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Relationships of Inflammation Trajectories with White Matter Volume and Integrity in Midlife

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Abstract

Objective: Elevated inflammation is associated with worse late-life cognitive functioning and brain health. Our goal was to examine the relationship between inflammation trajectories and white matter integrity in midlife.

Methods: Participants were 508 adults from the Coronary Artery Risk Development in Young Adults Study (CARDIA; 51% female). Latent class analysis was used to identify inflammation trajectories based on repeated measures of the inflammatory marker C-reactive protein (CRP) over the 18 years before brain magnetic resonance imaging (MRI). Outcomes were brain MRI measures of total and region-specific white matter volume and integrity at a mean age of 50.6±3.4 years. Linear regression was used to examine if inflammation trajectories were associated with brain MRI outcomes, adjusting for potential confounds in all models and for disease and health behaviors in follow-up models.

Results: Lower-stable (38%), moderate-increasing (7%), and consistently-higher (54%), trajectories emerged. Compared to the lower-stable group, the moderate-increasing group showed

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lower white matter volume (β = –0.18, 95% CI –0.29, –0.06) and worse white matter integrity as indexed by lower fractional anisotropy (FA; β = –0.37, 95% CI –0.70, –0.04) and higher mean diffusivity (β = 0.44, 95% CI 0.11, 0.78) in the whole brain. The consistently-higher group showed lower whole-brain FA (β = –0.20, –0.38, –0.03). In exploratory analyses, the moderate-increasing group showed lower white matter volume, lower FA and higher MD in the frontal, temporal, and parietal lobes compared to the lower-stable group. The consistently-higher group showed lower white matter volume in the parietal lobe and lower FA in the frontal, temporal, and parietal lobes, but similar MD, compared to the lower-stable group. Findings for the moderate-increasing, but not the consistently-higher, group were robust to adjustment for disease and lifestyle factors.

Conclusion: Increasing or high inflammation trajectories from early to mid adulthood are associated with worse brain health, as indexed by lower white matter volume and/or worse white matter integrity.

Keywords

Inflammation; White Matter; Midlife; Brain Structure; DTI

Introduction

As the global population ages, there is a pressing need to identify biomarkers and mechanisms of age-related cognitive decline.[1] Elevated inflammation has emerged as a predictor and potential mechanism of both cognitive impairment and dementia in older individuals.[2–4] Although the neural underpinnings of the relationship between inflammation and cognitive decline remain unclear, it appears that elevated peripheral inflammation negatively impacts brain structure, and particularly white matter integrity, in late life.[5–8] In turn, impairments in white matter integrity appear to play a role in age-related cognitive decline.[9–11] Given that cognitive impairment in late life typically emerges due to changes that occur over decades, it is critically important that we better understand the relationship of inflammation and brain health across the lifespan.

Research in non-human model systems has shown that neuroinflammation can lead to neurodegeneration, the death of neurons, and impair neurogenesis, the growth of new neurons.[12–16] *In vitro* evidence also indicates that neuroinflammation can damage neurons and oligodendrocytes.[13,16–18] A key issue is whether peripheral inflammation, which can be easily measured in humans, is related to the neuroinflammation that impacts brain structure. Although the brain was long considered an immune-privileged site, there is increasing recognition of great potential for crosstalk between peripheral and central immune systems.[19,20] In line with this, experimental studies in rodents have shown that peripheral inflammation can elicit neuroinflammation.[21–23] Moreover, circulating blood levels of the systemic inflammatory marker C-reactive protein (CRP) appear strongly associated with cerebrospinal fluid levels of multiple inflammatory markers including CRP in humans.[24] Thus, peripheral inflammation may be a valuable index of neuroinflammation and possibly even a clinically useful biomarker.

A large body of literature has documented cross-sectional associations of elevated peripheral inflammatory markers with reduced white matter volume and worse white matter integrity in

late life.[5,7,8,25] Accumulating evidence indicates that elevated inflammation may also prospectively predict late-life white matter volume and integrity.[26] A better understanding of the relationship between inflammation and white matter degradation will require that we clarify the effects of chronic patterns of inflammation on white matter. In this vein, an emerging literature has begun to define the trajectories of inflammatory activity in mid to late life that predict late-life white matter volume and integrity.[6,8,27] Overall, this literature indicates that increasing or consistently high levels of inflammation have particularly deleterious effects on late-life brain structure.[6,27] Trajectories of inflammation may also be important for white matter integrity in midlife, a time when intervention may be more effective.

Using prospective data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we examined whether early to midlife inflammation trajectories influence brain structure in midlife. We hypothesized that "problematic" trajectories of inflammation (i.e., increasing or consistently high) would be associated with lower white matter volumes and reduced white matter integrity, as assessed by lower fractional anisotropy (FA) and higher mean diffusivity (MD), at midlife.

Methods

Study Design and Sample

Participants are from CARDIA, a multi-site longitudinal study of 5,115 adults, initially healthy and aged between 18 and 30 years (55% female, 52% Black) at enrollment in 1985–1986.[28] CARDIA participants were recruited from four U.S. cities (Birmingham, AL; Minneapolis, MN; Chicago, IL; and Oakland, CA) and completed a baseline visit and eight follow-up visits at Years 2, 5, 7, 10, 15, 20, 25, and 30.[28,29] Among all CARDIA participants, 3,929 had at least three CRP measures from Years 7, 15, 20, or 25, which were in the 18 years prior to and the same year as the Brain MRI visit. Of these, 2,194 were eligible for inclusion in our trajectory analysis.

At the Year 25 visit, a subset of CARDIA participants completed neuroimaging as part of the CARDIA Brain Magnetic Resonance Imaging (MRI) Ancillary Study,[30] which is a sub-study designed to identify predictors of brain structure. This sub-study was conducted at three sites (Birmingham, AL; Minneapolis, MN; and Oakland, CA). The CARDIA Brain MRI sub-study enrolled participants at the time of scheduling of the Year 25 appointments. The sub-study aimed for balance within four strata of ethnicity/race (black, white) and sex (male/female), and across three CARDIA field centers (Birmingham, AL, Minneapolis, MN, and Oakland, CA). Each field center had a Brain MRI sub-study target sample size. When they reached their target enrollment, recruitment ceased. Exclusion criteria for the MRI substudy included any contra-indication to MRI or a body size that was too large for the MRI tube bore. Further details regarding the design of CARDIA and the Brain MRI ancillary study have been previously reported.[33]

Out of the 695 participants who had data available from the neuroimaging sub-study at Year 25, 508 (72%) were eligible for inclusion in our trajectory analysis. These 508 participants (mean age at brain scan = 50.6±3.4, 51% female, 34% Black) were included in the analytic

models to investigate the association between the inflammatory trajectories and midlife brain structure. Characteristics of individuals included versus excluded based on eligibility for the trajectory analysis are included in Supplementary Table 1. Participants with MRI data who were excluded from our models had a lower educational level, were more likely to be younger, male, White, and smokers, and to have elevated body mass index, lower levels of physical activity, and liver disease (BMI) ($p < 0.05$).

Participants provided written informed consent at each study visit and separately for participation in the CARDIA Brain MRI Ancillary Study. Study protocols were reviewed and approved by the institutional review boards at each site and by the CARDIA Coordinating Center.

Measures

Inflammation.—The systemic inflammatory marker CRP was measured in Years 7, 15, 20, and 25. Participants were asked to fast for at least eight hours and to avoid smoking and heavy physical activity for at least two hours before each blood collection. Plasma for CRP assays was separated from whole blood and stored at –70°C before being shipped on dry ice to a central laboratory for storage. A particle-enhanced immunonepholometric assay was conducted on a Siemens Dade Behring BN II Nephelometer to assess CRP levels in Years 7 to 20 (range: 0.175–1,000 mg/L). Intra-assay coefficients of variation (CVs) were 2.3–4.4% and inter-assay CVs were 2.1–5.7%. A Roche latex-particle enhanced immunoturbidimetric assay kit and the Roche Modular P Chemistry analyzer was used to assess CRP levels in Year 25 (range: 0.175–1,000 mg/L) with an intra-assay CV of 3.7%. Participants who had three detectable (0.175mg/L) CRP levels 10 mg/L were included in our analyses because at least three measures are required to define a trajectory over time.[31] CRP data was missing for 4.1%, 1.6%, 1.5% and 0.7% of participants at Year 7, 15, 20, and 25 respectively. Values >10 mg/L were excluded because of the possibility that they were due to acute inflammation from recent infection or injury, and our inability to distinguish between high inflammation due to acute illness or chronic factors.[32] Values > 10 mg/L were excluded for 5.7%, 7.2%, 4.8%, and 7% of cases in Years 7, 15, 20, and 25 respectively.

Brain Structure.—Structural MRI and diffusion tensor imaging (DTI) scans were completed in 3 Tesla (3T) magnetic resonance scanners (Philips 3T Achieva/2.6.3.6 platform in Birmingham, AL; Siemens 3T Tim Trio/VB 15 platform in Minneapolis, MN; and Siemens 3T Tim Trio/VB 15 platform in Oakland, CA) using standardized protocols in Year 25. More detailed neuroimaging methods are provided in Launer et al. (2015).[33] In brief, structural MRI images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using an automated multispectral computer algorithm that classifies all supratentorial brain tissue into gray matter, white matter, and CSF.[33] White matter was further characterized as normal and abnormal and then parcellated into regions of interest based on the Jakob Atlas.[34–36] We examined total, frontal, temporal, parietal, and occipital white matter volumes corrected for intracranial volume (ICV; sum of total brain volume plus cerebrospinal fluid) to account for variability in head size. Normal volumes in each lobe were combined across left and right hemispheres, then divided by ICV to calculate the volume to ICV ratio. DTI was used to compute voxel-wise maps of white matter integrity, as

indexed by FA and MD: Plane Axial Coil 12-channel Psd File name ep2d diff MDDW: TR 7300 TE 84 Fov 245 Thickness 2.2mm distance factor 0% Diff Directions- 33 Concatenations = 1 number sl = 64 Flip 90 Matrix 128×128 NSA 1 Center Freq. water Phase FOV = 100 Pixel BW = 1860 diff mode = Free Phase part fourier = 7/8 Echo spacing = .59 diff weighting = 1 Accel factor = 3 EPI factor = 112 Base Res 112 Phase res 100%; 2 times.[37] The FA measure estimates the degree or uniformity to which water diffuses along the direction of myelinated tracks in the white matter. FA scores range from 0 to 1 with lower scores indicating worse white matter integrity. The MD measure reflects the diffusivity of water such that reduced tissue density is associated with higher MD, indicating worse white matter integrity. We examined white matter integrity (FA, MD) overall and by lobe, such that mean values overall and within specific lobes were averaged across the left and right hemispheres.

Other Covariates.—We used covariates as assessed at Year 25, which was the same annual assessment as the Brain MRI. Demographics, current smoking (coded as smoker vs. non-smoker), and alcohol use (drinks per week) were based on self-report. BMI was defined as the average weight in kilograms divided by height in meters squared. Physical activity total scores were measured using the CARDIA Physical Activity questionnaire.[38] Presence of chronic disease (asthma, kidney problems, liver disease, heart problems, cancer/tumor, HIV, sleep apnea, stroke/TIA and multiple sclerosis) was assessed via a combination of self-report, physician diagnoses, and medication use. Cardiovascular risk factors including diabetes, hypertension, and high cholesterol were defined via a combination of self-report, medication use, and clinic assessments. The Center for Epidemiologic Studies (CESD) was used to assess depressive symptoms.[39]

Data Analysis

We generated inflammation trajectories using latent class growth analysis, a semi-parametric approach that differentiates groups of individuals based on their probability of following a similar trajectory on an outcome over time.[40,41] We used SAS PROC TRAJ to estimate trajectories of inflammation as indexed by CRP across visits at Years 7, 15, 20, and 25. We used natural log transformations for CRP to account for skewed distributions and modeled repeated CRP measurements as censored normal.[42] Model selection procedures were guided according to recommended procedures and we required that each trajectory include at least 5% of participants.[42] We fit 2-, 3-, and 4-class models[40,41] and for each model in which a given number of trajectories was selected, we evaluated cubic, quadradic, and linear terms to identify the trajectory shapes that best fit the data. We then determined the number of trajectories to keep by calculating the Log Bayes factor, which compares the Bayesian Information criterion (BIC) values between models and indicates that the more complex model with lower BIC better fits the data.[40]

Next, we selected the subset of original CARDIA participants who completed the neuroimaging sub-study and used descriptive statistics to compare characteristics of those with different inflammation trajectories in Year 25, the same year as the Brain MRI sub-study. To examine the association between inflammation trajectories and brain structure, we estimated a series of linear regression models. Our primary outcomes were whole-brain

measures of white matter volume, FA and MD. Exploratory outcomes included lobe-specific measures of white matter volume, FA and MD for the frontal, temporal, parietal, and occipital lobes. Model 1 was unadjusted. Model 2 adjusted for demographics (age, sex, race, and education) and study site in order to examine associations of inflammatory trajectories with brain health adjusted only for potential confounds. Models 3 and 4 additionally adjusted for potential contributors to the relationship between inflammation trajectory and brain health. First, Model 3 adjusted for Model 2 covariates plus medical illnesses (sleep apnea, diabetes, and hypertension) that differed between trajectory groups (p < .10) because these diseases could be a source of inflammation that contributes to the effects of inflammation on the brain.[43] Model 4 adjusted for Model 2 covariates plus lifestyle factors (BMI, physical activity, alcohol, smoking, and depression) that could cause inflammation that then impacts brain health.[44] Analyses were conducted in SAS version 9.4 and R version 3.4.3.

Data Availability Statement

Anonymized data are available from the CARDIA Coordinating Center (cardia.dopm.uab.edu/contact-cardia). A description of the National Heart, Lung, and Blood Institute policies governing the data and describing access to the data can be found online (cardia.dopm.uab.edu/study-information/nhlbi-data-repository-data).

Results

Inflammation Trajectories

Our trajectory analysis in the 2,194 participants who had at least three measures of CRP during the study period indicated that a 4-trajectory model was associated with improvements in model fit over a 3-trajectory model (For details, see Supplementary Table 2). However, this model had fewer than 5% of participants in one group. Therefore, we selected the 3-trajectory model for our follow-up models. The three identified inflammation trajectories reflected overall patterns of low, moderate, and high CRP during the 18-year period during young to middle age, with high inflammation defined as having CRP level the sample median across all years. We labeled the trajectories as lower-stable, moderate-increasing, and consistently-higher (Figure 1). The trajectories of the 2,194 participants were characterized as follows: lower-stable (n = 786 [36%]), moderate increasing (n = 169 [8%]), and consistently higher (n = 1,239 [56%]). Of those in the MRI sub-study (n = 508), 38% (n = 195) were classified as lower-stable, 7% (n = 38) as moderate increasing, and 54% (n = 275) as consistently higher.

Inflammation trajectory group membership was significantly associated with other participant characteristics including demographics, BMI, physical activity, alcohol consumption, current smoking, sleep apnea, diabetes, hypertension, and depression. Overall, the moderate-increasing and consistently-higher groups tended to have worse health behaviors and more health problems than those in the lower-stable group (Table 1). A similar, but not entirely overlapping, pattern of characteristics was observed in the larger cohort of 2,194 participants (Supplementary Table 3).

Inflammation Trajectories and White Matter Volume and Integrity

We first examined if inflammation trajectories were associated with white matter volume in the whole brain at midlife. In demographics-adjusted models, those in the moderate-increasing group showed lower ($\beta = -0.18$, 95% CI -0.29, -0.06), and the consistently-higher group showed similar, whole-brain white matter volume compared to the lower-stable group. Further adjustment for disease and lifestyle factors did not alter this pattern of results and the effect sizes remained similar to those in the demographics-adjusted models (Table 2).

We next examined if inflammation trajectories over time were associated with white matter integrity at midlife as indexed by whole-brain FA and MD. Compared to the lower-stable group, those displaying a moderate-increasing trajectory had worse white matter integrity as indexed by lower whole-brain FA ($\beta = -0.37$, 95% CI -0.70, -0.04) and higher whole-brain MD ($\beta = 0.44$, 95% CI 0.11, 0.78) after demographics adjustment. The consistently-higher trajectory group also displayed worse white matter integrity as indexed by significantly lower whole-brain FA ($\beta = -0.20$, 95% CI -0.38, -0.03) compared to the lower-stable group, but their levels of MD were similar. When we additionally adjusted for lifestyle factors and disease, the moderate-increasing group still showed significantly lower FA and higher MD in the whole brain, but the finding of lower FA in the consistently-higher group was not significant (Table 3). Thus, the moderate-increasing group showed lower FA and higher MD that remained significant when adjusting for disease and lifestyle factors, whereas associations of the consistently-higher trajectory with lower FA were no longer significant when adjusting for disease and lifestyle factors.

Inflammation Trajectories and Region-Specific White Matter Volume and Integrity

In exploratory analyses, we examined if inflammation trajectories were associated with white matter volume and integrity in specific brain regions. Compared to the lower-stable group, those in the moderate-increasing group showed lower white matter volume in the frontal ($\beta = -0.21$, 95% CI -0.36, -0.07) and parietal ($\beta = -0.17$, 95% CI -0.31, -0.01) lobes, and those in the consistently-higher group showed lower white matter volume in the parietal lobe ($\beta = -0.11$, 95% CI -0.20, -0.03), in demographics-adjusted models (Table 2). All of these findings remained significant in models additionally adjusted for disease and lifestyle factors.

With regard to region-specific white matter integrity, the moderate-increasing trajectory group showed lower FA in the frontal ($\beta = -0.33$, 95% CI -0.66, -0.01), temporal ($\beta = -0.43$, 95% CI -0.84, -0.15) and parietal lobes ($\beta = -0.38$, 95% CI -0.69, -0.07), but not in the occipital lobe, after demographics adjustment. Similarly, the moderate-increasing group showed significantly higher frontal ($\beta = 0.50$, 95% CI 0.16, 0.85), temporal ($\beta = 0.49$, 95% CI 0.15, 0.84), and parietal ($\beta = 0.38$, 95% CI 0.07, 0.69), but not occipital, MD compared to the lower-stable group in demographics-adjusted models. The consistently-higher trajectory group had significantly lower FA in the frontal ($\beta = -0.18$, 95% CI -0.36, -0.01), temporal ($\beta = -0.20$, 95% CI -0.70, -0.02), and parietal ($\beta = -0.24$, 95% CI -0.41, -0.08) lobes, but not the occipital lobe, compared to the lower-stable group, in demographics-

adjusted analyses. However, the consistently-higher group did not show significantly different MD than the lower-stable group in any regions.

Findings of lower FA for the moderate-increasing group in the temporal and parietal, but not the frontal, lobe remained significant when models were adjusted for disease and lifestyle factors (Table 3). With regard to MD, the moderate-increasing group showed higher MD in the frontal and parietal lobes, but not in the temporal lobe, when adjusting for disease and lifestyle factors. When we adjusted for lifestyle factors, the consistently-higher group only showed lower FA in the temporal and parietal lobes, and adjusting for disease rendered these associations non significant with marked reductions in effect sizes (Table 3).

Discussion

Results indicate that inflammation trajectories across almost two decades during early to middle adulthood are associated with worse white matter volume and integrity at midlife. Individuals showing a moderate-increasing trajectory of inflammation over time had lower white matter volume and worse white matter integrity, as indexed by lower FA and higher MD, in the whole brain, compared to a lower-stable trajectory group. Individuals in the consistently-higher group had lower whole-brain FA, but similar whole-brain white matter volume and MD, compared to the lower-stable group. Overall, these data indicate that moderate-increasing and consistently-higher trajectories of inflammation in early to mid adulthood might be risk factors for lower white matter quantity and quality in midlife. In turn, an accumulating literature has found that white matter volume and integrity are associated with cognitive impairment.[9,10] Thus, trajectories of inflammation may impact brain health even at midlife.

Our findings are in line with previous studies linking trajectories of inflammatory activity with white matter volume and integrity, although prior studies have examined brain outcomes in late life. In the Atherosclerosis Risk in Communities study, increasing levels of CRP levels during midlife predicted worse late-life white matter integrity.[6] Similarly, in a sample with an average age of 83 taken from the Health Aging and Body Composition Study, larger decreases in CRP values over a period of six years were associated with higher FA in several brain regions.[8] Thus, it appears that increasing levels of inflammation are most closely linked with degraded white matter. Our findings are also in line with prior work linking elevated peripheral inflammation with lower gray and white matter volume cross-sectionally.[45] Taken together, this literature raises the possibility that regulating inflammation, particularly to avoid increasing levels over time, may be beneficial for brain health throughout adulthood.

Identifying factors that contribute to deleterious inflammation trajectories, and particularly to increasing levels of inflammation, may point us in the direction of interventions that improve brain health across the lifespan. One possibility is that factors related to health behaviors, such as smoking, obesity, and physical inactivity, contribute to increasing levels of inflammation over time.[46–48] Stress-related psychiatric symptoms, including depressive symptoms, may also contribute to increases in inflammation.[49,50] Another possibility is that pathophysiological inflammatory processes associated with chronic diseases such as sleep

apnea, diabetes, and hypertension may contribute to rises in inflammatory activity.[51–53] All of these factors and conditions were less common in the lower-stable group in our analyses. However, adjusting for them reduced some, but not all, of the associations of inflammation trajectories with white matter volume and integrity. Notably, the characteristics of our different trajectory groups differed somewhat between those *with* (Table 1) and *without* (Supplementary Table 1) MRI data available. A comparison of the trajectory-group characteristics for the full sample of 2,194 and the MRI subsample of 508 indicates that women and Black people may be underrepresented in the moderate-increasing group in our MRI analyses. Although our models adjusted for both gender and race, data from key demographic groups may be missing. Findings for the moderate-increasing trajectory group were generally robust to adjustment for disease and lifestyle factors, whereas most results for the consistently-higher trajectory were not independent of these factors. Thus, interventions targeting health behaviors and disease may be particularly beneficial for white matter in those with consistently-higher levels of inflammation in early to mid-adulthood. Other mechanisms may be at play in the moderate-increasing trajectory group.

In exploratory analyses focused on region-specific white matter, we found that the moderate-increasing group showed lower white matter volume and worse white matter integrity in the frontal, temporal, and parietal lobes compared to the lower-stable group. The consistently-higher group showed reduced white matter volume in the parietal lobe and lower FA in the frontal, temporal, and parietal lobes, but similar MD, compared to the lower-stable group. There were no associations of inflammation trajectories with white matter volume and integrity in the occipital lobe. As these findings are based on exploratory analyses, they must be interpreted with caution. However, they suggest that inflammation trajectories may be associated with a general decrease in white matter volume and integrity across many brain areas, but perhaps less so in the occipital lobe. Previous research has indicated that the highest age-related changes in inflammation may occur in the temporal and frontal lobes,[54] and it will be important to understand how inflammation may impact brain-region specific changes in white matter that underlie different forms of dementia.[55]

Limitations

Several limitations should be considered when interpreting our findings. First, our moderate sample size may have limited our power to detect some effects. Our moderate-increasing trajectory group was particularly small and many of our findings are related to that group. Second, we rely on peripheral CRP as a marker of inflammation in this study. Although peripheral levels of CRP have been found to correlate highly with cerebrospinal fluid levels of inflammatory markers,[24] the inflammatory system is highly complex and future research should consider multiple markers as well as direct assessments of neuroinflammation. Moreover, although we attempted to exclude people with levels of CRP > 10 mg/L, which could be reflective of acute inflammation, it remains possible that some of the CRP measures are partly reflective of acute inflammation. In addition, our efforts to remove values reflective of acute inflammation may have led to the omission of extremely high CRP values reflective of high levels of chronic inflammation.[56,57] Future studies with larger samples will be needed to clarify the effects of extremely high inflammation on brain health. Third, although we examined a role for lifestyle and disease factors by including them as

covariates in our models, further research will be necessary to clarify the source of high and increasing levels of inflammation that may influence brain structure. Importantly, change in these factors over time may be crucial to understanding their impact on an individual's inflammation trajectory. Future studies should examine how change in lifestyle and disease factors influence trajectories of inflammation over time in population-based samples. In addition, our classification of covariates into the categories of "health behaviors" and "diseases" is imperfect. In particular, while BMI may index health behaviors, high BMI may also be a clinical condition. Moreover, apart from our adjustment for depressive symptoms, we did not assess the contribution of psychiatric disorders to our findings. Fourth, this paper is focused on brain health and did not examine cognitive functioning directly. Fifth, we did not adjust for multiple comparisons in this paper and our brain-region specific analyses were exploratory and should be interpreted cautiously. Finally, our study included only a subset of eligible participants from the CARDIA cohort who tended to have higher levels of education and were more likely to be older, female, White, and non-smoking, and to have less liver disease and lower BMI than those who were excluded (Supplementary Table 1). Population-based MRI studies will be needed to examine the generalizability of our findings.

Conclusions

Increasing and consistently high levels of inflammation in early to mid-adulthood are associated with reduced white matter volume and lower white matter integrity at midlife. Individuals who display such trajectories of inflammation in adulthood may be at risk for adverse neurological outcomes over time, which may index risk for accelerated cognitive decline. When considering when to intervene to enhance brain health in late life, we need to begin at least as early as midlife.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Highlights

- From early adulthood to midlife, inflammation trajectories fell into three groups.

- Moderate-increasing trajectory associated with lower midlife white matter volume.

- Moderate-increasing trajectory associated with worse midlife white matter integrity.

- Some evidence for worse midlife white matter integrity in consistently-higher group.

C-reactive protein levels over time
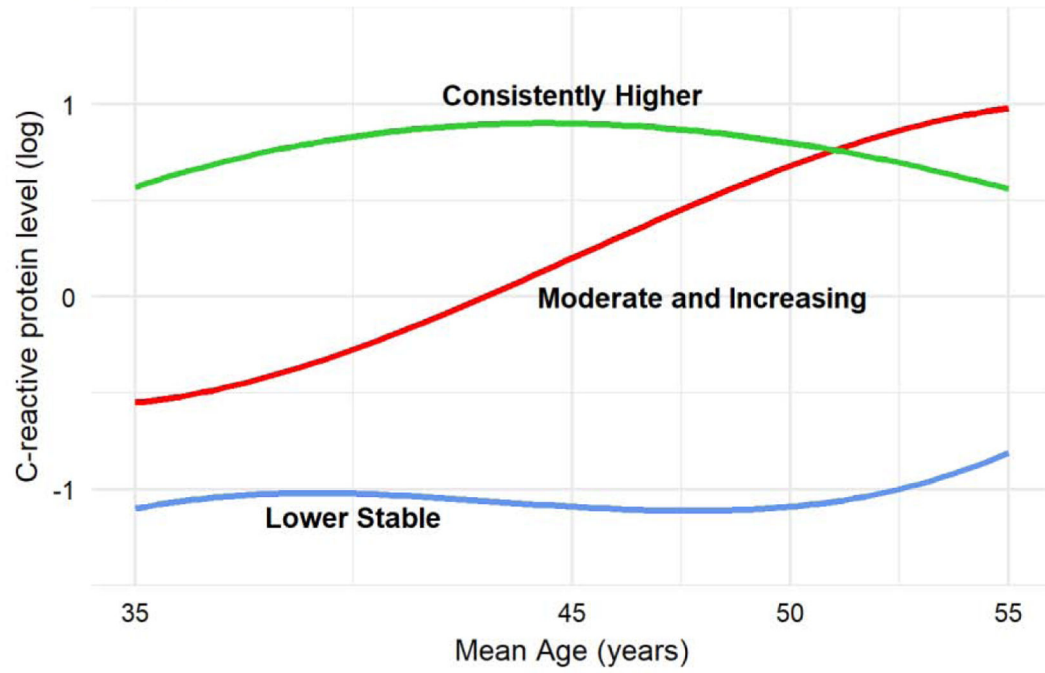
Figure 1.
C-reactive protein (CRP) latent class trajectories for the 2194 CARDIA participants who had at least 3 eligible CRP measures from Year 7 to Year 25.

Table 1.

Characteristics of sample with brain MRI by inflammatory trajectory

Characteristic mean (sd), n (%), or median (IQR)	Inflammatory Trajectory Group, No. (%)			
	Lower stable	Moderate-increasing	Consistently-higher	
	(n = 195)	(n = 38)	(n = 275)	p^a
Age, years	**51.0 (3.3)**	**48.8 (3.6)**	**50.6 (3.4)**	**<0.001**
Black	**146 (74.9)**	**19 (50.0)**	**170 (61.8)**	**0.001**
Female	99 (50.8)	16 (42.1)	141 (51.3)	0.56
Education, years	**15.5 (2.4)**	**15.2 (2.1)**	**14.7 (2.5)**	**0.003**
Smoking: current	**19 (9.7)**	**7 (18.4)**	**45 (16.4)**	**0.08**
Alcohol^b: drinks per week	**10 (4 – 20)**	**3 (0–5)**	**8(4–13)**	**0.05**
Body mass index: kg/m^2	**25.37 (3.7)**	**30.3 (4.5)**	**29.8 (5.6)**	**<0.001**
Physical activity	**416.3 (272.9)**	**361.1 (233.4)**	**356.0 (293.5)**	**0.06**
Asthma	10 (5.1)	3 (7.9)	24 (8.7)	0.33
Kidney problems	14 (7.2)	3 (7.9)	17 (6.2)	0.87
Heart problems	19 (9.7)	4 (10.5)	35 (12.7)	0.59
Liver disease	5 (2.6)	1 (2.6)	14 (5.1)	0.34
Cancer/tumor	16 (8.2)	1 (2.6)	24 (8.7)	0.43
Diabetes	**8 (4.1)**	**3 (7.9)**	**33 (12.0)**	**0.01**
HIV	3 (1.5)	0 (0.0)	2 (0.7)	0.55
Sleep apnea	**7 (3.6)**	**2 (5.3)**	**29 (10.5)**	**0.01**
Multiple sclerosis	19 (9.7)	4 (10.5)	35 (12.7)	0.59
Stroke/TIA	0 (0.0)	0 (0.0)	3 (1.1)	0.27
High cholesterol	14 (7.2)	6 (15.8)	23 (8.4)	0.21
Hypertension	**36 (18.5)**	**12 (31.6)**	**103 (37.5)**	**<0.001**
Depression: CESD > 16	20 (10.3)	5 (13.2)	49 (17.8)	0.07
CRP: median^c	**18 (9.2)**	**32 (84.2)**	**203 (73.8)**	**<0.001**

CARDIA, coronary artery risk development in young adults; sd, standard deviation; IQR, interquartile range; CESD, Center for Epidemiological Studies Depression scale.

^{a}P values are from 1-way analysis of variance for age, education, physical activity, and BMI; χ^2 tests for black race, female sex, smoking, self-reported medical conditions, cardiovascular risk factors, and depression; Kruskal-Wallis tests for alcohol.

^{b}Number of drinks per week among current drinkers.

CRP   median refers to CRP values across all years.

Table 2.

White Matter Volume by Inflammation Trajectory Group

Inflammation trajectory group	Standardized Difference in Each Brain Measure (95% CI)			
	Unadjusted Model β (95% CI)	Demographics Adjusted[a] β (95% CI)	Disease Adjusted[b] β (95% CI)	Lifestyle Adjusted[d] β (95% CI)
White matter (WM) brain volume				
Total WM				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.47 (−0.80, −0.13)**	**−0.18 (−0.29, −0.06)**	**−0.17 (−0.29, −0.06)**	**−0.18 (−0.30, −0.06)**
Consistently-higher	**−0.27 (−0.45, −0.09)**	−0.04 (−0.10, 0.01)	−0.04 (−0.10, 0.01)	−0.04 (−0.10, 0.02)
P-value	**0.001**	**0.01**	**0.01**	**0.01**
Frontal WM				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.47 (−0.84, −0.15)**	**−0.21 (−0.36, −0.07)**	**−0.21 (−0.36, −0.07)**	**−0.25 (−0.37, −0.07)**
Consistently-higher	**−0.27 (−0.38, −0.02)**	−0.01 (−0.07, 0.08)	0.01 (−0.06, 0.08)	0.01 (−0.07, 0.08)
P-value	**0.001**	**0.01**	**0.01**	**0.01**
Temporal WM				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.38 (−0.73, −0.04)**	−0.09 (−0.23, 0.03)	−0.10 (−0.24, 0.03)	−0.09 (−0.25, 0.02)
Consistently-higher	**−0.25 (−0.43, −0.07)**	−0.08 (−0.05, 0.05)	−0.02 (−0.09, 0.04)	−0.02 (−0.10, 0.05)
P-value	**0.01**	0.37	0.34	0.32
Parietal WM				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.47 (−0.81, −0.12)**	**−0.17 (−0.31, −0.01)**	**−0.16 (−0.32, −0.01)**	**−0.17 (−0.33, −0.01)**
Consistently-higher	**−0.34 (−0.53, −0.16)**	**−0.11 (−0.20, −0.03)**	**−0.10 (−0.18, −0.01)**	**−0.10 (−0.19, −0.01)**
P-value	**<0.001**	**0.01**	**0.02**	**0.03**
Occipital WM				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.43 (−0.78, −0.09)**	−0.16 (−0.34, 0.01)	−0.13 (−0.31, 0.05)	−0.08 (−0.27, 0.10)
Consistently-higher	**−0.10 (−0.42, −0.10)**	−0.06 (−0.16, 0.24)	−0.06 (−0.16, 0.02)	−0.03 (−0.13, 0.07)
P-value	**0.01**	0.14	0.22	0.64

CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval

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[a] Adjusted for age, sex, race/ethnicity, education, intercranial volume (WM models only), and site.

[b] Additionally adjusted for sleep apnea, diabetes, and hypertension.

[c] Additionally adjusted for BMI, alcohol, smoking, physical activity, and depression.

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Table 3.

White Matter Integrity by Inflammation Trajectory Group

Inflammation trajectory group	Standardized Difference in Each Brain Measure (95% CI)			
	Unadjusted Model β (95% CI)	Demographics Adjusted[a] β (95% CI)	Disease Adjusted[b] β (95% CI)	Lifestyle Adjusted[d] β (95% CI)
Fractional Anisotropy (FA)				
Total FA				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.29 (−0.62, −0.04)**	**−0.37 (−0.70, −0.04)**	**−0.34 (−0.67, −0.02)**	**−0.32 (−0.66, −0.01)**
Consistently-higher	**−0.23 (−0.41, −0.05)**	**−0.20 (−0.38, −0.03)**	−0.14 (−0.31, 0.03)	−0.13 (−0.31, 0.05)
P-value	**0.02**	**0.01**	0.06	0.12
Frontal FA				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.21 (−0.56, −0.13)**	**−0.33 (−0.66, −0.01)**	−0.32 (−0.66, 0.01)	−0.28 (−0.62, 0.05)
Consistently-higher	**−0.19 (−0.37, −0.01)**	**−0.18 (−0.36, −0.01)**	−0.11 (−0.29, 0.06)	−0.08 (−0.27, 0.09)
P-value	**0.04**	**0.04**	0.13	0.25
Temporal FA				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.37 (−0.72, −0.02)**	**−0.43 (−0.84, −0.15)**	**−0.46 (−0.78, −0.08)**	**−0.44 (−0.79, −0.08)**
Consistently-higher	**−0.24 (−0.42, −0.05)**	**−0.20 (−0.70, −0.02)**	**−0.39 (−0.39, −0.02)**	−0.16 (−0.35, 0.02)
P-value	**0.01**	**0.01**	**0.01**	**0.03**
Parietal FA				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.32 (−0.67, −0.01)**	**−0.38 (−0.69, −0.07)**	**−0.39 (−0.70, −0.08)**	**−0.35 (−0.68, −0.03)**
Consistently-higher	**−0.26 (−0.44, −0.07)**	**−0.24 (−0.41, −0.08)**	**−0.18 (−0.35, −0.02)**	−0.17 (−0.34, 0.02)
P-value	**0.01**	**0.01**	**0.01**	**0.04**
Occipital FA				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**−0.23 (−0.58, 0.11)**	−0.23 (−0.57, 0.11)	−0.22 (−0.58, 0.11)	−0.27 (−0.63, 0.08)
Consistently-higher	**−0.13 (−0.37, −0.10)**	−0.14 (−0.32, 0.03)	−0.09 (−0.28, 0.08)	−0.14 (−0.33, 0.05)
P-value	0.08	0.18	0.37	0.20

	Standardized Difference in Each Brain Measure (95% CI)			
Inflammation trajectory group	Unadjusted Model β (95% CI)	Demographics Adjusted[a] β (95% CI)	Disease Adjusted[b] β (95% CI)	Lifestyle Adjusted[d] β (95% CI)
Mean diffusivity (MD)				
Total MD				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**0.39 (0.05, 0.72)**	**0.44 (0.11, 0.78)**	**0.41 (0.08, 0.74)**	**0.42 (0.08, 0.76)**
Consistently-higher	0.10 (−0.06, 0.28)	0.13 (−0.05, 0.29)	0.05 (−0.10, 0.27)	0.05 (−0.13, 0.24)
P-value	**0.04**	**0.02**	**0.03**	**0.04**
Frontal MD				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**0.41 (0.06, 0.75)**	**0.50 (0.16, 0.85)**	**0.45 (0.10, 0.80)**	**0.44 (0.08, 0.79)**
Consistently-higher	0.12 (−0.05, 0.30)	0.14 (−0.03, 0.33)	0.07 (−0.10, 0.26)	0.06 (−0.12, 0.25)
P-value	0.04	**0.02**	**0.03**	0.05
Temporal MD				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**0.45 (0.10, 0.80)**	**0.49 (0.15, 0.84)**	0.47 (−0.02, 0.66)	0.31 (−0.04, 0.77)
Consistently-higher	0.04 (−0.06, 0.29)	0.13 (−0.48, 0.31)	0.07 (−0.16, 0.19)	0.01 (−0.20, 0.14)
P-value	**0.03**	**0.01**	0.16	0.18
Parietal MD				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	**0.32 (0.01, 0.67)**	**0.38 (0.07, 0.69)**	**0.36 (0.12, 0.82)**	**0.13 (0.02, 0.85)**
Consistently-higher	0.06 (−0.27, 0.40)	0.13 (−0.16, 0.44)	0.17 (−0.12, 0.47)	−0.10 (−0.13, 0.28)
P-value	**0.01**	**0.01**	**0.03**	**0.02**
Occipital FA				
Lower-stable	0 [Reference]	0 [Reference]	0 [Reference]	0 [Reference]
Moderate-increasing	0.27 (−0.06, 0.62)	0.25 (−0.09, 0.60)	0.26 (−0.09, 0.61)	0.26 (−0.08, 0.61)
Consistently-higher	0.04 (−0.13, 0.23)	0.03 (−0.14, 0.22)	−0.01 (−0.19, 0.18)	0.12 (−0.20, 0.45)
P-value	0.28	0.35	0.30	0.21

CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval

[a] Adjusted for age, sex, race/ethnicity, education, intercranial volume (WM models only), and site.

[b] Additionally adjusted for sleep apnea, diabetes, and hypertension.

[c] Additionally adjusted for BMI, alcohol, smoking, physical activity, and depression.