# Twin Analyses of Fatigue

**Ellen Schur, MD**[1], **Niloofar Afari, PhD**[2], **Jack Goldberg, PhD**[3], **Dedra Buchwald, MD**[1], and **Patrick F. Sullivan, MD, FRANZCP**[4]

[1]Department of Medicine, University of Washington School of Medicine, Seattle, WA

[2]Department of Psychiatry, University of California, San Diego & VA San Diego Healthcare System, San Diego, CA

[3]Department of Epidemiology, University of Washington & Vietnam Era Twin Registry, Seattle, WA

[4]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC

## Abstract

Prolonged fatigue of ≥1 month duration and chronic fatigue of ≥6 months duration are both commonly seen in clinical practice, yet little is known about the etiology or epidemiology of either symptom. Chronic fatigue syndrome (CFS), while rarer, presents similar challenges in determining cause and epidemiology. Twin studies can be useful in elucidating genetic and environmental influences on fatigue and CFS. The goal of this paper was to use biometrical structural equation twin modeling to examine genetic and environmental influences on fatigue and to investigate whether these influences varied by gender. A total of 1,042 monozygotic twin pairs and 828 dizygotic twin pairs who had completed the University of Washington Twin Registry survey were assessed for three fatigue-related variables: prolonged fatigue, chronic fatigue, and CFS. Structural equation twin modeling was used to determine the relative contributions of additive genetic effects, shared environmental effects, and individual-specific environmental effects to the three fatigue conditions. In women, tetrachoric correlations were similar for monozygotic and dizygotic pairs for prolonged and chronic fatigue, but not for CFS. In men, however, the correlations for prolonged and chronic fatigue were higher in monozygotic pairs than in dizygotic pairs. About half the variance for both prolonged and chronic fatigue in males was due to genetic effects and half due to individual-specific environmental effects. For females, most variance was due to individual environmental effects.

Fatigue is a common symptom in clinical practice; however, physicians have little empirical data on epidemiology or etiology. Fatigue is a presenting complaint for an estimated 7.6% to 13.6% of persons in primary care (Cathebras, Robbins, Kirmayer, & Hayton, 1992; Fuhrer & Wessely, 1995), and 5.0 to 7.7% of the general population suffers from prolonged fatigue (Jason et al., 1999). At the extreme end of the spectrum, where fatigue is disabling, is chronic fatigue syndrome (CFS). CFS is a clinically defined condition of unknown etiology that is characterized by profound fatigue of at least 6 months duration (Fukuda et al., 1994). Strictly defined, it appears to be comparatively rare in community-based samples (Jason et al., 1999; Reyes et al., 2003), and women are disproportionately afflicted (Afari & Buchwald, 2003; Reyes et al., 2003).

The etiology of the spectrum of fatiguing illness remains unclear. Recent family and twin studies have suggested a role for genetics in the etiology of prolonged and chronic fatigue as well as CFS (Buchwald et al., 2001; I. Hickie, Kirk, & Martin, 1999; I. B. Hickie, Bansal, Kirk,

Address for correspondence: Dr. Schur at Harborview Medical Center, Box 359780, 325 Ninth Avenue, Seattle, WA 98104; telephone 206-744-1824; FAX 206-744-9917; ellschur@u.washington.edu.

Lloyd, & Martin, 2001; Walsh, Zainal, Middleton, & Paykel, 2001). Recently, Sullivan et al. showed in a national Swedish Twin Registry that genetic effects for varying levels of fatigue were moderate, accounting for about 30% of the variance across fatigue definitions and gender strata (Sullivan, Evengard, Jack, & Pedersen, 2005). Because relatively little is known about the genetic epidemiology of fatigue, the goal of this research was to use biometrical structural equation twin modeling to investigate whether genetic and environmental factors differed by gender across three definitions of fatigue.

## METHODS

### Sample

All twins were participants in the University of Washington Twin Registry, a community-based registry of twin pairs derived from applications for drivers' licenses in Washington State. The construction and characteristics of the University of Washington Twin Registry and its sample population are described in full elsewhere (Afari et al., 2006). Briefly, because drivers' license numbers are assigned on the basis of an individual's name and date of birth, the Department of Licensing asks each new applicant whether s/he is a member of a twin pair to avoid issuing duplicate license numbers. The University of Washington receives lists of applicants who are twins, and each member of the pair is invited to join the University of Washington Twin Registry and complete a health survey. All University of Washington Twin Registry procedures and the data collection involved in this study were approved by the University of Washington Institutional Review Board. Informed consent was obtained from all twins.

### Zygosity Assignment

All twins completed a mailed questionnaire in which they were asked questions about childhood similarity to assess zygosity. Studies have shown that questions about childhood similarity in twin pairs can be used to correctly classify zygosity with an accuracy that is 95–98% of that achieved by using biological indicators (Eisen, Neuman, Goldberg, Rice, & True, 1989; Torgersen, 1979). The following questions were asked: "As children were you and your twin as alike as two peas in a pod or of ordinary family resemblance?" and "When you were children how often did [parents, other relatives, teachers, strangers] have difficulty in telling you apart?" The responses to these similarity questions were then used in a multi-step process to assign zygosity.

### Measures of Fatigue

Several different measures of fatigue-related variables were possible given the data collected by questionnaire. *Prolonged fatigue* was defined as the presence of self-reported fatigue of ≥1 month duration. *Chronic fatigue* was the self-reported presence of fatigue for ≥6 months. These definitions are consistent with other studies of the epidemiology and genetics of fatigue (Furberg et al., 2005; Sullivan, Evengard et al., 2005). Exclusionary criteria were not applied to these variables. *CFS* was coded via an affirmative response to the question "Has your doctor ever told you that you have chronic fatigue syndrome?" Pairs with missing data for CFS were excluded from these analyses.

### Statistical Analyses

As described at length elsewhere (Neale & Cardon, 1992), we applied a standard approach to structural equation twin modeling of a discrete trait. Briefly, our goal was to assess the magnitudes of latent components of variation underlying the observed trait (e.g., CFS). These analyses postulate that the observed similarity of members of a twin pair results from variance in three types of causes. Additive genetic effects ($a^2$) are the cumulative impact of multiple genes, individually of small effect, that contribute twice as much to the monozygotic as to the

dizygotic twin correlation, under the assumption that monozygotic twins are genetically identical while dizygotic twins share about half of their genes. Shared environmental effects ($c^2$) to which both members of a twin pair are exposed contribute equally to the correlation in monozygotic and dizygotic twins. Individual-specific environmental effects ($e^2$) reflect environmental experiences that are not shared by the members of a twin pair and tend to make them different in liability to illness. The sum of $a^2$, $c^2$, and $e^2$ is set to 1. The goal of univariate twin analysis is to decompose the variance in liability to the disorder in the population studied into the proportion due to $a^2$, $c^2$, and $e^2$ with 95% confidence intervals. Our primary intention was to assess the confidence intervals on $a^2$, $c^2$, and $e^2$ (Sullivan & Eaves, 2002). Mx was used for all analyses (Neale & Cardon, 1992), employing a script from the GenomEUtwin library {GenomEUtwin, #537} to analyze contingency tables perform confidence interval calculations (Neale & Miller, 1997).

# RESULTS

## Participants

At the time of these analyses, a total of 3,982 individual twins (1,991 twin pairs) had completed the University of Washington Twin Registry survey. Participants ranged from 18 to 90 years of age (mean=32.4 ± 14.7) and were predominantly female (61%). Most of the participants were White (87%); 33% were married; and 42% had fewer than 12 years of education. There were 1,042 monozygotic twin pairs (52%), 828 dizygotic twin pairs (42%), and 121 pairs of unknown zygosity (6%). The prevalence rate of prolonged fatigue was 16%; chronic fatigue was reported by 12%, CFS by 3%.

## Twin correlations

Tetrachoric correlations and associated data for the three definitions of fatigue by zygosity groupings are given in Table 1. For prolonged fatigue, the tetrachoric correlations between female monozygotic and dizygotic twins were similar (0.39 versus 0.32), while the difference in correlations between male monozygotic and dizygotic twins was substantial (0.55 versus −0.02). The female dizygotic twin correlation was substantially larger (0.32) than the other dizygotic correlations (−0.02, 0.05, −0.20).

The results for analyses of chronic fatigue were similar. The tetrachoric correlations between female monozygotic and dizygotic twins were comparable (0.36 versus 0.32), but the correlation for male monozygotic twins was substantially larger (0.51) than the correlation for male dizygotic twins (−0.07).

In contrast, the female monozygotic correlation for CFS exceeded the female dizygotic correlation (0.61 versus 0.40). The monozygotic male correlation for CFS was similar to the monozygotic male correlations for prolonged and chronic fatigue; however, due to low cell sizes, we were not able to calculate tetrachoric correlations for CFS among dizygotic males.

## Structural equation modeling

We next conducted structural equation twin modeling to estimate the genetic architecture of these three traits. Results of twin models are depicted in Table 2. For prolonged fatigue, the heritability ($a^2$) was estimated at 51% in males (95% CI: 13–69%) and considerably exceeded that in females (18%), whose 95% CI included zero. For males, about half the variance was due to genetic effects and half was due to environmental effects specific to individuals. For females, most of the variance was due to individual-specific environmental effects, but a substantial component of shared environmental effects could not be compellingly excluded.

For chronic fatigue, the same general pattern of results was found as for prolonged fatigue. However, the male heritability 95% CI included zero due to the smaller numbers of affected individuals and decreased statistical power. For CFS, the low prevalence in males (Afari & Buchwald, 2003) meant that several cells were empty in the zygosity contingency tables. As a consequence, twin models could be conducted only in females. Compared to the other fatigue definitions, the heritability estimate for CFS in females was larger (51%), and the precision was lower (95% CI: 0–82%). Environmental variance was split between shared (12%) and unshared (36%) components.

## DISCUSSION

The goal of this study was to examine genetic and environmental influences on fatigue and investigate whether these influences vary by gender. We found intriguing differences in the patterns of genetic influences for women and men. In women, correlations for prolonged and chronic fatigue were quite similar for monozygotic and dizygotic pairs, but not for CFS. This was in contrast to the much higher correlations in male monozygotic pairs than in male dizygotic pairs. Structural equation modeling results confirmed a possible genetic contribution to CFS in females. In contrast, for prolonged and chronic fatigue definitions, individual environmental effects predominated for females, whereas for males, approximately half the variance was due to genetic effects and half was due to individual-specific environmental effects. Shared environmental effects were minimal for both females and males, but could not be definitively excluded.

The prevalence of fatigue and its gender distribution were similar to findings in a Swedish Twin Registry (Evengard, Jacks, Pedersen, & Sullivan, 2005) and in U.S. samples (Furberg et al., 2005). However, studies of heritability among the Swedish twins did not find strong evidence for a genetic contribution as definitions of fatigue became more refined (Sullivan, Evengard et al., 2005). By contrast, our findings in this U.S. sample do suggest a genetic contribution to CFS, as evidenced among females in this study. Several other studies have examined interactions between gender and genetic contributions to fatigue, with inconsistent findings. One study investigated fatigue that interfered with daily activities for five days or more and found evidence for etiological heterogeneity, with a stronger genetic effect in women and shared environmental effects in men (Sullivan, Kovalenko, York, Prescott, & Kendler, 2003). More recently, however, a large study among 12, 407 Swedish twin pairs revealed remarkably consistent findings between women and men (Sullivan, Evengard et al., 2005). On the whole, the literature from twin research provides little consensus as to gender differences in genetic and environmental contributors for fatigue. Further research is needed, with an emphasis on recruiting adequate numbers of males into studies.

Recently, association studies and microarray analyses have revealed potential genes that may play an important part in chronic, disabling fatigue. Candidate genes that distinguished fatigued individuals from well individuals were identified (Carmel et al., 2006), as well as markers that consistently identified subjects with CFS (Goertzel et al., 2006). Associations were also found with 11 candidate genes involved in hypothalamic-pituitary axis functioning among CFS sufferers (Smith, White, Aslakson, Vollmer-Conna, & Rajeevan, 2006). These analyses take us one step closer to definitively classifying the spectrum of disabling fatiguing illness. The same line of research may also uncover the physiologic basis for this perplexing condition and guide clinicians in treating fatigue complaints.

A major strength of this study was the use of a community-based, U.S. registry of twins, distinguishing it from prior epidemiologic studies in Scandinavia (Evengard et al., 2005; Sullivan, Evengard et al., 2005) and disease-specific registries for chronic fatigue sufferers (Buchwald et al., 2001). In addition, our results are generalizable, because we obtained data

on a variety of definitions of fatigue with relevance to clinical settings. Finally, we performed analyses stratified by gender, which add a more nuanced understanding to the genetic epidemiology of fatigue.

This study does, however, have several limitations. While twin studies are exceptionally well-suited to examine hypotheses that polygenic or recessive genes, for example, might contribute to fatigue, we cannot verify the underlying assumptions of polygenic inheritance, nor can we confirm that monozygotic and dizygotic twins grew up in equal environments. Moreover, CFS was assessed by a single-item self-report of a doctor's diagnosis, which can be subject to response bias. This format also excludes symptomatic individuals who have not been formally diagnosed or have limited access to health care. Even when a clinical diagnosis of CFS has been made, there is concern that the 1994 CDC case definition of CFS may not accurately classify all individuals with impairing levels of fatigue (Sullivan, Pedersen, Jacks, & Evengard, 2005). Finally, small cell sizes in several analyses limit the conclusiveness of our findings, and we were in fact unable to complete analyses of CFS in males, because too few individuals were affected.

Nonetheless, this study adds further insight into the complexity of the genetic basis for fatigue. We would recommend further work on gender differences in fatigue presentation and among larger samples of men. Given the promising results of early association studies, continued investigation of genetics and gene-environment interactions in the etiology of persistent fatigue is warranted.

## Acknowledgments

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**Table 1**

Tetrachoric Correlations and Other Descriptive Data for Three Fatigue Definitions by Zygosity Groupings

| Phenotype | Zygosity | Tetrachoric correlation | ASE | Contingency table cell counts* (N) | | | |
|---|---|---|---|---|---|---|---|
| | | | | T1−/T2− | T1−/T2+ | T1+/T2− | T1+/T2+ |
| Prolonged fatigue | MZ-F | 0.39 | 0.07 | 474 | 82 | 66 | 39 |
| | DZ-F | 0.32 | 0.11 | 171 | 34 | 39 | 20 |
| | MZ-M | 0.55 | 0.10 | 316 | 20 | 31 | 14 |
| | DZ-M | −0.02 | 0.22 | 109 | 14 | 17 | 2 |
| | DZOS-MF | 0.05 | 0.17 | 133 | 38 | 15 | 5 |
| | DZOS-FM | −0.20 | 0.15 | 151 | 23 | 53 | 4 |
| Chronic fatigue | MZ-F | 0.36 | 0.08 | 521 | 63 | 55 | 22 |
| | DZ-F | 0.32 | 0.12 | 191 | 29 | 31 | 13 |
| | MZ-M | 0.51 | 0.12 | 329 | 18 | 25 | 9 |
| | DZ-M | −0.07 | 0.26 | 116 | 11 | 14 | 1 |
| | DZOS-MF | 0.16 | 0.18 | 146 | 30 | 11 | 4 |
| | DZOS-FM | −0.04 | 0.16 | 167 | 19 | 41 | 4 |
| Chronic fatigue syndrome[†] | MZ-F | 0.61 | 0.12 | 616 | 14 | 13 | 5 |
| | DZ-F | 0.40 | 0.21 | 237 | 11 | 8 | 2 |
| | MZ-M | 0.51 | 0.25 | 362 | 3 | 9 | 1 |
| | DZ-M | -- | -- | 139 | 2 | 1 | 0 |
| | DZOS-MF | -- | -- | 181 | 5 | 0 | 0 |
| | DZOS-FM | 0.72 | 0.24 | 217 | 1 | 5 | 1 |

* Counts of T1 by T2 for each phenotype-zygosity grouping; "−" means absent and "+" means present.

[†] Unable to calculate all correlations due to low cell sizes.

MZ=monozygotic; DZ=dizygotic; DZOS=DZ opposite sex; F=female; M=male; ASE=asymptotic standard error; T1=twin 1; T2=twin 2

**Table 2**

Structural Equation Twin Models for Three Fatigue Definitions

|  | **Prolonged fatigue** | **Chronic fatigue** | **Chronic fatigue syndrome** |
|---|---|---|---|
| Type of twin model | 6 group sex limitation | 6 group sex limitation | 2 group (females only) |
| Model GOF | $\chi^2$=18.7, df=11, p=0.07 | $\chi^2$=17.4, df=11, p=0.10 | $\chi^2$=2.91, df=3, p=0.41 |
| Male – $a^2$ (95% CI) | 51% (13–69%) | 47% (0–68%) | - |
| Male – $c^2$ | 0% (0–33%) | 0% (0–39%) | - |
| Male – $e^2$ | 49% (31–71%) | 53% (32–79%) | - |
| Female – $a^2$ | 18% (0–54%) | 12% (0–53%) | 51% (0–82%) |
| Female – $c^2$ | 23% (0–48%) | 26% (0–48%) | 12% (0–72%) |
| Female – $e^2$ | 59% (46–74%) | 62% (47–78%) | 36% (18–65%) |

GOF=goodness-of-fit; df=degrees of freedom; CI=confidence interval; $a^2$=proportion of variance in liability due to additive genetic effects;

$c^2$=proportion of variance in liability due to environmental effects common or shared between co-twins; $e^2$=proportion of variance in liability due to environmental effects unshared between co-twins.