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## The Comorbidity of Self-Reported Chronic Fatigue Syndrome, Posttraumatic Stress Disorder, and Traumatic Symptoms

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### Abstract

**Background**—Data from primary care and community samples suggest higher rates of posttraumatic stress disorder (PTSD) among individuals with chronic fatigue syndrome (CFS).

**Objective**—This study investigated the co-occurrence of CFS, PTSD, and trauma symptoms and assessed the contribution of familial factors to the association of CFS with lifetime PTSD and current traumatic symptoms.

**Method**—Data on lifetime CFS and PTSD, as measured by self report of a doctor's diagnosis of the disorder, and standardized questionnaire data on traumatic symptoms, using the Impact of Events Scale (IES), were obtained from 8,544 female and male twins from the community-based University of Washington Twin Registry.

**Results**—Lifetime prevalence of CFS was 2% and lifetime prevalence of PTSD was 4%. Participants who reported a history of PTSD were over 8 times more likely to report a history of CFS. Participants with scores  $\geq 26$  on the IES were over 4 times more likely to report CFS than those who had scores  $\leq 25$ . These associations were attenuated but remained significant after adjusting for familial factors through within-twin pair analyses.

**Conclusion**—These results support similar findings that a lifetime diagnosis of CFS is strongly associated with both lifetime PTSD and current traumatic symptoms, although familial factors such as shared genetic and environmental contributions played a limited role in the relationship between CFS, PTSD, and traumatic symptoms. These findings suggest that future research should

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investigate both the familial and the unique environmental factors that may give rise to both CFS and PTSD.

### Keywords

twins; chronic fatigue; posttraumatic stress disorder; trauma; traumatic symptoms; Impact of Events Scale; comorbidity

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### Introduction

Chronic fatigue syndrome (CFS) is a clinical condition characterized by unexplained prolonged and disabling fatigue, musculoskeletal pain, sleep disturbances, impairments in mood, and neurocognitive difficulties (1). Community-based prevalence studies suggest medically confirmed CFS point prevalence rates of 235 to 422 per 100,000 persons (2–3). Prevalence rates of chronic fatigue in twin registries range from 2.3 to 2.7% (4–5). A genetic basis for CFS has been suggested by twin studies of fatiguing illnesses and by the high frequency of fatiguing illnesses in certain families (6).

Psychosocial stressors also may be important in the development and maintenance of CFS among vulnerable individuals (6–7). Using a biopsychosocial model of CFS (8), several investigations have emphasized the relationship between CFS and traumatic or adverse life events such as victimization, sexual assault, or childhood abuse (9–10). A small percentage of individuals who experience these or other traumatic events go on to develop posttraumatic stress disorder (PTSD). PTSD is characterized by hyperarousal and by repeated and intrusive memories of the traumatic event that interfere with the individual's daily functioning (11). As with CFS, genetic factors may also play a significant role in developing PTSD after a traumatic event (12).

Community and clinical studies of CFS generally support an association between fatigue symptoms or CFS and PTSD and trauma symptoms (10, 13–14). For example, a general population study found that early childhood trauma was associated with a three- to eight-fold increase in risk for CFS, depending on trauma type (14), and a community-based study found that presence of childhood sexual abuse and total number of childhood abuse events were associated with increased likelihood of CFS (3). Several studies have also demonstrated an elevated rate of PTSD in individuals with CFS, with rates ranging from 18% to 29% (9, 14–16) compared to community-based PTSD prevalence estimates of 1–5% (17). Another population-based study of psychological stress found that of all measured variables, PTSD was most strongly associated with severe fatigue (18). Both trauma exposure and the severity of PTSD symptoms were significantly associated with a diagnosis of CFS in a clinical sample of patients with CFS (9). Likewise, the odds of being diagnosed with CFS increased three-fold in a clinical sample of girls and adolescents with PTSD (19). On the other hand, findings from clinical studies of the relation between severe fatiguing illness and PTSD have been mixed (18). Specifically, we found no relation between CFS and PTSD in a previous clinical study of our own (20), possibly for methodological reasons.

The present study had three main objectives. First, we wanted to extend the current literature by examining the co-occurrence of CFS, PTSD, and trauma symptoms in a large U.S. community-based twin registry. Second, given the hypothesized genetic contribution to both CFS and PTSD, we sought to elucidate the contribution of familial factors to the association of CFS with lifetime PTSD and current traumatic symptoms. Finally, we compared twins with CFS only to those with CFS and PTSD, in order to explore potential differences in sociodemographic and health characteristics.

## Methods

### Sample

All potential participants were members of the University of Washington Twin Registry, a community-based registry of twin pairs ascertained from driver license applications to the Washington State Department of Licensing (21). To avoid issuing duplicate licenses, the Department of Licensing asks each new applicant whether he or she is a member of a twin pair. A state agency data-sharing law permits the University of Washington to receive a weekly electronic list of all new driver license applicants who are twins. Each member of the twin pair is then invited to join the twin registry and complete a survey. All University of Washington Twin Registry procedures, as well as the data collection methods involved in this study, were approved by the University of Washington Institutional Review Board. Informed consent was obtained from all participants.

### Primary Measures

Lifetime CFS and PTSD were assessed by self-report of a doctor's diagnosis. Twins were given a list of conditions including CFS and PTSD and asked: "Has your doctor ever told you that you have any of the following conditions?" Current traumatic symptoms were identified by the Impact of Events Scale (IES) (22). The IES assesses distress by capturing qualities of conscious experiences that encompass stressful life events, such as bereavement or personal injuries from accidents, violence, illness, or surgery (22). In previous studies, the IES was strongly correlated with a diagnosis of PTSD (23), even though this instrument measures only the intrusion and avoidance symptom criteria for PTSD specified by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (11). Twins rated 11 IES items on a 4-point scale according to how often each had occurred in the past 7 days (0 = not at all, 1 = rarely, 3 = sometimes, 5 = often). Although the original IES has 15 items, we removed the 4 items that had the poorest correlation with the IES intrusion and avoidance subscales, based on findings from the cluster analysis conducted by the developers of the IES (22). The 11 remaining items were summed to create a total score that ranged from 0 to 55, with higher scores reflecting more stressful impact. Previous literature recommends grouping the scores into quartiles representing increasing levels of current subjective distress: 0–8 (subclinical), 9–25 (mild), 26–43 (moderate) and 44 (severe) (23). Given a dearth of responses in the subclinical and severe categories within our sample, we dichotomized IES scores into mild (scores  $\leq 25$ ) versus severe (scores  $\geq 26$ ) traumatic symptoms. We only included twins who answered at least 9 of the 11 IES items, with all missing values replaced by using the mean imputation method.

### Sociodemographic and Health Characteristics

Twins reported their sex, age, race (White, Black, Asian/Pacific Islander, Hispanic/Latino, Native American, Other), marital status, and education level. Other items asked about current weekly vigorous and moderate exercise levels; height and weight to calculate body mass index (BMI;  $\text{kg}/\text{m}^2$ ); whether they smoked 100 cigarettes in their lifetime (yes/no); general health status; and number of visits to a medical doctor, psychiatrist, or alternative practitioner in the past 3 months. We dichotomized race (White vs. non-White), marital status (married or living with partner vs. single, divorced, widowed, or separated), education (K-12 vs. at least college), and general health status (good/very good/excellent vs. fair/poor). Age, exercise levels, BMI, and number of visits to a care provider were examined as continuous variables.

## Statistical Analyses

Data were analyzed by using Predictive Analytics Software (24). Initial descriptive analyses examined the distribution of all variables according to sex. Next, odds ratios (OR) and 95% confidence intervals (CI) were calculated as measures of association between CFS status, PTSD, and categorized IES score. To account for the non-independence of twins within a pair, we used generalized estimating equations (GEE) that took into account the relatedness of twin pairs (25) and adjusted for age, race, and sex. A second set of analyses examined the within-twin pair associations of CFS with PTSD and categorized IES score; these within-twin pair analyses inherently control for the confounding effects of shared familial factors among co-twins. Within-twin pair effects were estimated by calculating the absolute difference between twins within a pair on CFS, PTSD, and IES, resulting in only twin pairs discordant for CFS to be included. These within-twin pair difference coefficients are then entered into logistic regression models to predict the odds of having CFS, while controlling for familial confounding (25).

To compare sociodemographic and health characteristics between CFS twins with and without PTSD, we used linear and logistic regression models, with GEE to adjust for the non-independence of members of a twin pair (25). Frequencies, ORs, and 95% CIs are presented for categorical variables, and least-squares means and standard errors (SE) are presented for continuous variables.

## Results

The sample included 8,544 individual twins. As shown in Table 1, twins ranged in age from 18 to 94 years (mean =  $32.4 \pm 15.7$ ) and were predominantly female (60.1%). Most twins described themselves as White (86.0%); 39% were married or partnered, and 37% had 12 years of education or less. Over 91% of twins ( $n = 7,841$ ) had complete IES data, while 2% of twins ( $n = 193$ ) had one or two items missing. Twins with three or more missing items ( $n = 510$ ) were excluded. The lifetime prevalence of self-reported physician-diagnosed CFS was 2%, and the lifetime prevalence of PTSD was 4%. Of the twins with complete data, 151 twin pairs were found to be discordant for a diagnosis of CFS. IES scores of at least 26 were observed for 30% of the sample. The prevalence of CFS, PTSD, and IES scores of at least 26 was higher for female than for male twins (all  $p$ -values  $< 0.001$ ).

We examined whether the associations between CFS, PTSD, and traumatic symptoms differed by sex; because no interactions were observed, we present results for men and women combined. Table 2 presents the associations between CFS, PTSD, and IES scores for the overall and the within-twin pair analyses. Twins who reported a lifetime physician diagnosis of PTSD were over 8 times more likely to report a diagnosis of CFS than those without PTSD (95% CI: 6.0–12.6). After adjusting for age, sex, and race, twins with PTSD were 7.5 times more likely to report CFS than those without PTSD (95% CI: 5.0–11.0). Further, in unadjusted and adjusted analyses, twins who had IES scores of at least 26 were over 4 times more likely to report a lifetime physician diagnosis of CFS than twins with IES scores lower than 26. For both PTSD and IES scores of at least 26, the OR for within-twin pair analyses was attenuated but remained significant.

The distributions of sociodemographic and health characteristics among CFS twins with and without PTSD are shown in Table 3 (categorical variables) and Table 4 (continuous variables). Among twins with CFS, those with PTSD were 70% less likely to be married or partnered than twins without PTSD (95% CI: 0.2–0.8). Twins with CFS and PTSD were also 50% less likely to report their health as being good, very good, or excellent than twins with CFS but no PTSD (95% CI: 0.3–1.0). No significant differences were observed for sex, race,

education level, smoking, age, BMI, exercise levels, or number of visits to a medical doctor, psychiatrist, or alternative practitioner.

## Discussion

We found that a lifetime diagnosis of CFS was strongly associated with both lifetime PTSD and current traumatic symptoms, as measured by the IES, in a large community-based twin registry. These findings are consistent with other studies of community and clinical samples that have found a substantial relationship between CFS, PTSD, and traumatic symptoms (18, 26). Investigation of within-twin pair associations from twin pairs discordant for CFS provided evidence for partial familial confounding. However, these findings suggest that familial factors such as shared genetic and environmental contributions play only a limited role in the relationship between CFS, PTSD, and traumatic symptoms. Because we did not find substantial familial confounding, our results indicate that unique factors may put an individual at risk for CFS, PTSD, and traumatic symptoms (14, 27). Such unique environmental factors may include childhood trauma and prolonged experiences of psychological distress (10, 13, 15). Another potential environmental factor is parental reaction to a traumatic event; for example, the ability of an individual parent to cope adaptively with experiences of PTSD has been directly associated with adolescents' ability to cope with PTSD (28). In terms of risk factors for CFS, a recent investigation in an ethnically diverse population found that anxiety, depression, physical inactivity, and social strain were all significant independent predictors of CFS (27). Additional research is necessary to determine the unique environmental factors that may predispose an individual to experience CFS while reducing his or her ability to cope adaptively with traumatic life events.

The stress-response system in general, and the hypothalamic-pituitary-adrenal (HPA) axis in particular, may play a role in the association between CFS and PTSD. Both animal and human studies have shown that traumatic early life stressors may permanently change the stress response system in ways that leave affected individuals more prone to the effects of other stressors and to stress-related disorders (29–31). With regard to people with CFS, abnormalities in HPA axis function, hormonal stress responses, and serotonin neurotransmission are among the most reproducible and robust findings (6, 32). Clinical studies of PTSD have yielded similar data in support of marked changes in HPA axis functioning, such as altered concentrations of the hormone norepinephrine in response to stressful events (31, 33).

Based on these and other findings in the literature, we have proposed a multidimensional conceptual model that can generate many testable hypotheses on the ways in which CFS and PTSD can develop (34). For example, genetic influences and life events can lead to the development of a maladaptive stress response system, such as abnormalities in the responses of the HPA, autonomic and central nervous systems, and immune system, especially in women. The resulting changes in the stress response system, in turn, predispose an individual to the development of CFS and PTSD. Environmental events, such as motor vehicle crashes, physical and psychological trauma, physical illness, and viral exposures, can then trigger the expression of symptoms in vulnerable individuals. After the onset of CFS or PTSD, abnormalities in sleep, evoked pain processing, and psychiatric and psychosocial functioning become evident. Consistent with our conceptual model and with previous epidemiological studies of CFS (3–4) and PTSD (35), we found that rates of CFS, PTSD, and traumatic symptoms were significantly higher in women than in men. Future studies that examine similarities and differences in physiological, psychological, and behavioral mechanisms that underlie each condition can advance our knowledge of both CFS and PTSD, and identify possible treatments.



We also found differences between twins with both CFS and PTSD compared to twins with CFS only. Twins with both conditions were less likely to be married and more likely to report fair or poor health. Although the CFS literature has not specifically compared individuals with both CFS and PTSD to those with CFS only regarding their available social support networks, research into quality of life has shown that individuals with CFS (36), as well as those with PTSD (37), are less likely to have extensive social support networks than individuals not affected by these disorders. For both CFS and PTSD, social activities are highly restricted by the nature of these illnesses, hindering the abilities of individuals with these disorders to maintain or form new relationships (37).

This study has several limitations. First, the use of self-reported physician diagnoses could have resulted in misclassification of both CFS and PTSD, and it excludes individuals whose symptoms have not been formally diagnosed or who have limited access to health care. Because of the large-scale epidemiological nature of this study, we did not conduct clinical assessments and cannot be certain how self-reported diagnoses would compare to such assessments. Second, we may have underestimated the prevalence of these disorders in our population because of undiagnosed conditions, or overestimated because of misdiagnosis or misperception of a physician's diagnosis. Of note, however, the 2% lifetime rate of CFS in our sample is similar to that observed in the Swedish Twin Registry (4) and other prevalence studies that used medically-confirmed diagnoses of CFS (2), as is our observation that the prevalence of CFS was higher for females than for males (4). Third, our sample consisted of relatively young individuals, potentially reducing the generalizability of our findings to older cohorts who may have experienced CFS and/or PTSD for longer periods of time throughout their lives.

In sum, our findings from a community-based twin registry support previous results on the comorbidity of CFS with PTSD, and they extend the literature to include the potential role of familial and unique environmental factors in the link between these two conditions. Our findings therefore have substantial relevance to practitioners and researchers alike. Clinicians should carefully and thoroughly consider the complex nature of CFS as it relates to other conditions, and follow a multifaceted treatment approach that addresses the potential common mechanisms, such as the hormonal changes previously discussed, that underlie both CFS and stress-related conditions. Future studies can fully examine the genetic, familial, and unique environmental mechanisms that link these conditions, especially with regard to the social support network available to individuals with these conditions and to potential differences between men and women.

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**Table 1**

Sociodemographic and clinical characteristics of twins in the University of Washington Twin Registry.

Characteristic	Total Sample <sup>1</sup> (N=8,544, 100%) n (%)	Males (n=3,413, 39.9%) n (%)	Females (n=5,131, 60.1%) n (%)	p-value <sup>2</sup>
<b>Mean Age, years (SD)</b>	32.4 (15.7)	32.1 (15.8)	32.6 (15.6)	.199
<b>Race</b>				
White	7306 (86.0)	2924 (86.2)	4382 (85.8)	0.70
Non-white	1911 (14.0)	200 (13.8)	723 (14.2)	
<b>Married or Partnered</b>				
Yes	3389 (39.8)	1234 (36.4)	2155 (42.1)	<0.001
No	5118 (60.2)	2160 (63.6)	2958 (57.9)	
<b>Education Level</b>				
K-12	3186 (37.5)	1430 (42.2)	1756 (34.4)	<0.001
College +	5309 (62.5)	1957 (57.3)	3352 (65.6)	
<b>CFS</b>				
Yes	175 (2.1)	39 (1.2)	136 (2.7)	<0.001
No	8265 (97.9)	3327 (98.8)	4938 (97.3)	
<b>PTSD</b>				
Yes	318 (3.8)	85 (2.5)	233 (4.6)	<0.001
No	8118 (96.2)	3281 (97.5)	4837 (95.4)	
<b>IES Score</b>				
26	2402 (29.9)	751 (23.7)	1651 (34.0)	<0.001
< 26	5632 (70.1)	2420 (76.3)	3212 (66.0)	

<sup>1</sup>Some variables do not add up to the population total (n = 8,544) because of missing values.

<sup>2</sup>P-values, which describe the association between sex and each characteristic, were derived from generalized estimating equations that took into account the relatedness of twin pairs.

**Table 2**

Unadjusted, adjusted, and within-twin pair odds ratios (OR) and 95% confidence intervals (CI) for the associations between CFS, PTSD, and IES.

Trauma Variables	Overall Unadjusted OR <sup>1</sup> (95% CI)	Overall Adjusted OR <sup>2</sup> (95% CI)	Within-twin Pair Adjusted OR <sup>3</sup> (95% CI)
<b>Lifetime History of PTSD</b>	8.7 (6.0–12.6)	7.5 (5.0–11.0)	5.2 (3.4–7.9)
<b>IES Score 26</b>	4.1 (3.0–5.7)	4.3 (3.1–6.0)	1.7 (1.2–2.4)

<sup>1</sup>ORs describe the association between CFS, PTSD, and dichotomized IES score while taking into account the relatedness of twin pairs.

<sup>2</sup>ORs describe the association between CFS, PTSD, and dichotomized IES score, adjusted for age, sex, and race, while taking into account the relatedness of twin pairs.

<sup>3</sup>ORs describe the association between CFS, PTSD, and dichotomized IES score, adjusted for age, sex, race, and familial confounding.

**Table 3**

Categorical sociodemographic and health characteristics of twins with CFS and with and without PTSD.

Characteristic	CFS with PTSD (n=39, 22.9%) n (%)	CFS without PTSD (n=131, 77.1%) n (%)	Adjusted OR <sup>1</sup> (95% CI)
<b>Sex</b>			
Males	9 (23.1)	28 (21.4)	1.1 (0.5–2.6)
Females	30 (76.9)	103 (78.6)	1.0
<b>Race</b>			
White	36 (92.3)	120 (93.8)	0.8 (1.2–3.1)
Non-White	3 (7.7)	8 (6.3)	1.0
<b>Married or Partnered</b>			
Yes	11 (28.2)	66 (51.6)	0.3 (0.2–0.8)
No	28 (71.8)	44 (48.4)	1.0
<b>Education level</b>			
K-12	17 (43.6)	36 (28.6)	0.5 (0.2–1.1)
College+	22 (56.4)	90 (71.4)	1.0
<b>Smoked at least 100 Cigarettes in Lifetime<sup>2</sup></b>			
Yes	15 (57.7)	53 (57.6)	0.9 (0.4–2.3)
No	11 (42.3)	39 (42.4)	1.0
<b>General Health Status<sup>2</sup></b>			
Good or Very Good or Excellent	19 (48.7)	84 (64.6)	0.5 (0.3–1.0)
Fair or Poor	20 (51.3)	46 (35.4)	1.0

<sup>1</sup>Odds ratios describe the association between each characteristic and CFS/PTSD status, adjusted for age, sex and race, while taking into account the relatedness of twin pairs.

<sup>2</sup>Values in the column for Smoking and General Health Status do not add up to the complete sample of CFS without PTSD because of missing values in these variables.

**Table 4**

Continuous sociodemographic and health characteristics of twins with CFS and with and without PTSD.

Characteristic	CFS with PTSD (n=39, 22.9%) LS Mean (SE) <sup>1</sup>	CFS without PTSD (n=131, 77.1%) <sup>1</sup> LS Mean (SE)	p-value
Age at survey (years)	38.2 (3.0)	38.7 (2.4)	0.85
Number of times/week did vigorous exercise	1.6 (0.4)	2.1 (0.3)	0.27
Number of times/week did moderate exercise	1.1 (0.7)	1.6 (0.4)	0.24
Body Mass Index (kg/m <sup>2</sup> )	26.6 (1.1)	27.7 (0.9)	0.32
Number of visits to a medical doctor in past 3 months	5.0 (1.4)	2.9 (1.1)	0.20
Number of visits to a psychiatrist in past 3 months	1.5 (0.7)	0.9 (0.5)	0.50
Number of visits to an alternative practitioner in past 3 months	1.4 (1.2)	0.5 (0.4)	0.53

<sup>1</sup>Least Square Mean and Standard Errors (LS Mean and SE) were obtained from mixed models that were adjusted for age (where appropriate), sex, and race, and took into account the relatedness of twin pairs.