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Chronic systemic inflammation is associated with symptoms of late-life depression: The ARIC Study

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Abstract

Objective: The current study examined how the pattern of systemic inflammation in the decades leading up to late-life relates to depression symptoms in older adults.

Methods: Within the Atherosclerosis Risk in Communities Study, we measured high-sensitivity C-reactive protein (CRP), a non-specific marker of systemic inflammation, at three visits: 21 years and 14 years before, and concurrent with the assessment of depression symptoms, defined using the 11-item Center for Epidemiologic Studies Depression (CESD) Scale. We categorized participants into one of four groups based on their 21-year longitudinal pattern of elevated

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(≥ 3 mg/L) versus low (<3 mg/L) CRP (stable low; unstable low; unstable elevated; stable elevated). Analyses excluded participants with suspected depression during midlife.

Results: A total of 4,614 participants were included (age at CESD assessment: 75.5[5.1]; 59% female; follow-up time 20.7 years [SD 1.0]). Compared to participants who maintained low CRP levels (stable low), participants who had elevated CRP at 2 of 3 visits (unstable elevated; $\beta=0.09$; 95% CI: 0.02, 0.17) and participants who maintained elevated CRP at all 3 visits (stable elevated; $\beta=0.13$; 95% CI: 0.05, 0.21) had greater depression symptoms as older adults, after adjusting for confounders. After excluding participants with late-life cognitive impairment, only participants with stable elevated CRP demonstrated significantly greater late-life depression symptoms. In a secondary analysis, stable elevated CRP was associated with increased risk for clinically significant late-life depression symptoms.

Conclusions: Chronic or repeated inflammation in the decades leading up to older adulthood is associated with late-life depression, even in the context of normal cognition.

Keywords

inflammation; immunology; depression; cognition; dementia

Introduction

Depressive symptoms are highly prevalent among older adults¹ and have been associated with reduced quality of life, disability, and elevated rates of mortality.^{2,3} Depression that emerges during older adulthood differs in several ways from depression symptoms that begin earlier in life with regard to associated comorbidity,⁴ genetic determinants,⁵ and response to anti-depressive treatment.⁶ Three hypotheses regarding the etiology of late-life depression, which are not mutually exclusive, have gained support: (1) the neurodegenerative hypothesis suggests that depression precedes or occurs concurrently with cognitive decline in the context of neurodegenerative disease;⁷ (2) the vascular hypothesis posits that the emergence of cerebral large and small vessel disease may promote depression symptoms;⁸ (3) the inflammatory hypothesis suggests that the continuous production of pro-inflammatory mediators in the periphery and central nervous system can cause neuro-molecular changes which manifest as reduced mood and neurovegetative symptoms.^{9,10} In support of the inflammatory hypothesis, previous work has demonstrated that individuals with late-life depression tend to have higher levels of circulating inflammatory markers compared to age-matched persons without depression.¹¹

Although a link between systemic inflammation and depression has been demonstrated, it remains unclear whether systemic inflammation plays a mechanistic or an associative role in the emergence of depression symptoms in late-life. Because much of the evidence supporting the inflammation hypothesis comes from cross-sectional studies, it is difficult to make inferences about the temporal association between inflammation and depression. To date, only a handful of prospective studies have begun to address this question of directionality.^{12–17} However, these studies have had relatively brief follow-up periods and few have assessed inflammation at multiple time-points, precluding the study of inflammation *chronicity* as a potential risk factor for late-life depression.

The goal of the current study was to provide insight into the relationship between long-term patterns of systemic inflammation and late-life depression symptoms using the Atherosclerosis Risk in Communities (ARIC) Study, a large community-based prospective cohort study. Specifically, we tested the hypothesis that individuals who maintained chronically elevated levels of systemic inflammation over a 21-year period spanning from middle-to late-life would have greater symptoms of depression as older adults. Because systemic inflammation has been previously associated with cognitive decline,¹⁸ and cognitive decline, with late-life depression (as suggested by the neurodegeneration hypothesis),⁷ we additionally examined whether the association between systemic inflammation and late-life depression symptoms was stronger in the context of late-life cognitive impairment and *APOE* $\epsilon 4$ allele possession (a major Alzheimer's disease risk factor).

Methods

Study Sample

The ARIC Study initially enrolled 15,792 adults in 1987–89. Participants were selected from 4 communities in the U.S.: Washington County, MD; Forsyth County, NC; Northwestern suburbs of Minneapolis, MN; and Jackson, MS. After an initial visit (Visit 1), participants returned every three years until Visit 4 (1996 to 1998). Approximately 15 years later, participants were invited back for Visit 5 (2011–13). A total of 6,538 participants attended Visit 5. The full study design and exclusionary criteria are presented in Figure 1A. ARIC study protocols were approved by the Institutional Review Boards at each site. All participants gave written informed consent.

Inflammatory Marker Measurement

To assess systemic inflammation, we measured high-sensitivity CRP levels (mg/L) at Visit 2 (1990–92), Visit 4, and Visit 5 from blood stored at -70°C. Visit 2 CRP levels (mg/L) were measured from serum in 2011–13 using an immunoturbidimetric assay on the Roche Modular P chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Visit 4 CRP levels (mg/L) were measured from plasma in 2010 using a nephelometric method on the Siemens Dade Behring BN II analyzer (Siemens Healthcare Diagnostics, Deerfield IL). Visit 5 CRP levels were measured from plasma in 2011–13 using an immunoturbidimetric assay on the Beckman Coulter Olympus AU400e analyzer (Beckman Coulter Inc., Brea, CA). An examination of differences in CRP measurements based on laboratory, assay methods, instruments, specimen type, and time of measurement found that variation was not large enough to warrant re-calibration (bias < 10%).¹⁹ Of note, CRP has been demonstrated to be a relatively stable biomarker of chronic inflammation.²⁰

To define 21-year CRP patterns, each participant was categorized as having “low” or “elevated” CRP levels at each visit using a clinical cut-off of 3 mg/L.²¹ Previous work suggests that a CRP level above 3 mg/L is suggestive of ongoing low-grade systemic inflammation.^{22,23} Using this “low” versus “elevated” CRP dichotomization, participants were grouped into one of four categories based on their patterns of CRP over three visits (see Figure 1B):

- *Stable low*: low CRP levels (<3 mg/L) at all three visits (Visits 2, 4, and 5)
- *Unstable low*: low CRP levels at 2 of 3 visits
- *Unstable elevated*: elevated CRP levels (≥ 3 mg/L) at 2 of 3 visits
- *Stable elevated*: elevated CRP levels at all three visits

Depression Assessment

Depression symptoms were assessed during Visit 5 using the Center for Epidemiologic Studies Depression Scale (CESD)²⁴ 11-item version.²⁵ This version of the CESD correlates highly with the original 20-item version of the CESD (Pearson $r=.95$).²⁵ Because it is less taxing, the 11-item version is preferred for an older adult population.²⁵ CESD depression symptoms, defined as a continuous parameter, was our primary outcome. We performed secondary analyses using a cutoff score of ≥ 9, above which has been previously defined as consistent with clinically significant depression.²⁶ The analogous cutoff defined using the full CESD (≥ 16) has been shown to have high sensitivity and specificity (as high as 100% and 88%, respectively) for detecting major depression among older adults.²⁷

To examine inflammation as a risk factor for *late-life* depression and reduce the potential for reverse causation (i.e., depression causing inflammation), we excluded participants who were suspected of having depression during midlife (Visit 2). Midlife depression symptoms were assessed using the 21-item Vital Exhaustion Questionnaire (VEQ).²⁸ The VEQ was developed as a measure of exhaustion, a trait which overlaps with depression. The VEQ was used in the current study because a traditional measure of depression was not administered during middle adulthood. The correlation between the VEQ and the Beck Depression Inventory (BDI) has been found to be relatively high (Pearson $r = 0.62$); most (77%) participants who were depressed according to the BDI were also exhausted on the VEQ.²⁹ Because the 12-month prevalence of major depressive disorder is approximately 5% for middle-aged adults,^{30,31} we excluded participants who scored in the top 5th percentile on the VEQ in our primary analyses. Because the VEQ was not designed to measure depression specifically, the current study examined alternative thresholds for midlife depression exclusion (i.e., no exclusion, top 10th percentile of VEQ), and we repeated analyses after additionally excluding persons on the basis of Visit 2 antidepressant medication use.

Covariate Assessment

Race (African American/white), sex, and education (less than high school/high school graduate or equivalent or vocational education/any college) were assessed at baseline by self-report. The following physiological variables were assessed at Visit 5, concurrent with the assessment of late-life depressive symptoms: body mass index (kg/m^2), calculated using measured height and weight and discretized into quartiles; total cholesterol (mg/dl); and total high-density lipoprotein (HDL) cholesterol (mg/dl). At Visit 5, we also assessed long-term use of anti-inflammatory medication (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], arthritis medication), current use of cholesterol-lowering medication, and cigarette use (current/former/ever) based on self-report. *APOE* $\epsilon 4$ status was assessed using the TaqMan assay (Applied Biosystems, Foster City, CA).

We assessed the following medical conditions at Visits 1 to 5. Hypertension was defined as a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or antihypertensive medication use. Coronary heart disease was defined based on self-report at baseline and adjudicated by a panel of physicians at subsequent study visits based on medical record documentation and ECG. Heart failure was defined based on heart failure medication use within the past two weeks or evidence of heart failure related hospitalization from the ARIC hospital surveillance. We defined diabetes as a fasting glucose ≥ 126 mg/dl or a non-fasting glucose ≥ 200 mg/dl, participant report of physician-diagnosed diabetes, or current diabetes medication use. Cancer was identified using information from ARIC hospital surveillance and cancer registries.

Statistical Analysis

To examine how the 21-year patterns of CRP related to Visit 5 CESD ratings, we first used an analysis of variance (ANOVA) to test for differences in CESD among the four CRP groups. This analysis was followed by a multivariable linear and logistic regression analysis, which compared participants with each 21-year CRP pattern to participants with *stable low* CRP. Analyses were adjusted for a set of demographic, physiological, and clinical characteristics which were selected a priori based on previous work indicating that these variables are jointly associated with depression symptoms and circulating inflammatory marker levels (confounders). Covariate associations with the primary outcome variable are presented in Supplementary Table 1. Model 1 adjusted for age, center-race, sex, education, Visit 5 physiological characteristics (i.e., BMI, HDL, total cholesterol), anti-inflammatory and cholesterol-lowering medication use, and cigarette use. To assess whether inflammation is associated with late-life depression independent of chronic medical comorbidity (which may act as a mediator), we examined a second model (model 2), which additionally adjusted for diagnoses of hypertension, CHD, heart failure, diabetes, and cancer occurring before or during the follow-up period up to the time of the late-life depression assessment (Visit 5). We used multiplicative interaction terms to examine the modifying effect of Visit 5 cognitive status (cognitively normal vs. mild cognitive impairment [MCI] or dementia; defined in the Supplementary Methods) and *APOE* genotype (0 vs. ≥ 1 $\epsilon 4$ alleles).

To assess the robustness of our findings, we performed several sensitivity analyses. First, we repeated analyses after excluding participants with MCI or dementia at Visit 5 to determine whether associations occurred independent of clinically significant cognitive impairment. Second, we excluded participants with clinical stroke before Visit 5 to determine whether the relationship between inflammation and depression occurred independent of stroke. Third, because depression and inflammation are associated with increased mortality and disability, we repeated analyses after applying inverse probability of attrition weighting (IPAW) to account for differential rates of study dropout (see Supplementary Methods and Supplementary Table 2). Fourth, to determine whether low-grade inflammation alone was associated with late-life depression, we repeated analyses after excluding all participants with one or more highly elevated CRP levels (≥ 10 mg/L), suggestive of an acute inflammatory response. We also repeated analyses using alternative methods to exclude participants with elevated depressive symptoms during midlife.

A series of secondary analyses were conducted to further evaluate the association of 21-year CRP characteristics with late-life depression. Specifically, we used multivariable linear regression to estimate the association of baseline CRP level, CRP slope, CRP variability, and the number of CRP observations at or above our clinically defined cut-points of 3mg/L and 10mg/L (independently and in combination) with late-life depression symptoms.³² Baseline CRP was defined at Visit 2. Linear regression was used to model CRP over time for each participant for the determination of individual CRP slopes and variability. CRP variability was defined as the root mean square error in a model with a linear trajectory. For this analysis, CRP values were log transformed and standardized to correct for skewness and facilitate interpretability. We used a two-sided p-value <0.05 as the cutoff for statistical significance. Analyses were conducted using Stata Version 14 (StataCorp, College Station, Tex., USA).

Results

Participant Characteristics

A total of 4,476 participants (mean age 75.5 (5.1), 58% women, 21% African American) were included in the primary analytic sample, which excluded 138 participants with suspected midlife depression. At the time of CESD assessment, 76% of participants were cognitively normal, 21% met criteria for MCI, and 3% met criteria for dementia. Participant demographic, physiological, and clinical characteristics are displayed in Table 1. There was significant between-subject heterogeneity in patterns of mid-to late-life CRP levels (Supplementary Figure 1).

21-Year CRP and Late-Life Depressive Symptoms

A one-way ANOVA showed a main effect of 21-year CRP pattern group on late-life depressive symptoms ($F[3, 4,472]=23.81$; $p<0.001$; $R^2=0.02$). Compared to participants who maintained low CRP levels, only participants with *unstable elevated* and *stable elevated* 21-year CRP patterns had significantly greater depression symptoms during late-life, after adjusting for demographic characteristics and cardiovascular risk factors using linear regression (Figure 2). The results were similar after additionally adjusting for prevalent medical comorbidity. The exclusion of participants with suspected midlife depression based on alternative Vital Exhaustion Questionnaire cut-points and midlife antidepressant use did not measurably change the primary results (Table 2). There was no evidence for effect modification by late-life cognitive status or *APOE* $\epsilon 4$ allele possession (p -interactions >0.05). After excluding participants with MCI or dementia during late-life ($n=1,094$), only participants with a *stable elevated* 21-year CRP pattern had higher depressive symptoms during late-life ($\beta=0.12$; 95% CI: 0.03, 0.21; $t=2.52$, $df=3,354$, $p=0.012$; Supplementary Table 3). A post-hoc analysis revealed that *unstable elevated* and *stable elevated* 21-year CRP patterns were significantly associated with greater somatic depression symptoms, but not with affective or interpersonal depression symptoms (Supplementary Table 4).

These results were similar in sensitivity analyses which excluded participants with previous clinical stroke ($n=159$; Supplementary Table 5) and in analyses which adjusted for differential attrition using IPAW (Supplementary Table 6). However, the association between

stable elevated CRP and late-life depression symptoms was significantly attenuated and no longer statistically significant after participants with one or more acutely elevated CRP levels ($\geq 10\text{mg/L}$; $n=688$) were excluded (Supplementary Table 7).

Secondary Analysis of CRP Characteristics and Late-Life Depressive Symptoms

In a linear regression model that included CRP slope, CRP variability, and number of elevated ($\geq 3\text{mg/L}$) CRP measurements, higher CRP variability and having two or three elevated CRP values was associated with significantly greater depression symptoms during late-life (Table 3). However, after adjusting for the number of acutely elevated ($\geq 10\text{mg/L}$) CRP values, these associations were attenuated (see Supplementary Table 8 for the fully adjusted model).

Secondary Analysis of 21-Year CRP and Clinically Significant Late-Life Depression

In total, 5.0% ($n=223$) of the analytic sample met CESD criteria for having clinically significant depression symptoms during late-life. Compared to the group with *stable low* CRP levels, participants with *unstable elevated* (Wald $\chi^2[\text{df}=1]=3.88$, $p=0.049$; odds ratio, 1.50; 95% CI: 1.00, 2.25) and *stable elevated* CRP (Wald $\chi^2[\text{df}=1]=5.36$, $p=0.021$; odds ratio, 1.64; 95% CI: 1.08, 2.45) had a greater odds of clinically significant late-life depression symptoms after adjusting for demographic characteristics and cardiovascular risk factors. After additionally adjusting for prevalent medical comorbidity, only the group with *stable elevated* 21-year CRP patterns had greater odds of clinically significant late-life depression symptoms (Wald $\chi^2[\text{df}=1]=4.00$, $p=0.046$; odds ratio, 1.53; 95% CI: 1.01, 2.32; Figure 3; Supplementary Table 9).

Discussion

Within a large biracial community sample of older adults, we examined the association of past 21-year patterns of systemic inflammation with late-life depression symptoms. We found that individuals who displayed repeated or chronic elevations in systemic inflammation over a two-decade period spanning middle-to late-life had greater symptoms of depression as older adults. Similarly, chronic systemic inflammation over this same time period was associated with an increased risk for clinically significant depressive symptom during late-life. These results, which were robust to adjustment for demographic characteristics, cardiovascular risk factors, and comorbid disease, suggest a relationship between chronic inflammation and late-life depression symptoms (especially somatic symptoms) that occurs independent of potentially confounding or mediating disease factors. These findings were essentially unchanged when analyses were restricted to persons without late-life cognitive impairment, and we found no evidence for effect modification by late-life cognitive status or *APOE* $\epsilon 4$ allele possession. In addition, these results suggest that inflammation variability may also be associated with late-life depression, and that *low-grade* inflammation alone may not be sufficient to account for the relationship between chronic inflammation and late-life depression symptoms.

A number of studies have examined the cross-sectional association between inflammation and depression, but only a handful have addressed the question of directionality using a

prospective study design. Some, but not all, of these studies suggest that a higher level of circulating inflammatory markers in older adults is associated with greater depression symptoms one to six years later.^{13–17} While these studies provide information about the temporal relationship between systemic inflammation and late-life depression, they measure systemic inflammation at only one time-point (typically during late-life) and therefore provide no information about how inflammation chronicity relates to the emergence of depression symptoms. The findings from this study, which suggest that persons with repeated or chronic inflammation in the decades leading up to older adulthood experience higher levels of depression symptoms during late-life, add to a body of literature which links chronic inflammation to adverse age-related outcomes.^{33,34} These findings are further substantiated by the results of a recent study, which found that older adults who maintained elevated CRP levels across two study visits spanning four years were at increased risk for new-onset depression symptoms.³⁵

The current results, which adjusted for the presence of cardiovascular risk factors and comorbid disease, suggest chronic inflammation is associated with late-life depressive symptoms independent of related disease or risk factors. This hypothesis is supported by previous work demonstrating that inflammation can exert a direct effect on the neurobiological pathways underlying depressive symptoms. For example, a number of studies have found that inflammatory signaling can lead to over-activation of the noradrenergic and HPA system and catabolism of neurotransmitters or their precursors, which can, in turn, promote depression symptomology, apathy, and anxiety.^{36–38} Although the present findings remained largely unchanged after the exclusion of participants with clinical stroke, it is possible that the association between chronic systemic inflammation and late-life depression symptoms is, at least in part, mediated by subclinical small vessel disease or white matter pathology, as systemic inflammation is believed to promote the emergence of microangiopathic white matter changes in older adults.³⁹

There are several caveats which need to be considered. First, although the current findings are robust, patterns of inflammation accounted for only a small degree of variation in late-life depression symptoms. However, the large proportion of individuals estimated to have chronically elevated inflammation in the population (16% in the current sample) translates to a sizable number of additional late-life depression cases that may be attributable, at least in part, to chronic inflammation. The clinical significance of this association is further supported by analyses which demonstrated that the participants with chronic inflammation had over a 50% higher odds of clinically significant late-life depressive symptoms compared to participants who maintained low inflammation. Second, our analyses suggest that chronic *low-grade* inflammation alone may not be sufficient to increase one's risk for late-life depression symptoms. It is possible there is a threshold for inflammation exposure (both in time and dose) that needs to be reached in order to initiate the physiological processes which bring about late-life depression symptoms. In a post-hoc analysis (Supplementary Table 10), we found that participants who had one or more acutely elevated CRP measurement were more likely to have hypertension, diabetes, and heart failure, chronic conditions which are known to act as potent inflammatory stimuli, especially if poorly controlled. Together, these results suggest that adults who experience one or more acute inflammatory event and

maintain persistently elevated levels of inflammation may be at especially high risk for experiencing depression symptoms in later life.

Strengths of the current study include the use of a large, biracial community-based sample, extended follow-up period, and repeated measures of inflammation. However, these results should be interpreted within the context of several limitations. First, although our primary analyses excluded participants with elevated symptoms on the VEQ during midlife (a proxy for depression), we may have inadvertently included a number of participants with depressive symptoms that emerged well before older adulthood. We acknowledge that the VEQ was not designed to measure depression. As such, for some participants, chronic or transient elevations in systemic inflammation may have occurred as a result of preexisting depression (i.e., reverse causation). Future studies will benefit from the use of structured clinical interviews to exclude participants with depression at study baseline. Additionally, there was a relatively long period between Visits 4 and 5 during which time CRP was not measured. Due to this extended follow-up period, it is possible that a transition from an inflammatory to a non-inflammatory state (or vice-versa) occurred over this time that went unmeasured. Additionally, although CRP is a widely used marker of systemic inflammation, there is evidence that inflammatory cytokines may play a more direct role in altering the neurobiological pathways underlying late-life depression.⁴⁰ Therefore, future studies should measure a broader array of inflammatory mediators, including pro-and anti-inflammatory cytokines. Despite these limitations, the current results provide novel insight into the relationship between longitudinal patterns of inflammation and late-life depression. Our findings suggest a potential etiologic role for repeated or chronic inflammation as a driver of late-life depression that is independent of cognitive decline, cardiovascular risk factors, and comorbid disease. The results suggest further that interventions aimed at reducing or avoiding a chronic inflammatory state during middle-and late-life (e.g., exercise, diet, or pharmacological) may help to limit the emergence of depressive symptoms in older adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

What is the primary question addressed by this study?

-This study examined long-term patterns of systemic inflammation in aging adults and determined whether individuals with chronic elevations in inflammation were at increased risk for having symptoms of depression as older adults.

What is the main finding of this study?

-Individuals with repeated or chronic elevations in systemic inflammation over a two-decade period spanning middle-to late-life had greater symptoms of depression as older adults. These associations occurred independent of medical comorbidity and did not differ based on late-life cognitive status or *APOE* ε4 genotype.

What is the meaning of the finding?

-These results highlight a potential etiologic role for chronic inflammation in late-life depression and suggest that interventions aimed at reducing or avoiding a chronic inflammatory state beginning in midlife may help to limit the emergence of late-life depressive symptoms.

Figure 1.

Study flowchart, inclusion criteria, and C-reactive protein pattern grouping

(A) Study design and primary inclusion and exclusion criteria. (B) Participants were categorized into one of four C-reactive protein (CRP) pattern groups based on CRP levels at Visits 2, 4, and 5. The dotted line denotes the hypothesized CRP level over time. A line above the tic mark indicates a CRP level ≥ 3 mg/L. CESD=Center for Epidemiologic Studies Depression Scale; CRP=C-reactive protein

^a We excluded 17 participants for non-white or non-black race, and 24 black participants living in Minneapolis or Washington County.

^b Of the 4,614 participants included in the study, 4,476 participants were included in the primary analytic sample, which excluded 138 participants with suspected midlife depression.

Figure 2.

Association between 21-year patterns of systemic inflammation and late-life depression symptoms

Linear regression models examined the covariate-adjusted associations between mid-to late-life C-reactive protein (CRP) patterns and late-life Center for Epidemiologic Studies Depression Scale (CESD) score. Model 1 adjusts for baseline age, sex, center-race, education, *APOE* ϵ 4 status, and Visit 5 BMI, total cholesterol, HDL, cigarette use, and cholesterol-lowering and anti-inflammatory medication use. Model 2 additionally adjusts for comorbid disease occurring up to the final visit (i.e., hypertension, diabetes, coronary heart disease, heart failure, and cancer).

^a $F(22, 4,453)=15.76$, $p<0.001$, $R^2=0.07$; p-values for beta coefficients were derived using two-tailed t tests (df=4,453).

^b $F(27, 4,448)=13.37$, $p<0.001$, $R^2=0.08$; p-values for beta coefficients were derived using two-tailed t tests (df=4,448).

Figure 3.

Probability of clinically significant late-life depression symptoms according to 21-year pattern of systemic inflammation

Logistic regression models were used to calculate the adjusted probability of clinically significant late-life depression according to the pattern of C-reactive protein (CRP) levels from middle-to late-life. Model 1 adjusts for baseline age, sex, center-race, education, *APOE* ε4 status, and Visit 5 BMI, total cholesterol, HDL, cigarette use, and cholesterol-lowering and anti-inflammatory medication use. Model 2 additionally adjusts for comorbid disease occurring up to the final visit (i.e., hypertension, diabetes, coronary heart disease, heart failure, and cancer).

^a $p < 0.05$ difference between group and Stable Low referent group (Wald χ^2 df=1); odds ratios and Wald χ^2 information is reported in the text and in Supplementary Table 9.

Table 1.

Visit 5 participant characteristics stratified by mid- to late-life C-reactive protein pattern

21-year longitudinal pattern of C-reactive protein					
Characteristic		Stable Low	Unstable Low	Unstable Elevated	Stable Elevated
	N	1,921	1,123	809	761
<i>Demographic variables</i>					
Age		75.5 (5.1)	75.8 (5.1)	75.6 (5.1)	74.7 (4.8)
Female		912 (47.5%)	627 (55.8%)	575 (71.1%)	587 (77.1%)
African American		298 (15.5%)	189 (16.8%)	191 (23.6%)	288 (37.8%)
<i>Education</i>					
Less than high school		210 (10.9%)	128 (11.4%)	103 (12.7%)	146 (19.2%)
High school/GED/vocational		777 (40.5%)	496 (44.2%)	353 (43.6%)	339 (44.6%)
College/graduate/ professional		934 (48.6%)	499 (44.4%)	353 (43.6%)	276 (36.3%)
<i>Apolipoprotein E e4 alleles</i>					
0		1,282 (66.7%)	828 (73.7%)	601 (74.3%)	593 (77.9%)
1		583 (30.4%)	276 (24.6%)	192 (23.7%)	155 (20.4%)
2		56 (2.9%)	19 (1.7%)	16 (1.9%)	13 (1.7%)
<i>Physiological & lab variables</i>					
Body mass index, kg/m ²		27.1 (4.5)	28.2 (5.1)	29.8 (5.6)	32.5 (6.5)
Total cholesterol, mg/dl		181.0 (40.0)	181.8 (42.5)	180.5 (43.9)	185.5 (41.3)
HDL, mg/dl		53.0 (14.4)	52.1 (14.2)	51.9 (13.7)	50.7 (12.7)
LDL, mg/dl		104.5 (32.5)	104.1 (35.0)	101.9 (36.9)	107.7 (35.5)
<i>Prevalent disease</i>					
Hypertension		1,320 (68.7%)	835 (74.4%)	639 (79.0%)	627 (82.4%)
Diabetes mellitus		466 (24.3%)	339 (30.2%)	327 (40.4%)	334 (43.9%)
Coronary heart disease		268 (14.0%)	179 (15.9%)	117 (14.5%)	88 (11.6%)
Heart failure		48 (2.5%)	65 (5.8%)	62 (7.7%)	58 (7.6%)
Cancer		166 (8.6%)	97 (8.6%)	90 (11.1%)	64 (8.4%)
<i>Medication</i>					
Cholesterol lowering (current)		1,078 (56.1%)	629 (56.0%)	488 (60.3%)	389 (51.1%)
Anti-inflammatory (regular use)		268 (14.0%)	186 (16.6%)	140 (17.3%)	145 (19.1%)
<i>Depressive symptoms</i>					
CES-D depression rating /22		2.6 (2.6)	2.9 (2.8)	3.3 (3.1)	3.7 (3.4)
Elevated CES-D depression		73 (3.8%)	66 (5.9%)	58 (7.2%)	73 (9.6%)
Vital Exhaustion Questionnaire /42		8.4 (7.8)	8.8 (7.7)	10.2 (8.2)	11.2 (8.7)

Values are displayed as means (SD) for continuous variables and frequencies (column percentages) for categorical variables, unless otherwise specified.

CESD=Center for Epidemiologic Studies Depression Scale

Table 2.

The association of 21-year patterns of systemic inflammation with late-life depression symptoms using alternative criteria for exclusion of participants with elevated depression symptoms during midlife

Longitudinal pattern of C-reactive protein	Late-life CESD score					
	Excluding no participants based on Visit 2 VEQ β (95%CI) ^{a, b} (N=4,614)	p-value	Excluding participants in top 10 th %tile of Visit 2 VEQ β (95%CI) ^{a, c} (N= 4,291)	p-value	Excluding participants in top 10 th %tile of Visit 2 VEQ and Visit 2 antidepressant medication users β (95%CI) ^{a, d} (N=4,177)	p-value
Stable Low	O(ref)	--	O(ref)	--	O(ref)	--
Unstable Low	0.02 (−0.05, 0.09)	0.564	0.03 (−0.04, 0.09)	0.475	0.03 (−0.04, 0.09)	0.442
Unstable Elevated	0.09 (0.01, 0.17)	0.021	0.09 (0.02, 0.17)	0.015	0.10(0.03,0.18)	0.009
Stable Elevated	0.14 (0.06, 0.23)	0.001	0.12 (0.04, 0.20)	0.005	0.12 (0.04, 0.20)	0.005

Linear regression models were used to examine the associations between mid-to late-life C-reactive protein (CRP) patterns and late-life Center for Epidemiologic Studies Depression Scale (CESD) score. Models are adjusted for baseline age, sex, center-race, education, *APOE* ϵ 4 status, and Visit 5 BMI, total cholesterol, HDL, cigarette use, and cholesterol-lowering and anti-inflammatory medication use, and comorbid disease occurring up to the final visit (i.e., hypertension, diabetes, coronary heart disease, heart failure, and cancer) (Model 2).

VEQ=Vital Exhaustion Questionnaire

^aThe standard deviation difference in Center for Epidemiologic Studies Depression (CESD) rating compared to the Stable Low referent group.

^bF(27, 4,586) = 15.25, p<0.001, R²=0.08; p-values for beta coefficients were derived using two-tailed t tests (df=4,586).

^cF(27, 4,263) = 11.75, p<0.001, R²=0.07; p-values for beta coefficients were derived using two-tailed t tests (df=4,263).

^dF(27, 4,149) = 11.63, p<0.001, R²=0.07; p-values for beta coefficients were derived using two-tailed t tests (df=4,149).

Table 3.

The association of longitudinal CRP characteristics with late-life depression symptoms

Model ^a	Measure	Model 1		
		β (95%CI) ^{a, b}	t(df)	p-value
		(N=4,476)		
CRP baseline only	Baseline	0.04(0.01,0.06)	2.44 (4,455)	0.015
CRP slope only	Slope	0.02 (−0.01, 0.04)	0.17(4,455)	0.174
CRP variability only	Variability	0.03 (0.00, 0.05)	2.05 (4,455)	0.040
CRP measurements 3mg/L only	0 CRP 3mg/L	Ref	--	--
	1 CRP 3mg/L	0.03 (−0.04, 0.10)	0.86 (4,453)	0.391
	2 CRP 3mg/L	0.11 (0.03,0.19)	2.84 (4,453)	0.005
	3 CRP 3mg/L	0.15(0.07,0.23)	3.52(4,453)	<0.001
CRP measurements 10mg/L only	0 CRP 10mg/L	Ref	--	--
	1 CRP 10mg/L	0.16(0.08,0.24)	3.86(4,454)	<0.001
	2CRP 10mg/L	0.14(0.01,0.28)	2.07 (4,454)	0.039
CRP baseline + slope + variability	Baseline	0.07 (0.03, 0.09)	3.61 (4,453)	<0.001
	Slope	0.05 (0.02, 0.08)	2.91 (4,453)	0.004
	Variability	0.02 (0.00, 0.05)	1.77(4,453)	0.077
CRP slope + variability + measurements 3mg/L ^b	Slope	0.02 (−0.01, 0.05)	1.37(4,451)	0.170
	Variability	0.03 (0.00, 0.06)	1.98(4,451)	0.048
	0 CRP 3mg/L	Ref	--	--
	1 CRP 3mg/L	0.00 (−0.07, 0.07)	-0.01 (4,451)	0.989
	2 CRP 3mg/L	0.10(0.02,0.17)	2.41 (4,451)	0.016
	3 CRP 3mg/L	0.15(0.06,0.23)	3.47(4,451)	0.001
	Slope	0.02 (−0.01, 0.04)	1.34(4,449)	0.179
	Variability	0.02 (−0.01, 0.05)	1.12(4,449)	0.262
	0 CRP 3mg/L	Ref	--	--
CRP slope + variability + measurements 3mg/L + measurements 10mg/L ^b	1 CRP 3mg/L	0.00 (−0.08, 0.07)	-0.13(4,449)	0.894
	2 CRP 3mg/L	0.08(0.00,0.16)	1.97(4,449)	0.049
	3 CRP 3mg/L	0.10(0.00,0.19)	2.02 (4,449)	0.043
	0CRP 10mg/L	Ref	--	--
	1 CRP 10mg/L	0.10(0.01,0.20)	2.20 (4,449)	0.028
	2CRP 10mg/L	0.09 (−0.07, 0.24)	1.12(4,449)	0.265

Linear regression models were used to examine the covariate-adjusted associations between C-reactive protein (CRP) characteristics and late-life Center for Epidemiologic Studies Depression Scale (CESD) score. Model 1 adjusts for baseline age, sex, center-race, education, *APOE* e4 status, and Visit 5 BMI, total cholesterol, HDL, cigarette use, and cholesterol-lowering and anti-inflammatory medication use. Results derived using model 2 are presented in Supplementary Table 8. Estimates for baseline CRP, CRP slope, and CRP variability, represent the standard deviation difference in CESD score per one standard deviation increase in baseline CRP, CRP slope, and CRP variability, respectively.

^a All models are adjusted for model 1 covariates.

^b Baseline CRP level was excluded from models that examined the number of elevated CRP measurements due to multicollinearity.