nature of LOD measurements in large multiplexed studies, and statistical power could be improved using observed values. We also conducted rank-based inverse normal transformations on raw protein values to standardize and reduce skewness.²¹

2.3 | Brain MRI measures

FHS Offspring cohort participants attending Exam 7 were approached for an opportunity to receive brain MRI and participate in a brain aging study beginning in 1999.¹⁷ Details about FHS brain MRI acquisition and quantification have been described previously.^{17,22} The majority of MRI machines were provided by Siemens and General Electric, with

RESEARCH IN CONTEXT

- 1. Systematic review:** Magnetic resonance imaging (MRI) and circulating inflammatory biomarkers play vital roles in the exploration of preclinical neurocognitive disorders. Nevertheless, existing literature tends to concentrate on a limited selection of inflammatory markers and lack an exploration of sex differences.
- 2. Interpretation:** We report links between several circulating inflammatory biomarkers and brain MRI measures, suggesting their roles in neurodegeneration. Elevated CDCP1, IL6, OPG, 4E.BP1, HGF, IL8, and MMP10 associate with smaller brain MRI volume, while SCF and TWEAK correlate with bigger MRI brain volume. Sex-specific differences are evident, with certain biomarkers affecting brain volumes exclusively in males.
- 3. Future directions:** The associations observed between various circulating inflammatory biomarkers and brain MRI, particularly in males, warrant further exploration using a longitudinal approach in a larger, more diverse sample. This could enhance understanding of the pathophysiological pathways underlying neurodegeneration, facilitating the development of early detection strategies and therapeutic targets.

a few machines being supplied by Philips.¹⁷ Participants underwent brain MRI in a machines ranging from 1 T to 1.5 T field strength, and brain MRI was obtained either at Framingham, MA, or offsite by other centers in the United States. No substantial differences were observed across sites according to analyses of MRI measures.¹⁷ All images were centrally read and blind to participants' personal identification information. Image evaluation involves the removal of non-brain elements through semiautomatic segmentation analyses, and the resulting total cranial volume (TCV) is used as a proxy of head size.^{17,23} Protocols for quantifying and segmenting total, regional brain volumes, and WMH volumes have been previously reported.^{17,24} Brain MRI measures of interest included TCBV, hippocampal brain volume (HPV), and WMH. In brief, TCBV is calculated as the ratio of total brain parenchymal volume to TCV. HPV and WMH were also computed as proportions of TCV to account for the head size. Five measures of gray matter volume were included due to different potential associations of regional gray matter in the disease progression of cognitive aging.^{25,26} Similarly, the same regional volumes for white matter were also considered since they are linked to cognition and brain activity.^{27–29} These ten measures were also regarded as outcomes, which were also calculated as proportions of TCV: cerebral gray matter volume (CGV), frontal gray matter volume (FGV), temporal gray matter volume (TGV), parietal gray matter volume (PGV), and occipital gray matter volume (OGV), cerebral white matter volume (CWV), frontal white matter volume (FWV), temporal

white matter volume (TWV), parietal white matter volume (PWV), and occipital white matter volume (OWV).

All 13 brain MRI measures except TCV were included as outcomes of interest and were rank-based inverse-normal transformed to attain a distribution with a mean of 0 and SD of 1. Some participants received brain MRIs multiple times. We identified a sample of 646 participants for whom MRI outcomes were measured within 5 years of the Exam 7 core visit, at which the blood sample for the biomarker panel was drawn. If multiple MRIs were available within 5 years of Exam 7, the MRI with the date closest to Exam 7 was selected.

2.4 | Pairwise association analyses

Pairwise associations were investigated between each of the 68 protein biomarkers and all 13 brain MRI outcomes. For each pair, a combined analysis for the full sample and stratified analyses within sex subgroups (male and female) were conducted. Two statistical models were considered for the analyses. The primary model (Model 1) included the covariates of age, age², sex, a sex × age interaction term, the time difference between the blood draw and the MRI measurement, and the additive coding for the number of APOE ε2 and ε4 alleles, as these are key variables associated with brain volumes and cognitive outcomes. Age and sex information were ascertained at Exam 7, and APOE genotypes were identified from polymerase chain reaction and restriction isotyping.³⁰ The terms age² and sex × age interaction were included due to the non-linear and sex-specific effects of age on the MRI measures.¹⁷

A secondary model (Model 2) was used to test for the robustness of the associations accounting for prevalent cardiovascular disease (CVD) and CVD risk factors, which included all covariates in Model 1 as well as: (1) indicators for prevalent CVD and prevalent atrial fibrillation (AF) at Exam 7 and (2) CVD risk factors including systolic and diastolic blood pressures (SBP, DBP, mmHg), diabetes status, treatment for hypertension, body-mass index (BMI, kg/m²), current smoking status, total cholesterol level (TC, mg/dL), high-density lipoprotein cholesterol levels (HDL, mg/dL), and use of lipid-lowering agents at Exam 7. The presence of CVD was established by diagnoses made before Exam 7 and confirmed by a panel of senior investigators including coronary heart disease (myocardial infarction, angina pectoris, coronary insufficiency), transient ischemic attack, intermittent claudication, and congestive heart failure.³¹ Diabetes status was defined by any of the conditions: use of antidiabetic medications, fasting blood glucose level ≥126 mg/dL, or random blood glucose level ≥198 mg/dL. The inclusion of additional prevalent CVD and CVD risk factors in Model 2 accounted for the mediation effects through the CVD pathways on biomarkers.

In stratified analyses, we performed sex-stratified analyses following the same analytical strategy and model covariates (excluding sex), and all pairwise analyses used separate linear mixed-effects models to test the associations between each of the 68 proteins (predictor) with each of the 13 brain MRI volumes (outcome), accounting for familial relationships via the kinship coefficient matrix. Effect sizes and 95%

confidence intervals (CIs) of proteins were reported and interpreted as effects in standard deviation units due to the standardization of both predictors and outcomes. False rejections of the true null hypotheses for the 68 × 13 = 884 correlated association tests were controlled by the false discovery rate (FDR).³² FDR ≤0.05 was set to declare significant associations. FDRs were computed within each stratum separately. All the statistical analyses were implemented by R-4.2.1 software³³ and the linear mixed-effect models were conducted by the `lme4` function in the `lme4` package.³⁴

2.5 | Sensitivity analyses

Two additional sensitivity analyses were conducted to further assess the robustness of the pairwise association analyses. First, we tested the associations between proteins and brain MRI outcomes using Model 1 in the subsample that excluded participants who underwent brain MRI more than 2 years before or after Exam 7 (subsample $n = 603$). Second, to examine if a specific subgroup of participants drove the significant associations, we performed analyses using Model 1 excluding participants who had prevalent chronic leukemia or lymphoma, who reported use of glucocorticoids at Exam 7, or who were identified as outliers by principal component analysis (PCA) using the 68 rank-normalized proteins (36 individuals excluded, subsample $n = 610$). We also performed another sensitivity analysis to examine potential effect modification by the APOE genotype. This was conducted by including and assessing the interaction term between each protein and the indicator for being APOE ε4 carriers using Model 1 (excluding the number of APOE ε2 and ε4 alleles, and instead using an indicator of APOE ε4 carriers) in the full sample ($n = 646$).

2.6 | Network analysis

Besides the marginal pairwise associations we have assessed, we also investigated the conditional associations of the 68 proteins and 13 brain MRI measures represented by Gaussian Graphical Models (GGMs). In GGMs, two nodes (variables) are connected by an edge if and only if this pair of nodes is conditionally dependent given all the other nodes in the network, and each edge weight corresponds to the conditional dependency between the node pair.³⁵ We used the Fused graphical lasso (FGL) to jointly estimate multiple sparse GGMs regarding related but distinct stratum groups, where the conditional dependency networks across groups are expected to share similar structures but also hold differential edges.³⁶ Based on the full data including 81 nodes (68 proteins and 13 outcomes), we identified the differential edges across sex groups, mainly focusing on protein–MRI outcome pairs to add insights into our sex-stratified pairwise analyses. Differential edges were defined as those pairs that have precision matrix entry differences between the male and female larger than 0.001, and those non-zero edges with differences across sex less than 0.001 were considered as similar edges. The FGL was conducted by function `JGL` in the `JGL` R package.

TABLE 1 Participant characteristics at Exam 7, time of plasma sample for inflammatory biomarker measurement.

Brain MRI sample	Full sample	Female	Male
Sample size, n, n (%)	646	338	308
Female, n (%)	338 (52.3%)	--	--
Age, mean(range)	61 (40, 88)	61 (41, 85)	60 (40, 88)
APOE ε2 carriers, n (%)	101 (15.6%)	56 (16.6%)	45 (14.6%)
APOE ε4 carriers, n (%)	142 (22.0%)	78 (23.1%)	64 (20.8%)
Attended college, n (%)	507 (78.5%)	254 (75.1%)	253 (82.1%)
Current smoker, n (%)	78 (12.1%)	50 (14.8%)	28 (9.1%)
BMI Kg/m2, mean (sd)	28 (5)	27 (5)	28 (4)
SBP mmHg, mean (sd)	125 (18)	124 (19)	126 (17)
DBP mmHg, mean (sd)	74 (9)	72 (9)	75 (9)
Hypertension Rx, n (%)	197 (30.5%)	91 (26.9%)	106 (34.4%)
Total cholesterol mg/dL, mean (sd)	200 (37)	207 (37)	192 (35)
Triglycerides mg/dL, mean (sd)	132 (76)	129 (71)	136 (82)
Lipid Rx, n (%)	128 (19.8%)	50 (14.8%)	78 (25.3%)
Fasting blood glucose mg/dL, mean (sd)	104 (27)	99 (22)	109 (30)
Type 2 diabetes Rx, n (%)	32 (5.0%)	13 (3.8%)	19 (6.2%)
MMSE, median (IQR)	29 (2)	29 (1)	29 (2)
≥ 1 parent with dementia Dx, n (%)	145 (22.4%)	71 (21.0%)	74 (24.0%)
Incident dementia through 2022, n (%)	65 (10.1%)	34 (10.1%)	31 (10.1%)
Blood cancer prevalent Exam 7, n (%)	6 (0.9%)	5 (1.5%)	1 (0.3%)
Blood cancer through 2019, n (%)	27 (4.2%)	12 (3.6%)	15 (4.9%)
Time difference between brain MRI and Exam 7, mean (sd)	0.75 (0.77)	0.74 (0.81)	0.76 (0.74)

Abbreviations: APOE, Apolipoprotein E; BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; Rx, prescription; SBP, systolic blood pressure; sd, standard deviation.

3 | RESULTS

3.1 | Participants characteristics

Table 1 presents the demographic characteristics of the participants in the brain MRI sample. The average age at Exam 7 was 61 years, approximately 52% of the participants were female, the median MMSE score was 29, and the proportion of APOE ε2 and ε4 carriers was roughly 16% and 22%, respectively. The brain MRI outcomes were measured on average 0.75 years (SD = 0.77 years) after Exam 7, 3% had MRIs > 3 years after Exam 7, and 0 had MRIs > 3 years before Exam 7. The mean and SD of the 68 proteins are shown in Table S2a. Table S2b presents the mean (SD) of brain MRI outcomes.

3.2 | Association analysis results

Figure 1 shows the forest plot of significant associations between the proteins and the 13 brain MRI measures in the full sample and in male and female strata. Figure 2 shows the same associations as well as any newly discovered significant associations after accounting for the Model 2 CVD and risk factor covariates. Most of the signifi-

cant protein associations were observed with TCBV and regional white matter volumes. In the combined analysis, higher levels of CDCP1, HGF, IL6, IL8, MMP10, OPG, and 4E.BP1 were significantly associated with smaller TCBV, with effect sizes ranging from -0.15 to -0.11 SD units per SD unit increase in protein levels. Higher levels of SCF ($\beta = 0.13$, SE = 0.029, FDR = 0.004, see Figure 1) and TWEAK ($\beta = 0.13$, SE = 0.030, FDR = 0.004, see Figure 1) were associated with larger TCBV. HGF, IL8, and MMP10 were also found to be significantly associated with CWV and FWV, with higher protein levels relating to smaller CWV and FWV. Effect sizes for HGF, IL8, and MMP10 on CWV were similar ($\beta = -0.14$, -0.13 , -0.12 , see Figure 1), as were their effect sizes on FWV ($\beta = -0.15$, -0.15 , -0.12 , see Figure 1).

In the sex-stratified analyses, we observed significant associations only in males ($n = 308$), where the effects were in the same directions, but of larger size compared with the combined analysis. For example, higher levels of CDCP1, HGF, IL6, IL8, MMP10, and 4E.BP1 were still significantly associated with smaller TCBV in the male stratum, with increased effect sizes ranging from -0.23 to -0.15 SD units per SD unit increase in protein levels. SCF ($\beta = 0.16$, SE = 0.039, FDR = 0.010, see Figure 1) and TWEAK ($\beta = 0.16$, SE = 0.043, FDR = 0.025, see Figure 1) were associated with larger TCBV, with increased effect sizes in the male stratum. Significant results found

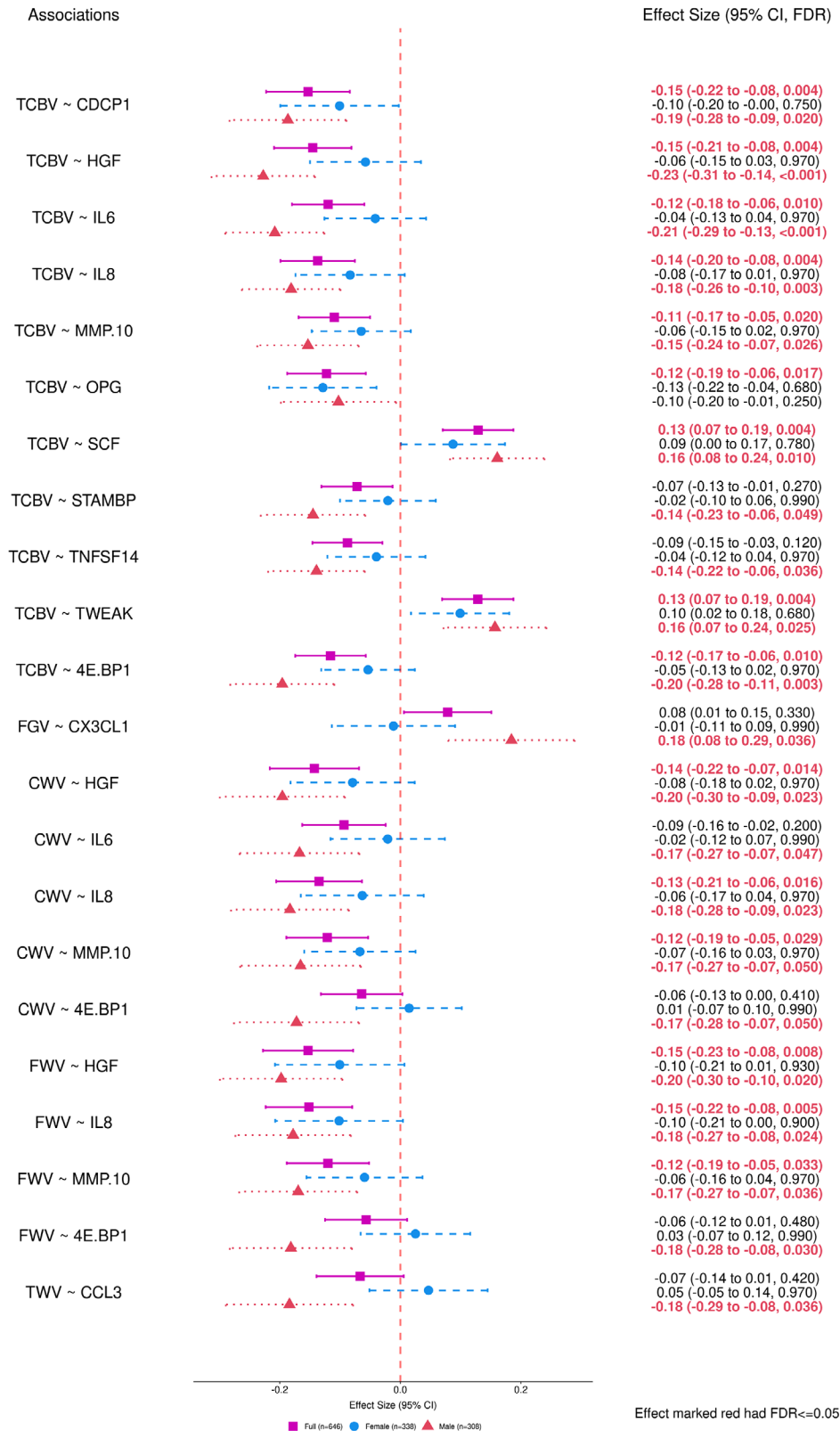


FIGURE 1 Forest plots of effect size for significant associations with the 13 brain MRI outcomes using Model 1 (FDR \leq 0.05). Model 1 covariates included: age, age², sex, an interaction term of sex \times age, the time difference between the blood draw (Exam 7) and the MRI measurement, and APOE genotype. The pink square represents the combined sample (n = 646), the blue circle represents the Female stratum (n = 338), and the red triangle represented the Male stratum (n = 308). APOE, apolipoprotein E; CI, confidence interval; CWV, cerebral white matter volume; FDR, false discovery rate; FWV, frontal white matter volume; MRI, magnetic resonance imaging; PGV, parietal gray matter volume; TCBV, total cerebral brain volume; TWV, temporal white matter volume.

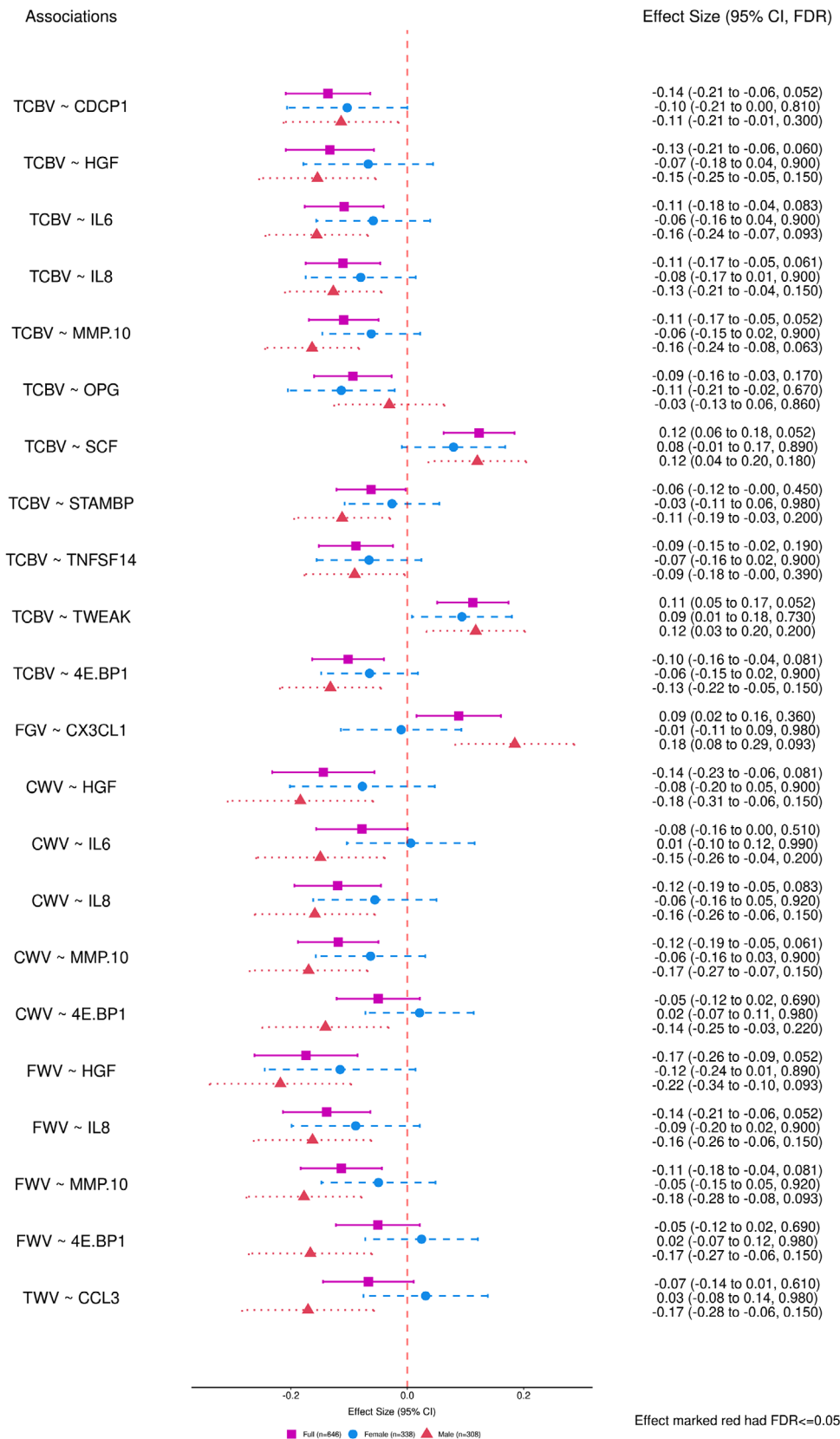


FIGURE 2 Forest plots of effect size for significant associations with the 13 brain MRI outcomes using Model 2 (FDR ≤ 0.05). Model 2 covariates included: age, age², sex, an interaction term of sex × age, the time difference between the blood draw (Exam 7) and the MRI measurement, APOE genotype, prevalent CVD, prevalent AF at Exam 7, and CVD risk factors such as systolic and diastolic blood pressures (mmHg), diabetes status, treatment for hypertension, body-mass index (kg/m²), current smoking status, total cholesterol level (mg/dL),

only in the male stratum include negative associations of STAMBP and TNFSF14 with TCBV ($\beta = -0.14$, -0.14 , see Figure 1), IL6 and 4E.BP1 with CWV ($\beta = -0.17$, -0.17 , see Figure 1), CCL3 with TWV ($\beta = -0.18$, SE = 0.053, FDR = 0.036, see Figure 1), and 4E.BP1 with FWV ($\beta = -0.18$, SE = 0.051, FDR = 0.030, see Figure 1), and a positive association of CX3CL1 with FGV ($\beta = 0.18$, SE = 0.053, FDR = 0.036, see Figure 1). In females ($n = 338$), all effects were closer to 0 than in the full sample, and none were significant, suggesting strong evidence for differential associations across sex subgroups.

As shown in Figure 2, after adjusting for the additional CVD-risk Model 2 covariates, all proteins significant in Model 1 showed consistent direction of effects, while displaying reduced effect sizes and lower levels of association significance. None remained significantly associated with the outcomes of interest at FDR ≤ 0.05 . Results for analyses of all proteins with all brain MRI measures, using both Model 1 and Model 2 adjustments are provided in [supporting information file 3](#).

3.3 | Sensitivity analysis results

The subsample of participants who underwent brain MRI within 2 years before or after Exam 7 excluded 43 individuals (remaining $n = 603$). The subsample excluding participants with prevalent chronic leukemia or lymphoma, participants who reported use of glucocorticoids at Exam 7, and participants who were identified as outliers by PCA using the 68 rank-normalized proteins excluded 36 individuals (remaining $n = 610$). Most of the significant associations between brain MRI measures and proteins using Model 1 in the full sample and male subgroups were still significant for these two sensitivity analyses, including CDCP1, HGF, IL6, IL8, MMP10, SCF, TWEAK, and 4E.BP1 with TCBV (Figure S2), as well as HGF, IL8, and MMP10 with CWV and FWV (Figure S3), with most changes in the absolute effect ranging within 0.02. The direction of effect and effect size were consistent with the primary analysis, suggesting that the observed associations are robust, even when considering the time lapse between protein measurement and brain MRI, as well as the potential inclusion of outliers (Figures S2 and S3). Still, no significant associations were observed in the females for both sensitivity analyses. Complete results for these two sensitivity analyses are provided in [supporting information file 3](#). An additional sensitivity analysis was conducted to investigate potential effect modification by the APOE genotype. This involved including and assessing the interaction term between each protein and the indicator for being APOE $\epsilon 4$ carriers using Model 1 (excluding the number of APOE $\epsilon 2$ and $\epsilon 4$ alleles, and instead using an indicator of APOE $\epsilon 4$ carriers) on the full sample ($n = 646$). Among all pairwise associations, none of the interactions were significant ([supporting information file 3](#)), and we conclude that

the APOE genotype did not modify the association between proteins and brain MRI measures in our sample.

3.4 | Network analysis results

To assess the differential associations observed between males and females from another perspective, we applied FGL to the complete cases of the full sample including 68 proteins and 13 brain MRI measures stratified by sex (male $n = 306$, female $n = 335$) to identify differential conditional dependencies across sex subgroups. As shown by the unweighted conditional dependency networks in Figure 3, there were a total of 320 differential edges and 242 similar edges inferred by FGL. We focused on the edges between proteins and outcomes only. In the male subgroup, we observed edges between pairs between IL8, IL6, SCF, and HGF, with TCBV, respectively. The proteins and outcomes were clustered into two parts separately in the network (Figure 3A), with the only path linking the two parts through TCBV. In the female subgroup, no edges existed between proteins and outcomes (Figure 3B). Thus, the four edges between IL8, IL6, SCF, and HGF, with TCBV were concluded to have conditional dependencies only in the male, consistent with the stratified pairwise associations observed in Figure 1. Directions of conditional dependencies (not shown) were consistent with the stratified pairwise analysis as well. These observations suggest that the other marginal pairwise associations observed in the male subgroup may be associated through TCBV due to the nature of conditional dependency.

4 | DISCUSSION

We examined the association of 68 circulating inflammatory biomarkers with 13 total and regional brain MRI volumetric measures in 646 participants from the FHS Offspring cohort. Our findings are several folds. First, higher CDCP1, IL6, OPG, and 4E.BP1 levels were associated with smaller TCBV, and higher levels of HGF, IL8, and MMP10 were associated with smaller TCBV, CWV, and FWV. Further, higher levels of two proteins, SCF and TWEAK, were associated with larger TCBV. However, associations were no longer significant in models adjusting for CVD risk factors, although the direction of effects were preserved. Further exploration in stratified analyses revealed that these associations were only present in males, where the effects were in the same direction and larger than observed in the full sample. Additional associations found only in males include 4E.BP1 levels with FWV and CWV, STAMBP and TNFSF14 with TCBV, CX3CL1 with FGV, IL6 with CWV, and CCL3 with TWV. Using GGMs, we observed a positive

high-density lipoprotein cholesterol levels (HDL, measured in mg/dL), and use of lipid-lowering agents at Exam 7. The pink square represented the combined sample ($n = 646$), the blue circle represented the Female ($n = 338$), and the red triangle represented the male ($n = 308$). AF, atrial fibrillation; APOE, Apolipoprotein E; CI, confidence interval; CVD, cardiovascular disease; CWV, cerebral white matter volume; FDR, false discovery rate; FWV, frontal white matter volume; MRI, magnetic resonance imaging; PGV, parietal gray matter volume; TCBV, total cerebral brain volume; TWV, temporal white matter volume.

(A) **Conditional dependency network for male (n=306)**

Blue edge: positive dependency, red edge: negative dependency

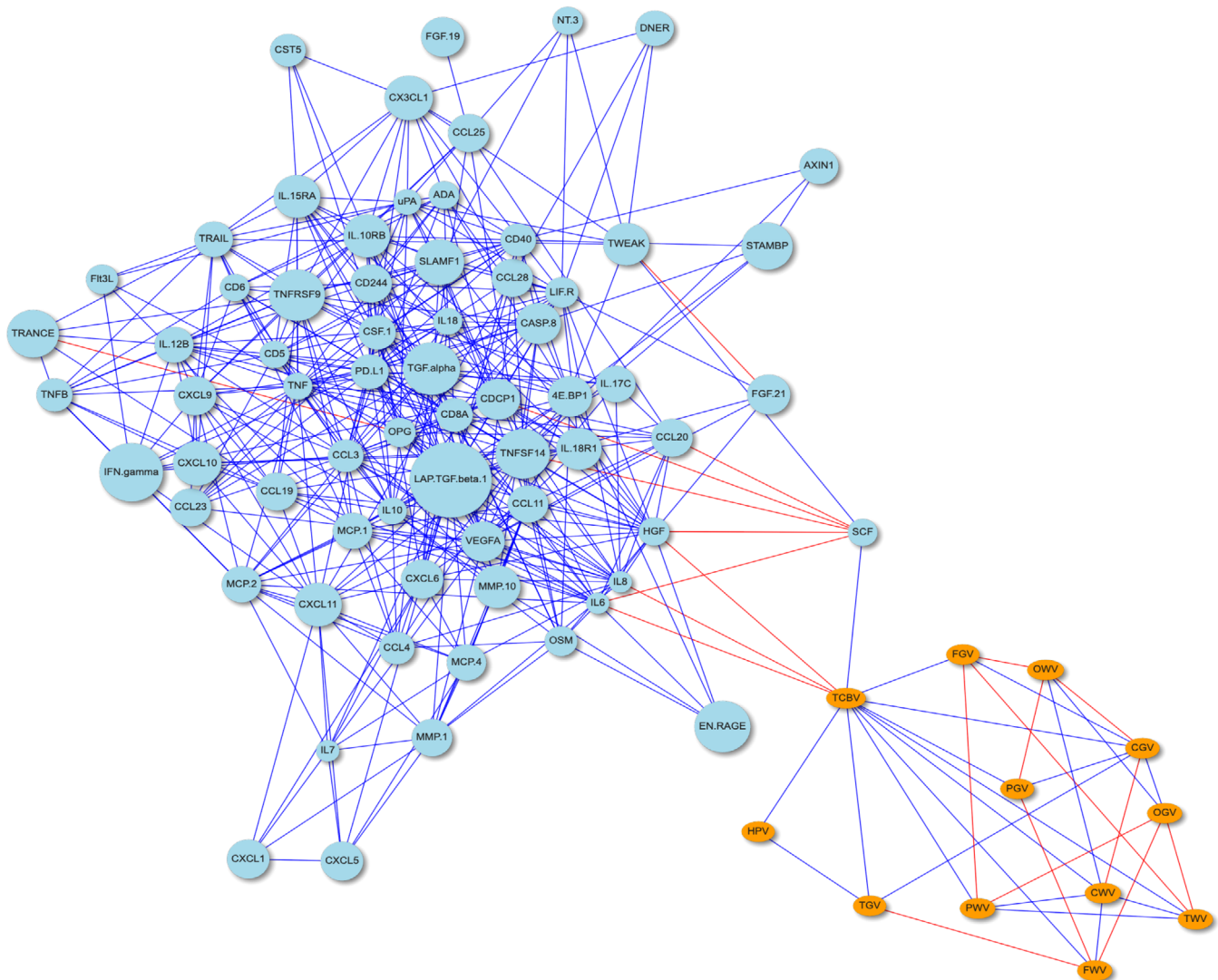


FIGURE 3 Unweighted conditional dependency networks inferred by FGL for male and female. For generating the networks, we include a total of 81 nodes, consisted of 68 proteins and 13 brain MRI measures. Nodes that have only degree of 1 will be excluded from being shown in the networks above. The sample size for the male (A) and female (B) is 306 and 335, respectively. FGL, fused graphical lasso; MRI, magnetic resonance imaging.

association between TCBV and SCF, and a negative association between TCBV and IL6, IL8, and HGF in males, whereas no associations were seen in females. These results underline differential associations between circulating inflammatory markers and brain imaging measures by sex. Our findings add to the knowledge base of the complex association of inflammation with dementia as we identify both protective and detrimental proteins related to early neuroimaging endophenotypes of dementia and AD.

A clear link has been established between intracranial brain volume and brain aging. Royle et al. showed that both the current and prior size of the brain serve as important indicators of current cognitive ability.³⁸ Wolf et al. also showed that intracranial volume could distinguish between cognitive normalcy and mild cognitive impairment (MCI) and between MCI and dementia.³⁹ It is hypothesized that a

larger brain volume has a greater neural reserve capacity, potentially contributing to a more extensive functional reserve. However, some studies showed no significant association between intracranial volume and risk of dementia.^{40–42} It is important to note that those studies had relatively small sample sizes and showed a similar direction of effect as the studies in favor of the hypothesis. Age-related alterations in the brain progress more rapidly in the presence of systemic inflammation. While inflammation is a nonspecific biomarker of dementia and AD, inflammatory markers play a significant role in the early stages of neurodegeneration. This role includes inhibiting angiogenic and neuroprotective mechanisms, leading to neuron loss and injury to myelin and a higher risk for cognitive impairment.⁴³ Our report showed an association between TCBV and circulating biomarkers related to different inflammatory cascades. For instance, IL6 and OPG are

(B) Conditional dependency network for female (n=335)

Blue edge: positive dependency, red edge: negative dependency

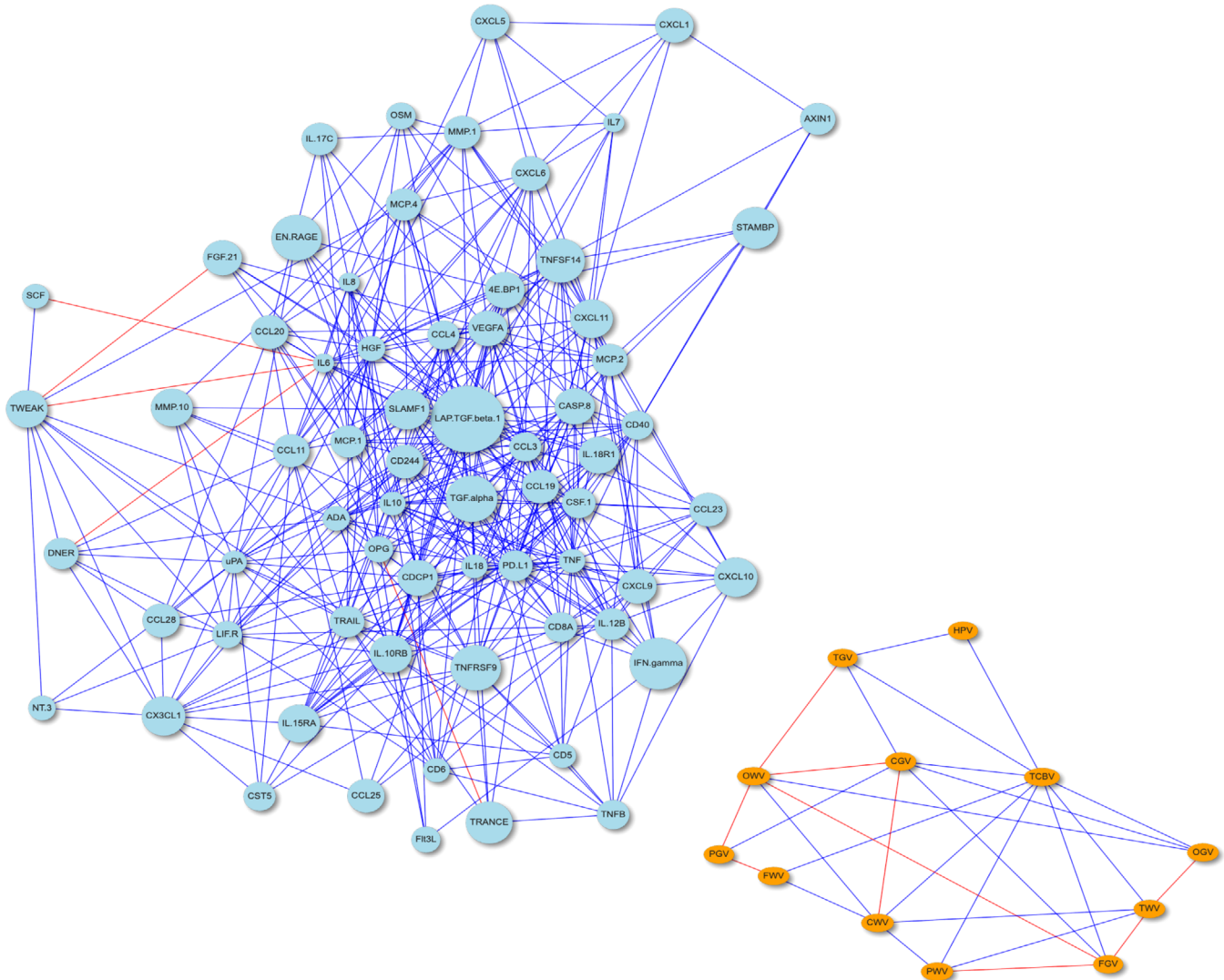


FIGURE 3 Continued

cardiovascular-related pro-inflammatory cytokines that have been associated with a higher risk for cardiovascular and neurodegenerative conditions.⁴⁴⁻⁴⁶ Moreover, CDCP1 (CD318) is an immunoinflammatory marker enhancing T-cell activation and infiltration, leading to increased production of proinflammatory cytokines.⁴⁷ Furthermore, 4E.BP1, part of the mTOR pathway, plays a role in regulating synaptic remodeling and regulating autophagy in neurons.⁴⁸ Higher levels of SCF and TWEAK were associated with larger TCBV, particularly in men. Consistent with our findings, research suggests SCF has neuroprotective properties in animal models.⁴⁹ Lower SCF plasma levels are associated with a faster cognitive decline in patients with AD.⁵⁰ Additionally, a small study of patients with AD receiving treatment with donepezil suggested that the treatment was associated with significantly higher SCF plasma levels and SCF levels correlated with improved cognitive scores.⁵¹ TWEAK, also known as tumor necrosis factor (ligand) superfamily member 12, participates in a wide range of

cellular activities, including proliferation, migration, apoptosis, inflammation, and angiogenesis. Importantly, previous work from our group identified an association between TWEAK and a lower risk of incident AD dementia,⁵² further supporting a potential protective role of TWEAK against neurodegeneration.

Age-related white matter changes are characterized by partial loss and pallor of myelin, loss of myelinated fibers, sparsely distributed macrophages, and malformation of myelin.⁵³ WMH is one of the major age-related white matter changes on MRI, partly due to small vessel disease related to aging and/or cardiovascular disease; however, the causes are multifactorial and non-specific. Another contributing factor is blood-brain barrier dysfunction, where small vessel alterations can lead to chronic fluid and macromolecule leakage in the white matter.⁵⁴ Cardiovascular risk factors such as hypertension and diabetes have been associated with WMH.^{55,56} Recent reports indicate that conventional cardiovascular risk factors contribute to the effect on white

matter as significantly as age does.⁵⁷ This is consistent with our data showing attenuated associations when adjusting for traditional CVD risk factors.

White matter atrophy has also been investigated as part of age-related changes. The Rotterdam study showed that age and cardiovascular risk factors are associated with smaller white matter volume.⁵⁸ The same cohort showed that white matter atrophy happened simultaneously with the formation of white matter lesions and not independently.⁵⁹

We report an association between CWV and FWV with three circulating biomarkers, namely HGF, IL8, and MMP10. We observed the association of these vascular related biomarkers in the frontal lobe which is the biggest and the most vulnerable cerebral lobe for vascular pathological insult.⁶⁰ Previous cross-sectional studies reported an association between high serum and CSF-HGF concentration and larger WMH in AD patients.^{61,62} HGF is a plasminogen-like growth factor with angiogenesis activity and plays a role in axon outgrowth, neuronal survival, and synaptic function.⁶³ IL8, a proinflammatory cytokine, has been associated with a higher risk for AD, but only in the presence of WMH.⁶⁴ Lastly, MMP-10 is a zinc-dependent enzyme. MMP-10 levels in CSF were associated with AD+ MCI and AD-dementia, while plasma MMP10 levels were not associated, despite a relatively high correlation between the two ($r = 0.312$, $FDR = 1 \times 10E-20$).⁶⁵

In sex-stratified models, several biomarkers were linked to reduced TCBV in males, while SCF and TWEAK were associated with larger TCBV. Two specific biomarkers, namely STAMP and TNFSF14, showed significant association with TCBV in male only. Both proteins have been reported to be associated with AD in human and mouse studies.^{66,67} Additionally, higher levels of CX3CL1 were associated with higher FGV. CX3CL1 is a CNS transmembrane chemokine which has been extensively investigated in the last few decades. Soluble form of CX3CL1 is suggested to be neuroprotective. Overexpression of the soluble CX3CL1 isoform reduced the effect of Tau, neuronal loss, and microglia activation in a mouse model.⁶⁸ Furthermore, an association between CCL3 and TWV was observed in the male subgroup. Reports suggested that CCL3 is involved in controlling glial activation and impacting cognitive functions.⁶⁹ In a transgenic mouse model of tauopathy called THY-Tau22, there was an observed increase in the levels of CCL3 along with the infiltration of T lymphocytes into the hippocampus.⁷⁰ CCL3 plays important role in trafficking of inflammatory cells across the blood brain barrier during inflammatory conditions.⁷¹

Despite a higher proportion of white matter changes in females, the impact of vascular risk factors such as hypertension and diabetes on the increased risk of developing WMH seems to be more pronounced in men.^{72,73} Midlife vascular risk factors have an impact on the rate of progression of vascular brain injury.⁷⁴

Sexual dimorphism in circulating protein levels has been reported in large-scale studies on healthy participants from the FHS and Dallas Heart Study.^{14,75} In our study sample males were observed to have a more adverse cardiovascular risk profile compared to females, and the associations between proteins and MRI outcomes were attenuated in models adjusting for cardiovascular covariates. This indicates the

involvement of cardiovascular pathways such as inflammation, adiposity, and fibrosis as mediators for these associations, which may explain the significant results observed in the male subgroup. Additionally, we do not discount the potential confounding effect influencing the observations.

Our study has several strengths, including the well-characterized, community-based cohort under continuous surveillance for dementia outcomes and with extensive, long-term data collection protocols for preclinical dementia phenotypes including neuroimaging. The inclusion of a wide array of inflammatory markers, alongside numerous total, and regional brain measures, significantly enriches our analytical scope, enhancing the exploration of the link between inflammation and structural brain changes. The inclusion of a dementia-free sample ensures a cross-sectional baseline measurement of the association between inflammatory biomarkers and brain changes.

Several limitations should be noted. First, the majority of FHS participants self-report as non-Hispanic White, potentially limiting the generalizability of our findings to other racial and ethnic populations. Second, the inflammatory biomarker data collection was conducted at a single time point, restricting our ability to capture longitudinal fluctuations in relation to brain volumes. Declines in inflammation over time have been observed to be associated with MRI indicators of brain health whereas transition to higher levels over time portend worsening white matter changes.⁵³ As our study is observational and cross-sectional, it cannot establish causal relationships. Additionally, the sample size may be a limitation, potentially obscuring some associations due to its scale.

To conclude, our analysis has revealed complex connections involving inflammatory biomarkers and brain volumes, offering insights into their potential roles in neurodegeneration. The initial model highlighted significant associations between increased levels of CDCP1, IL6, OPG, 4E.BP1, HGF, IL8, and MMP10, and adverse brain volume outcomes. Moreover, favorable brain volume changes were associated with SCF and TWEAK. Although some associations were moderated in the fully adjusted model, their trends remained. Furthermore, CX3CL1 demonstrated a significant connection with FGV, while HGF, IL6, IL8, MMP10, and 4E.BP1 displayed adverse associations with white matter volumes. Notably, CCL3 exhibited an adverse association with TWV. In males, certain biomarkers were associated with brain volume measures, unlike in females. Taken together, these findings underscore the complex interplay of specific inflammatory protein biomarkers in association with changes in brain structure, providing deeper insights into potential mechanisms underlying neurodegeneration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this study. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

Each participant provided written informed consent during each examination attended as part of the Framingham Heart Study (FHS), a procedure evaluated and approved by the Institutional Review Board (IRB) at Boston University Medical Center (BUMC). The IRB number for the ongoing FHS at BUMC is H-32132, whereas for the present study, it is H-39876.

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SUPPORTING INFORMATION

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

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