Prospective Association Between C-Reactive Protein and Fatigue in the Coronary Artery Risk Development in Young Adults Study

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Background: Fatigue is highly prevalent and causes serious disruption in quality of life. Although the underlying biological mechanism is unknown, increases in inflammation have been implicated. This prospective study examined the association between C-reactive protein (CRP), a biomarker of systemic inflammation, and fatigue 5 years later.

Methods: The Coronary Artery Risk Development in Young Adults (CARDIA) study is a population-based longitudinal study conducted in four U.S. cities. Highly sensitive CRP concentration and fatigue were measured in 2983 African American and white adults at both year 15 (2000–2001, ages 33–45 years) and year 20 (2005–2006) examinations. Fatigue was assessed using the vitality subscale of the 12-item Short Form Health Survey.

Results: Plasma CRP concentration at baseline (i.e., CARDIA year 15) was a significant predictor of fatigue level 5 years later (unadjusted $\beta = .126$, $p < .001$). After adjustment for potential confounders, this association remained significant (adjusted $\beta = .044$, $p = .033$). Additionally, baseline CRP independently predicted fatigue in the subgroup of participants without medical comorbidity (adjusted $\beta = .051$, $p = .039$). Fatigue was associated with a persistent elevation of CRP at both examinations but not with a transient elevation of CRP at only one of the examinations.

Conclusions: This is the first study to demonstrate a prospective association between an inflammatory marker and fatigue in a general population. Furthermore, the association between low-grade systemic inflammation and fatigue seems primarily driven by persistent immune activation and not explained by the presence or development of medical comorbidity.

Key Words: C-reactive protein, fatigue, inflammation, population-based prospective study

Fatigue is a highly prevalent symptom with up to 38% of community-dwelling individuals suffering from this subjective sense of weariness, tiredness, lack of energy, and low vitality (1,2). Fatigue is a comorbid symptom found across many major medical and psychiatric disorders—e.g., human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), cancer, multiple sclerosis, chronic fatigue syndrome, major depression, and schizophrenia—and causes serious disruption in quality of life (3–5). However, it also occurs independently, in otherwise healthy individuals, and can lead to disability and cost for society. United States workers with fatigue cost employers $136.4 billion annually in lost productivity (6)—far higher compared with $61.2 billion for pain (7) and $44.0 billion for depression (8).

The underlying biological mechanisms that contribute to fatigue are largely unknown, although recent basic research on neuroimmune interactions has suggested that inflammatory processes may play a role in fatigue through cytokine effects on the central nervous system. Indeed, animal studies have shown that peripheral immune activation and increases in proinflammatory cytokines—e.g., interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α—induce fatigue-like behaviors such as reduction in voluntary daily running distance (9,10). Intracerebrally administered recombinant TNF has also been found to induce such behaviors in mice (9). Similarly, human studies have shown administration of IL-6 and interferon-α, also a proinflammatory cytokine, induces fatigue in healthy men (11) and patients with malignant melanoma (12,13), respectively. However, these experimental strategies resulting in a highly robust and acute immune activation might not reproduce the effects of low-grade chronic inflammation, which is thought to be responsible for many pathological processes (14).

Evidence regarding the role of low-grade systemic inflammation on fatigue is limited to a small number of cross-sectional or case-control studies conducted primarily in medical populations (15–28). This prior work has examined the association between fatigue severity and circulating levels of IL-1, IL-6, TNF-α, and C-reactive protein (CRP) but has yielded conflicting results represented by positive, null, and even negative correlations. Furthermore, the design of these studies does not address the direction of causality and the generalizability of these data is constrained by sampling of patients with conditions such as cancer, multiple sclerosis, and chronic fatigue syndrome. Presence of severe medical comorbidity may either compound or obscure the associations between inflammation and fatigue, and small sample sizes have further contributed to conflicting results. No study, to our knowledge, has examined the association between markers of inflammation and fatigue in a large-scale community sample. Moreover, no data are available that have examined the prospective association between low-grade systemic inflammation and fatigue.

Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, an ongoing community-based

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cohort study, we examined whether high levels of CRP, a biomarker of systemic inflammation, were associated with fatigue 5 years later, assessed as low vitality, in a general adult population. Furthermore, we examined whether high CRP levels predicted fatigue in the subgroup without medical comorbidity—i.e., no comorbid disorders such as cardiovascular diseases, diabetes, and hypothyroidism. Lastly, we assessed whether a persistent, as opposed to a transient, elevation of CRP was associated with fatigue. We hypothesized that plasma CRP levels would predict fatigue levels 5 years later in the entire sample as well as in the subgroup without medical comorbidity and that this association would be most strongly driven by a persistent elevation of CRP.

Methods and Materials

Subjects

The CARDIA study is a longitudinal study of cardiovascular risk factors in white and African American men and women aged 18 to 30 years at study inception. Full details of the study design and methods have been published previously (29). Briefly, 5115 individuals were recruited from four US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) to take part in the baseline clinical examination (1985–1986). Of the 5115 individuals originally enrolled at year 0, 3178 participated in both year 15 and year 20, two CARDIA examinations when both CRP and fatigue were measured. For the purpose of the current article, year 15 (2000–2001) was considered as the baseline and year 20 (2005–2006) as the follow-up. After 195 subjects were excluded due to missing values of CRP or fatigue (n = 183) and outlying values of CRP (n = 12) at either baseline or follow-up, the remaining sample size was 2983.

Main Outcome Measure

Fatigue was measured as low vitality using the vitality subscale of the 12-Item Short Form Health Survey (SF-12) (30). The SF-12 is a valid and reliable shorter version of the 36-Item Short Item Health Survey (SF-36) with their subscales being highly correlated in clinical and general populations (30–33). The SF-12 vitality subscale consists of a single item ("Did you have a lot of energy?" referring to the past 4 weeks) on a 6-point scale: All of the time, 0; Most of the time, 1; A good bit of the time, 2; Some of the time, 3; A little of the time, 4; and None of the time, 5. Higher scores on this scale reflect more severe fatigue. The SF-12 vitality subscale score was treated as a continuous variable, given that ordinal variables with five or more categories are referred to as quasi-interval and can be treated as if they were continuous (34).

To ensure the suitability of using the SF-12 vitality subscale as the main outcome measure, we assessed its convergent validity using two datasets we had access to: the Whitehall II study, a prospective cohort study of British civil servants (35), and the Moving Beyond Cancer (MBC) study, a multisite randomized controlled trial of behavioral interventions (36). Both studies included the SF-36 and the latter also included the Fatigue Symptom Inventory (FSI) (37). Convergent validity was demonstrated by computing correlations between the individual energy item ("Did you have a lot of energy?") and the full vitality subscale of the SF-36. High correlations were observed in 7888 healthy adults from the Whitehall II study (r = .87; $p < .0001$) and in 557 breast cancer patients from the MBC study (r = .89; $p < .0001$). The individual energy item ("Did you have a lot of energy?") was also highly correlated with the FSI in the latter group (r = .64; $p < .0001$).

C-Reactive Protein

Highly sensitive CRP was measured using a Behring Nephelometer II (BN II) (Dade Behring, Deerfield, Illinois). Given the skewed distribution of CRP, the values were log transformed. Visual inspection of the distribution of log-transformed CRP identified 12 participants as having outlying values at either baseline or follow-up even after the transformation; consequently, these subjects were excluded from the analyses. Log-transformed CRP was used in all analyses as a continuous variable, except for graphic representation and the analysis of persistent CRP elevation. For the latter purposes, CRP values were categorized according to the Centers for Disease Control and Prevention/American Heart Association recommendations (<1 mg/L, 1–3 mg/L, and >3 mg/L) (38).

Potential Biobehavioral Confounders

Smoking status, originally classified as never, former, or current smoker, was recategorized as a binary variable (current smoker or not). A summary score of sleep quality was produced, summing up five items of the sleep questionnaire, with higher summary scores reflecting poorer sleep quality: daytime sleepiness (individual score 0 or 1), sleep onset problem (0 or 1), sleep maintenance problem (0 or 1), early awakening (0 or 1), and subjective sleep quality (0 to 4). All the other variables were used in the original format without further reduction or modification. They were binary (sex, ethnicity [white and African American], and regular use of aspirin) or continuous (age, years of education, body mass index [BMI], mean systolic blood pressure, self-reported average daily alcohol consumption, physical activity level, depressive symptoms, and pain). Pain was measured using the bodily pain subscale of the SF-12 (score range 0–4), with higher scores reflecting more severe pain. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), a valid and reliable measure of depressive symptoms in the general population. Physical activity level was assessed with the CARDIA Physical Activity History Questionnaire, eliciting frequency of participation in a range of specific heavy and moderate intensity activities during the previous 12 months. Physical activity score was computed and expressed in exercise units (EU). For reference, 300 EU roughly approximates the American College of Sports Medicine recommendations for the amount of exercise needed to support weight loss (39).

Analysis

Baseline characteristics of 2983 participants were described in terms of frequency, mean, or median by baseline levels of fatigue. Then, the study hypotheses were tested by performing linear regression analyses with standardized regression coefficients (β), which facilitate comparison across models. The prospective associations between CRP and fatigue were examined in both directions: 1) baseline CRP predicting fatigue at follow-up; and 2) baseline fatigue predicting CRP at follow-up. Selection of covariates for multivariable analysis relied on external clinical judgment rather than predetermined p value criteria; the latter approach, which selects factors for inclusion in a multivariable model only if the factors are statistically significant in bivariate screening, is considered less optimal (40). All covariates were assessed at baseline. Model 1 included sociodemographic variables (age, sex, ethnicity, and education). Model 2 further

included biological measures and medication (BMI, systolic blood pressure, and regular aspirin use). Model 3 further included fatigue-related symptoms (depressive symptoms, sleep quality, and pain). Finally, Model 4 further included health-related behaviors (smoking, alcohol consumption, and physical activity). Age, sex, ethnicity, and education were tested for potential effect modification. To avoid any artifact due to different sample sizes between the nested models, participants missing the covariates were excluded.

Since depression is a construct closely linked to the presence of fatigue in humans, the prospective associations between CRP and depressive symptoms were also examined. For this purpose, all the analytical procedures described above were repeated simply exchanging fatigue with depressive symptoms.

To examine whether high CRP levels predicted fatigue in those participants without medical comorbidity, a subgroup analysis was conducted. Based on the participants' medical history and laboratory data at follow-up, they were divided into two subgroups: those with or without medical disorders that are usually comorbid with fatigue. Then, the aforementioned multivariable models (models 1 to 4) were repeated for each subgroup. Given that CRP is an important risk marker for medical disorders comorbid with fatigue, such as cardiovascular disease, this subgroup analysis served to examine whether the prediction of fatigue at follow-up by baseline CRP was due to the presence or development of such medical disorders at follow-up. Presence of comorbid disorders was defined by any one of the following criteria: 1) lifetime history of chronic medical conditions comorbid with fatigue (e.g., coronary heart disease, diabetes, renal failure, hepatitis, cancer, hypothyroidism, inflammatory bowel diseases, and autoimmune diseases); 2) past year history of acute or subacute medical conditions comorbid with fatigue (e.g., asthma, pneumonia, and deep vein thrombosis); 3) fasting plasma glucose level at or above 126 mg/dL (as a criterion for diabetes mellitus); and 4) serum creatinine at or above 2.5 mg/dL (as a criterion for renal dysfunction).

These prospective associations between CRP and fatigue were graphically represented using mean fatigue score at follow-up in each of the three CRP categories at baseline. Crude and fully adjusted means (adjusted using model 4) in each category were represented as connected lines.

Lastly, to assess whether a persistent, as opposed to a transient, elevation of CRP was associated with fatigue, the participants were divided into four groups according to CRP levels at baseline and follow-up: group 1, the reference category with low levels (≤3 mg/L) at both examinations; group 2, high levels (>3 mg/L) at baseline and low levels at follow-up; group 3, low levels at baseline and high levels at follow-up; and group 4, high levels at both examinations. Then, multivariable linear regression was performed with this new categorization as the independent dummy variable and fatigue at follow-up as the dependent variable.

Results

Baseline Characteristics

Overall, mean fatigue score and median CRP concentration at baseline were 1.93 (standard deviation 1.15) and 1.36 mg/L (interquartile range .53–3.72), respectively (Figure 1 in Supplement 1). Fatigue score of 1.93 indicates "a lot of energy during a good bit of the time." Table 1 describes characteristics of the participants by levels of fatigue at baseline. A higher level of fatigue was associated with lower education level, higher BMI, more severe pain, lower physical activity level, higher depressive symptom level, poorer sleep quality, and higher CRP concentration. Those with a higher fatigue level were more likely to be female, currently smoking, and regularly using aspirin. The level of fatigue was not significantly associated with age, systolic blood pressure, or amount of daily alcohol consumption. Although those with low or intermediate fatigue level were more likely to be white and those with a high fatigue level were more likely to be African American, no linear trend was observed. Furthermore, the mean fatigue score was similar in these two ethnic groups (1.92 vs. 1.95, $p = .48$ by t test).

Cross-Sectional Associations Between CRP and Fatigue at Baseline

There was a significant positive cross-sectional association between CRP and fatigue at baseline (unadjusted $\beta = .154$, $p < .001$). The association remained significant after adjusting for age, sex, ethnicity, education, BMI, systolic blood pressure, regular aspirin use, depressive symptoms, sleep quality, pain, smoking, alcohol consumption, and physical activity (adjusted $\beta = .046$, $p = .013$).

Prospective Associations Between CRP and Fatigue

Figure 1 and Table 2 describe the prospective association of baseline CRP with fatigue at follow-up. High CRP concentration at baseline predicted fatigue at follow-up 5 years later (unadjusted $\beta = .126$, $p < .001$). This association remained significant in the subsequent multivariable models, including the fully adjusted model (model 4: adjusted $\beta = .044$, $p = .033$). C-reactive protein accounted for .9% of the variance in fatigue outcome. No effect modification was observed for age, sex, ethnicity, or education. Table 3 describes the prospective association in the opposite direction, baseline fatigue predicting CRP at follow-up. High fatigue level at baseline predicted CRP concentration at follow-up 5 years later (unadjusted $\beta = .152$, $p < .001$). This association remained significant in the subsequent multivariable models, including the fully adjusted model (model 4: adjusted $\beta = .053$, $p = .006$). Fatigue accounted for .7% of the variance in CRP outcome. No effect modification was observed for age, sex, ethnicity, or education.

Subsequently, we examined whether the following variables at follow-up mediate these independent associations between CRP and fatigue: BMI, depressive symptoms, sleep quality, pain, and physical activity. Sobel-Goodman mediation tests were performed examining each of these variables as a potential mediator of the associations between CRP and fatigue in both directions, maintaining the full set of baseline covariates (41). The only significant mediator was physical activity for the association between baseline fatigue and CRP at follow-up (10.2% of the total effect mediated, $p = .005$). As described in the Methods and Materials section, the time frame of physical activity assessment was a period of 12 months before the follow-up visit, therefore preceding the measurement of CRP and meeting a necessary condition for mediation.

Finally, we evaluated the prospective associations between CRP and depressive symptoms. High CRP concentration at baseline predicted depressive symptoms at follow-up 5 years later (unadjusted $\beta = .086$, $p < .001$). However, the fully adjusted model indicated that the prospective association of baseline CRP with depressive symptoms at follow-up was entirely explained by the confounding effects of the covariates (model 4: adjusted $\beta = -.006$, $p = .776$). Specifically, the most important confounders were sleep quality and fatigue, respectively accounting for

Table 1. Characteristics of 2983 Participants by Levels of Fatigue at Baseline

Variable (range)	Level of Fatigue[a] Low (n = 1334)	Intermediate (n = 1345)	High (n = 304)	p for Trend
Age (33–45 Years), Mean (SD)	40.2 (3.5)	40.3 (3.6)	40.4 (3.7)	.459
Sex, %				
Male	49.9	41.8	26.0	.001
Female	50.1	58.2	74.0	
Ethnicity, %				
White	53.7	60.0	46.1	.920[b]
African American	46.3	40.0	53.9	
Education (4–20 Years), Mean (SD)	15.2 (2.6)	15.0 (2.5)	14.4 (2.5)	.001
BMI (15.7–65.8 kg/m^2), Mean (SD)	27.6 (6.0)	29.1 (6.9)	30.7 (7.9)	.001
Daily Alcohol Consumption (0–564.9 mL), Mean (SD)	11.7 (29.7)	10.2 (20.7)	9.5 (24.2)	.088
Current Smoker, %				
No	83.0	77.8	75.0	.001
Yes	17.0	22.2	25.0	
Regular Use of Aspirin, %				
No	95.2	93.8	92.4	.031
Yes	4.8	6.2	7.6	
Pain Score (0–4), Mean (SD)	.33 (.66)	.60 (.88)	1.24 (1.33)	.001
Physical Activity Score (0–1818), Mean (SD)	423 (313)	307 (240)	223 (221)	.001
CES-Score (0–54), Mean (SD)	5.9 (5.6)	9.9 (7.1)	17.3 (10.6)	.001
Sleep Quality Score (0–8), Mean (SD)	1.7 (1.6)	2.5 (1.6)	3.6 (2.0)	.001
CRP (.15–35.6 mg/L), Median	1.15	1.47	2.16	.001

BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CRP, C-reactive protein; SD, standard deviation.

[a]For the purpose of the baseline description, fatigue levels were defined as follows: 1) low—a lot of energy "all of the time" or "most of the time"; 2) intermediate—a lot of energy "a good bit of the time" or "some of the time"; 3) high—a lot of energy "a little of the time" or "none of the time."

[b]Note that there was a significant nonlinear association between ethnicity and level of fatigue as assessed by chi-square test ($p < .001$).

17.7% and 13.4% of the variance, compared with .01% accounted for by CRP. Similarly, although high levels of baseline depressive symptoms predicted CRP at follow-up (unadjusted $\beta = .106$, $p < .001$), the association was no longer significant after the full adjustment (model 4: adjusted $\beta = -.010$, $p = .605$).

Prospective Association Between CRP and Fatigue in the Subgroup Without Medical Comorbidity

Of 2983 participants, 936 had comorbid medical disorders according to our criteria. C-reactive protein predicted fatigue only in the subgroup without comorbid disorders, and this prospective association was independent of age, sex, ethnicity, education, BMI, systolic blood pressure, regular aspirin use, depressive symptoms, sleep quality, pain, smoking, alcohol consumption, and physical activity (adjusted $\beta = .051$, $p = .039$). C-reactive protein accounted for 1.3% of the variance in fatigue outcome.

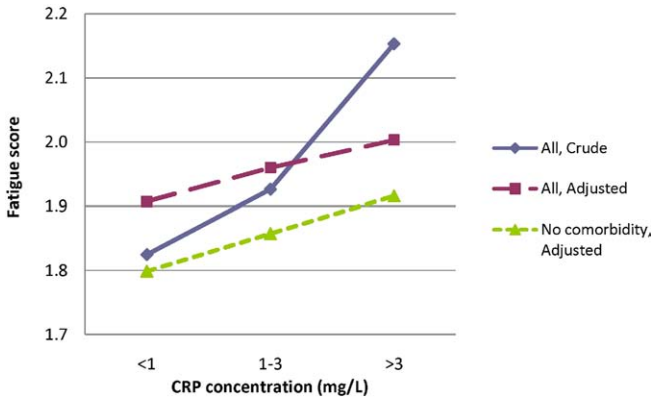

Figure 1. Crude and adjusted mean fatigue scores at follow-up according to the baseline level of C-reactive protein (CRP) in the entire sample (n = 2921) and in the subgroup with no medical comorbidity (n = 2012). The mean score was adjusted for age, sex, ethnicity, education, body mass index, systolic blood pressure, regular aspirin use, depressive symptoms, sleep quality, pain, smoking, alcohol consumption, and physical activity level.

Persistent Elevation of CRP and Fatigue

According to the categorization described in the Methods and Materials section using 3 mg/L as the cutoff for low versus high CRP, there were 1871 participants in group 1 (low CRP levels at both examinations), 354 in group 2 (high at baseline and low at follow-up), 219 in group 3 (low at baseline and high at follow-up), and 539 in group 4 (high at both examinations). Overall, a significant linear trend was observed with increasingly higher levels of fatigue at follow-up moving from one group to another, and this trend was independent of the aforementioned covariates (adjusted $\beta = .043$, $p = .032$) (Table 1 in Supplement 1). Pairwise comparisons revealed that group 4 had significantly higher fatigue levels at follow-up as compared with group 1 (adjusted $\beta = .042$, $p = .041$). However, neither group 3 nor group 2 had significant difference from group 1 (respectively, adjusted $\beta = .018$, $p = .312$; and adjusted $\beta = .007$, $p = .703$). In summary, fatigue was significantly associated with a persistent elevation of CRP but not with a transient elevation of CRP.

Additionally, to make the most of the continuous nature of CRP measure in showing the importance of persistent elevation, we performed another analysis using a newly generated variable, the mean of CRP values over baseline and follow-up. This new

Table 2. Prospective Association of Baseline CRP with Fatigue at Follow-up ($n = 2921$)

Adjustment[a]	β	*p*	R^2	ΔR^2 Due to CRP	% ΔR^2 Due to CRP
Unadjusted Model	.126	<.001	.016	.016	100%
Model 1: Sociodemographic Variables	.113	<.001	.038	.012	32.1%
Model 2: Model 1 + Biomedical Factors	.060	.006	.047	.002	5.3%
Model 3: Model 2 + Fatigue-Related Symptoms	.055	.008	.137	.002	1.5%
Model 4: Model 3 + Health-Related Behaviors	.044[b]	.033	.153	.001	.9%

β, standardized regression coefficient expressing the change in standardized fatigue score per one standard deviation in CRP concentration; CRP, C-reactive protein; R^2, R-square of the model; ΔR^2, change in R-square; % ΔR^2, percentage change in R-square.

[a]Sociodemographic variables include age, sex, ethnicity, and education. Biomedical factors include body mass index, systolic blood pressure, and regular aspirin use. Fatigue-related symptoms include depressive symptoms, sleep quality, and pain. Health-related behaviors include smoking, alcohol consumption, and physical activity.

[b]No effect modification was observed for age ($p = .259$), sex ($p = .542$), ethnicity ($p = .779$), or education ($p = .987$).

continuous variable, which reflects both time points with a higher mean corresponding to higher concentration over 5 years, was significantly associated with fatigue levels at follow-up (adjusted β = .065, $p = .002$).

Discussion

In a community sample, higher plasma CRP concentration predicted higher fatigue level 5 years later independent of a series of risk factors, such as BMI, depressive symptoms, sleep quality, pain, and physical activity. To our knowledge, this is the first study to demonstrate a prospective association between a marker of systemic inflammation and fatigue in a general population. In addition, among participants without comorbid medical disorders, the association between CRP and fatigue was significant, demonstrating that the prospective influence of CRP on fatigue cannot be explained simply by the presence or development of comorbid medical disorders. Moreover, fatigue was predicted by a persistent, as opposed to a transient, elevation of CRP. Lastly, the nature of the association between CRP and fatigue seems bidirectional, as higher fatigue level at baseline also independently predicted higher CRP concentration at follow-up 5 years later. Interestingly, the latter relationship was partly mediated by physical activity level, whereas the prospective effect of CRP on fatigue was not mediated by physical activity or any of the following variables including BMI, depressive symptoms, sleep quality, and pain.

Although an association between systemic inflammation and fatigue has been reported in cancer survivors (42,43), the implications of these data for a nonmedical community sample are unknown (see Miller *et al.* [44] and Schubert *et al.* [45] for a review) due to the confounding influence of cancer diagnosis and related treatments. Among persons with chronic fatigue syndrome as compared with control subjects, overproduction (15–20), reduced production (25), and no difference (21–24) of proinflammatory cytokines have been reported, with similar conflicting results in patients with multiple sclerosis (26–28). In a correlational study of 40 healthy young adults, no association of fatigue with TNF-α or CRP was found, although this could have been due to limited statistical power (46).

Derived from a community-based prospective study, the current data overcome the limitations of prior studies in humans and translate evidence generated in animals that systemic inflammation induces fatigue-like behaviors. The following features further strengthen the current findings. First, the possibility of selection bias or information bias was less likely than in previous studies, given that the study sample was randomly chosen from the community and the exposure variable was an objective biological measure. Second, as noted above, the association between CRP and fatigue was independent of a series of confounding variables such as obesity, depression, sleep quality, pain, and physical activity. Third, given that the findings were generated in community-dwelling adults including those without medical comorbidity, it does not appear fatigue is simply a byproduct of medical disorders and related inflammation. Fourth, there was twofold evidence of a dose-response relationship between CRP and fatigue: higher CRP levels were linearly associated with higher fatigue levels, and persistently elevated, but not transiently elevated, CRP concentration predicted fatigue.

The mechanisms that drive increases of inflammation and symptoms of fatigue in a healthy community-dwelling sample

Table 3. Prospective Association of Baseline Fatigue with CRP at Follow-up ($n = 2948$)

Adjustment[a]	β	*p*	R^2	ΔR^2 Due to Fatigue	% ΔR^2 Due to Fatigue
Unadjusted Model	.152	<.001	.023	.023	100%
Model 1: Sociodemographic Variables	.126	<.001	.098	.015	15.7%
Model 2: Model 1 + Biomedical Factors	.054	.001	.277	.003	1.0%
Model 3: Model 2 + Fatigue-Related Symptoms	.057	.002	.277	.002	.8%
Model 4: Model 3 + Health-Related Behaviors	.053[b]	.006	.281	.002	.7%

β, standardized regression coefficient expressing the change in standardized fatigue score per one standard deviation in CRP concentration; CRP, C-reactive protein; R^2, R-square of the model; ΔR^2, change in R-square; % ΔR^2, percentage change in R-square.

[a]Sociodemographic variables include age, sex, ethnicity, and education. Biomedical factors include body mass index, systolic blood pressure, and regular aspirin use. Fatigue-related symptoms include depressive symptoms, sleep quality, and pain. Health-related behaviors include smoking, alcohol consumption, and physical activity.

[b]No effect modification was observed for age ($p = .401$), sex ($p = .484$), ethnicity ($p = .301$), or education ($p = .553$).

are unknown. Experimental studies suggest that physical and psychological stressors activate the peripheral immune system, mounting an inflammatory response with the release of proinflammatory cytokines and acute phase proteins ("signal generated") (47). These peripheral inflammatory signals are then transduced to the brain through specific pathways across the blood-brain barrier such as vagal nerve afference and IL-1 receptors located on endothelial cells of brain venules ("signal received"), and the brain finally may produce sickness behaviors including fatigue ("response to signal") (48). While extensive research efforts have accumulated mechanistic evidence on the generation and reception of inflammatory signals (47), the specific mechanisms of how the brain responds to these signals producing the symptom of fatigue are still to be elucidated. To date, basal ganglia hypermetabolism—hence, altered dopaminergic activities—has been related to physical fatigue and anterior cingulate activation to mental fatigue during interferon-α therapy of patients with malignant melanoma (13,49). Interestingly, although systemic inflammation also has been linked to depressed mood, the nature and mechanism of this link seem to be distinct from the association between inflammation and fatigue. Among interferon-α treated patients, while fatigue has been related to alterations in dopamine neurotransmission in the basal ganglia, depressed mood has been linked to alterations in corticotropin-releasing hormone pathways and serotonin metabolism (50,51). Furthermore, fatigue occurs earlier in interferon-α therapy and responds less to antidepressant treatment (12), supporting distinct mechanisms for depression and fatigue.

Persistent inflammation may be a particularly important factor involved with fatigue. Interestingly, data from the CARDIA study reported elsewhere suggest that this persistent inflammation may be driven by genetic predisposition (CRP promoter gene polymorphisms) (52) and early life stress (low childhood socioeconomic status and harsh early family environment) (53). Furthermore, we have previously demonstrated that cytokine gene polymorphisms, which are thought to be associated with persistent elevations of inflammatory markers, correlate with fatigue in breast cancer survivors (54).

As to the association in which higher fatigue level leads to higher CRP concentration, physical activity level was shown to partly mediate it. Fatigued individuals may be less physically active, and low physical activity may lead to increased CRP level. Clinical trials have indeed shown physical exercise decreases CRP level (55,56).

The following limitations should be considered. First, the assessment of fatigue relied on a single item rather than a composite measure that evaluates the multidimensional nature of this construct. Thus, the current findings should be interpreted taking this limitation into account and future research should employ a more nuanced measure of fatigue, such as the Multidimensional Fatigue Symptom Inventory. However, as previously discussed, SF-12 vitality subscale is a valid and reliable measure of energy-fatigue. Additionally, supporting the usefulness of this measure, which inquires about energy level, is a previous report that the energy subscale of a composite fatigue measure was the best correlate of the biological substrate for cytokine-induced fatigue (13). Second, CRP was the only marker of systemic inflammation measured in the current study, although it is the most extensively researched and the most clinically useful inflammatory marker (57). Third, the magnitude of the association between CRP and fatigue was small, albeit statistically significant. Nevertheless, it was greater than the magnitude of the association between CRP and depressive symptoms in the current sample. The association between CRP and depression, examined by numerous previous studies, is currently considered an established research finding despite its small effect size. A recent meta-analysis has reported Cohen's *d* of .15 overall and .11 in community studies (58), both values considered small (59).

The findings of the current study suggest that plasma CRP, especially its persistent elevation, is an independent risk factor for fatigue. Despite the study limitations, these prospective observations provide novel information on the role of systemic inflammation on fatigue within the context of a large sample of nonmedical, community-dwelling persons. These data should also motivate further investigations to define the effects of proximal factors for persistent inflammation (e.g., CRP gene polymorphism, childhood stress) on fatigue risk. Testing of interventions that target inflammation might identify new strategies to constrain fatigue onset.

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Supplementary material cited in this article is available online.

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