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Cumulative Depression Episodes Predicts Later C-Reactive Protein Levels: A Prospective Analysis

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Abstract

Background—Depression is associated with elevated levels of the inflammation marker C - reactive protein (CRP), yet the direction of this association remains unclear. This study tested bi-directional longitudinal associations between CRP and depression in a sample of adolescent and young adults. The study compared the effects of current depression to the cumulative episodes of depression over time.

Methods—Nine waves of data from the prospective population-based Great Smoky Mountains Study (N = 1,420) were used, covering children in the community aged 9–16, 19, and 21 years old. Structured interviews were used to assess depressive symptoms, depression diagnosis, and cumulative depressive episodes. Bloodspots were collected at each observation and assayed for CRP levels.

Results—CRP levels were not associated with later depression status. In contrast, all depression-related variables displayed evidence of association with *later* CRP levels. The associations with depressive symptoms and diagnostic status were attenuated after controlling for covariates particularly body mass index, smoking, and medication use. The effect of cumulative depressive episodes, however, continued to be significant after accounting for a range of covariates. Body mass index, smoking behavior and recent infections may mediate a portion of the effect of cumulative episodes on later CRP, but cumulative depressive episodes continued to predict CRP levels independently.

Conclusions—The occurrence of multiple depressive episodes exerted the greatest effect on later CRP levels. This suggests that risk for the diseases of middle age - cardiovascular and metabolic disease – may begin in childhood and depend, in part, upon long-term emotional functioning.

Keywords

Inflammation; CRP; Depression; Epidemiology; Childhood; Adolescence

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Introduction

Dysregulated immune function and elevated inflammation markers are part of the phenomenology of depression (for reviews (1, 2)). Depression is associated with elevated levels of pro-inflammatory cytokines and the proteins released in response to increasing cytokine levels. The acute phase protein C-reactive protein (CRP) has been the focus of extensive epidemiologic investigation because of the association of elevated plasma CRP levels (>3 mg/L) with cardiovascular risk (3, 4) and aspects of metabolic syndrome (5–7). A recent meta-analysis of 51 cross-sectional clinical and community studies of the CRP-depression link found an overall effect size of 0.15 (95% CI =0.10, 0.21) (8). This association was attenuated but still significant after controlling for body mass index (BMI; d = 0.11; 95% CI = 0.06, 0.17). The link between CRP and depression appears to be unequivocal, yet the direction of this association remains unclear.

Four studies have examined at the longitudinal bi-directional associations between depressive questionnaire scores and CRP. The Whitehall II study of over 3000 adults found that baseline CRP predicted cognitive symptoms of depression at 12-year follow-up after controlling for baseline depressive symptoms (9). Cognitive symptoms of depression, however, did not predict CRP levels at follow-up, suggesting a unidirectional effect from inflammation to psychiatric status. Stewart and colleagues found little evidence for either pathway in a small sample of healthy adults followed over 6 years, although both effects were of a similar magnitude as that reported in other studies (10). In contrast, a large multi-ethnic study of 1781 older women supported both pathways over a 1–2 year follow-up period, although the association of depressive levels with later CRP was only marginally significant (11). Finally, a recent study of 2544 middle-aged adults found that depressive levels predicted later CRP levels 5 years later, but this effect was limited to African Americans (12). There was no evidence that CRP predicted later depression levels in either African Americans or whites.

It might be concluded from this small group of reports that both pathways are possible but that the size of the effects is sufficiently modest to produce varying findings across studies. These studies, however, share characteristics which may contribute to their heterogeneous findings: reliance upon questionnaire assessment of depression levels and use of middle-age or older samples. One lesson from the meta-analysis of cross-sectional inflammation-depression findings was the importance of method of assessing depression (8). For CRP, the moderate effect size of 0.26 (95% CI = 0.11, 0.40) for studies using depression assessed with *structured interviews* was halved in studies assessing depressive symptoms with *self-report questionnaires* (effect size of 0.12 (95% CI = 0.06, 0.18)). Hence, the effect of assessment approach "…may partly reflect the greater sensitivity of standardized clinical interview to detect depression…"p.180 (8). No studies looking at longitudinal associations have assessed depression with structured interviews.

The reliance upon middle-aged or older samples is understandable given that CRP is typically studied in the context of cardiovascular disease which has an age of onset many decades later than that of depression. At the same time, assessment at older ages introduces significant heterogeneity with respect to the "dose" of depression accumulated by individuals over their life course. Chronic or recurrent depression may exact long-term physiological costs that exceed that of a single depressive episode. The effects of such accumulated exposure may persist even if the current levels of depression are low (13). No longitudinal studies of CRP-depression have evaluated the impact of one's cumulative episodes of depression apart from current depression status. The aim of this study is to test three longitudinal pathways between CRP and depression: 1) The effect of CRP levels on

later depression status; 2) The effect of depression status on later CRP levels; and 3) The effect of cumulative depression episodes on later CRP levels.

Methods and Materials

Participants

The Great Smoky Mountains Study is a longitudinal study of the development of psychiatric disorder and need for mental health services in rural and urban youth (14, 15). A representative sample of three cohorts of children, age 9, 11, and 13 at intake, was recruited from 11 counties in western North Carolina. Potential participants were selected from the population of some 12,000 children using a household equal probability, accelerated cohort design. All children scoring above a predetermined cut point (the top 25% of the total scores) on the CBCL Externalizing scale, plus a 1 - in - 10 random sample of the remaining 75% of the total scores, were recruited for detailed interviews. This approach oversamples those at risk for psychiatric problems for the purpose of estimating prevalence rates for uncommon psychiatric disorders. All subjects were assigned a weight inversely proportional to their probability of selection, so that all results are representative of the population from which the sample was drawn and not biased from the oversampling procedure. About 8% of the area residents and the sample are African American, less than 1% are Hispanic, and 3% are American Indian. Of all subjects recruited, 80% (N=1420) agreed to participate.

Subjects were assessed annually to age 16 then again at ages 19 and 21. Participants were interviewed within 3 months of their birthday each year. Across all waves, participation rates averaged 84% (range: 74–94%).

Procedures

The parent (biological mother for 83% of interviews) and subject were interviewed by trained interviewers separately until the subject was 16, and subjects only thereafter. Before the interviews began, parent and child signed informed consent forms approved by the Duke University Medical Center Institutional Review Board. Each parent and child received an honorarium for their participation.

Using a previously described procedure (16), blood samples were obtained at the beginning of each in-person assessment, as follows: two finger-prick samples (yielding 10 spots total per visit) were collected at 20-minute intervals, applied to standardized collection paper, immediately refrigerated upon drying, and express shipped (without refrigeration) to the laboratory within two weeks of collection. Samples were then stored at −28°C until they were assayed. This protocol is consistent with the rigorous quality control program developed for newborn screening programs (17) and has been used in a number of epidemiologic studies involving blood spot CRP measures (18, 19).

Assessment

Depression—Depression variables were assessed using the *Child and Adolescent Psychiatric Assessment* until age 16, and its upward extension, the *Young Adult Psychiatric Assessment* thereafter (20, 21). These structured interviews were coded by a trained interviewer and each interview was then checked by a supervisor. A detailed glossary provides the operational rules for each item assessed. The time frame for determining the presence of most behaviors was the past three months (unless otherwise indicated) to minimize forgetting and recall biases, although onset dates were also collected for all symptoms. A symptom was counted as present if reported by either parent or child or both, as is standard in clinical practice. Scoring programs written in SAS by the senior authors combined information about the date of onset, duration, and intensity of each symptom to

create diagnoses according to the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (22). Depressive disorders included major depression, dysthymia, and depressive disorder, not otherwise specified. Two-week test-retest reliability of diagnoses is comparable to that of other highly-structured child psychiatric interviews (23). Construct validity as judged by 10 different criteria including comparison to other interviews and ability to predict mental health service use is good to excellent (20). Depression status was measured by two variables: Any current depressive disorder (binary) and the number of total current nonoverlapping depressive symptoms (range: 0–10). Cumulative depression episodes was assessed by looking at the total number of depressive episodes reported up until the current assessment (range: 0–3).

C-Reactive Protein—Our assay for CRP in whole-blood spots was a biotin-Streptavidin based immunofluorometric system improving on a previously published method (24). One assay was completed for each subject at each observation. Streptavidin A-coated microtiter plates bind a biotinylated capture antibody to CRP, clone C2. A second Europium-labeled antibody then binds to the Streptavidin A Biotin–C2–CRP complex; fluorescence of the resultant complex is directly proportional to the CRP concentration in each well. Minimum detectable dose for the assay is .010 mg/L. For low, medium, high, and very high controls (. 022, .259, 1.208, and 3.271 mg/L, respectively), within-assay coefficient of variation (CV) (precision) is 2.0%, 1.2%, 1.6%, and 1.4%, respectively, while between-assay CV (reliability) runs 14.4%, 13.9%, 12.3% and 10.9%, respectively. CRP remains stable in dried blood spots for at least 5 days at room temperature or 14 days at 4 °C, and stable for years at −26 °C.

A validation study was performed with matched serum and blood spot samples assayed for CRP (n=38). As has been reported for many other analytes including CRP {Worthman, 1997 #9972; McDade, 1997 #11241; McDade, 2004 #18001}, a close linear correlation was identified between serum and blood spot CRP values (n=29; R^2 = .98, p<.0001). Serum equivalents therefore were calculated using the following algorithm based on the serum-blood spot regression: serum (hsCRP) = 1.38*(Blood Spot CRP Value) – 0.97. Blood spot CRP measures have been used in a number of epidemiologic studies (18, 19, 26). Observations with values above 10 mg/L indicate frank infection and were removed from statistical analysis (N=190 from a total of 6000 observations), whereas values below that index the extent of chronic low grade systemic inflammation associated with cardiovascular and metabolic risk (27).

Covariates—Variables included as covariates were those associated with variation in CRP levels (28–30) or used as covariates in other longitudinal studies involving CRP (9–12). These included age, sex, race, BMI, medication use, substance use, low SES, and recent physical ailments. BMI was calculated from weight and height measurements completed at each assessment. For all assessments completed before subjects were 20, BMI values were corrected for age and sex (31). The substance use assessment of the CAPA and YAPA interviews assesses current nicotine, alcohol, and illicit drug use. Dichotomous variables were included to indicate recent use of these substances. A physical health problems survey adapted from Form HIS-1A (1998), US Department of Commerce for the U.S. Public Health Service was administered at all interviews to assess 39 common ailments (e.g., diabetes, anemia, mononucleosis). A binary variable indicating any health ailments within the last 12 months was used for all analyses. Analyses were also tested using the following separate health categories: atopic (e.g., food/digestive allergy, asthma, and, respiratory allergy), injuries, infections (tonsilitis, ear infection, frequent diarrhea or colitis, and urinary tract infections) and chronic diseases (e.g., diabetes, epilepsy, cancer and chronic heart disease). Medication use within the prior year was also assessed from the Child and Adolescent Services Assessment (32). That interview focuses on psychotropic medications, but it also

looked at prescribed medications not related to psychiatric problems. All analyses were tested using a broad-based medication use variables as well as categories for individual medication groups (e.g., antidepressant, stimulant, and other prescribed medications). Low SES coded whether the subject's family displayed any 2 of the following 3 indicators: income below the federal poverty line, low parental education attainment, and low parental occupation status. Additional physiological covariates studied with CRP in older samples at risk for cardiovascular problems (e.g., blood pressure, lipids, or insulin) were not assessed. Of all common covariates, the Howren meta-analysis suggests that BMI has the strongest effect on the CRP-depression association (8).

Analytic framework

CRP values were positively skewed and were $\log_{10}$-transformed after scaling for nonnegative values by adding 1. Models predicting depressive symptoms or cumulative depressive episodes employed Poisson regression, those predicting diagnostic status employed logistic regression and those predicting CRP employed linear regression. All models used values from the prior assessment to predict current levels of the outcome variable. As such, only subjects with multiple assessments were included and subjects with more than two assessments contributed multiple observations. For example, if a subject had 5 assessments, then they contributed 4 observations to the current analyses (wave 1 predicting wave 2, wave 2 predicting wave 3, wave 3 predicting wave 4, and wave 4 predicting wave 5). All associations were tested using weighted regression models in a generalized estimating equations framework implemented by SAS PROC GENMOD. The robust variance (sandwich type) estimates derived from generalized estimating equations adjust the standard errors of the parameter estimates for the stratified design and for subjects contributing multiple observations. The covariance matrix was specified as autoregressive in all analyses.

Missing data

By age 21, 8806 total assessments were completed. Of these, bloodspots were obtained for 6087 (69.1%). Bloodspots were not available either because the subject refused or because the interviews were completed by phone. For in-person interviews, 79.4% of subjects agreed to provide bloodspots. Comparisons of observations in which blood spots were collected to those in which the subjects refused indicated no significant differences on any of the depression outcomes. Of the 6087 bloodspots collected, 6000 (98.6%) were successfully assayed for CRP; 190 were removed due to CRP levels indicating infection. Of the 1420 study participants, 1,334 (93.9%) provided blood spot samples assayed for CRP in one year or more. The median number of CRP samples provided was 5 (mean =4.77 (SD=2.24); range =1–9).

Results

Sample characteristics

Table 1 shows the characteristics of the full analytic sample in person-observations (5810 observations of 1334 subjects). Depression-related outcomes tended to be associated with being female, older, higher BMI, alcohol use, nicotine use, illicit drug use, medication use, and current health ailments. CRP levels were associated with being older, higher BMI, nicotine use, alcohol use, other drug use, medication use, current health ailments and low SES. This pattern of findings is consistent with associations of CRP in adulthood and suggests that all these covariates merit inclusion.

CRP and depression

A series of regression models tested the bi-directional associations between CRP and all depression-related outcomes (table 2). For each outcome, two models were tested: 1) a simple model in which the outcome was predicted from the value of the predictor and outcome variable at the preceding assessment (e.g., prior CRP and depressive symptoms predicting current symptoms); and 2) a covariate-adjusted model that also included current levels of all covariates in table 1 as well as a variable indicating time past since the last assessment. Because all models control for prior outcome status, change in the outcome variable is predicted.

The first three rows display the results for models predicting the three depression-related outcomes from prior CRP levels. Prior CRP yielded evidence of predicting only depression diagnosis, although even this association did not met formal statistical criteria. This pattern was replicated in the covariate adjusted model, suggesting very limited evidence of any longitudinal association between CRP and later depression. In all covariate-adjusted models, depression status was predicted by medication use and prior depression status. Follow-up analyses including separate health and medication categories did not change the pattern of findings although both antidepressants and other prescribed medications were significant covariates in all models. Rerunning the models excluding subjects using antidepressant did not change the pattern of results.

The final three rows in table 2 display the results of each depression variable predicting later CRP levels. The simple models yielded evidence that each depression variable predicted later CRP. Only cumulative depressive episodes, however, continued to predict later CRP levels in the covariate adjusted models. CRP levels were also predicted by BMI, time since the last interview, medication use, nicotine use and prior CRP levels in all models. When models were retested with separate categories of health ailments and medications, the number of prior depressive episodes still predicted current CRP levels and both other prescribed medications and recent infections were significant covariates as predictors of CRP level. No changes were noted when models were rerun excluding subjects using antidepressants.

CRP levels increased in relation to the number of prior depressive (0 prior episodes: mean = 0.85 (SD=1.51); 1 prior episode: mean = 1.27 (SD=1.55); 2+ prior episodes: mean = 2.36 (SD=2.30)). CRP levels above 3 are considered an established risk factor for cardiovascular disease in adults (33). Nine point eight percent (SE = 0.80) and 11.4% (SE = 2.61) of those with 0 or 1 prior episodes of depression had elevated levels of CRP, respectively. In contrast, forty 42.0% (SE = 14.8) of those with 2 or more prior depressive episodes had elevated CRP levels.

Mediation Analyses

The pattern of attenuated effects of the depression variables on later CRP in covariate-adjusted models suggests that specific covariates may mediate this association. To test this possibility, each significant covariate was tested as potential mediator using a multistage regression approach (34, 35). (Mediation analyses were not tested for models of prior CRP levels on depressive variables given the lack of attenuated effects between simple and covariate-adjusted models.)

Identification of potential mediators was based on five criteria: 1) The depressive variable was associated with CRP; 2) The depressive variable was associated with the covariate (table 3, column 1); 3) In models controlling for the depressive variable, the covariate was associated with CRP (column 2); 4) In models controlling for the covariate, the association between the depressive variable and CRP was either no longer statistically significant or was

attenuated (column 3); and 5) A statistically significant indirect path existed between the depressive variable and CRP through the covariate, as measured by the Sobel test (36) (column 4). Time since last interview was not associated with the depressive variables and is not included in table 3.

Four of the five variables tested displayed some evidence of mediation. The association of prior depressive symptoms and diagnosis with later CRP levels was mediated by medication use and infections. The indirect pathway through smoking behavior was significant for depressive symptoms but not diagnosis. Indirect paths were significant from smoking, BMI and infections predicting CRP from cumulative depressive episodes. In each case, cumulative depressive episodes continued to predict CRP independently (see column 3) suggesting both direct and indirect pathways from cumulative depressive episodes to CRP levels. Although a significant covariate, other prescribed medications did not account for the effect of depressive variables on later CRP.

Discussion

All three depression-related variables predicted increased levels of CRP at the subsequent assessment. In the case of depressive symptoms and diagnostic status, these associations were attenuated after controlling for covariates, particularly medication use, nicotine use, and recent infections. The effect of cumulative depressive episode episodes, however, continued to be significant after accounting for a range of covariates. Although BMI, nicotine use, and recent infections were partial mediators of this association, cumulative episodes continued independently to predict later CRP. CRP levels were associated only with later depression *diagnostic* status and even this association did not meet formal statistical criteria ($p=0.06$). These findings confirm the longitudinal link between depression and CRP early in life, but do not support CRP as predicting later depression.

This study did not support the pathway from CRP to later depression early in the lifespan. This pathway has received support in both the Whitehall II study (9) and the Study of Women's Health Across the Nation (11). The mechanism by which the products of inflammation may affect behavioral and emotional functioning has been widely discussed (for reviews (1, 2)). Typically, conceptual models implicate stress-related HPA-axis and sympathetic system activation in eliciting the release of pro-inflammatory cytokines that result in short-term increases in levels of acute phase proteins. In the long term, these cytokines may exert neural effects through excitotoxicity, alterations in monoamine neurotransmission, and reductions in neurotrophic support. Together, these effects may elicit depressed mood and associated symptoms. This model is supported by studies demonstrating that administration of pro-inflammatory cytokines (such as interferon alpha) is associated with behavioral symptoms that overlap with depression (37–40). Our large study suggests that this pathway may not be prominent early in life.

Other studies have supported the effect of depression on later CRP (11, 12). The convergence between our findings and that of other reports is not trivial given the focus of previous research on middle- to older-aged subjects. The current study followed children into young adulthood and assessed CRP long before peak onset for many of the physical conditions that affect baseline CRP levels. Despite this fundamental difference, a longitudinal pathway identified in studies of older adults already was detectable in this largely pre-adult sample, suggesting the depression-CRP association holds across the lifespan.

Although less attention has been paid to this pathway, a possible mechanism behind it may lie within existing models of depression and inflammation. Raison and colleagues' model

presupposes an activation of the HPA axis and sympathetic systems triggered by stressful experiences (41). Production of pro-inflammatory cytokines is simulated within macrophages in direct response to these stress systems. It is plausible that depression itself may activate those stress response systems via a lower stress activation threshold, apart from any environmental stressors. In this sense, depression may be self-sustaining by producing a systemic stress response in the absence of external stressors (42, 43). McEwen suggests that the price to be paid for this constant adaption is “wear and tear” on physiological systems (44). This notion, which McEwen terms “allostatic load”, converges with our finding that the effect of depression is largely accounted for by one’s cumulative history or “dose” of depression. Such chronic exposures have been associated with resistance to the inhibitory effects of glucocorticoids on inflammatory responses (45, 46). In the current study, having had a history of multiple depressive episodes better predicted CRP levels than current depression status itself.

Limitations

The Great Smoky Mountains study has several strengths besides its longitudinal, prospective design: A population-based design that minimized selection biases; depression variables assessed repeatedly with structured interviews that allowed us to look at various aspects of depression; repeated collection of bloodspots that allowed for subjects to provide up to 9 values of CRP across 12 years; and assessment of a wide range of domains that allowed us to control for covariates of depression and CRP. But the sample is not representative of the U.S. population (Native Americans overrepresented and African Americans and Latinos underrepresented).

The time between any two assessments was never less than a year, yet both CRP levels and depressive symptoms vary over shorter periods. For example, levels of CRP begin to rise within hours following acute infection and peak within 48 hours. Follow-up periods in prior studies of this bidirectional association have tended to be over longer periods with some as long as 12 years. For evaluation of bi-directional associations, it is important to keep in mind that the pathways evident over longer periods of time (> 1 year) may differ from those over shorter periods (1 month or 1 hour).

Conclusion

Our study provides strong evidence supporting the long-term pathway from depression to later CRP levels, but not CRP to later depression. While the impact of any single depressive episode on later CRP may be modest, it is the cumulative effect or dose of multiple episodes that exerts the more robust effect on CRP. This is of particular interest given the role of CRP as an independent risk factor for later cardiovascular disease (3, 4) and metabolic disorders (5–7). Close to half of those with multiple prior depressive episodes display CRP levels that are commonly associated with risk for cardiovascular disease in adulthood. If confirmed, our findings suggest that risk for the chronic diseases of middle age, such as cardiovascular and metabolic disease, may begin in childhood and depend, in part, upon long-term emotional functioning.

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Table 1

Descriptive information and concurrent associations between primary variables and covariates

	Total sample (N=5810)	Depressive sx.[a]	Depressive dx.[c]	Cumulative episodes[b]	CRP[a]
Primary		**Odds or means ratio**	**Odds or means ratio**	**Odds or means ratio**	**Odds or means ratio**
Mean depressive sx.	0.80 (1.04)	--	--	--	--
Depression dx.	2.4% (169)	6.18 (5.61–6.80)	--	--	--
Cumulative episodes					
0	93.60% (5536)	2.13 (1.92–2.36)	4.86 (3.97–5.95)	--	--
1	5.00% (390)				
2+	1.4% (74)				
Mean CRP levels (mg/L)	1.04 (2.02)	1.25 (1.00–1.57)	2.58 (1.14–5.82)	1.59 (1.15–2.19)	--
Covariates					
Sex (% female)	48.7% (2766)	0.89 (0.78–1.02)	0.53 (0.32–0.87)	0.55 (0.33–0.92)	0.97 (0.95–1.00)
Mean age	14.21 (3.19)	1.00 (0.99–1.02)	1.08 (1.03–1.13)	1.14 (1.11–1.16)	1.02 (1.01–1.02)
Race (% White)	89.7% (3905)	1.10 (0.96–1.26)	0.79 (0.45–1.39)	0.76 (0.44–1.32)	1.04 (1.00–1.08)
Mean BMI	22.37 (5.62)	1.01 (1.00–1.02)	1.03 (1.00–1.07)	1.04 (1.02–1.06)	1.02 (1.02–1.02)
Alcohol use	12.8% (850)	1.10 (0.96–1.25)	1.67 (1.05–2.65)	1.24 (1.08–1.42)	1.06 (1.03–1.09)
Current nicotine use	13.5% (1143)	1.21 (1.04–1.41)	3.18 (1.90–5.32)	1.44 (1.10–1.89)	1.10 (1.06–1.13)
Other drug use	8.1% (571)	1.35 (1.13–1.60)	3.05 (1.85–5.02)	1.33 (1.09–1.61)	1.05 (1.01–1.09)
Medication use	30.2% (1842)	1.59 (1.44–1.76)	3.32 (2.19–5.03)	1.18 (1.06–1.32)	1.05 (1.03–1.08)
Recent health ailments	34.7% (2013)	1.34 (1.19–1.49)	1.90 (1.24–2.92)	1.15 (1.01–1.32)	1.04 (1.02–1.06)
Low SES	20.1% (1607)	0.99 (0.87–1.12)	0.63 (0.35–1.14)	0.93 (0.77–1.11)	1.04 (1.02–1.07)

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Means and standard deviations are reported for continuous variables and percentages and sample sizes are included for dichotomous variables. Reported CRP mean and standard deviation values are from untransformed variables. All associations between CRP and other variables use $\log_{10}$-transformed values. Associations of primary variable with other variables were tested with either linear[a], Poisson[b], or logistic[c] regression.

CRP=C-Reactive Protein; BMI = Body-mass index; SES= socioeconomic status. Sx = symptoms; Dx = diagnoses.

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Table 2

Bidirectional associations between CRP and depression-related variables

		Effect of prior predictor				
Predictor status at preceding assessment	**Outcome**	**Simple**		**Adjusted for covariates**		**Significant Covariates**
		β (SE)	***p***	**β (SE)**	***p***	
CRP	Depressive sx.[b]	0.12 (0.15)	0.42	0.07 (0.16)	0.64	3, 4, 9, 10
CRP	Depressive dx.[c]	1.08 (0.61)	0.08	1.10 (0.59)	0.06	6, 9
CRP	Cumulative episodes[b]	0.39 (0.32)	0.22	0.19 (0.30)	0.54	3, 5, 6, 9
Depressive sx.	CRP[a]	0.01 (0.005)	0.03	0.004 (0.005)	0.44	4, 5, 6, 9
Depressive dx.	CRP[a]	0.06 (0.03)	0.07	0.03 (0.04)	0.49	4, 5, 6, 9
Cumulative episodes	CRP[a]	0.08 (0.02)	< 0.0001	0.04 (0.02)	0.02	4, 5, 6, 9

Models were tested with either linear[a], Poisson[b], or logistic[c] regression. Simple models include prior status on the outcome variable.

Covariates include the following: 1= sex; 2= race; 3=age; 4 = time since last interview; 5=BMI; 6=current nicotine use; 7 = current alcohol use; 8= current illicit drug use; 9 = current medication use; 10=recent health ailments; 11= current low SES. CRP=C-Reactive Protein; BMI = Body-mass index; SES= socioeconomic status. Sx = symptoms; Dx = diagnoses.

Table 3

Tests of potential mediators of the association between depressive variables and later CRP

	1. Depression variable to mediator	2. Mediator to CRP	3. Depression variables to CRP	4. Sobel test
	β (SE)	**β (SE)**	**β (SE)**	***p***
Depressive sx.[a]				
Current nicotine use	0.17 (0.03)	0.04 (0.02)	0.007 (0.005)	0.02
BMI	0.17 (0.13)	0.02 (0.001)§	0.007 (0.005)	0.18
Infections	0.33 (0.04)§	0.06 (0.02)≠	0.006 (0.005)	0.005
Medication Use	0.20 (0.05)§	0.06 (0.01)§	0.009 (0.005)	0.002
Other Prescribed Meds	0.07 (0.04)	0.04 (0.01)≠	0.006 (0.005)	0.11
Depression status[b]				
Current nicotine use	0.39 (0.17)	0.04 (0.02)	0.05 (0.03)	0.09
BMI	0.36 (0.61)	0.02 (0.001)§	0.04 (0.04)	0.55
Infections	0.92 (0.30)≠	0.06 (0.02)≠	0.05 (0.03)	0.03
Medication Use	0.82 (0.22)§	0.06 (0.012)§	0.04 (0.03)	0.004
Other Prescribed Meds	0.26 (0.23)	0.04 (0.01)≠	0.05 (0.03)	0.28
Cumulative episodes[a]				
Current nicotine use	0.84 (0.17)	0.04 (0.02)	0.05 (0.02)≠	0.02
BMI	2.48 (0.98)≠	0.02 (0.001)§	0.05(0.02)≠	0.01
Infections	0.87 (0.16)§	0.06 (0.02)≠	0.04 (0.02)≠	0.009
Medication Use	0.32 (0.23)	0.06 (0.01)§	0.07 (0.01)§	0.17
Other Prescribed Meds	0.20 (0.12)	0.04 (0.01)≠	0.05 (0.02)≠	0.12

Models were tested with either Poisson[a] or logistic[b] regression. Columns numbered 2 and 3 provide results from models in which both depression variable and potential mediator predicted current CRP status. Models adjusted for demographic covariates and prior CRP status. Sobel test assess significance of indirect pathway.

CRP=C-Reactive Protein; BMI = Body-mass index. Sx = symptoms; Dx = diagnoses.

† $P \leq 0.05$;

‡ $P \leq 0.01$;

$^{\S}P \leq 0.0001$.