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Insulin-Like Growth Factor, Inflammation, and MRI Markers of Alzheimer's Disease in Predominantly Middle-Aged Adults

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CONFLICTS OF INTEREST

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Abstract

Background: Insulin-like growth factor 1 (IGF-1) signaling has been implicated in Alzheimer's disease pathogenesis, and further evidence suggests inflammation can be a moderator of this association. However, most research to date has been conducted on older adults.

Objective: To investigate the association of serum IGF-1 and IGF binding protein 3 (IGFBP-3) concentrations with MRI markers of Alzheimer's Disease in predominantly middle-aged adults, and further assess moderation by chronic inflammation.

Methods: We included participants from the Framingham Heart Study (n=1852, mean age 46±8, 46% men) and the Study of Health in Pomerania (n=674, mean age 50±13, 42% men) with available serum IGF-1, IFGBP-3, as well as brain MRI. IGF-1 and IFGBP-3 were related to MRI outcomes (i.e., total brain, cortical gray matter, white matter, white matter hyperintensities (WMH), and hippocampal volumes) using multivariable regression models adjusting for potential confounders. Subgroup analyses by C-reactive protein (CRP) concentrations were also performed. Cohort-specific summary statistics were meta-analyzed using random-effects models and corrected for multiple comparisons.

Results: Meta-analysis results revealed that higher IGF-1 concentrations were associated with lower WMH (estimate [β] [95% CI], −0.05 [−0.09, −0.02], p=0.006) and larger hippocampal volumes (0.07 [0.02, 0.12], p=0.01), independent of vascular risk factors. These associations occurred predominantly in individuals with CRP concentrations <75th percentile. We did not observe associations between IGFBP-3 and MRI outcomes.

Conclusion: Our findings suggest that IGF-1-related signaling may be implicated in brain health as early as midlife.

INTRODUCTION

Impaired insulin-like growth factor (IGF-1) signaling has been proposed as a contributing factor to Alzheimer's disease (AD) [1–4]. IGF-1 promotes cell survival and stimulates neurogenesis [5]. Furthermore, IGF-1 prevents abnormal oligomerization and aggregation of Aβ protein [1,6]. IGF-1 also regulates phosphorylation of tau [1]. Therefore, concentrations of bioavailable IGF-1, regulated by IGF binding proteins (IGFBP) [7], could be an important factor in the pathogenesis of AD. Prior studies [8–13] have related lower blood IGF-1 concentrations to an increased risk of cognitive impairment and brain atrophy. Other investigations suggest that once the disease has progressed, AD patients present with higher IGF-1 concentrations compared to non-demented controls [14,15] as the brains of individuals affected by AD may be resistant to IGF-1, particularly in the hippocampal region [16].

Prior studies relating blood IGF-1 concentrations to MRI have focused on older adults. However, studies investigating the relationship between IGF-1 concentrations and brain MRI measures in younger adults are lacking. Studies also suggest that inflammation disrupts IGF-1 signaling, leading to neurodegeneration [17], but associations between IGF-1 or IGFBP-3, and MRI have not been investigated in the context of inflammation. Elevated C-reactive protein (CRP), a marker of systemic inflammation, has been independently associated with neurodegeneration [18,19]. Therefore, our aim was to investigate the association of serum concentrations of IGF-1 and its binding protein, IGFBP-3, with MRI markers of early brain aging and Alzheimer's Disease, and additionally to assess these associations by serum CRP concentrations in predominantly middle-aged adults from the Framingham Heart Study (FHS) and the Study of Health in Pomerania (SHIP)-TREND.

METHODS

Study Design and Participants

The FHS is a community-based, longitudinal cohort study that began in 1948 in Framingham, Massachusetts [20]. Since its inception, three generations of participants have been enrolled [21,22], and the present study focuses on the Third-Generation cohort. This cohort began in 2002 with the recruitment of 4095 children of the offspring and grandchildren of the original cohort. Participants have been evaluated at two examination cycles and a third examination is currently underway, where detailed information on cardiovascular risk factors, blood pressure, anthropometric measurements, and prevalent cardiovascular disease are being collected. Our study sample includes dementia-free participants who provided blood samples at exam 1 (2002–2005) and who underwent brain MRI close to exam 2 (2008–2011).

The SHIP-TREND cohort is a community-based, longitudinal cohort study comprised of participants aged 20 to 79 years who were randomly selected from population registries in Northeast Germany [23]. The baseline examinations (SHIP-TREND-0) were performed from September 2008 until September 2012 (n=4420). The study has collected extensive information on risk factors and health measures through medical examinations and self-administered questionnaires. As with the FHS sample, SHIP-TREND participants that were included were dementia-free, provided blood samples, and underwent brain MRI close to the time of blood sampling.

Both cohorts excluded participants who experienced stroke events, had large cerebral brain infarcts, or had other neurological disorders that could substantially influence the measurement of brain volumes. The final sample included 1,852 FHS and 674 SHIP-TREND participants with both brain MRI and IGF-related measurements available. Detailed insights on the sample selection within both cohorts can be found in the flowchart (Supplemental Figure 1).

All participants in the FHS provided written informed consent, and the study was approved by the Boston University Medical Center Institutional Review Board. SHIP-TREND was approved by the University of Greifswald ethics committee and meets the recommendations

of the Declaration of Helsinki, and all participants gave written informed consent before taking part in the study.

Definition of independent variables and covariates

In FHS, a 3 mL blood sample was collected from each participant in the morning after overnight fasting. Samples were centrifuged, aliquoted, and stored at −80°C. Standard ELISA was used to measure both serum IGF-1 (R&D Systems Quantikine Human IGF-I Cat#DG100, SG100 and PDG100) and serum IGFBP-3 (R&D Systems Quantikine Human IGFBP-3 Cat#DGB300). The intra-assay coefficients of variation were 5.3% for the IGF-1 assay and 9.1% for the IGFBP-3 assay [24]. Diabetes mellitus was defined as fasting blood glucose of ≥126 mg/dL or use of an antidiabetic therapy. Smoking was defined as current smoker in the year preceding the FHS examination. Our definition of cardiovascular disease included TIA, coronary heart disease, congestive heart failure, and peripheral vascular disease. CRP was measured using a nephelometer (BN100; Dade Behring, Deerfield, IL).

In SHIP-TREND, a non-fasting blood sample was collected from each participant between 07:00 AM and 04:00 PM, and serum aliquots were prepared for immediate analysis and for storage at −80 °C in the Integrated Research Biobank (Liconic, Liechtenstein). Chemiluminescent immunometric assays were used to measure serum IGF-1 and IGFBP-3 (Immulite 2500, Siemens Healthcare Medical Diagnostics) and the inter-assay coefficients of variation were 3.5% or 8.3% at high level, 4.3% or 8.8% at median level, and 6.3% or 10% at low level in the IGF-1 or IGFBP-3 assay, respectively [25]. Diabetes mellitus was defined as Glycated hemoglobin HBA1c ≥6.1 % or treatment for diabetes. Smoking was defined as current or former smokers. The definition of cardiovascular disease included myocardial infarction and stroke. CRP was measured using a nephelometer (Behring Nephelometer II (Dade Behring)) [26].

CRP concentrations were dichotomized by the 75^{th} percentile (FHS=2.91 mg/L, SHIP-TREND=2.33 mg/L) into top quartile vs. bottom three quartile concentrations in each cohort, where the top quartile may be indicative of low-grade inflammation.

In additional sensitivity analyses, we excluded individuals with CRP levels indicative of acute inflammation or infection (CRP > 10 mg/L) from this top quartile [27]. The number of participants with CRP > 10 mg/L in FHS was N=22 and in SHIP-TREND was N=18.

MRI outcomes

Brain MRI for FHS participants was acquired using a 1.5T Siemens Avanto scanner (version syngo MR B15). We used 3D T1-weighted coronal spoiled gradient-recalled echo images and fluid attenuated inversion recovery (FLAIR) sequences. The segmentation and quantification of white matter hyperintensities (WMH) was performed on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure based on a previously published method of histogram fitting [28]. The segmentation of gray and white matter volumes was based on an Expectation-Maximization algorithm that iteratively refines its segmentation estimates to produce outputs that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness. The segmentation was refined using a Markov Random Field model and an adaptive priors

model [29]. Hippocampal volume was computed using a segmentation method that employs a standard atlas based diffeomorphic approach [30], with the minor modification of label refinement. We further modified this methodology to include the EADC-ADNI harmonized hippocampal masks as previously described [31]. Total intracranial volume was derived from 3D T1 after removal of non-brain tissues. The skull was removed using an atlas-based method [32] followed by human quality control to provide generally minor cleanup if needed.

Brain MRI in SHIP-TREND participants was acquired using a 1.5 T Siemens MRI scanner (Magnetom Avanto, Siemens Medical Systems). Axial MPRAGE and axial FLAIR sequences were used to derive WMH volumes [33] via a method based upon support vector machine [34]. The other brain phenotypes, including total intracranial volume, total brain volume, gray and white matter, and hippocampal volumes, were generated using FreeSurfer version 5.3.

Statistical Analysis

IGF-1 and WMH were natural-log transformed to normalize their skewed distributions. MRI volumetric measurements of total brain, cortical gray matter, white matter, WMH, and hippocampal volumes were separately regressed onto total intracranial volumes to account for differences in head size, and the residuals from each of these models were then standardized (mean=0, standard deviation=1) and used as the outcome measures. IGF-1 and IGFBP-3 concentrations were also standardized separately in each cohort (mean=0, standard deviation=1) to facilitate comparisons.

In each cohort, primary analyses consisted of assessing the association of IGF-1 or IGFBP-3 with each MRI outcome using multivariable linear regressions. Models were adjusted for age, age-squared, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and cardiovascular disease.

In secondary analyses, separately within each cohort, two sample t-tests were used to compare mean IGF-1 and IGFBP-3 concentrations by CRP subgroups (bottom three quartiles vs. top quartile). Each cohort also conducted stratified regression analyses by CRP subgroup adjusting for the same set of confounders included in the primary analysis. Finally, both the primary and CRP-based subgroup analyses were meta-analyzed using random effects models. Heterogeneity of effect sizes was assessed using Cochrane's Q tests and I^2 statistics. In addition to the stratified regression analyses, we included meta-analyses of the interaction of IGF-1 or IGFBP-3 and dichotomized CRP levels on the MRI outcomes.

Linear regressions for the stratified sensitivity analyses (excluding individuals with CRP > 10 mg/L) were conducted using the same models as the stratified secondary analysis and followed by an additional meta-analysis of the interaction by CRP levels.

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.4.2. Significance was set at a 5% threshold for main effects and CRP subgroup analyses. Finally, meta-analysis results were corrected for multiple comparisons using False

Discovery Rate (FDR) methods (reported as corrected p-values, p_c); we did not correct for multiple comparisons in the cohort-specific results as our main findings are derived from meta-analyses.

RESULTS

Baseline characteristics are reported in Table 1 and the age distributions of both cohorts can be found in Supplemental Figure 2. The participants in both cohorts were predominantly middle-aged adults (FHS: age 46.02±8.48, 46.17% men; SHIP: age 49.89±13.43, 42.43% men) with a low burden of cardiovascular disease. Compared to FHS, the SHIP-TREND cohort had higher systolic blood pressure, as well as a higher proportion of participants under antihypertensive medication and current smokers.

Cohort-specific and meta-analysis results adjusted for vascular risk factors are presented in Figure 1 for the main effects analyses. Meta-analysis results combining both cohorts showed that every SDU increase in IGF-1 concentrations was associated with reduced WMH burden (estimate [β] [95% CI], −0.06 [−0.09; −0.02], p=0.006). This association remained significant after correction for multiple testing (p_c=0.048). We also observed a protective association between IGF-1 and hippocampal volumes in meta-analysis combining both cohorts—every SDU increase in IGF-1 concentrations was associated with larger hippocampal volumes (0.07 [0.02; 0.12], p=0.01], which persisted after correction for multiple testing (p_c=0.048). Individually, these protective associations for WMH and hippocampal volume were nominally significant in FHS and had the same direction of effect in SHIP-TREND, although results did not reach nominal significance in this cohort alone.

Table 2 shows heterogeneity measures. Associations between IGFBP-3 and MRI outcome measures were heterogeneous between cohorts, particularly for total brain volume and white matter volume. We did not observe significant associations for IGFBP-3 in the meta-analysis.

In both FHS and SHIP-TREND, there were significant group differences between mean IGF-1 concentrations by CRP subgroups (p <0.001), but there were no group differences for IGFBP-3 concentrations (FHS p=0.933, SHIP-TREND p=0.073). Stratified association results by CRP subgroups are shown in Figure 2. Although we observed nominal associations for higher IGF-1 concentrations with lower WMH volumes (−0.05 [−0.09, −0.001], p=0.044) and larger hippocampal volumes (0.09 [0.03, 0.15], p=0.003) in participants with CRP concentrations <75th percentile, these results did not survive correction for multiple testing (p_c=0.07 and p_c=0.24, respectively). Another association at the nominal level was observed between higher IGF-1 concentrations and larger total brain volumes in participants with CRP concentrations ≥75th percentile (0.08 [0.01, 0.16], p=0.03, p_c=0.24). For the interaction analyses, we did not reveal any results that passed significance after correction for multiple testing. However, there was one nominal significant interaction of IGFBP-3 and CRP levels on cortical GM (−0.09 [−0.17, −0.01], p=0.02, p_c=0.20) (Figure 3).

The results of the sensitivity analyses (see Methods) by excluding individuals with CRP >10 mg/L from the ≥75th percentile were virtually unchanged (Supplementary Figure 3), for both the CRP subgroup and interaction analyses. Additional nominal significant interactions were observed for IGF-1 and CRP on WM (0.09 [0.00, 0.18], p=0.05, p_c=0.25) and for the interaction of IGFBP-3 and CRP on cortical GM (−0.10 [−0.18, −0.02], p=0.02, p_c=0.17) (Supplementary Figure 4).

DISCUSSION

Our findings suggest that circulating IGF-1 is associated with a lower burden of WMH and with larger hippocampal volumes, two important MRI predictors of early brain aging and AD, in predominantly middle-aged adults. Previous findings in older adults from FHS have shown that lower IGF-1 concentrations are associated with an increased risk of dementia and lower brain volumes [8]. The present work expands on those findings by showing that higher IGF-1 concentrations are associated with larger hippocampal volumes as early as the fifth decade across two population-based studies—twenty years before the usual age at which clinical dementia manifests. Additionally, we show that IGF-1 concentrations were related to reduced WMH burden, indicating not only a potential protective role in neurodegeneration, but also against cerebrovascular disease. Previous findings in adults with traumatic brain injury have shown that higher IGF-1 concentrations are associated with a greater improvement in white matter recovery over time [35]. Other studies have also reported that increases in IGF-1 concentrations are associated with decreased white matter damage after stroke in mice [36]. Together, our findings showing protective associations for IGF-1 with reduced WMH and preserved hippocampal volume supports existing reports of lower IGF-1 concentrations seen in AD patients [37–39]. IGF-1 is a neurotrophic factor that promotes cell differentiation, proliferation and myelination during brain development and maturation. In adults, IGF-1 modulates hippocampal neurogenesis and angiogenesis [40], which could explain part of the protective role to preserve the hippocampus and protect from vascular insults leading to WMH.

A recent Mendelian randomization study [41] suggested that epidemiologic studies have put undue emphasis on a relationship between circulating IGF-1 and IGFBP-3 concentrations and AD, as they found only one single nucleotide polymorphism in the FOXO3 gene, that impacts IGF-1 and IGFBP-3 concentrations, to be associated with AD risk. However, other reports [42–44] have found associations between IGF-1 related polymorphisms and dementia. These conflicting results might indicate that AD risk associated with IGF-1 and IGFBP-3 polymorphisms is dependent on other factors, such as age, environmental exposures (such as inflammation), or comorbidities.

Increasing focus is being given to the involvement of neuroinflammatory agents in the progression of AD [45]. While the relationship between systemic and CNS inflammation has yet to be established in this context, it has been shown that midlife systemic inflammation is associated with smaller current [46] and late-life brain volume on MRI [47]. Additionally, pro-inflammatory cytokines are able to cross the blood brain barrier and alter IGF-1 signaling [17]. IGF-1 can be complexed to IGFBP-3 in peripheral circulation, but unbound IGF-1 can freely cross the blood-brain barrier and modulate an effect in the CNS [48,49].

CNS and peripheral concentrations of IGF-1 and inflammatory markers often drive each other and are closely related, as shown in a rat model of sporadic AD [50]. Additionally, a positive association between concentrations of IGF-1 in the circulation and cerebrospinal fluid has been described in rats [51]. Our results of the CRP subgroup analyses showing that IGF-1 levels are related to larger hippocampal volumes predominantly in individuals with CRP concentrations <75th percentile compared to the upper percentile suggests, that CRP levels towards a low-grade systemic inflammation might alter IGF-1 signaling and its potential beneficial impact on brain health as indicated in other studies [52]. However, the lack of results in participants with CRP concentrations ≥75th percentile could simply reflect decreased power as this group is smaller. Considering that both the CRP-stratified results and the interaction test did not pass correction for multiple testing, these results should be interpreted with caution, and validation in a larger sample is needed to shed light on these findings. The lack of associations between IGFBP-3 and MRI outcomes, in contrast to IGF-1, may suggest that the regulation of IGF-1 bioavailability by IGF proteins may be less relevant for neuroimaging markers. We have recently shown that another binding protein member, IGFBP-2, although related to Alzheimer's Disease and all-cause dementia, was not associated with MRI measures in the Framingham Offspring cohort [31]. Additional research is needed to expand on these findings.

Strengths of this study comprise the inclusion of two community-based samples with large numbers of predominantly middle-aged adults with both blood biomarker and MRI data, and the adjustment for additional common vascular risk factors to control for potential confounding. A limitation of this study is the use of CRP, which is a non-specific marker of low-grade inflammation [53] and does not provide insight into which pathologies might be underlying chronic inflammation. Additionally, FHS and SHIP-TREND participants are largely of white European ancestry; therefore, our results might not be readily applicable to ethnically different populations until tested in separate, diverse samples. As indicated in Table 1, most of the cohort characteristics showed a statistically significant difference between FHS and SHIP-TREND which is not unexpected taking the underlying populations and large sample sizes into account where already small differences pass significance. However, the analyses were performed cohort-stratified correcting for these differences leaving only residual heterogeneity. Further, the algorithms to derive MRI measures were different in both cohorts and this might have introduced some heterogeneity, notably for total brain and white matter volume. Even though our analysis used standardized MRI measures, some heterogeneity may have remained. Finally, it is important to note that whereas SHIP performed MRI close to blood draw (about a month on average), in FHS, MRI was acquired 7.6 years on average after blood draw. This could potentially be another source of heterogeneity in our analysis. To address this limitation, cohort-specific analyses were corrected for the time interval between blood draw and MRI to obtain effect estimates independently of this time gap within cohorts, and have further performed random-effects meta-analysis to account for potential heterogeneity between cohorts. However, despite this discrepancy, we observed significant results, which indicate a robust association of IGF-1 with WMH and hippocampus volume. Our association of higher IGF-1 levels with higher hippocampus volume – a known marker for dementia, could at least partially explain the

association of higher IGF-1 with increased cognitive performance that was observed in other studies [54].

Thus, our study adds to the body of work investigating the role of IGF-1 in the progression of AD and its potential as a blood biomarker associated with early brain changes seen in predominantly middle-aged adults before the onset of dementia symptoms. IGF-1 has been put forth as a promising therapeutic target for AD given the evidence of its implications in the disease [50] and investigations into the link between the epidemiologic findings and possible molecular signaling mechanisms for the role of IGF-1 in AD are ongoing [55]. Animal studies have shown improvements of symptoms in AD models with administration of IGF-1. However, human trials administering IGF-1 or its homolog, insulin, to subjects with cognitive impairment have had limited success in achieving beneficial outcomes [6,56]. The continually growing evidence of a relationship between IGF-1 and Alzheimer's disease suggests that further human trials may still be worthwhile pursuits.

Our results suggest associations between IGF-1 and brain health in predominantly middle-aged adults. In the future, designing interventions targeted at individuals at high risk of AD (i.e. based on genetic, fluid, or neuroimaging biomarkers of AD) before the full manifestation of clinical symptoms could perhaps offer the most benefit from IGF-1 or insulin-based therapeutic strategies.

In summary, our findings suggest that IGF-1 signaling pathways could be implicated in abnormal brain aging as early as midlife. Further studies relating IGF-1 to brain aging and elucidating the potential role of inflammatory pathways are needed in other populations and experimental settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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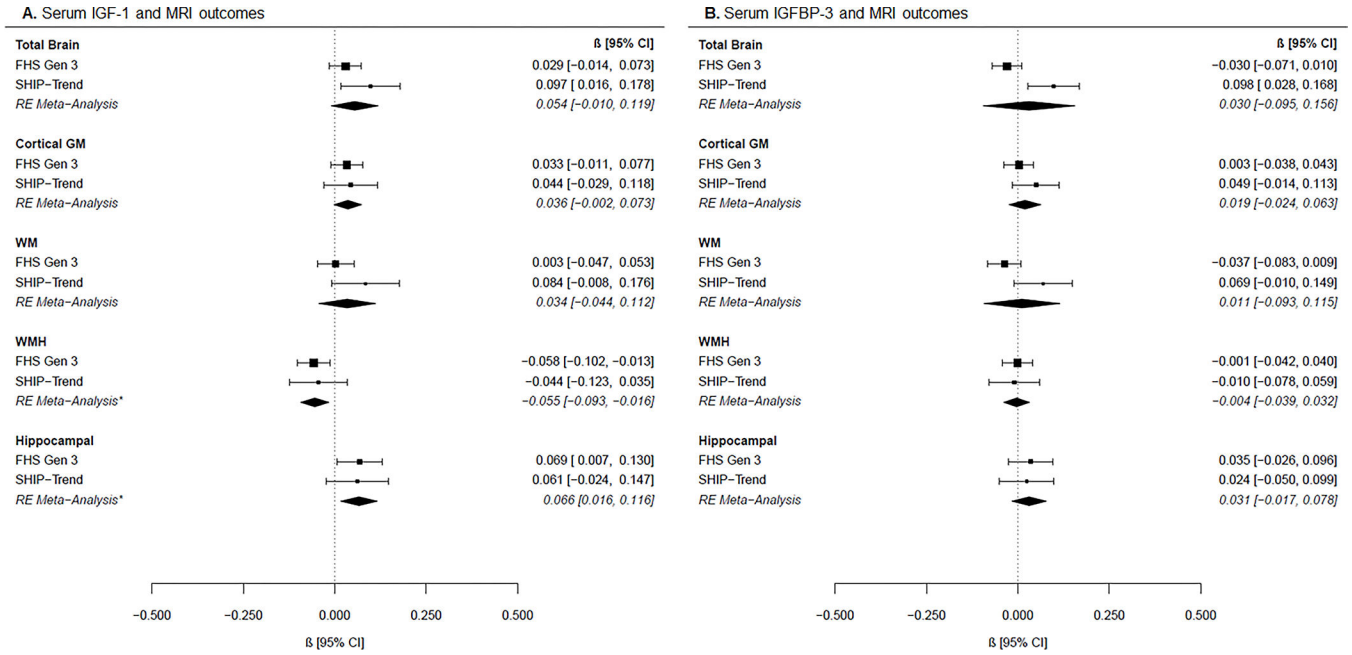

Figure 1. Associations between IGF-1 or IGFBP-3 with MRI outcomes.

Forest plots of cohort-specific and meta-analysis results for the associations between (A) IGF-1 and MRI measures, and (B) IGFBP-3 and MRI measures. Beta estimates and 95% confidence intervals (CI) are presented graphically in the center, where the square represents beta coefficients and the error bars the 95% confidence intervals per cohort according to the text on the right column. Meta-analysis results derived from random-effects (RE) models are presented with diamonds and italicized text. Models are adjusted for age, age-squared, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease. *p<0.05 after FDR correction.

Abbreviations: FHS: Framingham Heart Study Generation 3, SHIP: Study of Health in Pomerania Trend, RE Meta-Analysis: random effects meta-analysis, IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein-3, GM: gray matter, WM: white matter, WMH: white matter hyperintensity.

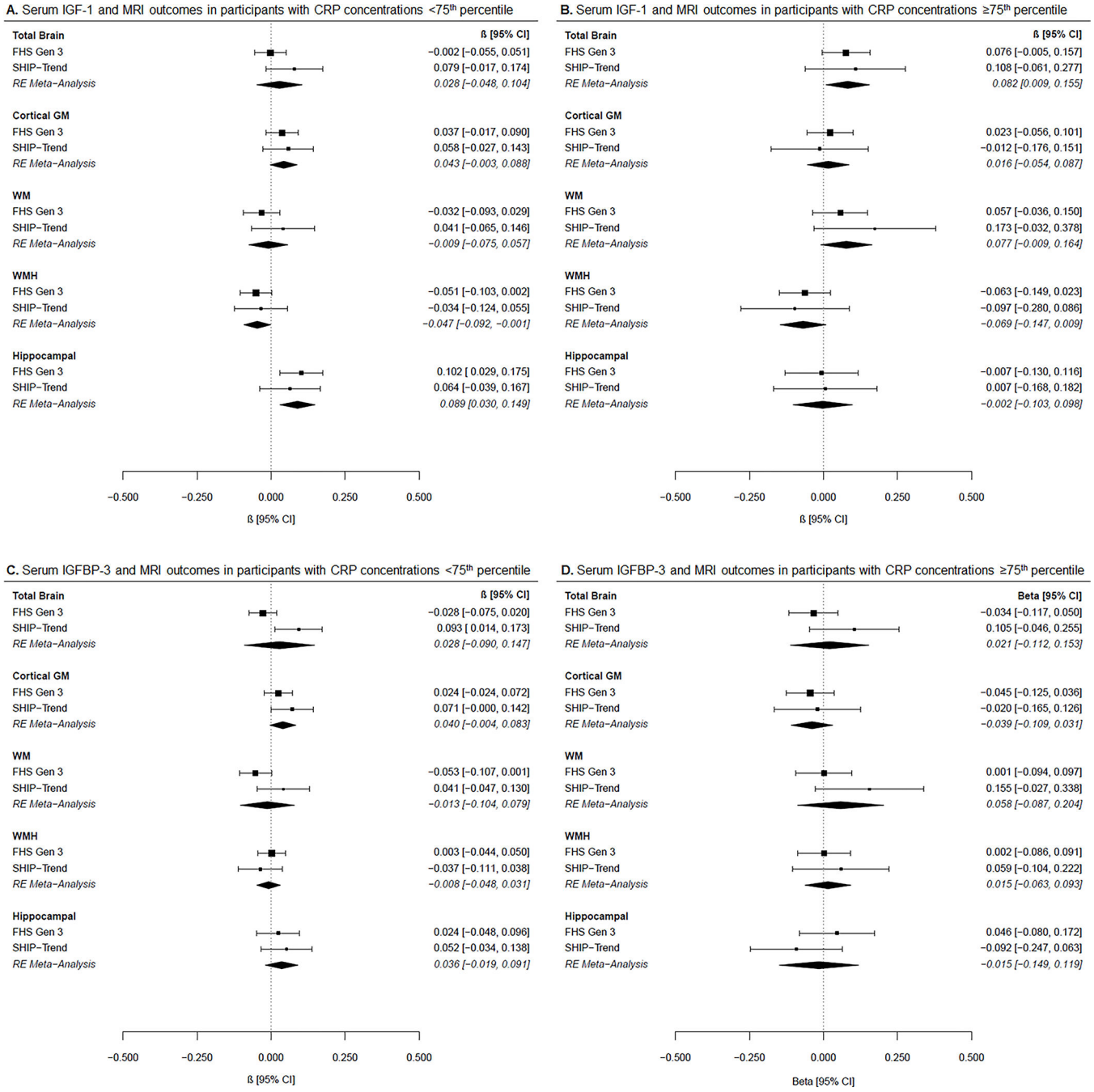

Figure 2. Associations between IGF-1 or IGFBP-3 with MRI outcomes by CRP subgroups.

Forest plots of cohort-specific and meta-analysis results for the associations between (A) IGF-1 and MRI measures in participants with CRP concentrations <75th percentile, (B) IGF-1 and MRI measures in participants with CRP concentrations ≥75th percentile, (C) IGFBP-3 and MRI measures in participants with CRP concentrations <75th percentile, and (D) IGFBP-3 and MRI measures in participants with CRP concentrations ≥75th percentile. Beta estimates and 95% confidence intervals (CI) are presented graphically in the center, where the square represents beta coefficients and the error bars the 95% confidence intervals

per cohort according to the text on the right column. Meta-analysis results derived from random-effects (RE) models are presented with diamonds and italicized text. Models are adjusted for age, age-squared, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease. *p<0.05 after FDR correction.

Meta-analysis results are derived from random-effects models and presented in italic. </P>Abbreviations: FHS Gen 3: Framingham Heart Study Generation 3, SHIP-TREND: Study of Health in Pomerania TREND, IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein-3, GM: gray matter, WM: white matter, WMH: white matter hyperintensity, CRP: C-reactive protein

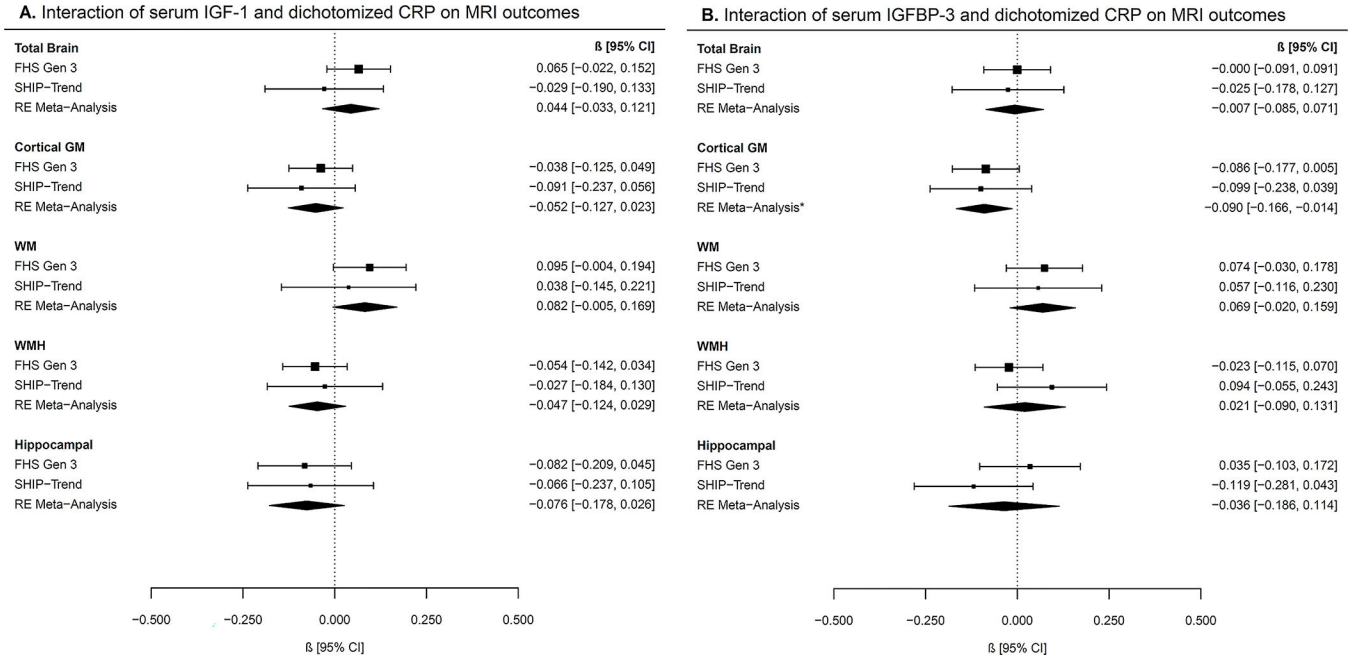

Figure 3: Interaction of IGF-1 or IGFBP-3 and CRP on MRI outcomes.

Forest plots of cohort-specific and meta-analysis results for the interactions of (A) IGF-1 and dichotomized CRP on MRI measures and (B) IGFBP-3 and dichotomized CRP on MRI measures. CRP was dichotomized according to the 75th percentile (<75th percentile, ≥75th percentile).

Beta estimates and 95% confidence intervals (CI) are presented graphically in the center, where the square represents beta coefficients and the error bars the 95% confidence intervals per cohort according to the text on the right column. Meta-analysis results derived from random-effects (RE) models are presented with diamonds.

Models are adjusted for age, age-squared, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease.

Abbreviations: FHS Gen 3: Framingham Heart Study Generation 3, SHIP-TREND: Study of Health in Pomerania TREND, IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein-3, GM: gray matter, WM: white matter, WMH: white matter hyperintensity, CRP: C-reactive protein

Table 1.

Characteristics of study cohorts

	FHS Gen 3 (n=1852)	SHIP-TREND (n=674)	p-value*
Men, n (%)	855 (46.17)	286 (42.43)	0.105
Age at blood draw, mean (SD)	46.02 (8.48)	49.89 (13.43)	<0.001
Blood draw to MRI interval (days), mean (SD)	2770.76 (327.55)	28.69 (64.84)	<0.001
Systolic blood pressure, mean (SD)	116 (14)	124 (17)	<0.001
Antihypertensive medication, n (%)	327 (17.69)	186 (27.60)	<0.001
Diabetes mellitus, n (%)	82 (4.43)	32 (4.75)	0.815
Current smoking, n (%)	164 (8.86)	136 (20.18)	<0.001
Prevalent cardiovascular disease, n (%)	33 (1.78)	5 (0.74)	0.086
Waist/hip ratio, mean (SD)	0.91 (0.08)	0.87 (0.09)	<0.001
CRP mg/L, median (Q1, Q3))	1.26 (0.59, 2.91)	1.13 (0.60, 2.33)	0.013
IGF-1 ng/mL, median (Q1, Q3)	125.57 (101.48, 153.15)	140.2 (110.3, 170.7)	<0.001
IGFBP-3 ng/mL, mean (SD)	3038.93 (1075.67)	4282 (1000.85)	<0.001
MRI volumes, cm^3			
Total Intracranial, mean (SD)	1261.34 (125.09)	1574.33 (154.80)	<0.001
Total Brain, mean (SD)	997.40 (102.06)	1115.47 (113.12)	<0.001
Cortical GM, mean (SD)	479.96 (46.29)	447.42 (49.27)	<0.001
WM, mean (SD)	472.31 (58.26)	476.80 (59.29)	0.088
WMH, median (Q1,Q3)	0.40 (0.21, 0.82)	0.16 (0.06, 0.40)	<0.001
Hippocampal, mean (SD)	6.85 (0.72)	4.00 (0.43)	<0.001

* p-values are based on t-tests for continuous and chi-square-tests categorical variables. For CRP, IGF-1, and WMH the t-tests are based on the log-transform of these variables.

Abbreviations: CRP: C-reactive protein, IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor binding protein 3, GM: gray matter, Q: quartile; SD: standard deviation; WM: white matter, WMH: white matter hyperintensity

Table 2.

Heterogeneity measures for the associations between IGF-1 or IGFBP-3 and MRI outcomes

Outcome	IGF-1 Heterogeneity			IGFBP-3 Heterogeneity		
	Q	Q p-value	I^2	Q	Q p-value	I^2
Total brain	2.09	0.15	52.13	9.65	<0.01	**89.63**
CRP (Q1–3)	2.08	0.15	51.91	6.58	0.01	**84.80**
CRP (Q4)	0.11	0.74	0.00	2.48	0.12	59.66
Cortical GM	0.07	0.79	0.00	1.46	0.23	31.48
CRP (Q1–3)	0.18	0.68	0.00	1.15	0.28	13.21
CRP (Q4)	0.14	0.70	0.00	0.09	0.77	0.00
WM	2.34	0.13	57.17	5.15	0.02	**80.58**
CRP (Q1–3)	1.35	0.25	25.82	3.15	0.08	68.29
CRP (Q4)	1.02	0.31	1.99	2.15	0.14	53.49
WMH	0.09	0.77	0.00	0.04	0.84	0.00
CRP (Q1–3)	0.10	0.76	0.00	0.77	0.38	0.00
CRP (Q4)	0.11	0.74	0.00	0.36	0.55	0.00
Hippocampal	0.02	0.89	0.00	0.05	0.83	0.00
CRP (Q1–3)	0.34	0.56	0.00	0.25	0.62	0.00
CRP (Q4)	0.02	0.90	0.00	1.83	0.18	45.24

Models are adjusted for age, age-squared, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease. Fields in bold font show associations with high heterogeneity.

Abbreviations: IGF-1: insulin-like growth factor 1, IGFBP-3: insulin-like growth factor binding protein-3, Q: quartile; WMH: white matter hyperintensity.