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# Chronic fatigue syndrome is associated with metabolic syndrome: results from a case-control study in Georgia

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**Abstract**

We hypothesized that persons with chronic fatigue syndrome (CFS) would have a higher prevalence of metabolic syndrome compared with well controls, and that unwell persons with insufficient symptoms or fatigue for CFS (termed *ISF*) would have a prevalence of metabolic syndrome intermediate between those with CFS and the controls. We also sought to examine the relationship between metabolic syndrome and measures of functional impairment, fatigue, and other symptoms. Our analysis was based on a population-based case-control study conducted in metropolitan, urban, and rural areas of Georgia, United States, between September 2004 and July 2005. There were 111 persons with CFS, 259 with ISF, and 123 controls. Metabolic syndrome was determined based on having at least 3 of 5 standard risk components (abdominal obesity, high triglycerides, high blood pressure, elevated fasting glucose, and decreased high-density lipids) according to the National Cholesterol Education Program Adult Treatment Panel III definition. Persons with CFS were 2-fold as likely to have metabolic syndrome (odds ratio = 2.12, confidence interval = 1.06, 4.23) compared with the controls. There was a significant graded relationship between the number of metabolic syndrome factors and CFS; each additional factor was associated with a 37% increase in likelihood of having CFS. The association of ISF with metabolic syndrome was weaker (odds ratio = 1.72, confidence interval = 0.94-3.16). Among persons with CFS, the number of metabolic syndrome factors was significantly correlated with worse fatigue on a standardized summary measure of fatigue ($r = 0.20$, $P = .04$). In conclusion, CFS was associated with metabolic syndrome, which further exacerbated fatigue.
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## 1. Introduction

Chronic fatigue syndrome (CFS) presents unique challenges for those who have the illness, for health care providers responsible for their evaluation and management, and for public health authorities. Many of the challenges reflect the lack of knowledge concerning the pathophysiology of CFS, the absence of characteristic clinical signs or diagnostic laboratory abnormalities in persons with CFS, and the uncertainty concerning treatment and the clinical course of the illness.

Because there are no characteristic clinical or laboratory markers, diagnosis of CFS is based on self-reported symptoms and exclusion of medical and psychiatric diseases with a similar clinical picture [1,2]. Around half the individuals in research studies who meet symptom criteria for CFS are determined to have a previously undiagnosed medical or psychiatric condition upon clinical evaluation, which likely explains their symptoms [3-6]. The most common explanatory medical conditions are thyroid disease, diabetes, and cardiovascular diseases. It is important to determine if persons with CFS are at increased risk for developing such diseases.

Although the etiology of CFS remains unknown, an increasing body of evidence supports the hypothesis that alterations of the hypothalamic-pituitary-adrenal (HPA) axis response to stress play a central role [7,8]. The HPA axis regulates endocrine and autonomic nervous system function and various immune pathways, and is central to the construct of allostatic load, a physiologic measure of the cumulative

This study adhered to human experimental guidelines of US Department of Health and Human Services and the Helsinki Declaration. The Centers for Disease Control and Prevention Human Subjects committee approved the study protocol, and all subjects gave informed consent.

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wear and tear on the body due to repeated cycles of attempts to adapt to change [9]. Allostatic load is determined based on measurements of primary mediators (cortisol, noradrenalin, epinephrine, dehydroepiandrosterone) and secondary outcomes, or physiologic effects of dysregulated primary mediators (blood pressure, waist to hip ratio, high-density lipids, total cholesterol, and glucose) [10]. In 2 population-based case-control studies, we found that persons with CFS are more than 2-fold as likely as healthy controls to have a high level of allostatic load; and the odds of having CFS increased with increasing levels of allostatic load in a significant dose-response relationship [11,12]. Increased allostatic load is a risk factor for cardiovascular disease; metabolic components of allostatic load largely account for this association [13,14]. Metabolic syndrome is a cluster of dyslipidemia, hypertension, glucose intolerance, and visceral fat accumulation and is associated with increased risks of maturity-onset diabetes, cardiovascular disease morbidity and mortality, and Alzheimer disease [15-20].

In the current study, we sought to measure metabolic syndrome status and describe the association of metabolic syndrome with CFS and with a less severe condition—unexplained unwellness with insufficient symptoms or fatigue to be considered CFS—termed *ISF*. We also sought to assess the relationships between metabolic syndrome and general health, functional impairment, fatigue severity, and overall symptom frequency/intensity. Persons with CFS and with ISF and well controls were identified in a study of defined metropolitan, urban, and rural populations of Georgia.

## 2. Subjects and methods

### 2.1. Study design

Between September 2004 and July 2005, we conducted a cross-sectional population-based case-control study in metropolitan, urban, and rural Georgia populations by using random-digit dialing to identify persons with CFS, unwell persons, and controls. *Unwell* household members included those with at least one of the common CFS defining symptoms (fatigue, cognitive impairment, unrefreshing sleep, muscle or joint pain) for at least 1 month, and *control* residents included those who had none of these symptoms for at least 1 month. Sampling methodology and subjects are described in detail elsewhere [21]. Briefly, we conducted a screening interview with a household informant aged at least 18 years to elicit demographic and health status of household members between the ages of 18 and 59 years. We then conducted detailed telephone interviews with adults identified as *unwell with fatigue*, randomly selected adults who were *unwell but without fatigue*, and a random sample of *control* household residents. Eight thousand eight hundred sixty-two subjects were selected for detailed interviews, and 5630 (75%) participated. Seven respondents were outside age criteria, and 1609 reported exclusionary medical or psychiatric conditions. The remaining 4014 were classified as having *CFS-like illness* (n = 469) if, on interview, they met 1994 CFS case definition criteria [1] but lacked medical, psychiatric, and laboratory evaluations to diagnose exclusionary conditions; as being *chronically unwell* (n = 1763) if they reported symptoms of unwellness for at least 6 months; or as being *well* (n = 1782) if they had no domain symptoms for more than 1 month. All those classified as CFS-like were invited to a 1-day clinical evaluation, and 292 (62%) participated. Five hundred five randomly selected chronically unwell subjects were invited to the clinic, and 268 (53%) participated. Finally, 223 controls who were frequency matched to the CFS-like subjects on age (±3 years), sex, race/ethnicity, and geographic strata attended the clinic.

### 2.2. Classification of subjects

Of the 783 subjects who completed the clinical examination, 280 (36%) had medical or psychiatric conditions considered exclusionary for CFS [1,2]; and 2 were missing data. The remaining 501 subjects were further classified for analysis. We diagnosed CFS according to the criteria of the 1994 research case definition [1]. To apply the 1994 criteria, we followed the recommendations of the International CFS Study Group [2] and evaluated functional impairment with the Medical Outcomes Survey Short Form–36 (SF-36) [22], fatigue with the Multidimensional Fatigue Inventory (MFI) [23], and occurrence and severity of the 8 CFS-defining symptoms by using the Centers for Disease Control and Prevention (CDC) CFS-specific Symptom Inventory (SI) [24]. We applied a classification algorithm based on subscale cutoffs per CDC recommendations [25] and classified 113 subjects with CFS, 264 with ISF, and 124 as well.

### 2.3. Clinical and laboratory data

Demographic information was obtained in a telephone interview and confirmed at the clinic visit. Physical functioning, general health, fatigue, and other symptoms were measured during the clinic visit based on subjects' responses to standardized questionnaires (SF-36, MFI, CDC SI).

A licensed nurse measured blood pressure at clinic after participants had rested recumbent for 30 minutes. Height, weight, waist, and hip circumference were measured in a standing position. Waist circumference was measured at the narrowest point between the iliac crest and the umbilicus. Hip circumference was measured at the maximum buttocks. Body mass index (BMI) was computed based on the ratio of the weight in kilograms to height in meters squared.

### 2.4. Laboratory data

All subjects had blood drawn by a research nurse at approximately 8:30 AM after fasting since midnight. Total cholesterol, high-density lipids, triglycerides, glucose, and insulin were measured using standard laboratory tests.

Insulin resistance was determined using the homeostasis model assessment algorithm (serum insulin [micro–international units per milliliter] × (fasting glucose [millimoles per liter]/22.5) and based on a cutoff of the 75th percentile for well controls [26].

### 2.5. Metabolic syndrome

We identified metabolic syndrome by using the 5 standard components (abdominal obesity, high level of triglycerides, low level of high-density lipids, high blood pressure, and high level of fasting glucose). We considered metabolic syndrome to be present if a subject's measurements for at least 3 factors were greater than or less than the risk cutoffs as defined by the revised Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel) definition [27]. Taking medication to lower lipids, blood pressure, or glucose also attributed 1 point each toward a subject's risk factor total, respectively (Table 2) [27].

### 2.6. Statistical methods

Throughout our analysis, we compared the 2 groups of ill participants (CFS and ISF) to the same control group. We used the Wilcoxon rank sum test to compare mean ages by case-control status and a $\chi^2$ or Fisher exact test to compare categorical demographic and metabolic factors by case-control status. Wilcoxon rank sum test was used to compare mean number of metabolic syndrome components present between cases and controls. Statistical significance for these tests was determined at $\alpha < .05$ level, and all tests were 2-tailed. Logistic regression analysis was used to generate odds ratios (ORs) as measures of the association of metabolic syndrome with CFS and ISF relative to the control. All matching factors were included as covariates in models predicting CFS (age [continuous values], sex, race, geographic stratum) because matching of CFS-like to controls in the source study was broken because of reclassification, precluding use of a matched analysis. For models predicting ISF, only age and sex were included as covariates. In addition, education (8 categories) and BMI (continuous) were examined as potential confounders. Model fit was assessed using the Hosmer-Lemeshow (HL) goodness of fit test; $P$ values >.05 were indicative of a good model fit.

We assessed the correlation of number of metabolic syndrome factors with continuous summary measures of physical and mental functioning (SF-36 physical and mental component scores), fatigue (total MFI summary score), symptom score (CDC SI score for CFS and non-CFS symptoms), and self-reported duration of fatigue among the CFS group using Spearman partial correlations, adjusting for age, sex, and BMI.

Age-standardized prevalence rates of metabolic syndrome were computed using the 2000 US Census population as the standard population. Ten-year age group proportions were derived from the standard population and multiplied by our crude prevalence estimates for each age group to obtain products that were summed to produce age-standardized rates per 100. EMM conducted all analyses using SAS version 9.0 (SAS Institute, Cary, NC).

## 3. Results

Eight (0.1%) of the 501 participants lacked complete clinical and laboratory data for all metabolic factors and were excluded from the analysis. Our analysis is based on 493 persons, including 123 controls, 111 persons with CFS, and 259 persons with ISF. Fourteen subjects had previously been diagnosed with type 2 diabetes mellitus or were taking diabetic medications at therapeutic levels (4 controls, 8 ISF, 2 CFS).

Our study sample comprised mostly middle-aged white women, and the largest proportion lived in rural areas (Table 1). Control, ISF, and CFS groups were demographically similar except for education level. Lower proportions of the CFS group completed post–high school education levels compared with the control ($P = .05$). In addition, both the CFS ($P = .06$) and ISF ($P = .005$) groups had a greater proportion of subjects in the overweight and obese categories of BMI compared with the control.

Metabolic syndrome was determined based on standardized criteria presented in Table 2. All study groups had a range of 0 to 5 metabolic factors that fell in the risk level for metabolic syndrome. Persons with CFS had an average of 2.12 (±1.45) metabolic factors in the high-risk range, which was significantly higher than an average of 1.59 (±1.14) among the control ($P = .006$). The ISF group also had a higher mean number of metabolic factors with values in the risk category (1.88 ± 1.41) compared with the control, although this difference was not significant ($P = .11$).

The prevalence of metabolic syndrome in the entire study sample was 31.0%; it was lowest among the controls (21.1%), intermediate among the ISF group (32.4%), and highest among the CFS group (38.7%). These prevalence rates were slightly higher than the age-standardized rates per hundred persons that were computed based on the age distribution of the US population: 15.8 for the controls, 25.4 for the ISF group, and 31.4 per hundred for the CFS group. The difference between our study prevalence rates and the age-standardized rates likely reflects the larger proportion (70%) of persons between the ages of 40 and 59 years in our study sample compared with the general US population (45%).

Persons with CFS were 2-fold as likely as controls to have metabolic syndrome, after adjusting for matching factors ($OR_{adjusted} = 2.65$, confidence interval [CI] = 1.43-4.81) (HL goodness of fit test $P$ value = .51). Additional adjustment for education did not appreciably alter the OR for the relationship between CFS and metabolic syndrome (OR = 2.62, CI = 1.40-4.91). Further adjustment for BMI

Table 1
Distribution of demographic and risk factors among subgroups of persons with CFS, persons with ISF, and healthy persons in Georgia

| Factors | Control (n = 123) | ISF (n = 259) | CFS (n = 111) | *P* value |
|---|---|---|---|---|
| Age (y) | | | | |
| Mean ± SD | 44.6 ± 10.5 | 43.1 ± 10.4 | 44.5 ± 10.0 | *P* = .80[a] |
| Range | (19-59) | (18-59) | (18-59) | *P* = .15[b] |
| Sex (n [%]) | | | | |
| Female | 93 (75.6) | 196 (75.7) | 90 (81.1) | *P* = .31[a] |
| Male | 30 (24.9) | 63 (24.3) | 21 (18.9) | *P* = .98[b] |
| Race (n [%]) | | | | |
| White | 94 (76.4) | 193 (74.5) | 83 (74.8) | *P* = .52[a] |
| Black | 28 (22.8) | 53 (20.5) | 20 (18.0) | *P* = .76[b] |
| Other[c] | 1 (0.8) | 13 (5.0) | 8 (7.3) | |
| Geographic stratum (n [%]) | | | | |
| Metropolitan | 22 (17.9) | 52 (20.1) | 22 (19.8) | *P* = .92[a] |
| Urban | 42 (34.1) | 89 (31.7) | 36 (32.4) | *P* = .83[b] |
| Rural | 59 (47.9) | 125 (48.3) | 51 (47.7) | |
| Education | | | | |
| Grades 1-8 | 0 | 3 (1.2) | 1 (0.9) | *P* = .05[a] |
| Some high school | 2 (1.6) | 7 (2.7) | 4 (3.6) | *P* = .14[b] |
| High school graduate | 12 (9.8) | 44 (17.0) | 27 (24.3) | |
| Trade/technical/ vocational | 11 (8.9) | 33 (12.8) | 9 (8.1) | |
| Some college | 25 (20.3) | 52 (20.2) | 24 (21.6) | |
| 2 y of college | 11 (8.9) | 18 (7.0) | 10 (9.0) | |
| 4 y of college | 27 (21.9) | 57 (22.1) | 19 (17.1) | |
| Postgraduate | 32 (26.0) | 41 (15.9) | 17 (15.3) | |
| Indeterminate[d] | 3 (2.4) | 3 (1.2) | 0 | |
| BMI (n [%]) | | | | |
| <25.0 | 58 (47.1) | 78 (30.1) | 35 (31.8) | *P* = .06[a] |
| 25.0-29.9 | 34 (27.6) | 94 (36.3) | 40 (36.4) | *P* = .005[b] |
| ≥30.0 | 31 (25.2) | 87 (33.6) | 35 (31.8) | |

[a] *P* values for comparison of CFS and control.
[b] *P* values for comparison of ISF and control.
[c] Other race was not included in statistical comparison.
[d] Indeterminate education was not included in statistical comparison.

reduced the strength of the association between CFS and metabolic syndrome, but it remained statistically significant ($OR_{adjusted}$ = 2.12, CI = 1.06-4.24) (HL *P* value = .68). There was a graded relationship between CFS and metabolic syndrome; each additional metabolic risk factor was associated with a significant 37% increased likelihood of having CFS (OR = 1.37, CI = 1.06-1.79), after adjusting for age, sex, race, geographic stratum, and BMI (HL *P* value = .75).

Similarly, persons with ISF were twice as likely as controls to have metabolic syndrome, after adjusting for age and sex ($OR_{adjusted}$ = 2.19, CI = 1.27-3.77) (HL *P* value = .15). Additional adjustment for education altered that OR only slightly (OR = 2.13, CI = 1.23-3.70) (HL *P* = .63). Further adjustment for BMI reduced the OR for the association of ISF and metabolic syndrome, and eliminated its statistical significance ($OR_{adjusted}$ = 1.72, CI = 0.94-3.16) (HL *P* value = .61). Each additional metabolic risk factor was associated with a 13% increased likelihood of having ISF (OR = 1.13, CI = 0.91-1.40) (HL *P* value = .53).

We examined the prevalence of the 5 components comprising the metabolic syndrome in the separate study groups (Fig. 1). All metabolic syndrome components were least prevalent in the control, intermediate in the ISF group, and most prevalent in the CFS group; and these trends were significant for high waist circumference ($P_{trend}$ = .04), high triglycerides ($P_{trend}$ = .004), and high glucose ($P_{trend}$ = .03). The prevalence of insulin resistance was lowest (25.0%) in the control, intermediate (37.8%) in the ISF group, and highest (42.7%) in persons with CFS (*P* = .01, *P* trend = .005). High waist circumference, high triglycerides, high glucose, and insulin resistance were significantly more common in persons with CFS than the controls (*P* = .03, *P* = .004, *P* = .04, and *P* = .005, respectively). The ISF group had significantly higher prevalence rates of high glucose (*P* =

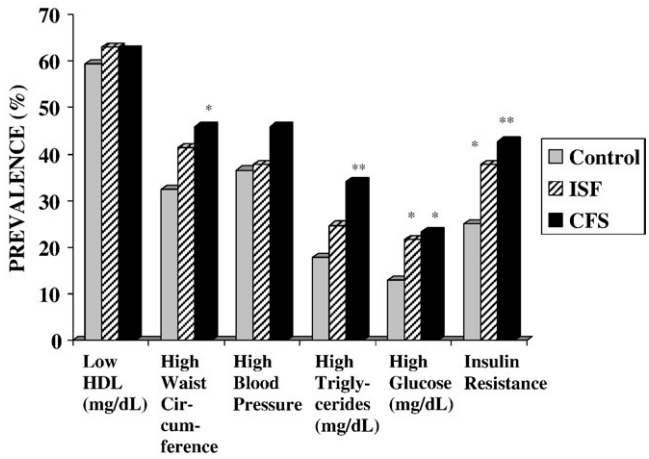


Fig. 1. Distribution of prevalence of metabolic syndrome components and insulin resistance by study group. Gray bars represent controls, striped bars represent the ISF group, and black bars represent the CFS group. *P* values represent statistically significant differences in metabolic syndrome components or insulin between the CFS or the ISF group relative to the control: **P* value < .05, ***P* value < .01, and ****P* value < .001. Compared with the control, the CFS group had significantly higher prevalence rates of high waist circumference (*P* = .03), high triglycerides (*P* = .004), high glucose (*P* = .04), and insulin resistance (*P* = .005). The ISF group had significantly higher prevalence rates of high glucose (*P* = .04) and insulin resistance (*P* = .02) compared with the control.

Table 2
Metabolic syndrome components and their respective risk levels

| Components | Risk levels |
|---|---|
| Abdominal obesity | |
| Men | Waist >102 cm (>40 in) |
| Women | Waist >88 cm (>35 in) |
| Triglycerides | ≥150 mg/dL or on lipid-lowering medication |
| High-density lipids | |
| Men | <40 mg/dL |
| Women | <50 mg/dL |
| Blood pressure | ≥130/≥85 mm Hg or on blood pressure medication |
| Fasting glucose | ≥100 mg/dL (5.6 mmol/L) or on glucose-lowering medication |

.04) and insulin resistance ($P$ = .02) compared with the control. Neither the CFS nor the ISF group differed significantly from the control with respect to the prevalence of low high-density lipids or high blood pressure. In addition, the ISF group did not differ significantly from the control with respect to the prevalences of high waist circumference and high triglycerides.

We examined the association between the number of metabolic syndrome factors present in a subject and summary scores for fatigue (total MFI summary score), impaired physical and mental functioning (physical component summary score, mental component summary score), and symptom scores (CDC SI) in the CFS group. The number of metabolic syndrome factors was linearly correlated with the fatigue summary score, indicating that increasing metabolic factors was weakly linearly associated with worse overall fatigue ($r$ = 0.20, $P$ = .04), after adjusting for age, sex, and BMI. The number of metabolic factors was not significantly linearly correlated with physical ($P$ = .21) or mental functioning ($P$ = .15) as measured by summary scores, or with the CFS-specific symptom score ($P$ = .93) or non-CFS symptom score ($P$ = .97).

Ninety-nine persons with CFS had information on self-reported duration of fatigue. The average duration of fatigue among the CFS group was 7.6 years (range, 0.04-49.6 years). Duration of fatigue was not linearly correlated with number of metabolic syndrome factors in this group ($r$ = 0.04, $P$ = .69).

## 4. Discussion

We examined the relationship between CFS and metabolic syndrome in a study of clinically confirmed CFS cases and controls ascertained from defined metropolitan, urban, and rural populations in Georgia. Compared with controls, persons with CFS were twice as likely to have metabolic syndrome after adjusting for BMI; waist circumference, triglycerides, and glucose were the metabolic syndrome factors that accounted for this difference. We found a similar relationship when comparing persons with ISF to the same control group; however, the strength of that association was weaker and became statistically nonsignificant after adjusting for BMI. The overall prevalence of metabolic syndrome in our study (31%) was similar to the total reported prevalence for the US general population of nonpregnant adults (34.5%) measured by the National Cholesterol Education Program Adult Treatment Panel III definition in 1999-2002 [28]. In addition to metabolic syndrome, we examined insulin resistance, as it is considered the pathophysiologic mechanism of metabolic syndrome [26,28]. We showed that persons with CFS as well as persons with ISF have significantly higher prevalences of insulin resistance compared with controls, with the highest prevalence detected among the CFS group. The prevalence of insulin resistance in the controls was similar to the crude prevalence among a survey of US adults 40 years and older [29].

To our knowledge, this is the first report of an association of CFS with metabolic syndrome, although there is precedent for this association. Fibromyalgia, a condition that shares many clinical features with CFS and also has fatigue as a core symptom, has been associated with metabolic syndrome; within that study, energy level was measured as a surrogate for fatigue and was inversely related to the level of glycosylated hemoglobin, a stable measure of glucose [30].

The number of metabolic syndrome factors was significantly correlated with a worse summary score for fatigue among the CFS group, but not with worse physical or mental functioning, or overall CFS-specific or non-CFS symptom scores. Our results on functional impairment are contrary to a study of obese persons seeking weight reduction that reported an association of metabolic syndrome with worse physical functioning [31]. Our study suggests that fatigue may be associated with metabolic syndrome. Additional studies of CFS in other populations are needed to confirm these findings.

Our results were generated from a cross-sectional study of CFS, which limits our ability to determine the temporal relationship between CFS and metabolic syndrome. It is equally possible that metabolic syndrome preceded or proceeded development of CFS. However, we did not find a significant correlation between number of metabolic syndrome risk factors and duration of illness, suggesting that metabolic syndrome did not develop because of illness duration. A further limitation is that persons with abnormal values for many standard laboratory tests were excluded from this analysis in accordance with the study design. Our findings may therefore be an underestimate of the prevalence of metabolic syndrome in the CFS and ISF groups that had larger proportions of exclusionary conditions than the control group [32].

A possible explanation of the relationship between CFS and metabolic syndrome is provided by an adaptation of the model for metabolic syndrome provided by Tentolouris et al [33]. Accordingly, high levels of insulin activate the HPA axis and the sympathetic nervous system (SNS) [34,35]. Increased activation of the SNS stimulates production of inflammatory molecules including the cytokines interleukin-6 and tumor necrosis factor–$\alpha$ by adipose tissue and macrophages, resulting in increased secretion of C-reactive protein (CRP) [36]. This model is supported by a growing body of evidence supporting a role for alteration of the HPA axis response to stress in CFS [7,8] and the findings that CFS is associated with decreased heart rate variability, consistent with increased SNS activity [37] and high levels of high-sensitivity (hs) CRP [38-40], although the relationship with hs-CRP was mitigated by symptoms of depression in one of these studies [40]. Thus, the insulinemia associated with metabolic syndrome may be triggering inflammation; and both could be impacting symptoms. In CFS, a high level of

hs-CRP was significantly associated with worse functioning due to physical symptoms, as measured by the physical component score of the SF-36 [40]; a high level of insulin was associated with worse fatigue, as measured by the reduced motivation subscale of the multidimensional fatigue inventory [12].

Prospective studies indicate that compared with persons without metabolic syndrome, persons with metabolic syndrome have approximately a 2- to 3-fold increased risk for atherosclerotic cardiovascular disease, an approximate 5-fold increased risk for type 2 diabetes mellitus, an approximate 2- to 4-fold increased risk of cardiovascular mortality [15-19], and a 2-fold increased risk for Alzheimer disease among the elderly [20]. Prospective studies of persons with CFS and controls are warranted to determine the temporal relationship between CFS and metabolic syndrome, in addition to the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and Alzheimer disease, among persons with CFS.

In conclusion, persons with CFS had a significantly elevated prevalence of metabolic syndrome compared with healthy individuals. Metabolic syndrome is a known risk factor for type 2 diabetes mellitus, cardiovascular disease, and Alzheimer disease. Metabolic syndrome should therefore be evaluated in persons with CFS. If detected, appropriate treatment of abnormal metabolic factors should be implemented.

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## References

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:933-9.

[2] Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res 2003;3:25.

[3] Reyes M, Nisenbaum R, Hoaglin DC, et al. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med 2003;163:1530-6.

[4] Reeves WC, Jones JF, Maloney E, et al. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metrcs 2007;5:5.

[5] Buchwald D, Umali P, Umali J, Kith P, Pearlman T, Komaroff AL. Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system. Ann Int Med 1995;123:81-8.

[6] Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. Arch Int Med 1999;159:2129-37.

[7] Van Den Eede F, Moorkens G, Van Houdenhove B, Cosyns P, Claes SJ. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. Neuropsychobiol 2007;55:112-20.

[8] Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. Trends Endocrinol Metab 2004;15:55-9.

[9] McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093-101.

[10] McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Ann NY Acad Sci 1999;896:30-47.

[11] Maloney EM, Gurbaxani BM, Jones JF, Coelho LdS, Pennachin C, Goertzel BN. Chronic fatigue syndrome and high allostatic load. Pharmacogenom 2006;7:467-73.

[12] Maloney EM, Boneva R, Nater UM, Reeves WC. Chronic fatigue syndrome and high allostatic load: results from a population-based study in Georgia. Psychosom Med 2009;71:549-56.

[13] Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation—allostatic load and its health consequences: MacArthur studies of successful aging. Arch Intern Med 1997;157:2259-968.

[14] Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Nat Acad Sci 2001;98:4770-5.

[15] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415-28.

[16] Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10 year cardiovascular disease risk in the Hoorn study. Circulation 2005; 112:666-73.

[17] Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24:683-9.

[18] Lakka HA, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002; 288:2709-16.

[19] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific statement executive summary. Circulation 2005;112: 2735-40.

[20] Vanhanen M, Koivisto K, Moilanen L, Helkla EL, Hanninen T, Soininen H, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology 2006;67:843-7.

[21] Reeves WC, Jones JF, Maloney E, et al. Prevalence of chronic fatigue syndrome in metropolitan, urban and rural Georgia. Popul Health Metr 2007;5:5. http://www.pophealthmetrics.com/content/5/1/5.

[22] Ware Jr JE, Sherbourne CD, The MOS. 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

[23] Smets EM, Garssen B, Bonke B, DeHaes JC. The Multidimensional Fatigue Inventory (MFI): psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315-25.

[24] Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC Symptom Inventory for assessment of chronic fatigue syndrome. Popul Health Metr 2005;3:8.

[25] Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome —a clinically empirical approach to its definition and study. BMC Med 2005;3:19. http://www.biomedcentral.com/1741-7015/3/19.

[26] Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999;16:442-3.

[27] Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003;26: 3160-7.
[28] Cheung BMY, Ong KL, Man YB, Wong LYF, Lau CP, Lam KSL. Prevalence of the metabolic syndrome in the United Sates National Health and Nutrition Examination Survey 1999-2002 according to different defining criteria. J Clin Hypertens 2006;8: 562-70.
[29] Li C, Ford ES, McGuire LC, Mokdad AH. Association of metabolic syndrome and insulin resistance with congestive heart failure: findings from the Third National Health and Nutrition Examination Survey. J Epidemiol Community Health 2007;61:67-73.
[30] Loevinger BL, Muller D, Alonso C, Coe CL. Metabolic syndrome in women with pain. Metabolism 2007;56:87-93.
[31] Tsai AG, Wadden TA, Sarwer DB, Berkowitz RI, Womble LG, Hesson LA, et al. Metabolic syndrome and health-related quality of life in obese individuals seeking weight reduction. Obesity 2008;16: 59-63.
[32] Jones JF, Lin JMS, Maloney EM, Boneva RS, Nater U, Unger ER, et al. An evaluation of exclusionary medical/psychiatric conditions in the definition of chronic fatigue syndrome. BMC Medicine 2009;7: 57, doi:10.1186/1741-7015-7-57.
[33] Tentolouris N, Liatis S, Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. Ann NY Acad Sci 2006;1083:129-52.
[34] Saper CB, Lowy AD, Swanson LW, et al. Direct hypothalamo-autonomic connections. Brain Res 1976;117:305-12.
[35] Chrousos GP, Gold PW. The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. JAMA 1992;267:1244-52.
[36] Bastard JP, Meachie M, Lagatha C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation and insulin resistance. Eur Cytokine Netw 2006;17:4-12.
[37] Boneva RS, Decker MJ, Maloney EM, Lin JM, Jones JF, Helgason HG, et al. Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: a population-based study. Auton Neurosci 2007;137:94-101.
[38] Cannon JG, Angel JB, ball RW, Abad LW, Fagioli L, Komaroff AL. Acute phase responses and cytokine secretion in chronic fatigue syndrome. J ClinImmunol 1999;19:414-21.
[39] Spence VA, Kennedy G, Belch JJ, Hill A, Khan F. Low-grade inflammation and arterial wave reflection in patients with chronic fatigue syndrome. Clin Sci (Lond) 2008;114:561-6.
[40] Raison CL, Lin JM, Reeves WC. Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. Brain Behav Immun 2009;23:327-37.