Brain, Behavior, and Immunity 23 (2009) 327–337

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Association of peripheral inflammatory markers with chronic fatigue in a population-based sample ☆

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ARTICLE INFO

Article history:
Received 26 June 2008
Received in revised form 25 November 2008
Accepted 26 November 2008
Available online 11 December 2008

Keywords:
Chronic fatigue syndrome
Unwellness
Major depression
Inflammation
c-reactive protein
Population-based

ABSTRACT

Alterations in the innate immune response may contribute to the pathogenesis of chronic fatigue syndrome (CFS). However, studies have been limited by small sample sizes, use of patients from tertiary care settings, inappropriate selection of controls, and failure to control for confounding demographic, medical and behavioral factors independently associated with immune activity. It is also not known whether specific symptoms account for observed associations between CFS and the innate immune response. To address these limitations, the current study examined plasma concentrations of high-sensitivity c-reactive protein (hs-CRP), white blood cell count (WBC) and a combined inflammation factor in a large population-based sample. Log-transformed mean plasma concentrations of hs-CRP were increased in subjects with CFS ($n = 102$) and in subjects with unwellness symptoms that did not meet diagnostic criteria for CFS (defined as "insufficient fatigue" [ISF]) ($n = 240$) when compared to subjects who were well ($n = 115$). Log transformed WBC was increased in ISF and was increased at a trend level in CFS. The combined inflammation factor was increased in both CFS and ISF. Subjects with CFS and ISF did not differ on any of the inflammation measures. In the entire subject population, the physical component summary score (PCS), but not the mental component summary score (MCS), from the Medical Outcomes Study Short Form-36 (SF-36) was negatively associated with each of the inflammation measures. Depressive symptoms were also associated with increased log hs-CRP. After adjustment for age, sex, race, location of residence, BMI, depressive status and immune-modulating medications, subjects classified as ISF continued to demonstrate increased log hs-CRP, WBC and elevations on the inflammation factor when compared to well controls; however, associations between CFS and log hs-CRP and the inflammation factor were no longer statistically significant. After adjustment, PCS score also remained independently associated with each of the inflammation measures. These findings support a role for innate immune activation in unexplained fatigue and unwellness, but do not suggest that immune activation is specific to CFS.

1. Introduction

Chronic fatigue syndrome (CFS) frequently devastates the lives of its sufferers (Buchwald et al., 1996; Komaroff et al., 1996; Solomon et al., 2003; Wessely et al., 1997). Yet despite almost two decades of intensive study the condition remains without diagnostic laboratory findings or an established pathophysiology (Cho et al., 2006; Henningsen et al., 2007). This lack of etiologic clarity contributes to the stigmatization of patients and represents a primary impediment toward progress in understanding and treating the condition.

Early conceptualizations of CFS focused on the role of viral infection and subsequent abnormal immune responses (DeFreitas et al., 1991; Jones et al., 1985; Landay et al., 1991; Straus et al., 1985). Although confidence in the link between infection and CFS pathogenesis has waned over subsequent years (Wessely et al., 1998), the immune system and interrelated central nervous system stress outflow pathways such as the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis have remained active areas of investigation (Aslakson et al., 2006; Cho et al., 2006; Demitrack et al., 1991; Glaser and Kiecolt-Glaser, 1998; Lyall et al., 2003). While initial studies generally suggested immunosuppression (Lyall et al., 2003), recent years have seen increased interest in the possibility that activation of the innate immune response might contribute to symptom development in patients with CFS (Cho et al., 2006; Kerr et al., 2008; Klimas and Koneru, 2007; Lyall et al., 2003).

Several lines of evidence suggest a role for activation of innate immune pathways in the pathogenesis of CFS. Studies have reported increased plasma concentrations and in vitro stimulated production of pro-inflammatory cytokines (Gupta et al., 1999) (for a review see (Lyall et al., 2003) and increased plasma concentrations of the acute phase reactant c-reactive protein (CRP) in

☆ Please see Brief Commentary by Carmine M. Pariante in this issue.

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doi:10.1016/j.bbi.2008.11.005

patients with CFS (Buchwald et al., 1997; Spence et al., 2007). More recently, increased production of the pro-inflammatory transcription molecule nuclear factor kappa beta (Maes et al., 2007), increased gene expression in pathways linked to cytokines and their receptors (Fang et al., 2006; Kerr et al., 2008) and increased prevalence of an allele in the tumor necrosis factor (TNF)-α gene associated with enhanced inflammatory activity (Carlo-Stella et al., 2006) have been reported to be associated with CFS. Moreover, chronic cytokine exposure, such as occurs during treatment with interferon-alpha, frequently leads to severe fatigue and other symptoms common in CFS (Capuron et al., 2002; Maddock et al., 2005), demonstrating that innate immune cytokines are capable of producing a CFS-like clinical picture. Consistent with these findings, a recent study indicates that a polymorphism in the promoter region of the TNF-α gene that increases inflammatory activity is associated with severity of fatigue in distressed, but medically healthy subjects (Jeanmonod et al., 2004). Conversely, the use of medications that block pro-inflammatory cytokines has been repeatedly shown to reduce fatigue and other symptoms common in CFS such as pain, in patients with autoimmune conditions (Strand and Singh, 2007; Tyring et al., 2006).

However, despite these positive findings the literature relating innate immune inflammatory processes to CFS remains mixed. A meta-analysis of studies published through 2003 found no convincing evidence for increased inflammation in the disorder, and several recent studies have also reported negative findings (Amel Kashipaz et al., 2003; Gaab et al., 2005; Lyall et al., 2003; Natelson et al., 2005; ter Wolbeek et al., 2007; Vollmer-Conna et al., 2007; Winkler et al., 2004). Consistent with this, in a previous population-based study by our group, no differences were observed in white blood cell count (WBC) or other immune measures between patients with CFS and well controls. (Mawle et al., 1997) A variety of factors may contribute to these discrepancies.

CFS is likely a heterogenous condition composed of more etiologically consistent subtypes (Aslakson et al., 2006; Janal et al., 2006; King and Jason, 2005; Nisenbaum et al., 2004; Wilson et al., 2001), only some of which may be associated with innate immune pathway activation, and clinical studies likely suffer from recruitment bias with respect to the subtypes. This is particularly likely because published studies of immune system function have evaluated patients identified through tertiary referral centers rather than through a population-based approach, so it is also possible that conflicting results reflect differences in systematic biases in the types of patients referred to each center (Wessely et al., 1997). Finally, although diagnostic criteria for CFS have been elaborated, published studies do not typically assess symptom domains with standardized measures that can be replicated across study sites, limiting the generalizability of immune findings between studies (Reeves et al., 2003).

Because immune markers in patients with CFS do not typically meet or surpass cut-offs for established disease processes, claims of immune abnormalities in CFS are always relative to a comparison group, with the result that study findings are as dependent upon the composition of these comparator groups as they are upon the identified patient population. In this regard, it is of concern that most studies include controls of convenience that are not identified through the same assessment or recruitment processes as the CFS patients, which greatly increases the risk that controls will not be epidemiologically comparable to cases. This is of direct relevance, given increasing evidence that demographic and lifestyle factors can themselves be associated with inflammatory biomarkers (Alley et al., 2006; Banks et al., 2006; McDade et al., 2006). Furthermore, much evidence suggests that fatigue and other CFS-defining symptoms (e.g., pain, sleep difficulties) are normally distributed in the population (Sha et al., 2005; Wessely, 2001). Thus, it is possible that differences in immune biomarkers that would be apparent between patients with CFS and completely healthy controls are diluted in studies in which some proportion of comparison subjects have even subsyndromal levels of fatigue or other symptoms. In support of this, Buchwald et al. found that patients with CFS had higher plasma concentrations of CRP than healthy controls, but did not differ from subjects with subsyndromal fatigue states (Buchwald et al., 1997).

Another potential confound is the unrecognized or unaccounted presence of other conditions associated with increased inflammation in either CFS patients or control subjects. For example, depression is highly comorbid with CFS (Deale and Wessely, 2000; ter Wolbeek et al., 2007; Wessely et al., 1996) and has been repeatedly reported to be associated with increases in inflammatory markers in both clinical (Cizza et al., 2008; Kling et al., 2007; Miller et al., 2005) and population-based samples (Cardiovascular Risk in Young Finns et al., 2006; Ford and Erlinger, 2004). Similarly, undiagnosed medical conditions or the use of medications that affect immune functioning may confound findings. Finally, it is unknown whether particular CFS symptoms are more likely than others to be associated with activation of inflammatory pathways (Dantzer et al., 2008).

Using a population-based approach, the current study attempted to address these issues by examining whether CFS is associated with increased high-sensitivity CRP (hs-CRP) and white blood cell count (WBC)—as well as an inflammatory factor composed of these two peripheral immune markers—when compared to both well controls and individuals with subsyndromic levels of fatigue or other CFS-defining symptoms. We identified persons suffering with CFS, those with subsyndromic levels of fatigue and other CFS symptoms, and well controls from defined metropolitan, urban, and rural populations to enhance the generalizability of findings to the general United States population. As recommended by the International CFS Study Group (Reeves et al., 2003), we used internationally validated standardized questionnaires to diagnose CFS (Reeves et al., 2005). All participants underwent rigorous medical and psychiatric evaluations and complete review of all current medications/supplements to identify exclusionary and comorbid conditions. To evaluate whether innate immune activity was more closely associated with physical or emotional functional impairment in the entire study population, we utilized the physical component summary (PCS) and mental component summary (MCS) scores from the Medical Outcomes Short Form (SF)-36 (Ware, 2000). We utilized hs-CRP as a primary marker of innate immune activation because it reflects summed activity of important inflammatory pathways and because of its health relevance, given that even mildly elevated values of hs-CRP have been consistently associated with increased risk for many medical conditions (e.g., vascular disease, diabetes, and dementia) (Hage and Szalai, 2007; Kuo et al., 2005; Pearson et al., 2003; Pradhan et al., 2001). We also examined white blood cell count and an inflammatory index that combined hs-CRP and WBC into a single measure (Danese et al., 2008).

2. Methods

This study adhered to human experimentation guidelines of the US Department of Health and Human Services and the Helsinki Declaration. The CDC Institutional Review Board approved the study protocol. All participants were volunteers who gave informed consent.

2.1. Population-based recruitment of study participants

This study was part of a larger effort to evaluate the occurrence of, and risk factors for, CFS in the 18 to 59 year-old population of Georgia, United States. A detailed description of the methodology of the larger Georgia Surveillance Study is available elsewhere (Reeves et al., 2007). Briefly, between September 2004 and July 2005 the surveillance study used random-digit dialing to contact a sample of households in metropolitan, urban and rural areas of Georgia. We screened 10,837 households with 21,165 residents (screening response rate 79%). Screening involved querying a household informant ($\geqslant$18 years) as to the age, sex, ethnicity and health status of each household member aged 18 or older. The informant was asked to identify unwell household members, who had at least one of four common symptoms of unwellness (fatigue, cognitive dysfunction, unrefreshing sleep, or muscle/joint pain) for $\geqslant$1 month, and well residents, who had none of these problems for $\geqslant$1 month. We attempted to conduct detailed telephone interviews with all 3851 who were identified as unwell with fatigue, and 2441 (63%) completed the detailed interview. We randomly selected 2136 of those noted to be unwell not fatigued and 1431 (67%) completed interviews. Similarly, 1758 (56%) of 3116 randomly selected household members identified as being well completed detailed telephone interviews.

Upon completion of the detailed telephone interview, subjects were provisionally categorized as having a CFS-like illness, as chronically unwell not CFS-like, or as well. CFS-like criteria included having continuous or relapsing fatigue for 6 months or longer, having four or more of the eight CFS-defining symptoms that were not made better by rest, and reporting that their illness substantially decreased their level of either social, educational, occupational or personal activity (Fukuda et al., 1994). Criteria for classification as unwell included having at least one of the CFS-defining symptoms for 1 month or more, but not meeting criteria for CFS-like. Criteria for being well were based on not having any of the eight CFS-defining symptoms for 6 months or more.

All persons identified as having a CFS-like illness (n = 469) and a random sampling of persons who were unwell but did not meet criteria for CFS—like illness (n = 505) were invited to participate in a 1 day clinical assessment. Two hundred ninety-two of the CFS-like (62%) subjects, and 268 (53%) subjects classified as unwell not CFS-like participated. Finally, 223 well controls frequency matched to the CFS-like group on age (+/− 3 years), sex, race and location of residence (metropolitan, urban, and rural) attended the clinic.

2.2. Medical evaluation

To screen for exclusionary medical conditions (Fukuda et al., 1994; Reeves et al., 2003), subjects who participated in the clinical assessment completed past medical history questionnaires and were requested to bring all their medications and supplements to the clinic. These were reviewed and if necessary clarified by a nurse practitioner or physician assistant. A specifically trained physician then performed a standardized physical examination, which was expanded as necessary to address any additional concerns (Reyes et al., 2003). Blood and urine specimens were obtained for laboratory screening tests to identify possible exclusionary medical conditions (Fukuda et al., 1994; Reeves et al., 2003). Laboratory tests included a complete blood count with differential, alanine aminotransferase (ALT), SGPT, albumin, alkaline phosphatase, aspartate aminotransferase (AST), SGOT, total bilirubin, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, total protein, sodium, urea nitrogen BUN, antinuclear antibodies, rheumatoid factor, TSH, free T4, and urinalysis.

2.3. Psychiatric evaluation

At the clinic visit a specifically trained licensed psychiatric social worker, clinical psychologist, or psychiatric nurse administered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002). The SCID provided diagnoses for psychiatric disorders considered exclusionary for CFS, including current melancholic major depression, any psychotic condition, bipolar disorder, active substance abuse/dependence, anorexia or bulimia (Fukuda et al., 1994). The SCID also classified subjects as having a current major depressive episode (current MDD), a past history of major depressive disorder (MDD) or no history of major depression. Current major depressive episode was defined per DSM-IV TR criteria. All SCID interviewers were trained by the SCID developer and certified. An independent SCID-certified interviewer observed all interviewers conducting their first SCID assessments to assure compliance with interview guidelines. Completed SCID interviews were reviewed by an independent SCID-certified and experienced interviewer for quality control. If discrepancies were observed in a completed SCID interview, the independent interviewer worked with the personnel who conducted the interview in question to resolve the discrepancy. Finally, a review committee of CDC and Emory clinicians (unaware of the subject's fatigue diagnostic category) reviewed all SCIDs.

Depressive symptom severity was assessed in all subjects with the 20-item Zung Self-Rating Depression Scale (SDS) (Zung, 1965). Items were rated 1–4 with higher scores representing greater symptom severity. Following standard practice, raw scores were converted to a 100-point scale (SDS Index) in which <50 = normal, 50–59 = mild depression, 60–69 = moderate to marked depression, and $\geqslant$70 = severe depression. To evaluate associations between depressive symptoms and hs-CRP, we used an SDS Index cut-off score $\geqslant$60 to identify subjects with moderate or greater symptom severity.

2.4. Defining symptoms, diagnostic categories and functional impairment

Two hundred and eighty (36%) of the participants who completed the clinical examination had medical or psychiatric conditions considered exclusionary for CFS (Fukuda et al., 1994), and two were missing data. The remaining 501 subjects were further classified for analysis. We diagnosed CFS according to the criteria of the 1994 research case definition (Fukuda et al., 1994). As recommended by the International CFS Study Group (Reeves et al., 2003), participants were classified as CFS or ISF, (i.e., unwell but not meeting criteria for CFS) or well based on standardized reproducible criteria that measure specifics of the 1994 case definition (Reeves et al., 2005). We used the multidimensional fatigue inventory (MFI) (Smets et al., 1995) to measure specifics of fatigue, the Medical Outcomes Survey Short Form-36 (Ware, 2000) to evaluate functional impairment, and the CDC CFS-specific Symptom Inventory (Wagner et al., 2005) to determine occurrence/frequency/severity of the eight CFS-defining symptoms. We applied cut-offs per CDC recommendations (Reeves et al., 2005). The MFI, SF-36 and symptom inventory are self-administered standardized validated questionnaires and interviewers do not assign patients to diagnostic categories. For final diagnosis of CFS (which requires evaluation of exclusionary medical and psychiatric conditions), a review committee of CDC and Emory University physicians and psychologists reviewed medical and psychiatric evaluations to determine the presence of medical and psychiatric conditions exclusionary for CFS. Members of the review committee were not aware of subjects' classification as CFS or not CFS.

Using this methodology, we classified 113 subjects with CFS. Two hundred an sixty four subjects who endorsed impairment

from at least one CFS-case defining symptom, but who failed to meet criteria for CFS were classified as insufficient fatigue (ISF). One hundred and twenty four subjects were classified as well.

In addition to medical and psychiatric conditions considered exclusionary for CFS, for the present study we further excluded subjects with a history of medical conditions that, while not exclusionary for CFS, might affect hs-CRP measures. These included vascular disease, neurological disorders, cancer (except treated cervical and non-melanoma skin cancer), diabetes, pulmonary disease or autoimmune disorders. In addition, three subjects lacked hs-CRP results. hs-CRP levels >10 mg/L often reflect undetected acute disease or autoimmune processes. For this reason, all subjects with hs-CRP > 10 mg/L were excluded (six CFS subjects, 14 ISF subjects, and four well subjects). Following these exclusions, 433 subjects comprised the study population.

2.5. Assessment of relationships between inflammation and physical and mental symptoms

To examine whether inflammation was more closely associated with physical or mental/emotional symptoms in the study population as a whole, we used the Physical Component Summary (PCS) and Mental Component Summary (MCS) measures from the SF-36 (Rush et al., 2000). These measures reflect higher order clustering of the SF-36's eight basic scales according to the physical and mental health variance they have in common. Multiple studies demonstrate that the PCS and MCS account for 80–85% of the reliable variance in the eight underlying SF-36 scales (Ware, 2000). The PCS reflects health status arising from physical symptoms. The scales that correlate most highly with PCS are physical functioning, role-physical and bodily pain. The MCS reflects health status arising from mental/emotional symptoms. The scales that correlate most highly with the MCS are mental health, role-emotional and social functioning. Supporting the clinical relevance of the PCS and MCS measures, scales that load highest on the PCS are most responsive to treatments that improve physical morbidity, whereas scales loading highest on the MCS respond most to interventions that target mental health (Ware, 2000). Values on each summary score range from a maximum of 100 (i.e., best functioning) to 0 (worst functioning).

2.6. Assessment of inflammation

We assessed two measures of inflammation: hs-CRP (mg/L) and white blood cells (10^3/mcl). hs-CRP was measured by a commercial laboratory (Esoterix, Inc. Austin, TX) with a turbidimetric assay using an LX-20 Beckman instrument. WBC was measured on a Coulter GEN-S machine for complete blood cell counts. For primary analyses, we assessed hs-CRP and WBC as continuous measures, log transformed to improve normality. Based on recent work linking inflammation to depression (Danese et al., 2008), as well as evidence that both hs-CRP and WBC predict future disease development (Danesh et al., 1998), we also examined correlations between log hs-CRP and log-WBC for the purposes of constructing an inflammation factor that might benefit from the combined predictive values of each variable while minimizing measurement errors of the single components (Danese et al., 2008). Supporting the utility of such an inflammation factor, we found that logged hs-CRP and logged WBC were highly correlated ($r = 0.39$, $p < 0.0001$). A principal-component analysis confirmed that the inflammation factor accounted for 69% of the variance in continuous measures of hs-CRP and WBC in the study population. Finally, to enhance the clinical relevance of our data, we conducted a secondary analysis of hs-CRP as a categorical measure based on a cut-off value of >3 mg/L that has been associated with increased risk for the development of a number of disease states (Hage and Szalai, 2007; Pradhan et al., 2001; Ridker, 2000).

2.7. Statistical analysis

Simple linear regression models were used to examine bivariate associations between inflammation measures (hs-CRP plasma concentration, WBC, and Inflammation Index) and the following covariates: (1) unwellness diagnostic group (CFS, ISF or well); (2) functional impairment reflected in the physical component summary measure (0–100 scale); (3) functional impairment reflected in the mental component summary measure (0–100 scale); (4) presence or absence of current MDD; (5) presence or absence of moderate or greater severity depressive symptoms (SDS Index $\geqslant 60$); (6) sex; (7) age; (8) BMI (underweight/normal, overweight, obese), (9) race (black vs. other); (10) location of residence (metropolitan, urban, rural); and (11) use of medications previously reported to affect inflammatory signaling pathways (including statins, antidepressants, non-steroidal anti-inflammatory agents and oral glucocorticoid agonists). When indicated, Tukey–Kramer tests were employed to test significance of post-hoc multiple subgroup comparisons. To evaluate independent associations between these variables and hs-CRP, multiple linear models were employed. For all analyses, hs-CRP and WBC were log-transformed to improve the distribution of these variables. Multiple linear models were used to examine the association between inflammation measures and CFS with a progression of adjustments including: (1) adjusting for sociodemographic factors, and (2) further adjusting for body mass index (BMI), depressive symptoms and use of medications as well as sociodemographic factors. All tests of significance were two-tailed with the α level set at 0.05. Analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

3. Results

Table 1 presents demographic characteristics of the study population. We classified 96 subjects as CFS, 226 as ISF and 111 were classified as well. These groups did not differ in terms of sex, age, race or place of residence. CFS and ISF subjects were more likely than well subjects to have a BMI in the overweight or obese range, but did not differ from each other. As would be expected, CFS and ISF subjects had significantly higher scores on each of the five MFI fatigue subscales, but lower scores in PCS and MCS in the SF-36 (with lower scores indicating worse functioning) (Table 2). Interestingly, although not a selection criteria for group assignment, all participants with either current major depression ($n = 30$) or who met criteria for moderate or greater depressive symptom severity (i.e., SDS Index $\geqslant 60$) ($n = 60$) were in the CFS or ISF groups.

Plasma concentrations of log hs-CRP were significantly higher in subjects with CFS (geometric mean = 0.40 mg/L, $p = 0.0399$) and ISF (geometric mean = 0.50 mg/L, $p = 0.0009$) than in well subjects (geometric mean = −0.01 mg/L, i.e., mean = $e^{-0.01} = 0.99$ mg/L); however, persons with CFS and ISF were not different from each other ($p = 0.7841$); (Fig. 1 and Table 3). 34% of subjects with CFS, 38% of subjects with ISF and 21% of well subjects had hs-CRP levels >3 mg/L. Other variables associated with increased plasma hs-CRP included PCS score, presence of depressive symptoms (SDS Index $\geqslant 60$), sex, and BMI (Table 3). Overall, PCS score was significantly and negatively associated with plasma logged hs-CRP (coefficient $\beta = -0.0277$, $e^{\beta} = 0.9727$, $p < 0.0001$) (Table 3). Presence of depressive symptoms was significantly associated with logged hs-CRP ($\beta = 0.3840$, $e^{\beta} = 1.4681$, $p < 0.0228$ for SDS Index $\geqslant 60$ [geometric mean = 0.68 mg/L; mean = 1.97 mg/L] vs. <60 [geomet-

Table 1
Demographic characteristics of the study population as a whole and by diagnostic category (CFS, ISF, and Well).

	All (n = 433)		CFS (n = 96)		ISF (n = 226)		Well (n = 111)	
Age, mean (SD), year	43.0	(10.4)	43.6	(10.1)	42.4	(10.5)	43.9	(10.5)
Range	18–59		18–59		18–59		19–59	
Sex, No. (%)								
Female	327	(75.5)	76	(79.2)	167	(73.9)	84	(75.7)
Male	106	(24.5)	20	(20.8)	59	(26.1)	27	(24.3)
Race, No. (%)								
Caucasian	326	(75.3)	71	(74.0)	168	(74.3)	87	(78.4)
African-American	87	(20.1)	18	(18.8)	46	(20.4)	23	(20.7)
Other	20	(4.6)	7	(7.3)	12	(5.3)	1	(0.9)
Residency, No. (%)								
Metropolitan	85	(19.6)	21	(21.9)	46	(20.4)	18	(16.2)
Urban	140	(32.3)	31	(32.3)	71	(31.4)	38	(34.2)
Rural	208	(48.0)	44	(45.8)	109	(48.2)	55	(49.6)
BMI (kg/m^2)								
Mean (SD)	27.3	(5.1)	27.7	(4.7)	27.6	(5.0)	26.4	(5.3)
Range	16.7–39.5		17.7–39.5		16.7–38.7		18.1–38.6	
BMI[a], No. (%)								
Under/Normal Weight (<24.9)	152	(35.1)	29	(30.2)	72	(31.9)	51	(46.0)
Overweight (24.9–29.9)	156	(36.0)	36	(37.5)	88	(38.9)	32	(28.8)
Obese (> = 29.9)	125	(28.9)	31	(32.3)	66	(29.2)	28	(25.2)

[a] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Table 2
Clinical characteristics of study population as a whole and by diagnostic category (CFS, ISF, and Well).

	All (n = 433)		CFS (n = 96)		ISF (n = 226)		Well (n = 111)	
PCS, mean (SD)^{****,a,b,c}	48.69	(9.50)	38.44	(9.35)	49.62	(7.90)	55.65	(3.04)
Range	18.12–67.97		18.12–58.26		23.46–67.97		49.19–65.40	
MCS, mean (SD)^{****,a,b,c}	46.55	(11.90)	38.19	(12.71)	44.93	(10.45)	57.06	(3.92)
Range	6.44–65.83		6.44–63.78		16.62–65.83		40.01–63.80	
MFI, Mean (SD)								
General fatigue^{****,a,b,c}	12.12	(4.75)	16.74	(2.62)	12.73	(3.86)	6.90	(2.29)
Physical fatigue^{****,a,b,c}	10.01	(4.14)	13.94	(3.28)	10.19	(3.55)	6.24	(2.07)
Mental Fatigue^{****,a,b,c}	10.28	(4.45)	13.53	(3.81)	10.67	(4.10)	6.69	(2.88)
Reduced activity^{****,a,b,c}	8.61	(3.88)	11.47	(4.04)	8.78	(3.63)	5.76	(1.61)
Reduced motivation^{****,a,b,c}	8.97	(3.63)	11.82	(2.99)	9.24	(3.38)	5.97	(2.10)
Current MDD, No. (%)****								
Present	30	(6.93)	21	(21.87)	9	(3.98)	0	(0)
Absent	403	(93.07)	75	(78.13)	217	(96.02)	111	(100)
Past MDD, No. (%)****								
Present	151	(35.03)	41	(43.16)	91	(40.44)	19	(17.12)
Absent	280	(64.97)	54	(56.84)	134	(59.56)	92	(82.88)
SDS Index, No. (%)****								
⩾60	60	(14.05)	39	(42.39)	21	(9.33)	0	(0)
<60	367	(85.95)	53	(57.61)	204	(90.67)	110	(100)
Immune medication, No. (%)*								
Taking	244	(56.35)	66	(68.75)	121	(53.54)	57	(51.35)
Not-taking	189	(43.65)	30	(31.25)	105	(46.46)	54	(48.65)

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
**** $p < 0.0001$ for the overall F test across three classification groups: CFS, ISF, and Well, and chi-square or Fisher exact test for categorical variables.
MCS, SF-36 mental component summary; PCS, SF-36 physical component summary.
[a] p-Value for post-hoc comparison between CFS and ISF with Tukey p-adjustment less than 0.05.
[b] p-Value for post-hoc comparison between CFS and Well with Tukey p-adjustment <0.05.
[c] p-Value for post-hoc comparison between ISF and Well with Tukey p-adjustment <0.05.

ric mean = 0.30 mg/L; mean = 1.35 mg/L]). Subjects who met criteria for current major depressive episode had marginally higher logged hs-CRP levels ($p = 0.066$). MCS score, race, location of residence and use of medications with potential immune system effects were not associated with plasma logged hs-CRP.

Logged WBC was increased in ISF subjects when compared to well subjects ($\beta = 0.1068$, SE (β) = 0.0345, $e^{\beta} = 1.1127$, $p = 0.0021$), and a trend toward increased logged WBC was observed in CFS subjects ($\beta = 0.0773$, SE (β) = 0.0416, $e^{\beta} = 1.0804$, $p = 0.0639$) (Fig. 2 and Table 4). CFS and ISF subjects did not differ (5.8 vs. 5.9 10^3/mcl, $p = 0.6957$). The inflammation index was also elevated in subjects with CFS and ISF when compared to well subjects ($\beta = 0.3467$, SE (β) = 0.1375, $e^{\beta} = 1.4144$, $p = 0.0120$ for CFS; $\beta = 0.4638$, SE (β) = 0.1140, $e^{\beta} = 1.5901$, $p < 0.0001$ for ISF), with no differences noted between CFS and ISF (Fig. 3 and Table 5). Other variables associated with logged WBC included PCS score and BMI (Table 4). Variables associated with the inflammation index were PCS score and BMI (Table 5).

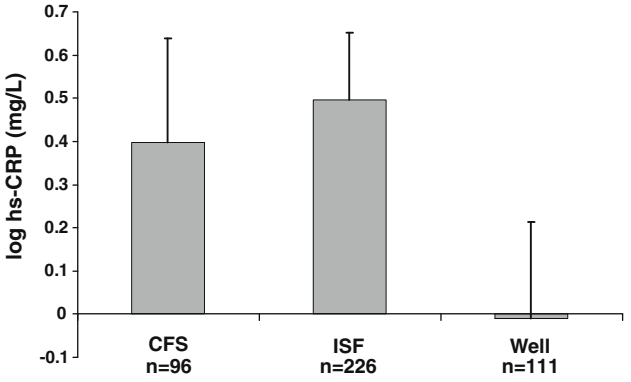

Fig. 1. Log normalized (log) mean plasma concentrations of high-sensitivity c-reactive protein (hs-CRP) were increased in subjects who met diagnostic criteria for chronic fatigue syndrome (CFS) and in subjects with unwellness symptoms who did not meet diagnostic criteria for CFS (defined as "insufficient fatigue" [ISF]) when compared to subjects who were well. Mean log hs-CRP plasma concentrations did not differ between subjects with CFS and ISF.

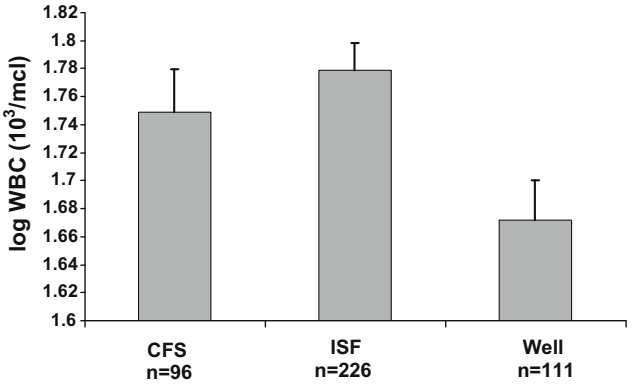

Fig. 2. Log normalized (log) white blood cell count was increased in subjects with unwellness symptoms who did not meet full criteria for CFS (termed "insufficient fatigue" [ISF]) when compared to subjects who were well. Subjects with CFS demonstrated a trend toward increased WBC when compared to well subjects. WBC did not differ between subjects with CFS and ISF.

Table 3
Bivariate associations between log-normalized high-sensitivity c-reactive protein (hs-CRP) (mg/L) and subject characteristics.

	β	exp(β)	SE	p-Value
PCS[a]	−0.0277	0.9727	0.0060	<0.0001
MCS[a]	−0.0089	0.9911	0.0049	0.0696
Fatigue diagnosis				0.0013
CFS	0.4075	1.5031	0.1670	0.0151
ISF	0.5046	1.6563	0.1389	0.0003
Well	Reference			
Age, years	0.0102	1.0103	0.0056	0.0696
Sex				
Female	0.3136	1.3683	0.1350	0.0207
Male	Reference			
Race				
Black	0.2552	1.2907	0.1453	0.0797
Other	Reference			
Residency				0.3943
Metropolitan	0.0279	1.0283	0.1563	0.8582
Urban	−0.1608	0.8515	0.1327	0.2264
Rural	Reference			
BMI				<0.0001
Under/normal weight (<24.9)	Reference			
Overweight (24.9–29.9)	0.7925	2.2089	0.1244	<0.0001
Obese (⩾29.9)	1.3267	3.7686	0.1318	<0.0001
Current MDD				
Present	0.3860	1.4711	0.2293	0.0930
Absent	Reference			
SDS Index				
⩾60	0.3840	1.4681	0.1681	0.0228
<60	Reference			
Immune medication				
Taking	0.0143	1.0144	0.1178	0.9036
Not-taking	Reference			

β indicates the coefficient in the linear model and SE indicates the standard error of β estimate.
[a] PCS, SF-36 physical component summary; MCS, SF-36 mental component summary.

Table 4
Bivariate associations between log-normalized white blood cell counts (WBC) (10^3/mcl) and subject characteristics.

	β	exp(β)	SE	p-Value
PCS[a]	−0.0051	0.9949	0.0015	0.0008
MCS[a]	−0.0013	0.9987	0.0012	0.2944
Fatigue diagnosis				0.0086
CFS	0.0773	1.0804	0.0416	0.0639
ISF	0.1068	1.1127	0.0345	0.0021
Well	Reference			
Age, years	−0.0014	0.9986	0.0014	0.3137
Sex				
Female	−0.0006	0.9994	0.0336	0.9867
Male	Reference			
Race				
Black	−0.0930	0.9112	0.0358	0.0097
Other	Reference			
Residency				0.2748
Metropolitan	−0.0619	0.9400	0.0387	0.1099
Urban	−0.0132	0.9869	0.0328	0.6882
Rural	Reference			
BMI				0.0001
Under/normal weight (<24.9)	Reference			
Overweight (24.9–29.9)	0.0639	1.0660	0.0336	0.0576
Obese (⩾29.9)	0.1522	1.1644	0.0357	<0.0001
Current MDD				
Present	0.0706	1.0732	0.0577	0.2219
Absent	Reference			
SDS Index				
⩾60	0.0267	1.0271	0.0421	0.5268
<60	Reference			
Immune medication				
Taking	−0.0023	0.9977	0.0292	0.9374
Not-taking	Reference			

β indicates the coefficient in the linear model and SE indicates the standard error of β estimate.
[a] PCS, SF-36 physical component summary; MCS, SF-36 mental component summary.

We employed two models to evaluate the effect of potential confounders on independent relationships between fatigue diagnostic categories (i.e., CFS, ISF and well) and inflammatory measures. In a first model that adjusted for sociodemographic variables, including age, sex, race, and location of residence, both CFS and ISF remained significantly associated with elevated logged hs-CRP and the inflammation index when compared to well subjects (For CFS vs. Well, logged hs-CRP: coefficient $b = 0.41$, SE (b) = 0.17, $e^{\beta} = 1.51$, $p = 0.0137$; inflammation index: coefficient $b = 0.35$, Standard Error: SE (b) = 0.14, $e^{\beta} = 1.42$, $p = 0.0119$; For ISF vs. Well, logged hs-CRP: coefficient $b = 0.53$, SE (b) = 0.14, $e^{\beta} = 1.70$, $p = 0.0001$; inflammation index: coefficient $b = 0.48$, Standard Error: SE (b) = 0.11, $e^{\beta} = 1.62$, $p < 0.0001$). ISF remained associated with increased WBC, and CFS remained associated with

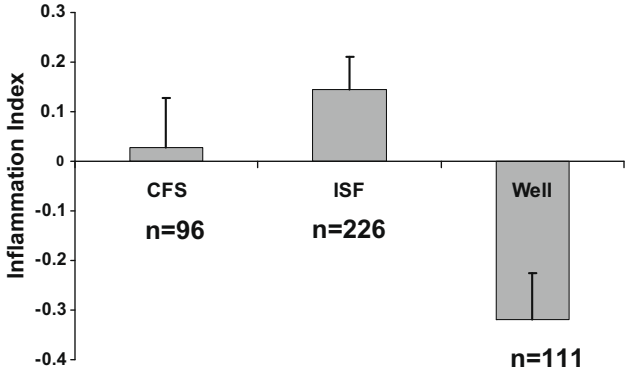

Fig. 3. An inflammatory factor derived by factor analysis that included high-sensitivity c-reactive protein (hs-CRP) and white blood cell count (WBC) was elevated in subjects who met diagnostic criteria for chronic fatigue syndrome (CFS) and in subjects with unwellness symptoms who did not meet diagnostic criteria for CFS (defined as "insufficient fatigue" [ISF]) when compared to subjects who were well. The inflammatory factor did not differ between subjects with CFS and ISF.

Table 5
Bivariate associations between the inflammation factor (WBC and hs-CRP) and subject characteristics.

	β	exp(β)	SE	p-Value
PCS[a]	−0.0237	0.9766	0.0050	<0.0001
MCS[a]	−0.0068	0.9932	0.0040	0.0926
Fatigue diagnosis				0.0003
CFS	0.3467	1.4144	0.1375	0.0120
ISF	0.4638	1.5901	0.1140	<0.0001
Well	Reference			
Age, years	0.0022	1.0022	0.0046	0.6307
Sex				
Female	0.1514	1.1635	0.1117	0.1759
Male	Reference			
Race, No. (%)				
Black	−0.0567	0.9449	0.1201	0.6368
Other	Reference			
Residency				0.5653
Metropolitan	−0.1055	0.8999	0.1290	0.4139
Urban	−0.1015	0.9035	0.1095	0.3546
Rural	Reference			
BMI				<0.0001
Under/normal weight (<24.9)	Reference			
Overweight (24.9–29.9)	0.5207	1.6832	0.1055	<0.0001
Obese (⩾29.9)	0.9568	2.6034	0.1120	<0.0001
Current MDD				
Present	0.3052	1.3569	0.1919	0.1125
Absent	Reference			
SDS Index				
⩾60	0.2301	1.2587	0.1399	0.1007
<60	Reference			
Immune medication				
Taking	−0.0015	0.9985	0.0971	0.9878
Not-taking	Reference			

β indicates the coefficient in the linear model and SE indicates the standard error of β estimate.

[a] PCS, SF-36 physical component summary; MCS, SF-36 mental component summary.

a trend toward increased WBC (For CFS vs. Well, logged WBC: coefficient $b = 0.08$, Standard Error: SE (b) = 1.08, $e^{\beta} = 1.07$, $p = 0.0629$; For ISF vs. Well, logged WBC: coefficient $b = 0.11$, Standard Error: SE (b) = 0.03, $e^{\beta} = 1.12$, $p = 0.0022$).

However, in a second model that added BMI, depressive status and use of potential immune-modulating medications to the sociodemographic variables, CFS was no longer independently associated with either logged hs-CRP or the inflammation factor (logged hs-CRP: coefficient $b = 0.17$, SE (b) = 0.17, $e^{\beta} = 1.19$, $p = 0.3194$; logged WBC: coefficient $b = 0.07$, Standard Error: SE (b) = 0.05, $e^{\beta} = 1.07$, $p = 0.1554$; inflammation index: coefficient $b = 0.21$, Standard Error: SE (b) = 0.14, $e^{\beta} = 1.23$, $p = 0.1376$). On the other hand, ISF remained significantly associated with all inflammatory measures (logged hs-CRP: coefficient $b = 0.37$, Standard Error: SE (b) = 0.13, $e^{\beta} = 1.45$, $p = 0.0031$; logged WBC: coefficient $b = 0.09$, Standard Error: SE (b) = 0.03, $e^{\beta} = 1.10$, $p = 0.0062$; inflammation index: coefficient $b = 0.37$, Standard Error: SE (b) = 0.11, $e^{\beta} = 1.45$, $p = 0.0005$).

After adjusting for all variables in the second model plus fatigue diagnostic categories (CFS, ISF, well), PCS score also remained independently associated with logged hs-CRP, logged WBC and the inflammation index (logged hs-CRP: $\beta = -0.0254$, $e^{\beta} = 0.9749$, SE (β) = 0.0072, $p = 0.0004$; $r^2 = 0.29$ for the multiple linear model; logged WBC: $\beta = -0.0068$, $e^{\beta} = 0.9932$, SE (β) = 0.0020, $p = 0.0006$; $r^2 = 0.12$ for the multiple linear model; inflammation index: $\beta = -0.0261$, $e^{\beta} = 0.9742$, SE (β) = 0.0061, $p < 0.0001$; $r^2 = 0.24$ for the multiple linear model). Conversely, subjects with hs-CRP plasma concentrations >3 mg/L, which is widely recognized as a risk factor for the development of cardiovascular disease (Pearson et al., 2003), had significantly lower PCS scores than did subjects with hs-CRP values ⩽3 mg/L (44.86 vs. 48.69, unequal variance t statistics = 3.02, df = 239, $p < 0.01$) (Fig. 4). After adjustment, depressive symptoms (SDS Index score) were no longer associated with logged hs-CRP, logged WBC or the inflammation index.

When examined as a categorical variable (based on a cut-off of >3 mg/L), hs-CRP was significantly higher in subjects with CFS (34.38%) and ISF (38.05%) than in well controls (20.72%) (CFS: OR = 2.00, 95% CI = 1.08–3.74; ISF: OR = 2.35, 95% CI = 1.38–4.00). Other variables associated with hs-CRP >3 mg/L included sex, race, PCS score, BMI, and SDS depression score. After adjustment for age, sex, race, location of residence, BMI, depressive status and use of immune modulating medications, subjects classified as ISF continued to demonstrate increased logged hs-CRP (adjusted OR = 2.34, 95% CI = 1.29–4.27, p = 0.0120). After adjustment, the association between hs-CRP >3 mg/L and CFS did not remain significant (adjusted OR = 1.62, 95% CI = 0.75–3.53, p = 0.8569).

4. Discussion

Results from this population-based study indicate that persons with CFS had increased markers of peripheral inflammation when compared to well controls, but had a similar inflammatory profile when compared to unwell subjects who did not meet criteria for CFS (i.e., those considered ISF). However, despite observing no differences in inflammatory markers between subjects with CFS and

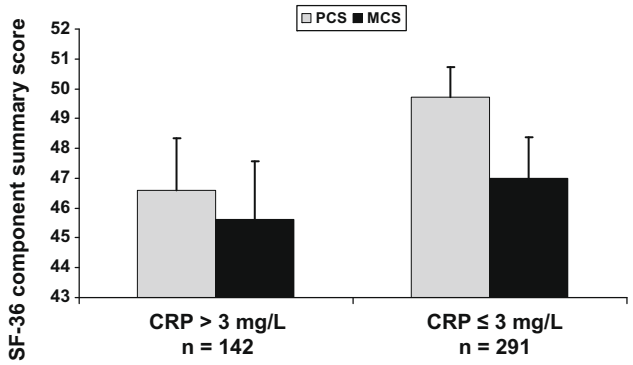

Fig. 4. Scores on the physical component summary (PCS) scale of the Medical Outcomes Study Short Form-36 (SF-36) were higher in subjects with plasma concentrations of high-sensitivity c-reactive protein (hs-CRP) >3 mg/L when compared to subjects with hs-CRP plasma concentrations ⩽3 mg/L. SF-36 mental component summary (MCS) scores were not different between subjects with hs-CRP > 3 mg/L vs. ⩽ 3 mg/L.

ISF, multivariate modeling indicated that ISF, but not CFS, remained independently associated with increases in these measures after adjustment for age, sex, BMI, race, depressive symptoms, and use of medications. It is of note that these findings are consistent with results from two previous clinically-based studies that examined plasma CRP concentrations in smaller groups of CFS patients (Buchwald et al., 1997; Spence et al., 2007). Both studies found CFS to be associated with increased plasma CRP when compared to non-fatigued control groups; however, the one study that examined the issue also found that CRP levels were not different between subjects with CFS and subjects with subsyndromic levels of fatigue (Buchwald et al., 1997). It should be noted that neither study adjusted for factors independently associated with CRP such as age, sex, BMI or depressive status, so it is unclear whether either CFS or subsyndromic fatigue was independently associated with CRP in these populations or whether, as in the current study, independent associations would have been observed in subjects with subsyndromic fatigue, but not CFS.

To our knowledge the current study is the first to examine the potential contribution of depressive symptoms to immune abnormalities in subjects with CFS. Replicating prior population-based data (Elovainio et al., 2006; Ford and Erlinger, 2004), depressive symptoms were associated with increased CRP. Our results indicate, however, that the increased hs-CRP observed in subjects with CFS and ISF was not entirely accounted for by the presence of comorbid depression, even though CFS and ISF subjects had significantly higher depressive scores than did well subjects. Consistent with this, emotional symptoms such as sadness, which form the core of the depression construct (1994) and that are reflected in the MCS scale of the SF-36 (Ware, 2000), were not associated with CRP in our study population, given our finding that MCS score was not associated with hs-CRP in the study population as a whole. On the other hand, functional impairment related to physical complaints and limitations, which are captured in the PCS scale of the SF-36, were independently associated with increased CRP, even after adjustment for diagnostic category (i.e., CFS, ISF, well). This finding is consistent with other recent population-based studies that have observed stronger relationships between exhaustion and inflammatory markers than between depressive symptoms and these markers (Janszky et al., 2005; Kop et al., 2002). Although many studies have linked major depression and depressive symptoms with increased indices of inflammation (for a review see Raison et al., 2006), little is known regarding whether certain symptoms or symptom clusters within depression are more or less likely to be associated with increased inflammation (Dantzer et al., 2008). Our results highlight the need for such analyses and suggest that—at least in subjects with significant physical complaints—associations between depression and increased inflammation may primarily reflect the neurovegetative symptoms that occur in the vast majority of depressed individuals (Silverstein, 1999).

We were puzzled that inflammation levels were not different between subjects with ISF and CFS, given that CFS is—by definition—associated with more severe symptoms that cause more disability. In considering potential explanations for this apparent paradox, we wondered whether the fact that the ISF group was nearly twice as large as the CFS group might have produced a statistical artifact that accounted for the independent association of ISF but not CFS with inflammatory measures in our multivariate model. To address this possibility, we re-ran our analyses employing a bootstrapping methodology which demonstrated that our findings did not result from the larger sample size in the ISF group (statistics not shown). We next wondered whether a stronger association between ISF and inflammatory measures might be "swamping" the contribution of CFS to the second multiple linear model that included BMI, depressive symptoms and medications in addition to sociodemographic variables. To test this possibility, we removed ISF from the model, however even with ISF removed, CFS failed to remain independently associated with either logged hs-CRP or the inflammation factor (statistics not shown).

The finding that individuals with CFS did not significantly differ from other unwell subjects (i.e., the ISF group) in terms of hs-CRP or the combined inflammation factor raises the intriguing (and clinically relevant) possibility that the use of diagnostic categories such as CFS may exclude many unwell individuals who are physiologically more similar to patients with CFS than to non-affected comparison subjects. If so, a more inclusive strategy that set the boundary of illness between generalized unwellness and wellness (as opposed to between conditions such as CFS and fibromyalgia or between such conditions and healthy individuals), might more effectively "cleave nature at the joints". Other studies support such a broadening of diagnostic boundaries and are consistent with evidence that unwellness symptoms, including fatigue, are normally distributed in the population (Nisenbaum et al., 2004; Pawlikowska et al., 1994; Wessely, 2001). Given the negative health implications of even mildly increased CRP (Hage and Szalai, 2007; Kuo et al., 2005; Pearson et al., 2003; Pradhan et al., 2001), results from the current study suggest that within the realm of functional somatic symptoms the boundary between sickness and health might profitably be lowered. Moreover, the robust association between functional impairment from physical symptoms (reflected in the PCS score of the SF-36) and hs-CRP, WBC and the inflammatory factor in the entire subject population further highlights the potential health relevance of evaluating fatigue and other unwellness symptoms as spectrum conditions rather than rigidly defined diagnostic entities such as CFS.

We would suggest that these observations point to how best to interpret the literature reporting associations between symptom-based disease states (such as CFS, fibromyalgia or major depression) and inflammatory markers. Because it is almost certainly true that these syndromes are not etiologically unitary (Aslakson et al., 2006; Borish et al., 1998; Janal et al., 2006), but rather reflect final common pathway phenomena for a variety of physiological imbalances, it is also very unlikely that a condition such as CFS "causes" increased inflammation. Rather, patients who meet criteria for fatiguing conditions (in our study either CFS or ISF) are likely to evince unwellness symptoms for a variety reasons. One such reason may be an increase in peripheral inflammatory signaling, based on overwhelming evidence that inflammatory cytokines are capable of inducing all the cardinal symptoms of CFS in humans (Capuron et al., 2002; Dantzer et al., 2008).

However, in our view it is unlikely that inflammatory biomarkers offer much promise as supports for the creation of new, pathophysiologically-based, nosologic schemas for functional somatic syndromes, because abnormalities in these biomarkers reflect the summed activity of numerous factors that typically co-aggregate in the same individuals. Thus, it is almost certain that no single driver of increased inflammation will ever be found to dominate in individuals with CFS who demonstrate immune activation, let alone in the larger and even more heterogenous group of individuals who suffer with unwellness symptoms. Fig. 5 articulates this notion by suggesting that the risk for developing a condition such as CFS is increased by any combination of factors known to promote increased inflammatory signaling, many of which are highly comorbid, such as obesity (Alley et al., 2006; Kern et al., 2001), early life adversity (Danese et al., 2007), sedentary lifestyle (Kohut et al., 2006; McTiernan, 2008), poor dietary patterns (Dai et al., 2008), life stress (Kiecolt-Glaser et al., 2005, 2003; Steptoe et al., 2007), maladaptive personality structure (Bouhuys et al., 2004; Kahl et al., 2006), depression (see below for a discussion of depression) (Raison et al., 2006) and incipient, but undiagnosed medical illness. As one would predict if inflammation contributes

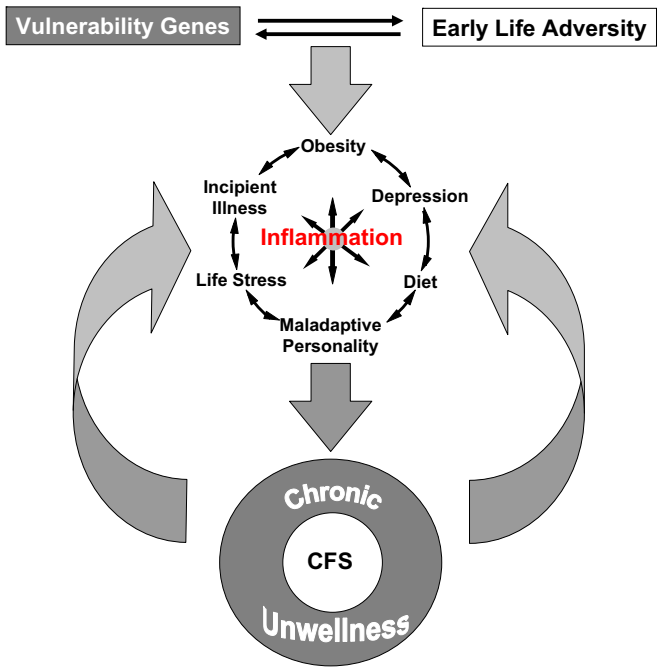

Fig. 5. Findings from the current study are consistent with other lines of emerging data suggesting that states of syndromic unwellness such as chronic fatigue syndrome (CFS) arise and are maintained by bi-directional interactions between numerous variables, many of which promote increased activity in peripheral inflammatory signaling pathways. Studies suggest that the risk for developing symptoms common in CFS (and related/comorbid conditions such as fibromyalgia and major depression) is greatly increased by complex interactions between vulnerability genes and early life experience. Maladaptive interactions between genetic make-up and early adversity also greatly increase the risk of a number of conditions and behaviors that have been associated with the development or worsening of CFS, or related unwellness conditions, including obesity, depression, poor dietary choices, maladaptive personality and coping styles, increased life stress and the presence of incipient illness (e.g., insulin resistance, silent vascular dysfunction). Interestingly, these factors are also well known to increase peripheral inflammation, strongly suggesting that inflammatory pathways may represent an important mechanism for transducing these risk factors into symptomatic illness. Finally, once CFS or a related unwellness condition has developed the condition itself feeds back to further promote the risk factors that led to disease development in the first place, with a resultant amplification of peripheral inflammatory tone.

to the pathogenesis of at least some unwellness states, many of the factors articulated in Fig. 5 that increase inflammation have also been repeatedly associated with the development or worsening of CFS (Frankenburg and Zanarini, 2004; Heim et al., 2006; Joyner and Masuki, 2008; Kato et al., 2006; Lutgendorf et al., 1995; Neumann et al., 2008; Van Houdenhove et al., 2001; Viner and Hotopf, 2004). Moreover, once an individual has developed symptoms consistent with CFS or a related unwellness condition, these symptoms themselves are likely to promote further inflammatory activation through a number of pathways, such as increased life stress as a result of disability, reduced physical activity, weight gain and the development of depression.

If our findings linking unwellness to increased inflammation offer no diagnostic holy grail, they nonetheless may have important prognostic implications for individuals with CFS and related unwellness conditions. Given increasing evidence from well populations that even mild elevations in peripheral inflammatory markers significantly increase the risk of subsequently developing vascular disease (Hage and Szalai, 2007), metabolic disorders (Pradhan et al., 2001)and dementia (Kuo et al., 2005), it may be that states of unwellness such as CFS might be more profitably conceived of as way stations on the journey to diagnosable pathology rather than as static and clearly demarcated conditions best served by the application of reifying disease monikers. In the same vein, increased WBC and interleukin-6 (the primary stimulus for CRP production in the body) have been associated with age-related frailty (Leng et al., 2007) and inflammation has been repeatedly linked to hastened mortality in elderly individuals (Franceschi et al., 2005; Graham et al., 2006). This might suggest viewing symptoms common to CFS and other unwellness syndromes as manifestations of premature aging processes in these individuals. Nonetheless, available data do not support a link between CFS and increased mortality from other medical conditions (Smith et al., 2006), but the types of large, prospective, population-based studies required to address the issue adequately have yet to be conducted. Interestingly, symptoms common in CFS, such as fatigue, pain and sleep disturbance have been associated with increased mortality in older adults, even after adjusting for presence of medical conditions and affective symptoms (Avlund et al., 1998; Sha et al., 2005)

Several limitations in the current study warrant consideration. The use of a cross-sectional design makes it impossible to determine the degree to which increased peripheral inflammatory activity contributes to the symptoms of CFS/ISF as opposed to the degree to which factors associated with CFS/ISF might promote increased inflammation. An important next step will be to conduct longitudinal studies in large populations of unwell individuals to better determine directions of causality between increased peripheral inflammation and symptom development. Although a number of potentially confounding demographic and lifestyle factors were addressed by our analyses, it is possible that associations between CFS/ISF and CRP were mediated by covariates that we failed to examine, such as life stress and physical activity/immobility. Given evidence that unwellness conditions such as CFS and fibromyalgia are characterized by alterations in central nervous system (CNS) functioning (Caseras et al., 2006, 2008; Schmidt-Wilcke et al., 2007), it is a limitation that we did not assess CNS inflammatory status in the current study. Nevertheless, the potential relevance of the current study is accentuated by recent data indicating that peripheral inflammatory pathways are capable of activating innate immune signaling in the CNS in ways that promote symptoms common to CFS and other unwellness states (Raison et al., 2008). Finally, although studies suggest that hs-CRP is fairly stable in individuals across time (Miller et al., 2002), our results would have been strengthened had repeated measures of inflammatory biomarkers been obtained.

In summary, we found using a population-based methodology that individuals with CFS or subsyndromic levels of fatigue and/or other CFS-defining symptoms had increased levels of peripheral inflammatory biomarkers when compared to well subjects, but did not differ from each other. Physical component summary score from the SF-36, but not the mental component summary score was associated with increased CRP, suggesting that emotional distress did not play a primary role in the increased hs-CRP in our population of medically healthy, but symptomatically unwell individuals. Combined with evidence that activation of peripheral inflammatory pathways produce fatigue and other CFS symptoms, results from the current study are consistent with a role for immune abnormalities in CFS spectrum disorders, but do not suggest that immune activation is specific to CFS or that hs-CRP or WBC might serve as biomarkers for the condition. However, the current findings suggest that behavioral and pharmacological strategies aimed at reducing inflammatory signaling pathways may deserve more intensive study as interventions for individuals afflicted with a range of disabling unwellness symptoms.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agency.

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