

A longitudinal study of physical activity and body mass index among persons with unexplained chronic fatigue

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Abstract

Objective and Methods: A cohort of 100 patients with unexplained chronic fatigue (CF) was assessed longitudinally for 1.5 years to determine if physical activity (kcal expended), exercise capacity (VO₂max), perceived exertion, and body mass index (BMI) changed over time and were associated with changes in CF-related clinical status. **Results:** BMI increased significantly over time but did not predict changes in clinical status. Increasing energy

expenditure was associated with increasing vitality and decreasing CF symptom severity over time, and decreasing perceived exertion was associated with increasing physical functioning. However, increasing perceived exertion was also associated with increasing CF symptoms. **Conclusions:** These data do not support models that posit associations between CF and deconditioning.

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Introduction

Syndromes of unexplained chronic fatigue (CF) occur along a continuum of symptom severity. Chronic fatigue syndrome (CFS) is an illness of unknown etiology, associated with significant disability; characteristic symptoms include profound fatigue for 6 months or more, impaired memory or concentration, sore throat, tender lymph nodes, myalgia, arthralgia, headaches, unrefreshing sleep, and postexertion malaise [1]. Another such illness, idiopathic chronic fatigue (ICF), is similar but has fewer symptoms than CFS does [1]. No physical examination signs are specific to CFS or ICF, and no diagnostic tests identify these syndromes.

Poor physical functioning and feeling poorly after exertion characterize patients with CF. Cognitive-behavioral models of CF (e.g., Ref. [2]) posit that patients' concerns that

activity will result in the exacerbation of symptoms lead to the avoidance of activity. In turn, avoidance may result in disuse, deconditioning, and disability. Disuse may result in less tolerance for activity that patients become uncomfortable when they are active, leading to further avoidance, further disuse, etc. This model has received support from research among patients with chronic pain (see Ref. [3] for a review) and CF [4].

Only a few longitudinal studies of CF have examined physical activity as a predictor of outcome, and all used subjective measures of exercise. Sharpe et al. [5] found that self-reported limiting of exercise as a way to cope with the illness was associated with more functional impairment approximately 1 year later. Among patients with ICF, Hartz et al. [6] observed an inverse relationship between body mass index (BMI), which may be an indicator for insufficient physical activity given the calories consumed, and improvement in fatigue 2 years later, but improvements in fatigue were not significantly associated with self-reported exercise or hours per day of TV. In a study by Vercoulen et al. [7], avoidance of physical activity at baseline did not predict

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outcome 1.5 years later. In cross-sectional investigations using objective measures of exercise, patients with CFS had significantly lower maximal oxygen uptake ($VO_2\text{max}$) than controls did [8–12]. On the other hand, in the work of Bazelmans et al. [13], physical fitness based on watts/beat from a maximal exercise test of patients did not differ from that of the controls. Likewise, Sargent et al. [14] observed that maximal oxygen uptake was within the normal range for patients with CFS. Moreover, $VO_2\text{max}$ did not differ for men with CFS compared with that of the controls, but women with CFS had lower $VO_2\text{max}$ than their healthy counterparts did. Finally, although the comparison of patient values with established age-predicted norms is another method to examine functioning, few such studies have been conducted. These studies have found that $VO_2\text{max}$ values among patients with CFS were in the normal range (approximately 100% of age-predicted values; [12,14]), even if they were less than that of the controls [12].

Several studies have compared the physiological parameters of exertion with the perceptions of exertion in CF. Generally, levels of perceived exertion were significantly higher among CF patients than among controls at equivalent [13,15] or lesser [12] levels of physiological exertion. Overprediction of physical discomfort during exertion has been associated with greater BMI and lower physical fitness and physical functioning among the general population [16], but these associations have not been assessed in CF. Lastly, in a sample of patients with CFS, beliefs about negative consequences of activity predicted less behavioral persistence (or more avoidance) of exercise [4].

Weight gain among persons with CF has not been examined, to our knowledge, but other chronic illnesses have been associated with inactivity and weight gain [17–19]. Weight gain could contribute to disability; alternatively, illnesses that result in decreased activity could lead to weight gain.

Previous longitudinal research linking physical activity to clinical outcomes in CF has relied on self-reported activity. The purpose of this study was to describe changes in objective measures of physical activity (maximal oxygen consumption, BMI, and energy expenditure) and perceived exertion over an 18-month period among patients with CF. A second aim was to determine if these variables predicted CF clinical status and, if so, to examine their temporal association.

Methods

Participants and procedures

Participants were selected from a tertiary care clinic at an academic medical center. Potential participants were between the ages of 18 and 65 and met criteria for CFS or ICF, as defined by Fukuda et al. [1], and had an appointment at the clinic.

The medical records of the patients were reviewed prior to their clinic appointment to determine if CFS/ICF inclusion and exclusion criteria were still met (persistent or relapsing fatigue for 6 months or longer and ≥ 4 symptoms for CFS or < 4 symptoms for ICF, and no exclusionary conditions, including endocrine and metabolic disorders; see Ref. [1]). Within 6 months of the clinic appointment at which the patient was recruited for participation, a comprehensive medical and psychiatric evaluation was conducted to exclude other causes of CF. This evaluation consisted of the following: (a) physical examination; (b) set of laboratory tests that included a complete blood count with differential, erythrocyte sedimentation rate, 12-factor automated chemical analysis, liver function tests, thyroid stimulating hormone, and any other tests deemed medically necessary to fully evaluate the potential causes of fatigue (including endocrine and metabolic disorders); (c) review of the patient's current and former medical records; (d) self-report questionnaire that probed for the presence and absence of all elements of the CFS case criteria; and (e) computer-assisted structured psychiatric diagnostic interview, the Diagnostic Interview Schedule (DIS) Version III-A [20].

After the screening process, eligible participants received a description of the study and were invited to participate. The study involved four research appointments at 6-month intervals, for a total of 1.5 years: the index visit, and visits 6, 12, and 18 months subsequent to the index visit. An appointment for the index visit was scheduled, and the participants were given questionnaires to complete and return at the time of their research appointment. At each appointment, a physical examination and structured interviews were conducted, and questionnaires and a blood sample were obtained. Participants who were unable or unwilling to come to research appointments subsequent to the index visit were asked if they would complete the questionnaires by mail and interviews by phone. Participants who were unable to be contacted or refused further participation were considered lost to follow-up. Participants were paid US\$35 for completing each of the four research appointments. The study was reviewed and approved by the appropriate Institutional Review Board. All participants provided written informed consent.

Clinical status measures

CF symptom severity

We designed a questionnaire to assess the severity of nine CFS/ICF symptoms: fatigue, memory or concentration problems, sore throat, painful lymph nodes, muscle pain, joint pain, headaches, unrefreshing sleep, and feeling poorly after exertion. Participants rated how often they experienced each symptom on a five-point scale (0=*not at all* to 4=*constantly*), yielding a possible range of scores of 0–36. For the index visit, the alpha coefficient for the symptom severity items was .65, and patients with ICF had lower

scores ($M=18.0$, $S.D.=4.4$) than did those with CFS [$M=22.5$, $S.D.=4.4$; $t(97)=2.6$, $P<.05$]. Thus, the scores show evidence of discriminant validity, although the value of the alpha coefficient at the index visit approached, but did not achieve, the standard criterion of .70 for acceptable internal consistency; the coefficients for all subsequent visits did ($\alpha=.73$, .79, and .82, at the second, third, and fourth visits, respectively).

Illness outcome

The Medical Outcomes Study Short Form-36 (SF-36; [21]) was used to evaluate functional status. This 36-item questionnaire consists of eight scales that reflect physical functioning, role-physical functioning, role-emotional functioning, social functioning, mental health, bodily pain, vitality, and health perceptions. Higher scores indicate better functioning (range, 0–100), with the normal range considered to be 80 and above. We retained two scores, physical functioning and vitality, as analysis on the basis of these scores' demonstrated tendencies to be more sensitive to change over time [22] and the particular relevance of their content for persons with CF.

Predictors of clinical status

Demographic variables

Age, gender, years of CF, years of education, race (recoded as either Caucasian or non-Caucasian), relationship status (recoded as either married or living with an intimate partner versus single, widowed, or divorced), and employment status (recoded as either working part or full time vs. not working) were retained for analysis.

Body mass index

BMI was defined as weight in kg/(height in meters)². In addition, participants were categorized according to the standard clinical definitions [23] as underweight (BMI <18.5), normal weight (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥30). A BMI ≥45 is exclusionary for unexplained CF [1]; thus, all the participants' BMIs were <45 (see Table 1 for descriptive data).

Maximal oxygen uptake, perceived exertion, and perceived–actual exertion comparison

Participants completed a submaximal exercise test. The standardized methods and protocol of Siconolfi et al. [24] were used. The protocol consisted of stepping up and down on a sturdy wooden box that was 10 in. high, 18 in. long, and 12 in. wide for 3 min per trial, for a maximum of three trials. Heart rate was monitored by a strap containing ECG electrodes and a transmitter, around the chest (Polar, Woodbury, NY). The signal was transmitted to a watch, which displayed the heart rate, worn by the participant. After fitting the participant with the heart rate monitor, the participant listened to tape-recorded instructions. The tape began with a description of the procedure, then the tape was stopped so the research assistant could demonstrate the stepping. The tape was restarted, with a brief practice trial so the participant could practice stepping up and down in time with the stepping rate supplied on the tape. The first 3-min trial consisted of 17 steps per minute; the stepping rates of the second and third trials were 26 and 34 steps per minute, respectively. For each trial, heart rate was recorded by the research assistant at 2:30, 2:45, and 3:00 (min:s). If, at the end of the first trial, the participant had not attained 65% of the predicted maximal heart rate (calculated as 220 minus age), based on an average of the three readings, the participant proceeded to the second trial after 1 min of sitting rest. The procedure was repeated for the second trial, and if the participant did not attain the heart rate criterion, the third trial was performed. Oxygen uptake ($VO_2\max$ in l/min) was calculated using the equations supplied by Siconolfi et al. [24], based on the trial during which the participant attained the heart rate criterion and their weight.

The participants were asked to rate their perceived exertion (RPE) immediately after stopping the test at their point of maximal exertion, based on either the participants' request or the attainment of their target submaximal heart rate. Participants answered the question, "How hard were you working...?" using a scale from 6 (*no exertion at all*) to 20 (*maximal exertion*) [25]. This scale was used because previous research has

Table 1

Clinical status measures, BMI, and physical activity variables and perceived exertion at each research appointment

	Visit 1	Visit 2	Visit 3	Visit 4
Clinical status				
CF symptom severity	22.1 (4.5)	21.3 (5.0)	20.9 (5.7)	20.7 (6.0)
Physical functioning	43.5 (23.9)	47.3 (23.7)	49.6 (26.3)	49.4 (25.5)
Vitality	16.6 (14.7)	23.5 (18.1)	23.8 (18.2)	25.4 (19.4)
BMI and physical activity variables				
BMI	28.0 (6.3)	28.2 (6.2)	28.1 (6.4)	27.8 (6.2)
$VO_2\max$	2.4 (0.8)	2.4 (0.7)	2.4 (0.8)	2.3 (0.7)
kcal/day expended	2697.5 (735.5)	2691.0 (683.5)	2717.5 (697.0)	2699.0 (667.8)
RPE	13.9 (2.5)	14.3 (2.7)	13.8 (2.7)	13.6 (2.4)

The values in the cells are means, with standard deviations in parentheses. CF Symptom Severity scores range from 0 (*low*) to 36 (*high*).

shown that such ratings on this scale are approximately 1/10th of the heart rate among healthy young adults [26]. The RPE was added to the protocol after approximately one-third of the index visits; 286 nonmissing observations are available.

Because of the previously demonstrated association between RPE and heart rate in young, healthy persons [25], a ratio of perceived to actual exertion was calculated by subtracting the maximum heart rate from 10 times the RPE positive scores, indicated as the overestimation of exertion (compared with exertion based on actual maximal heart rate), and negative scores, indicated as the underestimation of exertion.

Physical activity

Participants completed a standardized questionnaire [27] that asks participants to recall the number of hours spent sleeping, and doing activities in each of three categories (moderate, hard, and very hard) for the last weekend and the last five weekdays. Although the questionnaire gives household, occupational, and sports examples of activities in each category of exertion (for example, cleaning windows is moderate; singles tennis is very hard), many participants miscategorized activities, thus, all data were checked and recoded into correct, consistent categories across participants. The hours spent in each category that week were totaled and subtracted from 168 h (24 h × 7 days) to calculate the hours spent in light activities. The number of hours in each activity category was multiplied by its metabolic rate and divided by seven and the participant's weight in kilograms, to obtain the expended kcal/day. Previous studies have found 2-week test–retest coefficients for kcal/day to be 0.67 [27].

Statistical analysis

Descriptive statistics were used to characterize the sample. Univariate parametric (t tests) or nonparametric (χ^2) tests were used to compare the variables for participants who refused to complete the step tests for one or more of the four research appointments versus those who did not refuse. Because of the repeated measures involved in the data, general linear mixed model regression analysis was used to examine the main study questions of the ability of the physical activity variables (BMI, maximal oxygen uptake, perceived exertion, and expended kcal/day) to predict change in outcome (CF symptom severity and vitality and physical functioning from the SF-36) over time. The number of days elapsed between research appointments was used as a time-varying covariate. To conform with the normality of residuals, Box-Cox transformations were performed for physical functioning and vitality [28]. The level of statistical significance was set at $P < .05$.

Results

Participant characteristics

The 100 participants averaged 43.7 years of age (S.D.=9.7), 14.6 years of education (S.D.=2.4), and reported having CF an average of 6.2 years (S.D.=4.0) at the time of their index visit. Consistent with the characteristics of clinical samples of CF patients (e.g., Ref. [29]), 82% of the sample was female, 92% was Caucasian, 60% were partnered (married or living with an intimate partner), and 40% were employed (21% full time and 19% part time). Of the persons who were unemployed, 33% were receiving disability compensation, and 27% were not. Ninety-three percent of the participants met case criteria for CFS, and the remaining 7% met case criteria for ICF.

Of the initial cohort of 100 participants, 86% supplied partial or complete data for all four research appointments; 7% for three of the four appointments, 5% for two of the four appointments, and 2% provided data for the first appointment only.

Comparison of participants who did versus did not refuse the step test

Of the 100 participants, 15 declined to complete the step test at one or more of the four visits. A comparison of clinical status variables at the index visit revealed no differences between those who did and did not refuse to complete one or more step tests on all variables, except physical functioning, which was significantly lower among participants who refused one or more step tests ($M=26.6$, S.D.=22.6) than among those who did not [$M=46.4$, S.D.=23.0; $t(94)=3.0$, $P < .01$].

Change over time

Although the planned interval between each research appointment was 6 months, the actual interval between appointments was somewhat longer than 6 months, on average. For those who completed the first and second appointments, the average interval was 195.8 days ($n=94$, S.D.=22.9). An average of 192.4 days ($n=90$, S.D.=31.0) separated the second and third appointments, 189.8 days ($n=86$, S.D.=28.8) separated the third and fourth appointments, and 576.1 days ($n=91$, S.D.=45.2) separated the first and fourth (last) appointments.

Table 1 shows the average CF symptom severity, physical functioning, vitality, BMI, VO_2 max, kcal/day expended, and RPE at each research appointment. The general linear mixed model analysis for the effect of elapsed days on the predictor variables revealed that BMI increased significantly over time [$t(257)=3.31$, $P < .01$; 354 observations available for analysis], such that the passage of a year was associated with an increase in BMI of 0.30 units. None

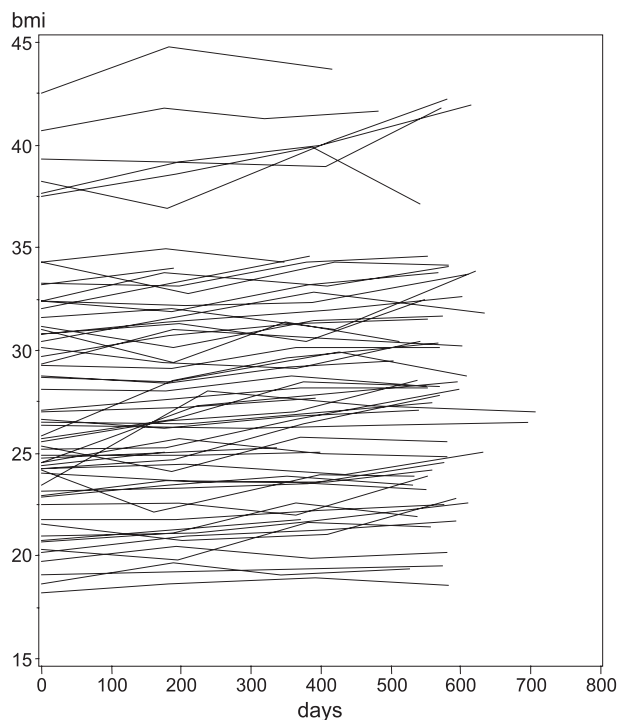


Fig. 1. BMI over time for 62 patients with positive trends.

of the other variables (VO_2 max, kcal/day expended, and RPE) changed significantly over time.¹ Figs. 1 and 2 show the individual trajectories in BMI over time for participants with BMI data at the index visit and at least one other appointment ($n=96$). Fig. 1 includes all participants with increasing BMI over time ($n=62$, the majority of the sample). Fig. 2 includes all participants with decreasing BMI over time ($n=34$) and additionally includes a thicker, smoothed line indicating the overall positive trend line for the entire sample.

Comparison with norms

The majority of participants were overweight or obese at all appointments, with 25–30% being overweight, and 35–37% being obese at each appointment. The expected values of oxygen consumption for our modal participant, a 44-year-old female, at the 50th percentile would be 3.1 l/min; the average values for this sample are below the 10th percentile for women 40–49 years of age [31]. On average, the comparison of perceived with actual exertion indicated the overestimation of exertion (based on RPE times 10 min minus the maximum heart rate) by 12–17 beats/min across research appointments. Despite statistically significant improvement over time, the average subscale scores for

physical functioning and vitality from the SF-36 did not approach the normal range.

Predictors of change in clinical status

Only 97 participants were included because there was at least one missing variable for each of the time points for three excluded participants.

For CF symptom severity, a total of 274 observations was available, and the overall test was significant [$F(4,219)=6.65$, $P<.001$]. Decreasing symptom severity was associated with decreasing VO_2 max [an increase of 1.7 points of CF symptom severity for each l/min increase in VO_2 max; $t(263)=2.41$, $P<.05$], decreasing RPE [a decrease of 0.3 CF symptom severity points for each unit decrease in perceived exertion; $t(269)=3.09$, $P<.01$], and greater energy expenditure [a decrease of 0.001 CF symptom severity points for each additional kcal expended; $t(262)=-2.00$, $P<.05$].

For the SF-36 physical functioning subscale, 278 observations were available for analysis, and the overall test was significant [$F(4,234)=6.64$, $P<.001$]. Over time, decreasing physical functioning was associated with increasing VO_2 max [a decrease of 1.6 points on the physical functioning scale for each l/min increase in VO_2 max; $t(270)=-2.18$, $P<.05$] and increasing perceived exertion [a decrease of 0.45 points in physical functioning for each unit increase in RPE; $t(257)=-4.29$, $P<.001$].

There were 274 observations available for the SF-36 vitality subscale, and the overall test was significant

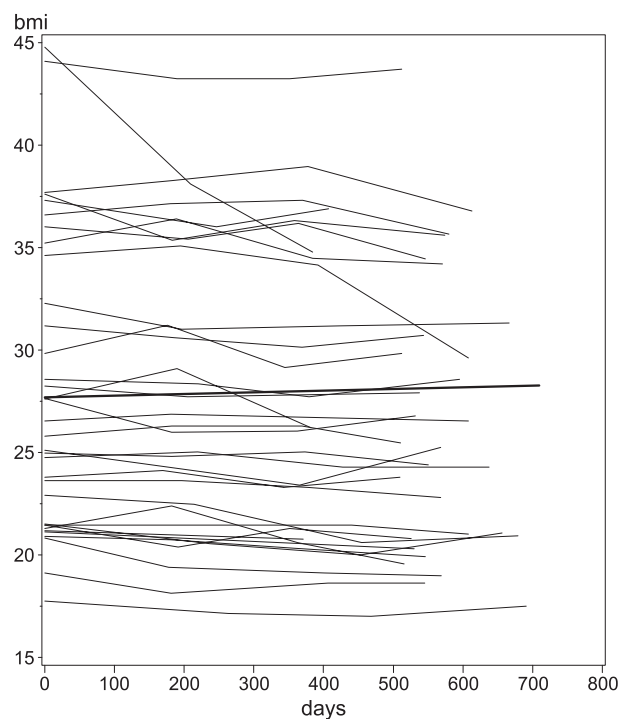


Fig. 2. BMI over time for 34 patients with negative trends and overall positive trend line.

¹ As we reported elsewhere [30], vitality increased significantly over time, physical functioning demonstrated a marginally significant trend to increase, and CF symptom severity did not change significantly over time in this sample.

[$F(4,199)=2.96$, $P<.05$]. Increasing energy expenditure was predictive of increasing vitality over time [an increase of 0.002 points on the vitality scale for each additional kcal expended; $t(242)=2.31$, $P<.05$].

Discussion

This study followed a cohort of patients with CF over a year and a half and found that BMI increased significantly over time. Compared with published norms, these patients were overweight, deconditioned, and perceived exercising to be harder than was reflected in physiological parameters of exertion. Other studies of CF have reported that their samples were overweight [10], deconditioned [8–11], and overestimated their level of exertion compared with their heart rate [13,15].

As we noted earlier, the overestimation of exertion has been associated with greater BMI in the general population [16], in addition to being characteristic of patients with CF [12,13,15]. Therefore, persons with CF who also are overweight or obese may be particularly likely to overestimate exertion. While not tested in the present study, it is possible that persons with CF are unnecessarily limiting their activity based on perceptions of exertion, when they may have more functional capacity. Monitoring physiological parameters may be useful to provide feedback and reassurance to persons with CF regarding their functional capacity. Physical rehabilitation programs, including graded exercise programs (used with CF; e.g., Ref. [32]), involve exercising to a preset criterion (such as time, distance, or heart rate or other physiological parameters) rather than limiting or extending activity on the basis of the presence or absence of discomfort. Such programs typically result in increased functional capacity that may or may not (e.g., Ref. [33]) be accompanied by decreased discomfort. Future research may examine the utility of heart rate monitoring and feedback on activity tolerance and perceived exertion among patients with CF.

The annual rate of increase in BMI among the participants in this study (0.30) was greater than that observed in a long-term longitudinal study of the natural history of weight gain among Caucasian women (0.25; [34]). Although BMI increased over time in this study, and we previously reported that vitality increased over time [30], BMI did not predict changes in vitality or other clinical outcomes. Similarly, in their longitudinal study of fibromyalgia, Mengshoel and Haugen [35] observed that patients gained weight but reported less pain and fatigue over time. However, greater BMI was associated with worsened fatigue at a 2-year follow-up among persons with ICF [6], and being overweight or obese has been correlated with poorer physical functioning and vitality in a population-based study [36]. Further studies to clarify the longitudinal associations between BMI and clinical changes in CF are warranted.

Increasing energy expenditure was associated with increasing vitality and decreasing CF symptom severity

over time, and decreasing perceived exertion was associated with increasing physical functioning and decreasing fatigue symptoms. More activity and more comfort with exerting oneself are not surprisingly associated with improved clinical status. In this regard, treatment outcome studies of behavioral activation, such as graded exercise programs, have demonstrated beneficial effects for CF (see Refs. [32,37] for reviews).

As noted earlier, this sample demonstrated an oxygen uptake that was below normal. Although CFS patients might be expected to be deconditioned, these data do not support an association between CF and deconditioning (e.g., Refs. [2,4]), as our most direct measure of exercise capacity, $VO_2\max$, demonstrated an unexpected longitudinal association with clinical status. If deconditioning was the result of, or resulted in, CF, one would predict increased CF symptoms and decreased physical functioning as conditioning worsened. However, physical conditioning worsened (oxygen uptake decreased) as CF symptom severity and physical functioning measures improved. One interpretation is that, on the whole, the cohort was symptomatic, deconditioned, and overweight throughout the entire study, thus, a relative ‘floor’ effect or lack of a dynamic range to the data may limit the clinical significance of these associations.

This study has several limitations. First, the results may not be representative of other less highly selected patients with CF or of community-based samples. Second, 15% of the sample declined one or more exercise tests. Participants who declined the exercise tests had poorer physical functioning at the index visit than did participants who did participate in the test.² Incomplete data exerted unknown effects on the results. Third, there were insufficient numbers of men in the sample to conduct separate or comparative analyses by gender, which would be an interesting area for future research. Fourth, unmeasured and unexamined confounding variables, such as occult illnesses, not detected by our evaluation procedures, may also have exerted unknown effects on the results. Finally, the external validity of the $VO_2\max$ measure, i.e., how it translates into real-life levels of exercise, is not known in the CF population.

In conclusion, weight gain was not associated with poorer clinical outcomes. With nearly 300 observations, it is unlikely that the lack of statistically significant associations of BMI with clinical outcomes was due to a lack of power. Weight gain, however, is an added health burden for patients with CFS, who are already chronically ill and poorly functioning. Because most successful weight loss programs include components of dietary therapy, behavior therapy, and

² Post hoc analyses of variance of the three outcome variables comparing Visits 1 and 4 data for participants who did and did not refuse one or more step tests revealed one significant time-by-participant-group interaction for CF symptom severity ($P<.05$). Although no differences for symptom severity were found at the index visit, participants who declined one or more step tests demonstrated worse symptom severity, whereas participants who did not decline demonstrated lessened symptom severity.

physical activity [23], it may be necessary to emphasize graded increases in physical activity among patients with CF who are attempting to lose weight [32,37]. Future studies should further evaluate the complex longitudinal relationship between fatigue, functioning, BMI, and physical activity.

Acknowledgments

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