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Association of C-reactive protein and interleukin-6 with new-onset fatigue in the Whitehall II prospective cohort study

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Abstract

Background—Although basic research on neuroimmune interactions suggests that inflammatory processes may play a role in the development of fatigue, population-based evidence on this association is limited. This study examined whether plasma C-reactive protein (CRP) and interleukin-6 (IL-6), biomarkers of systemic inflammation, predict fatigue onset.

Methods—The Whitehall II study is a large-scale cohort study conducted in 20 civil service departments in London. Plasma CRP and IL-6 were measured in 4847 non-fatigued participants at Phase 3 (1991-1993, ages 39-63 years). Fatigue was assessed using the Vitality Subscale of the 36-item Short Form Health Survey (SF-36) at Phase 3 and Phase 4 (1995-1996).

Results—During a mean follow-up of 3.1 years, 957 new fatigue cases (19.7%) were identified using the pre-established cutoff score 50 or less on the Vitality Subscale. CRP values were dichotomized as low (<1.0 mg/L) or high (≥ 1.0 mg/L) using the Centers for Disease Control/American Heart Association recommendations. Similarly, IL-6 values were also dichotomized as low (<1.5 pg/mL) or high (≥ 1.5 pg/mL). After full adjustment for sociodemographic and biobehavioral covariates, the odds ratios for new-onset fatigue were 1.28 (95% confidence interval 1.09-1.49, P=0.003) for high CRP and 1.24 (1.06-1.45, P=0.008) for high IL-6. Similar results were found when CRP and IL-6 were treated as continuous variables.

Conclusions—Plasma CRP and IL-6 were prospectively associated with new-onset fatigue, supporting the hypothesis that low-grade inflammation has a role in the development of fatigue.

Keywords

C-reactive protein; fatigue; inflammation; interleukin-6; prospective cohort study

Introduction

Fatigue, i.e., a subjective sense of weariness, tiredness, lack of energy, and low vitality, is a highly prevalent symptom with prevalence rates up to 38% in community-dwelling individuals and 43% among primary care patients (Valdini, 1985; Pawlikowska *et al.*, 1994; Cho *et al.*, 2009a). Fatigue can be a comorbid symptom for many major medical and

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Declaration of Interest
None.

psychiatric disorders (e.g. HIV/AIDS, cancer, multiple sclerosis, chronic fatigue syndrome, major depression, and schizophrenia) (Anderson and Ferrans, 1997; Curt, 2000; Amato *et al.*, 2001), but it also occurs independently, in otherwise healthy individuals, and can lead to disability and cost for society. In the US, for example, workers with fatigue are estimated to cost employers \$136.4 billion annually in lost productivity (Ricci *et al.*, 2007) – far higher compared to \$61.2 billion for pain (Stewart *et al.*, 2003b) and \$44.0 billion for depression (Stewart *et al.*, 2003a). The burden imposed by fatigue in clinical practice is also significant. It is often a difficult symptom to be managed because the available treatments for fatigue are at most of moderate effectiveness, e.g., cognitive behavioral therapy in chronic fatigue syndrome (White *et al.*, 2011), amantadine in multiple sclerosis (Compston and Coles, 2002), and modafinil in major depression (Fava, 2006), and also because fatigue can be a side effect of the treatments targeting the underlying disorders, such as anticancer (Miller *et al.*, 2008), antidepressant (Zajecka, 2000), and antipsychotic pharmacotherapy (Ritsner *et al.*, 2002).

Recently, inflammatory processes have been suggested as playing a role in fatigue through cytokine effects on the central nervous system (Dimsdale and Dantzer, 2007). Studies have shown that administration of proinflammatory cytokines such as interleukin (IL)-6 and interferon (IFN)- γ induces fatigue in healthy men (Spath-Schwalbe *et al.*, 1998) and patients with malignant melanoma (Capuron *et al.*, 2002; Capuron *et al.*, 2007), respectively. Similarly, inflammatory challenge with endotoxin administration, which leads to an acute elevation of IL-6 and tumor necrosis factor (TNF)- α , increases fatigue level in healthy subjects (Eisenberger *et al.*, 2010). 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 (Danesh *et al.*, 2000).

To date, research on the association between low-grade systemic inflammation and fatigue has yielded conflicting results represented by positive, null, and even negative – i.e., systemic inflammation being associated with lower risk of fatigue – correlations (summarized in online eTable 1) (Chao *et al.*, 1991; Buchwald *et al.*, 1997; Cannon *et al.*, 1997; Gupta *et al.*, 1997; Cannon *et al.*, 1999; LaManca *et al.*, 1999; Moss *et al.*, 1999; Zhang *et al.*, 1999; Giovannoni *et al.*, 2001; Kashipaz *et al.*, 2003; Flachenecker *et al.*, 2004; Collado-Hidalgo *et al.*, 2006; Heesen *et al.*, 2006; ter Wolbeek *et al.*, 2007; Vollmer-Conna *et al.*, 2007). Furthermore, evidence is limited to a small number of cross-sectional or case-control studies conducted primarily in clinical populations, such as patients with cancer, multiple sclerosis, and chronic fatigue syndrome (Chao *et al.*, 1991; Buchwald *et al.*, 1997; Cannon *et al.*, 1997; Gupta *et al.*, 1997; Cannon *et al.*, 1999; LaManca *et al.*, 1999; Moss *et al.*, 1999; Zhang *et al.*, 1999; Giovannoni *et al.*, 2001; Kashipaz *et al.*, 2003; Flachenecker *et al.*, 2004; Collado-Hidalgo *et al.*, 2006; Heesen *et al.*, 2006; ter Wolbeek *et al.*, 2007; Vollmer-Conna *et al.*, 2007). The design of these studies does not address the direction of causality, and the presence of severe medical comorbidity may either compound or obscure the associations between inflammation and fatigue.

We have previously demonstrated that high levels of C-reactive protein (CRP), a biomarker of systemic inflammation, were associated with fatigue five years later in a general adult population, using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a community-based prospective cohort study (Cho *et al.*, 2009b). However, the only marker of systemic inflammation measured was CRP, an acute phase reactant that does not cross the blood-brain barrier, and no pro-inflammatory cytokines were included in the study. Furthermore, the assessment of fatigue relied on a single item rather than a composite measure, hence not allowing a comprehensive evaluation of this construct. This limitation also impeded the identification of fatigue cases, a categorical classification

approach that would assist in translating the research findings into the clinical context and in generating data on the incidence or new-onset of illnesses/symptoms.

Therefore, using data from the Whitehall II study, an ongoing large-scale occupational cohort study, we examined whether low-grade systemic inflammation, measured by CRP and IL-6, a pro-inflammatory cytokine, predicted the onset of fatigue three years later, assessed using the Vitality Subscale of the 36-item Short Form Health Survey (SF-36), a valid and reliable four-item measure of energy-fatigue supported by both observational and experimental data (Ware, 1993). By adopting this measure, which has a pre-established cutoff score for well-being versus limitation/disability related to fatigue, we were able to identify cases of fatigue. Specifically, we first aimed to confirm the findings of our prior work (Cho *et al.*, 2009b) by assessing prospective associations between inflammatory markers and fatigue as continuous variables, and then aimed to provide new information within the clinical context of case prediction by assessing prospective associations between inflammatory markers and new onset cases of fatigue as categorical variables.

Methods

Subjects

The Whitehall II study is a prospective cohort study of 10308 civil servants (6895 men and 3413 women) working in 20 departments based in London, aged 35-55 years at study inception in 1985-1988 (Phase 1). Since then, there have been seven further data collection phases. Odd-numbered phases include both a clinical examination and a self-administered questionnaire, while even-numbered phases are questionnaire only. Informed consent was obtained from all participants. Ethical approval was obtained from the University College London Medical School Committee on the Ethics of Human Research. Full details of the study design and methods have been published previously (Marmot and Brunner, 2005).

For the purpose of the current study, Phase 3 (1991-1993) is considered the baseline, as it was the first clinical examination with a measurement of inflammatory markers. Phase 4 (1995-1996) is considered the follow-up. Initially, for the analysis of cross-sectional associations at baseline, 7509 participants were selected as they had inflammatory markers – either CRP or IL-6 – and fatigue assessed at baseline (aged 39 to 63 years). For the analysis of prospective associations, 819 participants were excluded as they did not have fatigue assessed at follow-up, hence leaving 6690 for the prospective analysis (mean follow-up time 3.1 year, range 1.9-4.6 years). These 6690 individuals were slightly older, more likely to be male, more likely to be white, and more likely to have high employment grades compared to those excluded (online eTable 2). However, the differences were small, reaching statistical significance mostly due to the large sample size. In addition, given the focus of the study on fatigue onset, 1843 participants were excluded as they evidenced fatigue ‘caseness’ at baseline, with SF-36 Vitality Subscale at 50 or less (Ware, 1993). Hence, the remaining 4847 non-fatigued individuals were considered for the analysis of the associations between inflammatory markers and new-onset fatigue. Specifically, 4822 were included in the analysis of CRP and 4786 in the analysis of IL-6. Compared to the rest of the sample, these 4847 non-fatigued individuals were older, included a higher proportion of males, and had higher employment grades (online eTable 3).

Inflammatory markers

Venous blood was taken in the fasting state or at least 5 hours after a light, fat-free breakfast. CRP was measured using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). IL-6 was measured using a high-sensitivity ELISA assay (R & D Systems, Oxford, UK). Values lower than the detection

limit (0.154 mg/L for CRP and 0.08 pg/mL for IL-6) were assigned a value equal to half the detection limit. To measure short-term biological variation and reproducibility of the assessment, a repeated sample was taken from a subset of 150 participants for CRP and 241 for IL-6 (average time between samples 32 days). Reliability (Pearson r) between samples was $r=0.77$ for CRP and $r=0.61$ for IL-6 (Gimeno *et al.*, 2011).

Given the skewed distribution of CRP and IL-6, the values were log transformed. Initially, log-transformed CRP and IL-6 as continuous variables were used for the analyses of cross-sectional and prospective associations between inflammatory markers and fatigue without excluding fatigue cases at baseline. Subsequently, in order to investigate the prediction of new-onset fatigue by inflammatory markers, both CRP and IL-6 were categorized. CRP values were dichotomized as low (<1.0 mg/L) or high (≥ 1.0 mg/L) using the Centers for Disease Control/American Heart Association (CDC/AHA) criteria, originally recommended for the risk assessment of cardiovascular disease (Pearson *et al.*, 2003). Using 1.0 mg/L as the cutoff, Liukkonen *et al.* previously found a significant association between CRP and depression in a large cohort (Liukkonen *et al.*, 2006). In the current sample, this cutoff approximately corresponded to the median and defined 54.6% of the initially selected 7509 participants as having low CRP. The categorization of CRP into three groups using the CDC/AHA criteria (<1.0 mg/L, 1.0-3.0 mg/L, and >3.0 mg/L) yielded almost identical results, supporting the use of dichotomized CRP (online eTable 4). Similarly, IL-6 values were also dichotomized as low (<1.5 pg/mL) or high (≥ 1.5 pg/mL). As there is no available guideline for the categorization of IL-6, we chose the cutoff that would roughly reproduce the distribution of participants determined by the CRP categorization. Consequently, the cutoff of 1.5 pg/mL approximately corresponded to the median and defined 55.3% of the initially selected 7509 participants as having low IL-6. Finally, to explore the combined effect of CRP and IL-6, we generated a composite variable of both inflammatory markers with the following four categories: low CRP and low IL-6 (i.e., absence of inflammation); high IL-6 and low CRP (i.e., acute inflammation that is not of sufficient magnitude or duration to induce CRP); low IL-6 and high CRP (i.e., indicative of inflammation that may have been initiated but is no longer sustained by activation of IL-6); and high IL-6 and high CRP. IL-6 induces CRP; hence elevated levels of both IL-6 and CRP are indicative of activation of proximal as well as distal components of systemic inflammation, and might be indicative of an ongoing and persistent state of inflammation (Pepys and Hirschfield, 2003; Cole *et al.*, 2011).

Main outcome measure

Fatigue was measured using the Vitality Subscale of the 36-item Short Form Health Survey (SF-36), referring to the past four weeks (Ware *et al.*, 1996). The SF-36 Vitality Subscale is a valid and reliable four-item measure of energy-fatigue supported by both observational and experimental data (O'Connor, 2004). Moreover, the SF-36 Vitality Subscale is one of the most frequently used measures of energy-fatigue in a variety of subject groups including arthritis patients, cancer survivors, and general population, and correlates highly with other fatigue measures such as the Chalder Fatigue Questionnaire and the Piper Fatigue Scale (Andrykowski *et al.*, 1998; O'Connor, 2004; Wolfe, 2004; Dagfinrud *et al.*, 2005). The standardized scores range from 0 to 100, higher scores reflecting higher vitality, i.e., less severe fatigue, and scores greater than the midpoint of 50 represent well-being, whereas scores 50 or less represent limitations or disability related to fatigue (Ware, 1993). This variable was first used as a continuous variable and then dichotomized using a cut-off of 50, therefore defining fatigue caseness as a score 50 or less.

Potential biobehavioral confounders

Potential biobehavioral confounders to be included in the multivariable analysis were obtained from Phase 3. Sociodemographic variables included age, sex, ethnicity (white or non-white), and socioeconomic position based on participant's last known civil service employment grade, categorized as high (administrators), middle (executives, professionals and technical staff), and low (clerical and office support staff) (Kumari *et al.*, 2004). Biomedical variables, measured according to standard protocols, included body mass index (BMI in kg/m²), systolic blood pressure (mmHg), presence of common medical conditions (diabetes, diagnosed heart disease, or respiratory illness), and use of prescription medications that could affect systemic inflammatory status or fatigue severity (lipid lowering drugs, aspirin, oral steroids, oral contraceptives, hormone replacement therapy, antidepressants, and hypnotics). Health-related behaviors included current smoking status (yes or no) and alcohol consumption (units of alcohol in last week) (Kumari *et al.*, 2004). Fatigue-related symptoms included symptoms of psychological distress (i.e. symptoms of depression and anxiety as measured by the 30-item General Health Questionnaire) (Goldberg, 1972; Stansfeld and Marmot, 1992) and sleep difficulty (presence or absence in last 14 days).

Analysis

First, the cross-sectional associations between inflammatory markers and fatigue at baseline were examined by performing multivariable linear regression analyses, using these variables as continuous. To facilitate comparison across models, standardized regression coefficients () were calculated, which express the change in standardized fatigue score per one standard deviation in log-transformed CRP or IL-6 concentration. Similarly, the prospective associations between baseline inflammatory markers and fatigue at follow-up were examined by performing multivariable linear regression analyses, again using these variables as continuous. Subsequently, the prospective associations between inflammatory markers and newly onset cases of fatigue were examined by performing multivariable logistic regression analyses, using these variables as categorical. Covariates were selected based 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 (Steyerberg *et al.*, 2000). All covariates were assessed at baseline. Models were adjusted for age, sex, and ethnicity since they influence the distribution of the inflammatory markers (Wener *et al.*, 2000). Further multivariable models also included each of the following sets of variables in turn: socioeconomic position (employment grade), biomedical factors (BMI, systolic blood pressure, common medical conditions, and use of prescription medication that could affect systemic inflammatory status), health-related behaviors (smoking and alcohol consumption), and fatigue-related symptoms (depression/anxiety and sleep difficulty). Finally, the analysis was repeated with simultaneous adjustment for all the above covariates. Age, sex, and ethnicity were tested for potential effect modification. Analyses were performed using STATA version 12.0 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

Table 1 describes the characteristics of 7509 participants who had data on either of the inflammatory markers and fatigue at baseline by sex. Levels of CRP and IL-6 were higher in women than men. Women had lower vitality and consequently were more likely to be classified as fatigue cases. Overall, regardless of sex, 27.9% of 7509 participants were classified as fatigue cases. Women were older, included a higher proportion of non-white participants, and were more likely to be from the low employment grade. Women had higher

BMI and higher likelihood of using prescription medications that could affect systemic inflammatory status or fatigue severity but had lower blood pressure and lower prevalence of common medical conditions. Women had a better profile of health-related behaviors, smoking less and drinking less. Women presented with a higher level of psychological distress (i.e. depression/anxiety) and reported more sleep difficulty than men. CRP and IL-6 levels were positively correlated ($r=0.37$, $P<0.0001$).

Cross-sectional associations between inflammatory markers and fatigue

At baseline, there were significant cross-sectional associations between inflammatory markers (CRP and IL-6) and fatigue, both treated as continuous variables, after adjustment for age, sex, and ethnicity (Table 2). More specifically, higher levels of inflammatory markers were associated with lower levels of vitality (as represented by negative values of β), hence higher levels of fatigue. These associations remained statistically significant in the subsequent multivariable models, including the fully adjusted model, which further controlled for socioeconomic position, body mass index, systolic blood pressure, presence of common medical conditions, use of prescription medications that could affect systemic inflammatory status or fatigue severity, smoking, alcohol consumption, symptoms of depression/anxiety, and sleep difficulty (adjusted $\beta = -0.032$ for CRP with $P=0.003$; adjusted $\beta = -0.027$ for IL-6 with $P=0.013$) (Table 2). In practical terms, -0.032 means that, for every 1 standard deviation increase of log-transformed CRP, there was a decrease of 0.59 in SF-36 Vitality subscale.

Prospective associations between inflammatory markers and fatigue

Table 3 describes the prospective associations of baseline inflammatory markers (CRP and IL-6) with fatigue at follow-up, both treated as continuous variables. High plasma concentrations of inflammatory markers at baseline predicted fatigue at follow-up about 3 years later when adjusted for age, sex, and ethnicity. These associations remained statistically significant in the subsequent multivariable models, including the fully adjusted model (adjusted $\beta = -0.025$, $P=0.048$ for CRP; adjusted $\beta = -0.025$, $P=0.044$ for IL-6). In practical terms, -0.025 means that, for every 1 standard deviation increase of log-transformed CRP, there was a decrease of 0.49 in SF-36 Vitality subscale.

Among the covariates, the fully adjusted model with CRP indicated depression/anxiety as having the strongest effect on fatigue (adjusted $\beta = -0.237$, $P<0.001$). Similarly, the fully adjusted model with IL-6 also indicated depression/anxiety as having the strongest effect on fatigue (adjusted $\beta = -0.237$, $P<0.001$).

Prospective associations between inflammatory markers and new-onset fatigue

Of 4847 participants free of fatigue at baseline, 957 (19.7%) developed new fatigue at follow-up. As shown in Table 4, after adjustment for age, sex, and ethnicity, those with high CRP at baseline had 35% higher odds of developing fatigue compared to those with low CRP (odds ratio 1.35, 95% confidence interval [CI] 1.17-1.56, $P<0.001$), and those with high IL-6 at baseline had 27% higher odds of developing fatigue compared to those with low IL-6 (odds ratio 1.27, 95% CI 1.10-1.47, $P=0.001$). Table 4 also describes the contribution of the four sets of covariates to the associations between inflammatory markers at baseline and new-onset fatigue at follow-up. The full adjustment indicated both CRP and IL-6 were significant independent predictors of new-onset fatigue. After adjusting for age, sex, ethnicity, socioeconomic position, BMI, systolic blood pressure, presence of common medical conditions, use of prescription medications, smoking, alcohol consumption, depression/anxiety, and sleep difficulty, the respective odds ratios for CRP and IL-6 were 1.28 (95% CI 1.09-1.49, $P=0.003$) and 1.24 (95% CI 1.06-1.45, $P=0.008$). No effect modification was observed for age, sex, ethnicity, or education.

The categorization of CRP into three groups using the CDC/AHA criteria (<1.0 mg/L, 1.0-3.0 mg/L, and >3.0 mg/L) yielded almost identical results (online eTable 4). A similar pattern was observed when IL-6 was categorized into three groups using the cutoffs that would roughly reproduce the distribution of participants determined by the CRP categorization (<1.5 pg/mL, 1.5-2.5pg/mL, and >2.5 pg/mL) (online eTable 4).

Combined effect

Additional analyses explored whether the combination of elevated CRP and IL-6 had additive predictive effects on fatigue caseness. Having both inflammatory markers at low levels was defined as the reference category, and this included 40.0% of the participants. The category of low CRP & high IL-6 included 16.0% of the participants and that of high CRP & low IL-6 included 16.4%. The last category with both markers at high levels included 27.6% of participants. As shown in Table 5, after adjustment for age, sex, and ethnicity, only the membership in the last category was significantly associated with increased risk of developing fatigue compared to the reference category (odds ratio 1.51, 95% CI 1.26-1.81, $P<0.001$). This association remained significant after the full adjustment for age, sex, ethnicity, socioeconomic position, BMI, systolic blood pressure, presence of common medical conditions, use of prescription medications, smoking, alcohol consumption, depression/anxiety, and sleep difficulty (odds ratio 1.45, 95% CI 1.19-1.77, $P<0.001$).

Discussion

In a large sample of British civil servants, higher levels of circulating inflammatory markers, CRP and IL-6, were cross-sectionally and prospectively associated with fatigue. Furthermore, higher levels of circulating CRP and IL-6 predicted new-onset fatigue about three years later. These associations were independent of a series of risk factors such as sociodemographic characteristics, BMI, systolic blood pressure, presence of common medical conditions, use of prescription medications, smoking, alcohol consumption, symptoms of depression/anxiety, and sleep difficulty. Additionally, when the data were analyzed using CRP and IL-6 as a combined variable rather than separately, participants with both markers at high levels were at a significant risk of developing fatigue, while those who had only one of the markers at high levels were not. Elevated levels of both of these inflammatory markers are more likely in the setting of ongoing (e.g., elevations of IL-6) and persistent (e.g., elevations of CRP) inflammation rather than temporarily heightened inflammation.

Comparison with other studies

Although an association between systemic inflammation and fatigue has been reported in cancer survivors, the implications of those data for non-medical general adult population is unknown due to the confounding influence of cancer diagnosis and related treatments (see Miller et al. (Miller *et al.*, 2008), Schubert et al. (Schubert *et al.*, 2007), and Saligan & Kim (Saligan and Kim, 2012) for a review). Among persons with chronic fatigue syndrome (see Klimas et al. (Klimas *et al.*, 2012) for a review of recent work), overproduction (Chao *et al.*, 1991; Buchwald *et al.*, 1997; Cannon *et al.*, 1997; Gupta *et al.*, 1997; Cannon *et al.*, 1999; Moss *et al.*, 1999), reduced production (ter Wolbeek *et al.*, 2007), and no difference (LaManca *et al.*, 1999; Zhang *et al.*, 1999; Kashipaz *et al.*, 2003; Vollmer-Conna *et al.*, 2007) of proinflammatory cytokines have been reported as compared to controls, with similar conflicting results in patients with multiple sclerosis (Giovannoni *et al.*, 2001; Flachenecker *et al.*, 2004; Heesen *et al.*, 2006) (see online eTable 1 for a summary). In a correlational study of 40 healthy young adults, no association of fatigue with TNF- or CRP was found although this could have been due to limited statistical power (Corwin *et al.*,

2002). Our previous analysis using the CARDIA study data overcame the limitations of the previous studies, however, it was still limited because the assessment of fatigue relied on a single item rather than a composite measure and CRP was the only marker of systemic inflammation measured (Cho *et al.*, 2009b).

Strengths and limitations

Derived from a large prospective cohort study, the current data largely overcome the limitations of prior studies and suggest that low-grade systemic inflammation plays a role in the development of fatigue. The main outcome was assessed using a valid and reliable composite measure of fatigue supported by both observational and experimental data (Ware, 1993). The current study employed two systemic inflammatory markers involved in different steps of the inflammation process, a proinflammatory cytokine and an acute phase reactant, respectively corresponding to a proximal and a distal step of the cascade. By including only fatigue-free participants at baseline, the prediction of new onset fatigue was evaluated. Given that the findings were obtained from a non-medical occupational cohort, it does not appear fatigue is simply a byproduct of medical disorders and related inflammation. Lastly, as noted above, the association between inflammatory markers and fatigue was independent of a series of confounding variables such as obesity, depression/anxiety, sleep difficulty, use of prescription medications, and presence of common medical conditions.

The following limitations should be considered. First, this was not an incidence study as the study design only allowed the identification of fatigue present during the 4 weeks prior to the follow up assessment. It is possible that some participants may have had transient fatigue sometime between the baseline and the follow up, hence not identified by the study. For this reason, we could not estimate any incidence and purposely used the term ‘new-onset’ instead of ‘incident’. Second, although we carefully performed multivariable analyses considering a series of potential risk factors, it is still possible that there is some residual confounding since this was not a randomized controlled trial, the only approach that can eliminate the confounding effect entirely. There could be unmeasured confounding variables accounting for some of the association between inflammatory markers and fatigue. Hence, although this study suggests a possible causal link between low-grade systemic inflammation and fatigue, no definite causality can be established. Third, we measured inflammatory markers only at one point in time. Further research is needed to examine whether duration of inflammation, based on repeat data, is associated with the risk of new-onset fatigue in a dose-response manner.

Possible mechanisms

The mechanisms that drive increases of inflammation and symptoms of fatigue in a non-clinical adult population such as the current sample 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’) (Black, 2002). 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’) (Dantzer *et al.*, 2008). While extensive research efforts have accumulated mechanistic evidence on the ‘generation’ and ‘reception’ of inflammatory signals (Black, 2002), 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 IFN- α therapy of patients

with malignant melanoma (Capuron *et al.*, 2005; Capuron *et al.*, 2007). The current findings extend the existing mechanistic knowledge of inflammatory biology to the study of fatigue.

Conclusion and implication

Population-based evidence on a robust association of CRP and IL-6 with new-onset fatigue is consistent with the hypothesis that low-grade systemic inflammation may play an important role in the development of fatigue. No validated prediction algorithms or specific pharmacotherapies with demonstrated effectiveness are currently available for fatigue. These findings suggest that inflammatory markers might provide an incremental component to risk prediction models for fatigue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1
Characteristics of the participants at baseline (N = 7509^{*})

| Variable | Men (5219) | Women (2290) | P [§] |
|--|------------------|------------------|----------------|
| Main variables | | | |
| CRP (mg/L), median (interquartile range) | 0.85 (0.43-1.72) | 1.01 (0.47-2.36) | <0.001 |
| IL-6 (pg/mL), median (interquartile range) | 1.35 (0.99-1.93) | 1.57 (1.11-2.45) | <0.001 |
| SF-36 Vitality score, mean (SD) | 63.9 (17.4) | 57.9 (19.8) | <0.001 |
| Fatigue, N (%) | 1267 (24.3) | 829 (36.2) | <0.001 |
| Sociodemographics | | | |
| Age (years), mean (SD) | 49.3 (6.0) | 50.2 (6.1) | <0.001 |
| Ethnicity (white), N (%) | 4822 (92.4) | 1951 (85.2) | <0.001 |
| Employment grade (low), % | 346 (6.6) | 909 (39.7) | <0.001 |
| Biomedical | | | |
| BMI (kg/m ²), mean (SD) | 25.1 (3.2) | 25.7 (4.7) | <0.001 |
| Systolic blood pressure (mmHg), mean (SD) | 121.8 (13.2) | 117.7 (14.1) | <0.001 |
| Presence of common medical conditions [†] , N (%) | 883 (16.9) | 327 (14.3) | 0.005 |
| Use of prescription medications [‡] , N (%) | 218 (4.2) | 348 (15.2) | <0.001 |
| Health-related behaviors | | | |
| Current smoking, N (%) | 651 (12.7) | 368 (16.5) | <0.001 |
| Alcohol consumption (unit in last week), mean (SD) | 12.3 (13.8) | 5.3 (7.4) | <0.001 |
| Fatigue-related symptoms | | | |
| Depression/anxiety (GHQ-30 score), mean (SD) | 2.8 (4.9) | 3.4 (5.4) | <0.001 |
| Sleep difficulty, N (%) | 1314 (25.2) | 759 (33.2) | <0.001 |

CRP = C-reactive protein; IL-6 = interleukin-6; SF-36 = the 36-item Short Form Health Survey; SD = standard deviation; BMI = body mass index; GHQ-30 = the 30-item General Health Questionnaire

^{*} Participants with data on inflammatory markers (either CRP or IL-6) and fatigue at baseline

[§] P-value from chi-square test, t-test, or Wilcoxon rank-sum test, respectively, for proportion, mean, or median

[†] Diabetes, diagnosed heart disease, or respiratory illness

[‡] Use of prescription medications that affect systemic inflammatory status or fatigue severity, including lipid lowering drugs, aspirin, oral steroids, oral contraceptives, hormone replacement therapy, antidepressants, and hypnotics

Table 2
Cross-sectional associations between circulating inflammatory markers (CRP and IL-6) and fatigue at baseline

| Adjustment* | CRP as predictor | | IL-6 as predictor | |
|-------------------------------|------------------|---------------|-------------------|---------------|
| | N | P | N | P |
| Age, sex, ethnicity (Model A) | 7476 | -0.055 <0.001 | 7422 | -0.044 <0.001 |
| A + Socioeconomic position | 7471 | -0.056 <0.001 | 7417 | -0.046 <0.001 |
| A + Biomedical factors | 7408 | -0.033 0.006 | 7358 | -0.031 0.010 |
| A + Health-related behaviors | 7328 | -0.050 <0.001 | 7274 | -0.037 0.002 |
| A + Fatigue-related symptoms | 7466 | -0.049 <0.001 | 7412 | -0.040 <0.001 |
| Fully adjusted | 7249 | -0.032 0.003 | 7199 | -0.027 0.013 |

CRP = C-reactive protein; IL-6 = interleukin-6; β = standardized regression coefficient expressing the change in standardized fatigue score per one standard deviation in log-transformed CRP or IL-6 concentration

* Biomedical factors include body mass index, systolic blood pressure, presence of common medical conditions, and use of prescription medications that could affect systemic inflammatory status. Health-related behaviors include smoking and alcohol consumption. Fatigue-related symptoms include psychological distress and sleep difficulty at baseline.

Table 3
Prospective associations of circulating inflammatory markers (CRP and IL-6) at baseline with fatigue at follow-up

| Adjustment* | CRP as predictor | | IL-6 as predictor | |
|-------------------------------|------------------|---------------|-------------------|--------------|
| | N | P | N | P |
| Age, sex, ethnicity (Model A) | 6658 | -0.052 <0.001 | 6614 | -0.042 0.001 |
| A + Socioeconomic position | 6654 | -0.052 <0.001 | 6610 | -0.042 0.001 |
| A + Biomedical factors | 6600 | -0.033 0.011 | 6559 | -0.031 0.013 |
| A + Health-related behaviors | 6532 | -0.047 <0.001 | 6488 | -0.035 0.005 |
| A + Fatigue-related symptoms | 6649 | -0.046 <0.001 | 6605 | -0.039 0.001 |
| Fully adjusted | 6465 | -0.025 0.048 | 6424 | -0.025 0.044 |

CRP = C-reactive protein; IL-6 = interleukin-6; = standardized regression coefficient expressing the change in standardized fatigue score per one standard deviation in log-transformed CRP or IL-6 concentration

* Biomedical factors include body mass index, systolic blood pressure, presence of common medical conditions, and use of prescription medications that could affect systemic inflammatory status. Health-related behaviors include smoking and alcohol consumption. Fatigue-related symptoms include symptoms of depression/anxiety and sleep difficulty at baseline.

Table 4
Prospective associations of circulating inflammatory markers (CRP and IL-6) at baseline with new-onset fatigue cases at follow-up

| Adjustment* | CRP as predictor | | | | IL-6 as predictor | | | |
|-------------------------------|------------------|--------------------|----------------------------------|--------|-------------------|--------------------|----------------------------------|-------|
| | Low [§] | Total [§] | Odds ratio [†] (95% CI) | P | Low [§] | Total [§] | Odds ratio [†] (95% CI) | P |
| Age, sex, ethnicity (Model A) | 2708 | 4822 | 1.35 (1.17-1.56) | <0.001 | 2700 | 4786 | 1.27 (1.10-1.47) | 0.001 |
| A + Socioeconomic position | 2706 | 4819 | 1.34 (1.16-1.55) | <0.001 | 2700 | 4783 | 1.27 (1.09-1.47) | 0.002 |
| A + Biomedical factors | 2684 | 4782 | 1.34 (1.15-1.56) | <0.001 | 2768 | 4747 | 1.25 (1.07-1.46) | 0.004 |
| A + Health-related behaviors | 2673 | 4737 | 1.31 (1.13-1.51) | <0.001 | 2658 | 4701 | 1.24 (1.07-1.44) | 0.005 |
| A + Fatigue-related symptoms | 2705 | 4816 | 1.34 (1.16-1.56) | <0.001 | 2699 | 4780 | 1.29 (1.11-1.50) | 0.001 |
| Fully adjusted | 2644 | 4689 | 1.28 (1.09-1.49) | 0.003 | 2635 | 4654 | 1.24 (1.06-1.45) | 0.008 |

CRP = C-reactive protein; IL-6 = interleukin-6; CI = confidence interval

* Biomedical factors include body mass index, systolic blood pressure, presence of common medical conditions, and use of prescription medications that could affect systemic inflammatory status. Health-related behaviors include smoking and alcohol consumption. Fatigue-related symptoms include symptoms of depression/anxiety and sleep difficulty at baseline.

[§] Number of individuals in low categories and total number

[†] CRP and IL-6 were dichotomized using the respective cutoff points of 1.0 mg/L and 1.5 pg/mL. Odds ratios were calculated taking low categories (CRP <1.0 mg/L and IL-6 <1.5 pg/mL) as the reference.

Table 5
Prospective associations of the composite variable of CRP and IL-6 at baseline with new-onset fatigue cases at follow-up

| Adjustment | Level* | N | Odds ratio (95% CI) | P |
|-----------------------------|----------------------|------|---------------------|--------|
| Age, sex, ethnicity | Low CRP & Low IL-6 | 1906 | 1 | |
| | Low CRP & High IL-6 | 761 | 1.07 (0.86-1.34) | 0.526 |
| | High CRP & Low IL-6 | 780 | 1.15 (0.93-1.43) | 0.198 |
| | High CRP & High IL-6 | 1314 | 1.51 (1.26-1.81) | <0.001 |
| Fully adjusted [§] | Low CRP & Low IL-6 | 1863 | 1 | |
| | Low CRP & High IL-6 | 741 | 1.07 (0.85-1.35) | 0.544 |
| | High CRP & Low IL-6 | 759 | 1.10 (0.88-1.37) | 0.419 |
| | High CRP & High IL-6 | 1267 | 1.45 (1.19-1.77) | <0.001 |

CRP = C-reactive protein; IL-6 = interleukin-6; CI = confidence interval

*The respective cutoff points for CRP and IL-6 were 1.0 mg/L and 1.5 pg/mL.

[§]Adjusted for age, sex, ethnicity, socioeconomic position, body mass index, systolic blood pressure, presence of common medical conditions, use of prescription medications that could affect systemic inflammatory status, smoking, alcohol consumption, symptoms of depression/anxiety, and sleep difficulty.