ORIGINAL ARTICLE

Premorbid Predictors of Chronic Fatigue

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Context: Chronic fatigue syndrome is a disabling problem characterized by persistent fatigue lasting at least 6 months with a number of ancillary symptoms. Although the etiology of chronic fatiguing illness is unknown, some evidence suggests that stress may confer increased risk for development of the disorder. Moreover, subjects with chronic fatiguing illness may have distinctive personality traits, although this finding could reflect confounding by other mechanisms.

Objective: To assess the prospective association of premorbid self-reported stress and personality with chronic fatigue–like illness.

Design: Prospective nested case-control study in a population-based sample.

Setting: General community.

Participants: From the Swedish Twin Registry, 19 192 twins born between January 1, 1935, and December 31, 1958.

Main Outcome Measures: Information about current chronic fatiguing illnesses was obtained from computer-assisted telephone interviews conducted between 1998 and 2002. Self-reported stress (based on a single question) and personality scales (emotional instability and extraversion in the Eysenck Personality Inventory) were measured from 1972 to 1973 by a mailed questionnaire. Relative risks were estimated with case-control analyses (matched for age and sex) and co-twin control analyses (comparing discordant pairs).

Results: Higher emotional instability and self-reported stress in the premorbid period were associated with higher risk for chronic fatigue–like illness in matched case-control analyses (odds ratios, 1.72 and 1.64, respectively). In co-twin control analyses, relative risk of emotional instability decreased to 1.02 whereas that of stress increased considerably to 5.81. There was no association between extraversion and fatigue.

Conclusions: Elevated premorbid stress is a significant risk factor for chronic fatigue–like illness, the effect of which may be buffered by genetic influences. Emotional instability assessed 25 years earlier is associated with chronic fatigue through genetic mechanisms contributing to both personality style and expression of the disorder. These findings suggest plausible mechanisms for chronic fatiguing illness.

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CHRONIC FATIGUE SYNdrome (CFS) is characterized by disabling fatigue associated with muscle pain, multijoint pain, and alterations in mood, sleep, and neurocognition.[1-5] In clinical settings, substantial comorbidity has been frequently observed between CFS and fibromyalgia, irritable bowel syndrome, and temporomandibular disorder.[6,7] Subjects with CFS also have higher rates of some psychiatric disorders such as major depression and generalized anxiety disorder.[8] Despite extensive study of the prevalence and comorbidity of CFS, little is known about its etiology.

Stress may play a pivotal role in the etiology of chronic fatigue. It has been reported that subjects with chronic fatigue experienced considerably more life events[9] or child abuse[10] prior to the onset of chronic fatigue than healthy controls, although some investigators found no association.[11,12] As such, stressful life events may act as triggers necessary for initiating disease symptoms. Little is known, however, about the role of self-perceived stress in disease etiology. A key feature of coping with stress is personality style, which may also be associated with chronic fatiguing illness. The few studies addressing the relationship between chronic fatiguing illness and personality indicate an association with significantly higher scores for emotional instability (eg, emotionality, neuroticism, or harm avoidance) in subjects with CFS as compared with control subjects.[13-15]

Critically, in all of the previous studies, state and trait effects were confounded. It is not known whether the association between stress coping or personality charac-

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Table 1. Descriptive Statistics of the Like-Sexed Respondents and Chronic Fatigue Syndrome–like Illness Cases

Characteristic	Subjects, No.	Men, No. (%)	Women, No. (%)
Like-sexed respondents	19 192	9040 (47.1)	10 152 (52.9)
MZ	7751	3538 (45.6)	4213 (54.4)
DZ	11 441	5502 (48.1)	5939 (51.9)
Case definition*			
Chronic impairing fatigue	1120	308 (27.5)	812 (72.5)
MZ	465	123 (26.5)	342 (73.5)
Like-sexed DZ	655	185 (28.2)	470 (71.8)
CFS-like illness	447	84 (18.8)	363 (81.2)
MZ	196	38 (19.4)	158 (80.6)
Like-sexed DZ	251	46 (18.3)	205 (81.7)

Abbreviations: CFS, chronic fatigue syndrome; DZ, dizygotic; MZ, monozygotic.

*Subjects who reported having fatigue at the time the questionnaire was administered from 1972 to 1973 were excluded.

teristics and chronic fatiguing illness is causal, a consequence of a disabling illness, or due to confounding with some unmeasured variable. In addition, most studies attempted to make comparisons between cases identified at clinics and controls recruited in a different manner. These study designs are susceptible to multiple forms of bias.[16,17]

In this study, we investigated the relationship between chronic fatigue–like illness and self-perceived stress as well as scores on 2 major personality scales (extraversion and emotional instability) in the population-based Swedish Twin Registry. The stress and personality measures were assessed from 1972 to 1973, and chronic fatigue was assessed from 1998 to 2002. Our prospective study design enables us to evaluate the role of premorbid personality and stress as predictors of having chronic fatigue. Inclusion of twins as subjects also permits comparison with unaffected co-twins, an effective way of adjusting for unmeasured genetic and family environmental influences.

METHODS

SUBJECTS

This study is based on the Swedish Twin Registry. This is the largest population-based twin registry in the world,[18,19] comprising all twin births in Sweden since 1886.

We screened all living, contactable, interviewable, and consenting twins born in Sweden before January 1, 1959, for a range of disorders including chronic fatigue. Data collection was performed from 1998 to 2002 with a computer-assisted telephone interview by trained interviewers. Owing to the confounding influence of aging, questions about chronic fatigue were only asked of twins born between January 1, 1935, and December 31, 1958 (aged 42-64 years). Only like-sexed twins from the interviews from 1998 to 2002 were included, as the data from 1972 to 1973 were only available for like-sexed twin pairs (as discussed later). Zygosity was established based on responses to a series of standard questions of physical similarity.[18] This method was validated as having greater than 98% accuracy by using DNA markers in a pilot study prior to the commencement of full-scale screening. The data collection procedures were reviewed and approved by the Swedish Data Inspection Board, Stockholm, Sweden, and the Regional Ethics Committee of the Karolinska Institutet, Stockholm. All of the participants provided verbal informed consent during the telephone interview, and this was later confirmed by postcard. Descriptive statistics of the subjects are summarized in **Table 1**.

MEASURES OF STRESS EXPERIENCE AND PERSONALITY

Stress and personality data were collected as part of the questionnaire sent in 1972 to 1973 to twins of like-sexed pairs. In the early 1970s, it was standard not to study unlike-sexed dizygotic pairs, as their utility had not yet been widely appreciated. Stress was assessed by the question, "Do you experience your daily existence as being very 'stress filled'?" with the answers coded as yes or no. Personality was assessed as indexed by measures of extraversion and emotional instability (also known as neuroticism) using a short form of the Eysenck Personality Inventory,[20] which has been widely used in previous Scandinavian twin studies.[21-23] Each scale score was based on the sum of yes and no responses to 9 items. We used mean imputation if 1 item for a particular scale was missing. Individuals having more than 1 missing item for a particular scale were excluded. Raw scale scores were standardized using a regression technique[24] to adjust for the effects of age, sex, and age × sex interaction.

ASSESSMENT OF CHRONIC FATIGUE

A complete description of the screening procedure and case definitions for the project were reported previously.[25] The screening module for chronic fatigue in the telephone interview was based on the Centers for Disease Control and Prevention consensus criteria for CFS.[1] The stem question, "Have you felt abnormally tired during the last 6 months?" was used to code fatigue. The time frame was the 6 months prior to interview, as assessment of lifetime fatigue was believed to be considerably less reliable. Subjects who endorsed this item were then asked about the continuousness of fatigue in the prior 6 months and about the duration of continuous fatigue. Impairment was considered present if subjects believed that fatigue made them too tired to live a normal life, had caused social problems, or had caused work incapacity of 25% or greater. Finally, subjects were asked about 8 ancillary symptoms during the period of abnormal tiredness (substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multijoint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting >24 hours). The presence of 4 or more of these ancillary symptoms is a component of the definition of CFS.[1]

FATIGUE-RELATED DEFINITIONS

We defined *fatigue* as the presence of self-reported abnormal tiredness in the absence of an exclusionary condition. Exclusionary conditions were determined from multiple sources as described elsewhere.[25] In brief, information about exclusions was obtained from the following sources: (1) the telephone interview (eg, morbid obesity, lifetime history of an eating disorder); (2) Swedish national registers (eg, malignant neoplasm, hospitalization owing to narrow definitions of schizophrenia, schizoaffective disorder, and bipolar disorder); and (3) physician review of all available medical records that revealed the presence of any other exclusionary diagnosis

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Table 2. Mean Standardized Scores of Personality Scales and the Proportion of Subjects With Stress in Cases and Unaffected Controls

	Emotional Instability Scale Score, Mean (SD)*			Extraversion Scale Score, Mean (SD)*			Report of Stressful Daily Life		
Case Definition	Cases†	Controls	*P* Value‡	Cases†	Controls	*P* Value‡	Cases, %†	Controls, %	*P* Value§
Chronic impairing fatigue	0.43 (1.08)	−0.09 (0.96)	<.001	−0.16 (0.98)	0.03 (1.00)	<.001	22.8	13.3	<.001
CFS-like illness	0.55 (1.10)	−0.09 (0.96)	<.001	−0.18 (1.05)	0.03 (1.00)	<.001	23.1	13.3	<.001

Abbreviation: CFS, chronic fatigue syndrome.

*Raw personality scores (0-9 as measured by the short form of the Eysenck Personality Inventory) were standardized for like-sexed respondents (n = 19 150) and adjusted for age at the time the questionnaire was administered, sex, and age × sex interaction by using a regression technique. After the standardization, each score has a grand mean of 0 and SD of 1.

†Subjects who reported having fatigue at the time the questionnaire was administered (n = 42) were excluded.

‡Analyzed by the *t* test.

§Analyzed by the χ^2 test.

(eg, drug or alcohol dependence, sleep disorder with adequate workup, infection with hepatitis B or C or human immunodeficiency virus).

The following definitions were made in the absence of the exclusionary conditions mentioned earlier: (1) *prolonged fatigue* was the presence of fatigue with a duration of 1 month or longer; (2) *chronic fatigue* was the presence of fatigue with a duration of 6 months or longer; (3) *chronic impairing fatigue* was the presence of fatigue with a duration of 6 months or longer plus impairment; and (4) *CFS-like illness* was the presence of fatigue with a duration of 6 months or longer, impairment, and 4 or more ancillary symptoms. For clarity, only the latter 2 definitions (ie, chronic impairing fatigue and CFS-like illness, which correspond to CF-B and CF-C in our previous report[25]) were used in the subsequent analyses.

STATISTICAL ANALYSES

Analyses were performed by 3 steps of matched case-control designs: generalized estimating equations (GEE), co-twin control analyses using both monozygotic and dizygotic twin pairs who were discordant in terms of case status, and co-twin control analyses using discordant monozygotic twin pairs only. The design of GEE is conceptually equivalent to matched case-control design, controlling for the clustering of twins within a pair. Subjects were considered controls if they did not endorse the stem question about fatigue. In the co-twin control design, twin pairs in whom 1 twin was the case and the co-twin was unaffected were identified. Subjects were excluded from the analyses in the case of unknown zygosity, unlike-sexed dizygotic twins, or the presence of fatigue at the time the questionnaire was administered from 1972 to 1973 based on the question about the duration of continuous fatigue in the telephone interview.

If there is overlap in genes for stress or personality and chronic fatigue, the association could reflect confounding by the genes. Using twins discordant for case status is more informative than using unrelated case-control samples, as it allows matching for unmeasured familial factors that could be genetic or environmental. In particular, discordant monozygotic twins are ideal case-control pairs with whom all genes and environmental effects in early life are shared. Thus, if the association found in GEE analyses decreases in co-twin analyses, it suggests that there is familial confounding; if the association further decreases when monozygotic twins are used, it suggests genetic confounding. In contrast, if a significant association remains when using monozygotic twins only, it means that the association is influenced by factors other than genetic and early environmental effects. If there is a temporal order of exposure and outcome, the association in monozygotic twins indicates a direct relationship.

Odds ratios and 95% confidence intervals were obtained by GEE analyses using the PROC GENMOD procedure and by conditional logistic regression analyses using the PROC LOGISTIC procedure in SAS statistical software version 9 (SAS Institute, Inc, Cary, NC). The variables (standardized extraversion, standardized emotional instability, and stress) were evaluated first separately and then simultaneously in the same model along with their interactions (eg, emotional instability × stress).

RESULTS

Of 41 499 individual twins who were eligible for chronic fatigue screening, 31 406 (75.7%) responded to the interview. After excluding unlike-sexed twins and twins with unknown zygosity, 19 192 subjects were obtained, 40.4% of whom were monozygotic twins. Among the 19 192 subjects, 4002 (20.8%) endorsed abnormal tiredness in the prior 6 months, 15 001 (78.2%) denied abnormal tiredness in the prior 6 months, and 189 (1.0%) provided no usable answer. To focus our analyses on incident cases, we excluded 42 subjects who reported that fatigue had been present at the time the questionnaire was administered from 1972 to 1973, leaving 1570 twins who reported fatigue lasting 6 or more months (defined as chronic fatigue), 1120 of whom endorsed impairment (chronic impairing fatigue) and 447 of whom had 4 or more ancillary symptoms (CFS-like illness) (Table 1).

Table 2 shows standardized scores for personality scales and the proportion of subjects who endorsed their daily life as stressful, comparing cases and controls. The differences in mean scores for the personality scales were statistically significant between cases and controls in both case definitions (*t* test, $P<.001$). The differences in proportions of subjects with stress were also statistically significant for both case definitions (χ^2 test, $P<.001$).

The **Figure** shows the results of matched case-control analyses using GEE, co-twin control analyses using both monozygotic and dizygotic twins, and co-twin control analyses using monozygotic twins only. In GEE analyses, both definitions of chronic fatigue were significantly associated with emotional instability. These results can be thought of as the same as analyses of an unselected population, and they indicate that there is a 55% to 72% increase in the risk

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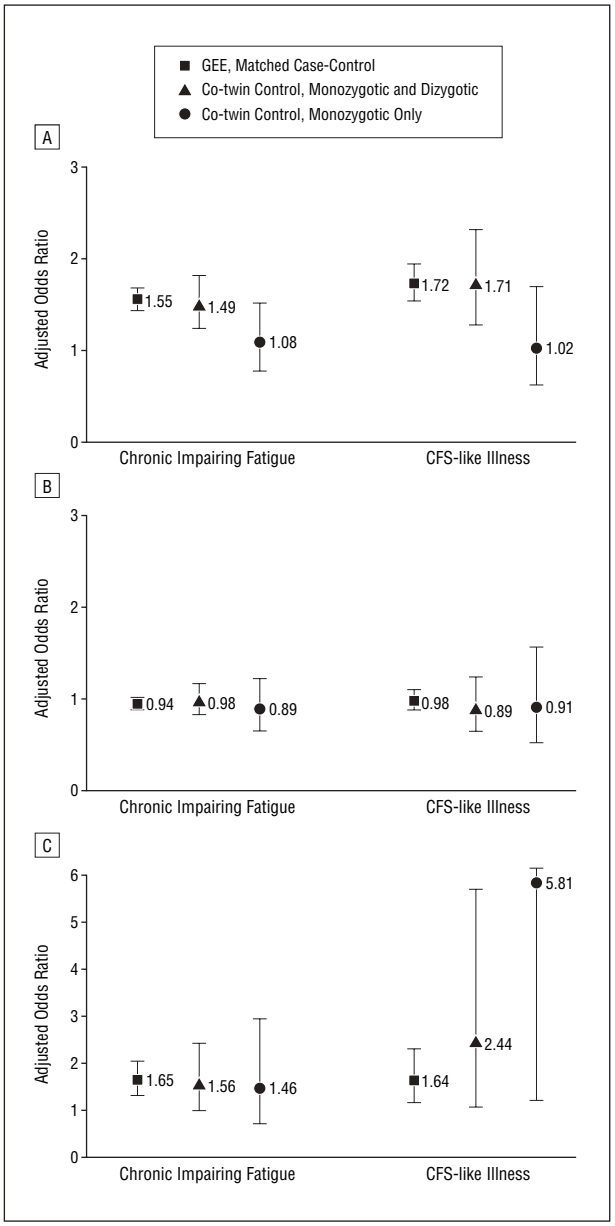

Figure. Adjusted odds ratios with 95% confidence intervals for the associations of chronic impairing fatigue and chronic fatigue–like illness with emotional instability (A), extraversion (B), and stress (C). CFS indicates chronic fatigue syndrome; GEE, generalized estimating equations.

of these definitions of chronic fatigue with each standard deviation increase in emotional instability (after correction for stress and extraversion). In the second series of analyses, using monozygotic and dizygotic twins, the point estimates dropped only slightly and were still significant. In the final set of analyses, based on monozygotic twins only, the point estimates approached 1.0 and neither definition was significant. These results indicate that the association between emotional instability and chronic fatigue primarily reflects genetic factors that are important for both emotional instability and fatigue. The emotional instability × stress interaction term was not significant in any of the analyses.

Extraversion was not associated with either case definition in any of the analyses in the Figure. Self-reported stress displayed an interesting pattern of results. In the matched case-control analyses, stress was a modest predictor of chronic impairing fatigue; those experiencing their life as stressful between 1972 and 1973 had a 64% to 65% greater risk of developing fatigue later in life. For CFS-like illness, however, risk estimates increased with increasing degrees of adjustment for family environmental and genetic factors. Thus, when genetic influences are controlled, the impact of premorbid stress becomes more pronounced. This suggests that some genes may serve as a buffering effect whereas other sensitive individuals are more susceptible to the impact of stress.

COMMENT

Using a population-based, genetically informative sample, we have characterized the importance of premorbid emotional instability and self-reported stress for developing chronic fatigue–like illness up to a quarter of a century later. The combination of prospective risk assessment and a genetically informative sample of twins allowed us to evaluate the extent to which the effect of potential risk factors reflects family environmental and/or genetic mechanisms. Premorbid self-reported stress confers a 64% to 65% greater risk for the occurrence of chronic fatigue. Genetic factors tend to buffer the impact of stress; risk increases from 64% to more than 5-fold after accounting for genetic factors. Emotional instability is predictive of chronic fatiguing illness; this association can be entirely attributed to familial (genetic and family environmental) mediation. Thus, certain genetic propensities may ameliorate or exacerbate the effect of stress. At the same time, genetic influences on emotional instability also contribute to the development of fatiguing symptoms.

Although a number of studies have reported the risk of specific types of stress for chronic fatiguing illness, the literature to date for stress in general is inconclusive. In contrast to emotional instability, premorbid stress clearly predicted risk for chronic fatigue even when controlling for familial factors, suggesting that premorbid stress is a direct environmental risk for fatigue. Stress is thought to affect health through down-regulation of the hypothalamic-pituitary-adrenal axis, resulting in persistent fatigue and other symptoms.[26] Like depression,[27] certain combinations of susceptibility genes for chronic fatiguing illness that are expressed only when the subject is exposed to stress may exist.

A key feature of stress coping is personality,[28] yet our results indicate that the impact of stress on chronic fatigue is independent of the level of emotional instability. Thus, it is notable that perceived stress was a significant predictor of fatigue beyond the influence of 2 measures of personality. Previous associations with emotional instability[13-15] were based on cross-sectional and retrospective studies and were thus unable to ascertain whether higher emotional instability exists premorbidly or whether the chronic fatigue influences the outcome of personality assessment. Our results clearly indicate that greater emotional instability does exist premorbidly and is predictive of more than a 50% greater

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risk of developing chronic fatigue some 25 years later. The co-twin analyses, which resulted in decreasing risk estimates, indicate that unmeasured familial influences contribute to the association and are thus implicated as mechanisms. In contrast to stress, the association between emotional instability and fatigue is more likely to be endogenous. Because we found considerable influences attributable to genetic and early environmental factors, our results suggest biological mechanisms that mediate the relationship between emotional instability and chronic fatigue. Likely candidates are those genes related to neurotransmission that have been implicated in depression and emotional instability.[29]

The trait of emotional instability that we studied in this article is clearly defined.[30] Emotional instability is a quantitative personality trait defined as an individual's tendency to experience psychological distress that can be reliably measured by self-report and is relatively stable in an individual over time. Individuals with high scores are characterized by low self-esteem and feelings of anxiety, depression, and guilt.[31] The construct of emotional instability is extraordinarily robust[32]: emotional instability or a very similar construct can be found in essentially every major theory of personality and is identifiable across the socioeconomic spectrum and in a diverse range of cultures.

Unfortunately, the useful construct of emotional instability is also known as "neuroticism," which is generally confounded with the imprecise, pejorative, and even dismissive terms "neurosis" and "neurotic."[33] We recommend that these terms *not* be used in regard to our findings—their use is not consistent with clarity, precision, and a dispassionate and logical perspective on the complex problem of chronic fatigue.

In addition, the salient findings from this article consist of correlations of chronic fatiguing illness with self-reported emotional instability and the perception of a stressful life. Although temporality is a singular strength of our findings and the correlation is unlikely to be owing to chance given the low *P* values, we cannot definitively distinguish between direct causality and confounding. Nonetheless, our co-twin control findings strongly suggest that the association is entirely explained by (ie, confounded by) unmeasured family environmental and genetic factors. Therefore, we also recommend that our findings *not* be described as a demonstration that "neuroticism" causes chronic fatigue, as such an interpretation is undoubtedly simplistic and not consistent with our findings.

A notable strength of our study is that it is a nested case-control study in a prospective, population-based cohort. The associations based on clinical studies could be not only susceptible to referral bias but also induced by uneven distributions of socioeconomic status between cases and controls. Neither risk factors nor chronic fatigue were assessed with prior knowledge about any particular health problem that each participant might have had at the time the study was conducted. Nevertheless, 3 limitations should be noted. First, cases were diagnosed by telephone interviews without clinical assessment. The duration of chronic fatigue as well as the exclusion of other fatigue-inducing causes could therefore be inaccurate. Inaccuracy of the age at onset may also lead to misclassification of subjects who felt stress due to fatigue that already existed at the time the questionnaire was administered from 1972 to 1973. However, we were able to exclude 42 individuals who reported onset of fatigue prior to that time. Second, the subjects were aged 42 years or older at the time of the interview. Although most cases have gone through the window of time with the greatest incidence of chronic fatiguing illness,[34] a number of cases might have been misclassified owing to recovery or recall bias by the time of the interview. We believe, however, that the misclassification could only result in underestimation of the risk. Third, stress was measured only once based on a subjective self-report (coded as a dichotomous variable) that may not necessarily reflect actual stressful events in real life. However, the fact that the risk estimates were magnified in the co-twin control analyses suggests differences in familial influences between stress experience and emotional instability measured in this study.

In conclusion, we found strong support for the predictive capacity of premorbid stress and emotional instability for chronic fatiguing illness several decades later. Our findings suggest that although both stress and emotional instability are important, emotional instability has endogenous, moderating effects mediated by familial factors whereas stress has exogenous, direct effects on the occurrence of chronic fatigue.

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