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*ORIGINAL RESEARCH*

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Major Depressive Disorder  
in Chronic Fatigue Syndrome:  
A CDC Surveillance Study

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**ABSTRACT.** *Background:* Controversy continues to exist as to whether Chronic Fatigue Syndrome is a psychological/psychiatric disorder. To further understand this condition the Centers for Disease Control (CDC) conducted a Surveillance Study. The CDC partitioned 565 subjects with

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The study utilizes the Chronic Fatigue Syndrome Surveillance System data set provided by James G. Dobbins, PhD, Chronic Fatigue Syndrome Research Group, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.

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fatiguing illnesses into four diagnostic groups, one of which met the 1988 CDC criteria for CFS. The non-CFS groups had either insufficient severity (idiopathic), medical exclusions or prior psychiatric disorders.

*Objectives:* The present study reports on the psychiatric features in that study, estimates the time of onset of Major Depressive Disorder (MDD) and looks for possible relationships between 1988 CDC criteria for Chronic Fatigue Syndrome and psychiatric disorders.

*Methods:* The study design is cross-sectional. The Diagnostic Interview Schedule (DIS) assessed for four Axis I psychiatric disorders. Time of onset of MDD was estimated from the DIS and validated by an examination of the medical records. Odds ratios and confidence intervals were calculated as tests of association between 1988 CDC criteria and psychiatric disorders.

*Results:* Subjects classified as CFS and non-CFS had similar rates of psychiatric disorders. A minority of subjects had preexisting MDD. Three 1988 CDC criteria were associated with current MDD whilst no criteria were associated with prior MDD.

*Conclusions:* CFS subjects did not demonstrate any unique patterns of psychiatric disorders. MDD may not be an important predisposing factor for CFS or the other fatiguing illnesses. Some 1988 CDC criteria may be preferentially endorsed by subjects with current MDD. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2004 by The Haworth Press, Inc. All rights reserved.]

**KEYWORDS.** Chronic fatigue syndrome, major depressive disorder, predisposing factor, phenotypes

## INTRODUCTION

The literature on Chronic Fatigue Syndrome (CFS) is polarized into those who view the disorder(s) within a psychological/psychiatric context and those who view it within a neurological context. The former and traditional view often called neurasthenia notes the predominance of psychiatric disorders in CFS (primarily major depression) as a culturally sanctioned form of illness behavior. The later or more recent view

notes that many of the 1988 CDC criteria for CFS including: prolonged debilitating fatigue worsened after physical exertion, painful lymph nodes, sore throat and sudden onset are less commonly observed in Major Depressive Disorder (MDD) and point to a different underlying etiology.

The CDC now places CFS at the top priority of new and reemerging infectious diseases (1). Markers of persistent infection (2) and acquired immune dysregulation (3-5) have been reported in CFS. While to date CFS has no widely acceptable biological markers it is clearly a disabling condition with features that suggest neurobehavioral and multi-system involvement.

Damasio (6) suggested that Descartes' theory that the mind and body are separate has had an adverse influence on the Western approach to illness. Ray (7) stated that disorders with a psychological component may not necessarily primarily have a psychological basis. The issue is pertinent because the literature suggests that MDD is a predominant psychiatric disorder accompanying CFS. Possible interpretations are that (1) MDD results in CFS, (2) MDD-like symptoms follow CFS, (3) MDD and CFS share common etiological factors, and (4) CFS is a heterogeneous condition where only some phenotypes have MDD. Van Hoof et al. (8) proposed that MDD-like symptoms following CFS represent not atypical depression but sickness-response behaviors.

If a temporal relationship between MDD and CFS were to be established there might be a better understanding of CFS. To investigate this issue we reviewed studies that utilized an accepted CFS case definition, administered a standardized instrument to diagnose MDD (9) and estimated a temporal relationship between CFS and MDD.

Four reviewed studies were selected. The proportions of CFS subjects with a concurrent onset of MDD (acquired) were: 45.3% (10), 45.8% (11), 30% (12) and 20% (13). The proportions where MDD began prior to CFS (preexisting) were: 16.4%, 12.5%, 15%, and 0%, respectively. Comparatively low reported levels of preexisting MDD suggest that MDD may not be a necessary risk factor for CFS. However, it is difficult to draw firm conclusions regarding temporality because of the paucity of studies, possibilities of selection bias, small sample sizes,

and the retrospective nature of the inquiry. There is also a problem of heterogeneity of the subjects (14).

When four published CFS case definitions were compared (14-17), they were shown to have an overlapping of caseness (18). According to De Becker, McGregor, and De Meirleir (19) the case definition could be improved by modifying its criteria. They suggested that the symptom "arthralgia" be deleted. However, Axe (20) found correlations between arthralgia and neurocognitive difficulty. For the present study, we used the 1988 CDC criteria because the CDC could not guarantee a reliable reclassification of subjects for the 1994 CDC criteria.

The present study utilizes data from the CDC's Chronic Fatigue Syndrome Surveillance System (21), one of the largest and richest epidemiologic investigative studies pertaining to this subject. It will ascertain if CFS subjects have unique psychiatric features, judge whether MDD is a risk factor for CFS subjects and investigate whether 1988 CDC criteria are associated with psychiatric disorders.

## ***METHOD***

### ***Sites and Subject Selection***

The study adhered to the human experimentation guidelines of the U.S. Department of Health and Human Services. Four geographically distinct metropolitan areas were selected as study sites. Atlanta, Georgia was chosen for its proximity to the CDC. Wichita, Kansas and Grand Rapids, Michigan had populations demographically representative of the United States and Reno, Nevada was close to Incline Village, the site of an outbreak of CFS-like illness in 1986.

The CDC intended to locate primary care physicians who were likely to provide health care to CFS patients and report them to the system. They selected family practitioners, infectious disease specialists, internists, osteopaths, rheumatologists and pediatricians from local tele-

phone and medical directories. These sentinel physicians referred patients to Surveillance nurses at the local site.

Entry criteria were: debilitating fatigue leading to reduced activity and greater effort required to accomplish one's usual activities, plus a six month history of having at least two out of seven listed symptoms (21). Patients who met the entry criteria were invited to participate.

### ***Case Definition***

The 1988 CDC case definition for CFS was more stringent than the entry criteria (15). It required a reduction of daily activity to less than 50% of the premorbid level. The nurse asked about daily activity before and after illness, hours of employment, physical activity (three levels), energy level, social and sexual activity, and sleep patterns. The case definition also required at least eight out of 11 Holmes CFS defining symptoms or at least six symptoms plus two or three listed physical criteria. The nurse inquired about symptoms through a series of questions.

### ***Study Design***

The study design is cross-sectional. The time of onset of psychiatric disorders was assessed through the DIS, a subjective measure of recall subject to recall bias. However the CDC was able to confirm the time of onset of the psychiatric disorder through medical records.

### ***Assignment of Diagnostic Groups***

The CDC's Physician Review Committee classified subjects into four Diagnostic Groups. Everyone enrolled in Surveillance had a fatiguing illness but only Group I met the 1988 CDC criteria for CFS. It included 130 subjects (23.0%). Group II with 99 subjects (17.5%) had insufficient symptoms or fatigue severity (idiopathic). Group III had 101 subjects (17.9%) with a medical condition that might explain their

fatigue (medical exclusionary). Group IV had 235 subjects (41.6%) and were excluded because of prior psychiatric disorders. The classification was based on the 1988 criteria, the Diagnostic Interview Schedule (DIS), and the medical records (21).

### ***Physical Examination***

Trained personnel from the CDC performed limited physical evaluations which included taking the temperature, and evaluating the pharynx and lymph nodes.

### ***The Diagnostic Interview Survey (DIS)***

The goal of the Diagnostic Interview Schedule (DIS) was to make it possible for lay interviewers to make psychiatric diagnoses comparable to those of a psychiatrist. Details of the psychometrics including measures of validity (sensitivity and specificity) and reliability for the DIS may be found in an article by Robins et al. (9).

The CDC assessed subjects for four of the Axis I disorders in the DIS: Major Depressive Disorder (MDD), Generalized Anxiety Disorder, Panic Disorder, and Somatization Disorder (9). They did not report scores for each subject or stipulate the algorithm used to make a psychiatric diagnosis.

### ***Statistical Analyses***

Statistical analyses were conducted using the SAS version 6.08 (SAS Institute, Cary, NC). F-tests were performed on continuous data while Pearson's Chi-square tests were performed for discrete data on the demographic and sociological characteristics and current psychiatric disorders across the groups. Subjects were categorized according to time of onset MDD with respect to the fatiguing illnesses. Mantel-Haenszel Chi-square tests were conducted to test for a positive dose-response effect between psychiatric disorders and 1988 CDC criteria. To look for a

pattern of 1988 CDC criteria that might be associated with psychiatric disorders, odds ratios and confidence intervals were estimated. All statistical tests were two-tailed, and significance was determined at an alpha level of .05.

## **RESULTS**

### ***Subjects and Group Designations***

Some of the demographic and sociological characteristics of the study population are illustrated in Table 1. The mean age was 40 years and the average duration was 6 years. The study population was mostly white (94%) and female (81%). Some 17% had a high school education or less, and 43% attended technical school or had some college education. Of the 40% who completed college, 18% attended graduate school. Group II subjects (idiopathic) had the highest income and were most likely to be living as couples with children. These results are as expected and reflect the milder designation for Group II. Subjects in Group III (medical exclusionary) were older. This result conforms to expectations that number of medical conditions increase as people age.

The 1994 CDC criteria for CFS would have allowed subjects classified as Group IV who had prior MDD without melancholic features to be reclassified as Groups I, II, or III (21). Recently the CDC have further refined their Diagnostic groups (22).

### ***Psychiatric Disorders***

As shown in Table 2, the predominant psychiatric disorder was MDD. It was seen in 50% of the men and 54% of the women. Rates for other disorders were: Generalized Anxiety Disorder: 12% in men and 14% in women, Panic Disorder: 6% in men and 10% in women and Somatization Disorder: 2% in men and 6% in women.

TABLE 1. Demographic and Sociological Characteristics by Group

Characteristics	Gr I (n = 130)	Gr II (n = 99)	Gr III (n = 101)	Gr IV (n = 235)	F	P
Mean age	37.0 yr	38.1 yr	43.4 yr	40.9 yr	8.1	<.001
Duration	6.6 yr	6.2 yr	5.7 yr	5.7 yr	0.5	.7
Gender					$\chi^2$	P
<i>Female</i>	(n = 111) 85%	(n = 77) 78%	(n = 78) 77%	(n = 193) 82%	3.4	.3
<i>Male</i>	(n = 19) 15%	(n = 22) 22%	(n = 23) 23%	(n = 42) 18%		
Education <sup>a</sup>						
0-12	(n = 22) 17%	(n = 14) 14%	(n = 18) 18%	(n = 39) 17%	3.7	.7
13-15	(n = 56) 44%	(n = 40) 41%	(n = 38) 39%	(n = 108) 47%		
$\geq 16$	(n = 50) 39%	(n = 44) 45%	(n = 42) 43%	(n = 82) 36%		
Income <sup>b</sup>						
\$0-20K	(n = 23) 19%	(n = 9) 10%	(n = 12) 13%	(n = 52) 24%	15	.02
\$20-50K	(n = 55) 46%	(n = 48) 51%	(n = 46) 48%	(n = 103) 49%		
>\$50K	(n = 42) 35%	(n = 37) 39%	(n = 37) 39%	(n = 57) 27%		
Living arr. <sup>c</sup>						
1	(n = 39) 31%	(n = 38) 40%	(n = 34) 35%	(n = 73) 32%	31	.008
2	(n = 31) 24%	(n = 25) 26%	(n = 28) 28%	(n = 67) 29%		
3	(n = 8) 6%	(n = 3) 3%	(n = 5) 5%	(n = 15) 6%		
4	(n = 50) 39%	(n = 30) 31%	(n = 31) 32%	(n = 74) 32%		

<sup>a</sup> Frequency missing for education = 12.

<sup>b</sup> Frequency missing for income = 44.

<sup>c</sup> Frequency missing for living arrangements = 14.

Note: 1 = Couples with children; 2 = Couples without children; 3 = Single parent 4 = Living with parents, roommates, relatives, other, or alone.

TABLE 2. Current Psychiatric Disorders by Gender and Group

Men Only												
Current Psychiatric Disorder <sup>a</sup>	Gr I n = 19		Gr II n = 22		Gr III n = 23		Gr IV n = 42		Total n = 106		$\chi^{2,b}$	P
	No	%	No	%	No	%	No	%	No	%		
Any	9	47	12	55	9	39	25	60	55	52	2.7	.4
MDD	9	47	11	50	9	39	24	57	53	50	2.0	.6
Anxiety	1	5	0	0	3	13	9	21	13	12	FE <sup>c</sup>	.05
Panic	0	0	1	5	2	9	3	7	6	6	FE <sup>c</sup>	.8
Somat.	0	0	0	0	0	0	2	5	2	2	FE <sup>c</sup>	.7

  

Women Only												
Current Psychiatric Disorder <sup>a</sup>	Gr I n = 111		Gr II n = 77		Gr III n = 78		Gr IV n = 193		Total n = 459		$\chi^{2,b}$	P
	No	%	No	%	No	%	No	%	No	%		
Any	61	55	34	44	39	50	142	74	276	60	27	<.001
MDD <sup>b</sup>	56	51	32	42	33	42	127	66	248	54	21	<.01
Anxiety	9	8	5	7	5	6	46	24	65	14	26	<.001
Panic	11	10	3	4	10	13	20	10	44	10	4	.3
Somat.	5	5	2	3	3	4	16	9	26	6	FE <sup>c</sup>	.3

<sup>a</sup> Major Depressive Disorder, Anxiety Disorder, Panic Disorder, Somatization Disorder.

<sup>b</sup>  $\chi^2$  tests were 2-tailed.

<sup>c</sup> Fishers Exact.

Note: Rates of Major Depressive Disorder and Anxiety were higher in Group IV women but were similar in women across Groups I-III ( $\chi^2_{MDD} = 1.9$ ,  $p = 0.4$ ; and  $\chi^2_{Anxiety} = 0.3$ ,  $p = 0.9$ ).

In males, the rates of Current MDD were similar by Group ( $\chi^2 = 2.0$ ,  $P = 0.6$ ). In females MDD was higher in Group IV ( $\chi^2 = 21$ ,  $P = 0.01$ ). These results may be attributed to the presence of prior MDD in Group IV which could inflate the risk for current. MDD was not elevated in Group I. This observation suggests that MDD may not be a unique feature of CFS.

### *Time of Onset of MDD in the Fatiguing Illnesses*

To advance our understanding of associations between various events the groups were combined for the remainder of the analyses. Subjects were partitioned into mutually exclusive possibilities according to time of onset of MDD (Table 3). They were: (a) Never (no prior or current MDD), (b) Resolved (MDD prior only), (c) Acquired (MDD current only) and (d) Preexisting (both prior and current MDD). It should be noted that only subjects designated as Acquired or Preexisting had current MDD. The distribution was as follows: (a) Never 38.9%, (b) Resolved 7.8%, (c) Acquired 35.4%, and (d) Preexisting 17.9%. Current MDD was diagnosed in 301 (53%) of the subjects. Of those, 200 (35%) were acquired and 101 (18%) were preexisting. Of the 264 (47%) without current MDD, 220 (39% of the total group and 83% of those without current MDD) never had it and in 44 (8% of the total group and 17% of those without current MDD) it had resolved.

### *Psychiatric Disorders and 1988 CDC Criteria*

To assess for a positive dose response effect in subjects with psychiatric disorders, i.e., whether subjects with psychiatric disorder reported more 1988 CDC criteria, Mantel-Haenszel Chi-Square tests were performed. There was no association seen with any prior psychiatric disorder (results not shown). In contrast, the results for current psychiatric disorders (shown in Table 4) were as follows:  $\chi^2_{\text{MDD}} = 4.1$ ;  $P = 0.04$ ;  $\chi^2_{\text{Anxiety Disorder}} = .7$ ;  $P = 0.4$ ;  $\chi^2_{\text{Panic Disorder}} = 0.9$ ;  $P = .3$ ;  $\chi^2_{\text{Somatization Disorder}} = 4.5$ ;  $P = 0.03$ . The data show positive dose response effects for current MDD and Somatization.

To determine which if any psychiatric disorders are associated with particular 1988 CDC criteria, odds ratios and confidence Intervals were calculated. With respect to prior psychiatric disorders, all confidence intervals traversed zero indicating that no associations were found (data

TABLE 3. Major Depressive Disorders by Time of Onset in the Fatiguing Illnesses

Prior MDD	Current MDD		Total
	No	Yes	
No	a (n = 220) 38.9% Never	c (n = 200) 35.4% Acquired	(n = 420) 74.3%
Yes	b (n = 44) 7.8% Resolved	d (n = 101) 17.9% Preexisting	(n = 145) 25.7%
Total	(n = 264) 46.7%	(n = 301) 53.3%	(n = 565) 100.0%

a. Never (220/565) 38.9%.

b. Resolved-Onset and termination prior to a fatiguing illness.

c. Acquired-Onset concurrent with a fatiguing illness.

d. Preexisting-Onset prior to a fatiguing illness and continuing.

TABLE 4. Positive Dose Response Effects: 1988 CDC Criteria in Current Psychiatric Disorders in the Fatiguing Illnesses

Current Psychiatric Disorder	Mantel-Haenszel Chi-Square	P-value
MDD	4.064	<b>0.04*</b>
Anxiety	0.758	0.4
Panic Disorder	0.985	0.3
Somatization Disorder	4.532	<b>0.03*</b>
Any of the Above	6.320	<b>0.01*</b>

\*Associations were seen for Current MDD and Current Somatization disorder.

not shown). Table 5 reflects data on current psychiatric disorders. Only current MDD was associated with the 1988 CDC criteria and the associations were for three criteria. They were headache OR = 1.4 (CI = 1.0-1.9), neurobehavioral OR = 3.4 (CI = 1.6-7.6); and sleep disturbance OR = 1.7 (CI = 1.1-2.6).

TABLE 5. Odds Ratios and Confidence Intervals: 1988 CDC Criteria in Current Psychiatric Disorders in the Fatiguing Illnesses

REPORTED SYMPTOM <sup>c</sup>	% <sup>b</sup>	PSYCHIATRIC DISORDERS <sup>a</sup>				
		MDD	Anx.	Panic	Somat.	Any
		OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Weakness	74	1.2 0.8-1.8	1.4 0.8-2.5	1.6 0.8-3.5	2.1 0.7-6.2	1.4 0.9-2.0
Head Ache	59	1.4 1.0-2.0	0.7 0.4-1.2	1.6 0.9-3.1	3.3 1.3-8.5	1.3 0.9-1.9
Joint Pain	84	0.9 0.6-1.9	1.2 0.7-2.0	0.9 0.5-1.6	1.7 0.7-4.1	1.0 0.7-1.4
Neuro-Behav	95	3.5 1.6-7.6	2.4 0.5-9.8	0.9 0.2-3.0	1.5 0.2-11	4.4 2.0-9.4
Sleep Disturb	82	1.7 1.1-2.7	1.4 0.7-2.8	1.6 0.7-4.0	1.9 0.5-6.4	2.0 1.3-3.1
Fever	71	1.2 0.8-1.7	0.9 0.5-1.6	1.3 0.6-2.6	1.9 0.7-5.1	1.3 0.9-1.9
Sore Throat	69	1.1 0.7-1.5	0.8 0.5-1.4	1.1 0.6-2.1	1.6 0.6-4.1	1.1 0.8-1.6
Lymph Nodes	83	1.3 0.9-1.9	0.8 0.5-1.4	1.1 0.6-2.1	1.2 0.5-2.8	1.3 0.9-1.9
Muscle Ache	78	1.1 0.7-1.7	1.6 0.8-3.2	1.1 0.5-2.3	1.7 0.6-5.1	1.3 0.8-1.9
Exert Fatigue	84	1.1 0.8-1.6	1.0 0.6-1.6	1.3 0.7-2.5	1.7 0.7-4.1	1.2 0.8-1.7
Sudden Onset	32	1.0 0.7-1.4	1.6 0.9-2.9	1.0 0.5-1.8	1.1 0.5-2.7	0.9 0.6-1.3

<sup>a</sup> Major Depressive Disorder, Anxiety, Panic, Somatization, Any of the four disorders.

<sup>b</sup> Percent reporting.

<sup>c</sup> Three physical criteria (nurse-recorded fever, sore throat, and lymph nodes) had low percentages reporting and had non-significant results. They were omitted.

## DISCUSSION

While high rates of psychiatric disorders were seen in the present study, the effect was largely seen for one disorder, namely MDD. This finding is consistent with the literature where for the most part MDD was the predominant disorder. The test instrument used in the present

study to assess psychiatric disorders was the DIS, while the reviewed studies used the Structured Clinical Interview for DSM-III-R (SCID). Despite the different test instruments, rates of MDD in the present study were comparable to two reviewed studies (10,11). Lower rates found in the other two studies may be explained by a possibility of selection bias. Krupp (12) excluded subjects with high scores on the Center for Epidemiological Studies Depression Scale (23) and Pepper (13) lost subjects referred to psychiatry. Taylor and Jason (24) favor the SCID, however further work is needed to determine which may be the better test instrument.

In this study, 46.7% were not currently depressed and 38.9% were never depressed. The fact that MDD had resolved in the remaining 7.8% also suggests that MDD is an unlikely risk factor for the fatiguing illnesses. Hickie et al. (25) reported that the prevalence of premorbid psychiatric disorders in CFS was similar to that of a normal population estimate (ECA) which further dampens prevailing views on the role of prior MDD in these disorders. A low proportion of Somatization Disorder (4.9%) brings to mind that the traditional neurasthenia hypothesis may also not be a predominant cofactor in the fatiguing illnesses.

In an effort to further delineate psychiatric disorders, we investigated whether subjects with psychiatric disorders reported more 1988 criteria. A dose-response effect was not seen in subjects with prior psychiatric disorders. A positive dose-response was seen in subjects with current MDD and Somatization. However, when using the same data (2) and stratifying subjects by age, education, and gender these differences ceased to exist.

We investigated whether psychiatric disorders were associated with individual 1988 CDC criteria. There was no association for prior psychiatric disorders whatsoever. Subjects with only current MDD preferentially endorsed two 1988 CDC criteria: sleep disturbance and cognitive complaints (neurobehavioral). A body of research confirms associations of MDD with sleep disturbance and polysomnographic abnormalities (27). With respect to cognitive complaints the present data set assessed for forgetfulness, confusion, difficulty thinking, and difficulty with concentration. Wearden and Appleby (28) noted that reports

of general cognitive functioning were associated with mood in CFS patients. Noting a disparity between cognitive complaints and test performance they suggested that cognitive complaints be distinguished from cognitive difficulty. The literature supports our findings that sleep disorders and cognitive complaints correlate with psychiatric disorders.

The frequency of psychiatric disorders in the present study was similar in CFS and non-CFS subjects. These results raise concerns regarding the 1988 CFS criteria and suggest that *a priori* sub typing of persons be abandoned in favor of empirically-driven phenotypes that partition the apparent heterogeneity more testable and meaningful subgroups using variables external to the subtype classification for validation.

A second candidate variable in this context would involve neurocognitive functioning. A comprehensive study of CFS patients (29) found associations between poor neurocognitive functioning and immune system abnormalities which persisted after controlling for depression. The authors concluded that cognitive impairment in CFS patients could not solely be explained by depression. Results from a recent unpublished dissertation study (20) found a cognitive disorder phenotype with a pattern of psychomotor speed and executive impairment similar to that seen in immunocompromized HIV patients (30). The dissociation between depression and cognitive performance (but not cognitive complaints) has been reported in other CFS studies and in HIV studies (25,30,32,33).

The information gained in this study may be useful to future researchers to reduce heterogeneity. For example, the MDD subtypes shown in Table 2 represent a classification system that might provide insights into etiology and treatment. Two clinical phenotypes offer a potentially useful approach in the search for a neurobiological mechanism or substrate-namely: (a) those patients who never had major depression, and (d) those with preexisting depression. The former is hypothesized to represent a more homogenous neurobiological type, unconfounded by psychiatric factors. The latter might be a predominantly psychiatric or neurasthenic group consistent with the traditional views.

But what about those with an onset of depression acquired after the fatiguing illness (c) some of whose members, as in subgroup (a), have been shown to have cognitive impairment? It would be imprudent to dismiss a separate underlying neurobiological substrate in this group despite the presence of current major depression. In this case treatment strategies would have to consider both neurological and psychiatric disorders. Because these hypotheses go beyond the scope of the present data they should be viewed as speculative at this time.

This study has some limitations. It originated in primary care settings (7) which are subject to more referral bias than studies that describe CFS in the community. It lacked normal internal control subjects. It also used prevalence measures which are not as useful as incidence measures (34). More recent CDC studies incorporate incidence measures (35). The CDC did not make available raw DIS scores or the algorithm used to make a psychiatric diagnoses. The present study could not analyze the individual responses in the DIS used to establish the psychiatric diagnoses.

This study benefited from having a richness of data and a large sample size, although in males the Diagnostic Groups were sometimes rather small. The first classification used compared subjects according to the Diagnostic Groups. The subjects were later stratified differently to characterize the times of onset of MDD and test for quantitative and qualitative associations between MDD and 1988 CDC criteria. These stratifications may be useful to guide future studies and disentangle some of the ambiguity associated with current views of CFS.

## REFERENCES

1. Jason LA, Richman JA, Friedberg F, Wagner L, Taylor R, Jordan KM. Politics science and the emergence of a new disease: The case of chronic fatigue syndrome. *Am Psychol* 1997;52:973-983.
2. Suhadolnik RJ, Reichenbach NL, Hitzges P, et al. Upregulation of the 2-5A synthetase/RNase L antiviral pathway associated with chronic fatigue syndrome. *Clin Infect Dis* 1994;18 Suppl 1:S96-S104.

3. De Meirleir K, Bisbal C, Campine I, et al. A 37kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med* 2000; 108:99-105.
4. De Meirleir K, De Becker P, Nijs J, et al. CFS etiology, the immune system, and infection. In: Englebienne P, De Merlier, editors. *Chronic fatigue syndrome: A biological approach*. City: CRC Press; 2002. pp. 201-228.
5. Englebienne P, Verhas M, Herst CV, De Meirleir K. Type I interferons induce proteins susceptible to act as thyroid receptor (TR) corepressors and to signal the TR for destruction by the proteasome: Possible etiology for unexplained chronic fatigue. *Med Hypotheses* 2003;60:175-180.
6. Damasio, AR. *Descartes' error: Emotion, reason, and the human brain*. New York: Avon, Lippencott-Raven; 1994.
7. Ray C. Chronic fatigue syndrome and depression: Conceptual and methodological ambiguities. *Psychol Med* 1991;21:1-9.
8. Van Hoof E, Cluydts R, De Meirleir. Atypical depression as a secondary symptoms in chronic fatigue syndrome. *Med Hypotheses* 2003;61:52-55.
9. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: Its history, characteristics and validity. *Arch Gen Psychiatry* 1981;38:381-389.
10. Fischler B, Cluydts R, De Gucht V, Kaufman L, De Meirleir K. Generalized anxiety disorder in chronic fatigue syndrome. *Acta Psychiatr Scand* 1997;95:405-413.
11. Hickie I, Lloyd A, Wakefield D, Parker G. The psychiatric status of patients with chronic fatigue syndrome. *Br J Psychiatry* 1990;156:534-540.
12. Krupp LB, Sliwinski, M, Masur DM, Friedberg F, Coyle PK. Cognitive functioning and depression in patients with chronic fatigue syndrome and multiple sclerosis. *Arch Neurol* 1994;51:705-710.
13. Pepper C, Krupp LB, Doscher C, Coyle PK. A comparison of neuropsychiatric characteristics in chronic fatigue syndrome, multiple sclerosis and major depression. *J Neuropsychiatry Clin Neurosci* 1993;5:200-205.
14. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953-959.
15. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: A working case definition. *Ann Intern Med* 1988;108:387-389.
16. Lloyd AR, Wakefield D, Boughton C, Dwyer J. What is myalgic encephalomyelitis? *Lancet* 1988;1:1286-1287.
17. Sharpe MC, Archard LC, Banatvala JE, et al. A report-chronic fatigue syndrome: Guidelines for research. *J Roy Soc Med* 1991;84:118-121.
18. Bates DW, Buchwald D, Lee J, et al. A comparison of case definitions of chronic fatigue syndrome. *Clin Infect Dis* 1994;18 Suppl 1:S11-S15.
19. De Becker P, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. *J Intern Med* 2001;250:234-240.

20. Axe ERK. Neuropsychological and psychiatric correlates in chronic fatigue syndrome [dissertation]. Los Angeles (CA): UCLA; 1999.
21. Reyes M, Gary HE, Dobbins JG, et al. Surveillance for chronic fatigue syndrome—four U.S. cities, September 1989 through August 1993. *MMWR CDC Surveill Summ* 1997;46:3-14.
22. Solomon L, Nisenbaum R, Reyes M, Papinicolaou DA, Reeves WC. Functional status of persons with chronic fatigue syndrome in the Wichita, Kansas population. *Health Qual of Life Outcomes* 2003;1:48-51.
23. Radloff LS, Locke BZ. The community mental health assessment survey and the CES-D scale. In: Weissman MM, Meyers JK, editors. *Community survey of psychiatric disorders*. New Brunswick: University Press; 1986. pp. 177-187.
24. Taylor RR, Jason LA. Comparing the DIS with the SCID: CFS and psychiatric comorbidity. *Psychol Health* 1998;13:1087-1104.
25. Harker JO, Satz P, D'Elia L, Miller EN, Jin S. Measurement of depression and neuropsychological impairment in HIV-1 infection. *Neuropsychology* 1995;9:10-17.
26. Axe E, Satz P. Depressive comorbidity in the fatiguing illnesses. *J Chronic Fatigue Syndr* 2001;8:23-29.
27. Emslie GJ, Rush AJ, Weinberg WA, Rintelmann JJ, Roffwarg HP. Sleep EEG features of adolescents with major depression. *Biol Psychiatry* 1994; 36:573-581.
28. Wearden A, Appleby L. Cognitive performance and complaints of cognitive impairment in chronic fatigue syndrome (CFS). *Psychol Med* 1997;27:81-90.
29. Lutgendorf S, Klimas NG, Antoni M, Brickman A, Fletcher MA. Relationships of cognitive difficulties to immune measures, depression and illness burden in chronic fatigue syndrome. *J Chronic Fatigue Syndr* 1995;1:23-41.
30. DeLuca J, Johnson SK, Ellis SP, Natelson BH. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. *J Neurol Neurosurg Psychiatry* 1997;62:151-155.
31. Miller EN, Satz P, Visscher B. Computerized and conventional neuropsychological assessment of HIV-1 infected homosexual men. *Neurology* 1991;41: 1608-1616.
32. Drebbling CE, Van Gorp WG, Hinkin C et al. Confounding factors in the measurement of depression in HIV-1. *J Personality Assess* 1994; 62:68-83. impairment in HIV-1 infection. *Neuropsychology* 1995;9:10-17.
33. Vercoulen JHMM, Bazelmans E, Swanink CMA, et al. Evaluating neuropsychological impairment in chronic fatigue syndrome. *J Clin Exp Neuropsychol* 1998;20:144-156.
34. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippencott-Raven; 1998.
35. Reyes M, Nisenbaum R, Hoaglin DC, et al. Prevalence and incidence of 5 chronic fatigue syndrome in Wichita, Kansas. *Arch Int Med* 2003;163:1530-1535.