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Subtyping Patients with Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) By Course of Illness

Jamie Stoothoff^{1,*}, Kristen Gleason², Stephanie McManimen³, Taylor Thorpe⁴, and Leonard A. Jason⁵

^{1,2,3,4,5}Center for Community Research, DePaul University, Chicago, IL, USA

Abstract

Past research has subtyped patients with Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) according to factors related to illness onset, illness duration, and age. However, no classification system fully accounts for the wide range of symptom severity, functional disability, progression, and prognosis seen among patients. This study examined whether illness trajectories among individuals with CFS were predictive of different levels of symptomology, functional disability, and energy expenditure. Of the participants ($N=541$), the majority described their illness as Fluctuating (59.7%), with 15.9% Constantly Getting Worse, 14.1% Persisting, 8.5% Relapsing and Remitting, and 1.9% Constantly Getting Better. The illness courses were associated with significant differences in symptomology on select domains of the DSQ, functioning on select subscales of the SF-36, and on overall levels of energy expenditure. The significant symptomatic and functional differences between groups suggest that subtyping patients with CFS according to illness course is a promising method for creating more homogeneous groups of patients.

Keywords

Myalgic Encephalomyelitis; Chronic Fatigue Syndrome; Subtypes; Illness Course

Introduction

Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) are debilitating illnesses, often presenting with neurological, immunological, gastrointestinal, musculoskeletal and hormonal symptoms [1–4]. The severity of symptoms and levels of functional disability experienced can vary drastically from patient to patient, suggesting there may be distinct clinical courses that have yet to be identified. In the most extreme cases, patients are bedbound and depend entirely on caretakers for support. Community based studies have determined that approximately 25% of patients are housebound and

*Corresponding authors: Jamie Stoothoff, Center for Community Research, DePaul University 990 W. Fullerton Ave., Suite 3100 Chicago, IL, USA, 60604-2201, Tel.: (773) 325-2018; Fax: (773) 325-4923, jstootho@depaul.edu.

Declarations

Ethical Approval

The ethical standards of the American Psychological Association were upheld throughout the study period. All procedures were approved by the DePaul University Institutional Review Board.

64.3% are on disability, with only 15.1% of patients currently employed [5–7]. In short, those diagnosed with these illnesses represent a heterogeneous group of individuals who experience differing patterns of symptom severity and levels of functional disability [8].

It is possible that combining potentially diverse patient subtypes into one sample pool may account for the inconsistent findings and the lack of reproducibility that has often plagued research related to the etiology, diagnosis, epidemiology, and treatment of ME and CFS [8]. Past studies have attempted to categorize patients based on type of illness onset [9–11], the duration of the illness, and the age of patient [12–15]. However, there is no classification system yet that fully accounts for the diversity of symptom severity, functional disability, progression, and prognosis of this illness. It is, therefore, pertinent to further explore methods of sub typing individuals with ME and CFS in order to more accurately describe the wide range of patient experiences.

Research has distinguished between two different onset patterns: 1) sudden onset, in which symptoms appear over a few days or weeks and 2) gradual onset, in which symptoms develop over a period of months or years. Sudden onset has often been linked with viral and infectious illnesses [16], including: Epstein-Barr Virus infection (EBV) and enterovirus infections [17,18]. One study found that patients who experienced a sudden onset had poorer health outcomes than patients who described their onset as gradual [9]. Conversely, other findings suggest that patients with a sudden onset have a better prognosis than those with a gradual onset, while others have found no significant differences in prognosis between sudden and gradual onset subgroups [10–12]. With such a range of mixed results, sub typing patients by type of onset cannot fully account for the variability seen in symptom severity and the course of the illness.

Additionally, researchers have explored illness duration and current age as related factors that may impact prognosis and symptom severity. Research has found that patients with a longer illness duration (10 years or more) experienced poorer cognitive functioning compared to those with a shorter illness duration (7 years or less) [13]. However, another study has found that the physical functioning of patients tended to improve over the course of their illness [14]. Further studies were unable to reproduce these findings and have suggested that the length of the illness experience does not have a significant effect on patient outcome [12]. In general, older age has also predicted poorer prognosis among patients [15]. In one study, researchers sought to examine how both age and duration of illness can interact to affect illness severity and functioning. Within this sample, older patients with longer illness duration (10 years or more) displayed better mental health functioning than younger patients and older patients with shorter illness duration. However, younger patients with an illness duration of 10 years or more reported more severe immune and autonomic symptoms than older patients whose illness experience also spanned 10 years or more [16].

The categorization system developed to describe differing clinical courses in patients with Multiple Sclerosis (MS) is an illustrative example of the importance of defining subtypes of a chronic illness. The International Advisory Committee on Clinical Trials of MS has defined four distinct subtypes of illness course: clinically isolated syndrome, relapsing-

remitting, primary progressive and secondary progressive. Clinically isolated syndrome describes patients who have experienced their first episode of neurological symptoms. The relapsing-remitting course is characterized by attacks of new neurologic symptoms, followed by periods of partial or complete recovery, while primary progressive describes patients who have experienced consistently worsening neurologic functioning without relapses or remissions. The final subtype, secondary progressive, describes a worsening of neurological symptoms over time, following a relapsing and remitting course [20].

Using the MS typology described above as a template, the current study explored the feasibility of a similar system of classifying differing experiences of CFS and ME symptomology. Specifically, we examined whether differing self-reported patient illness courses are predictive of different levels of symptom severity and functional disability. Further, we assessed the relationship between these illness course subtypes, maintenance of the energy envelope, illness duration, and age.

Methods

Research Participants

The sample for the present study was derived from multiple settings in various geographical locations. Participants included individuals at least 18 years of age with a current diagnosis of CFS or ME. Participants from the DePaul sample had self-report diagnoses, while the remaining samples required diagnoses to be confirmed by a physician. Of the 882 individuals available, only participants with complete data on the primary illness course variable ($N = 541$) were included.

The overall sample was 84.5% female and 15.5% male. Most participants identified as Caucasian/White (98.2%); 0.4% were Asian or Pacific Islander, and 1.4% indicated their race as “other.” For current work status, 62.5% reported being on disability, 17.3% reported they were working, and the remaining 20.2% were not currently employed (student, homemaker, retired, or unemployed). Most participants in this sample (55.8%) were married or living with someone; 29.1% were single and 15.1% were either divorced, separated, or widowed. In terms of education, 30.4% of participants had a high school diploma or lower level of education, 11.6% attended college for at least a year, 33.6% held a standard college degree, and 24.4% had a graduate degree. The mean age was 46.3 years ($SD = 13.2$).

DePaul Sample

The largest portion of participants for the present study ($n = 213$, 39.4%) came from the DePaul convenience sample pool. This sample was recruited through support groups, internet forums, and by contacting past participants of DePaul studies. Participants were English speakers at least 18 years old who self-identified as having a CFS or ME diagnosis. Those eligible completed informed consents and surveys either electronically, by hard-copy, or verbally over the phone. A large majority of the DePaul participants were female (84.2% versus 15.8% male) and most identified as Caucasian/White (97.7%). An additional 0.4% identified as Asian and 1.9% reported their race as “other.” The mean age for the DePaul Sample group was 51.9 ($SD = 11.3$).

Newcastle Sample

Another 18.1% of the participants ($n = 98$) in the present study came from the Newcastle Sample. Individuals 18 years of age and older with a suspected CFS diagnosis were referred to the Newcastle-upon-Tyne Royal Infirmary clinic for a medical assessment. A physician completed a comprehensive medical history and medical examination for each participant. All informed consents and measures were completed by hard copy. Most of the Newcastle Sample group (84.2%) identified as female and 15.8% identified as male. Almost all participants from this group identified as Caucasian (99.0%), and 1 participant selected “other” as their primary race. The mean age was 45.7 years ($SD = 14.0$).

Norway 1 Sample

The Norway 1 Sample database contributed 34.4% of the participants in the present study ($n = 168$). Participants living in the suburbs of Oslo, Norway, were recruited to participate in a CFS self-management trial program, through referrals from healthcare professions as well as through CFS patient organizations and education programs. Patients were required to be 18 years of age or older, have a current CFS diagnosis, and be physically able to attend the self-management program. Participants completed an informed consent that included permission to request a confirmation of their CFS diagnosis. Within this sample of 168 individuals, 87.4% were female and 12.6% were male. Nearly all participants identified as Caucasian (99.4%), and 1 participant identified as “other”. The mean age was 43.4 years ($SD = 11.6$).

Norway 2 Sample

The final 11.5% of the sample in the present study came from the Norway 2 Sample database. Participants from this database were recruited from an inpatient medical facility and an outpatient CFS/ME Center. Participants were required to be between 18 and 65 years of age. An experienced physician completed a comprehensive medical history interview and medical examination for individuals suspected of having a CFS diagnosis. In addition, a psychologist examined each individual to rule out exclusionary conditions. All informed consent and other study measures were completed by hard copy. Again, the majority of participants were female (82.3%) and 17.7% were male. Regarding race, 95.0% identified as Caucasian, 1.7% as Asian and 3.3% identified as “other.” The mean age was 34.8 years ($SD = 11.7$).

Illness Course Groups

Participants were placed in one of five illness course groups based upon their response to an item asking about the progression of their illness. This item provided the choice of five labels: “constantly getting worse,” “constantly improving,” “persisting (no change),” “relapsing and remitting (having ‘good’ periods with no symptoms alternating with symptomatically ‘bad’ periods),” and “fluctuating (symptoms periodically get better and get worse, but never disappear completely).”

Measures

SF-36—Participants completed the Medical Outcomes Study 36-item short-form health survey (SF-36) to measure their current physical and mental functioning [21]. The

questionnaire measures functioning on eight subscales: Physical Functioning, Role Physical, Bodily Pain, General Health, Social Functioning, Mental Health, Role Emotional, and Vitality. This measure is scored on a 100-point scale, where higher scores indicate higher functioning, and lower scores indicate lower functioning. The SF-36 has been found to have good internal consistency and discriminate validity among subscales [22].

DePaul Symptom Questionnaire (DSQ)

The DePaul Symptom Questionnaire (DSQ)^[7] consists of 54 self-report items assessing CFS-related symptomatology, as well as demographic, occupational, and social history. Patients were asked to rate the frequency of their symptoms over the past 6 months on a 5-pt Likert scale as follows: 0 = none of the time, 1 = a little of the time, 2 = about half the time, 3 = most of the time, and 4 = all of their time. Patients were also asked to rate the severity of their symptoms over the past 6 months on a 5-pt Likert scale as follows: 0 = symptom not present, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. Symptom frequency and severity were converted to a 100-point scale, and were averaged to create one composite score for each symptom. Symptoms were compiled into domains^[23] based on symptomology suggested by the Canadian Clinical Criteria for ME/CFS^[2] and select other symptoms categories that were empirically identified through factor analysis [23,2,7]. The domain composite scores were calculated by converting the frequency and severity for each symptom in the domain and averaging them to create one score. The DSQ has proven to have good test-retest reliability, as well as good convergent and discriminate validity [24,25]. The DSQ has been made available at Research Electronic Data Capture (REDCap): <https://redcap.is.depaul.edu/surveys/?s=tRxytSPVVw>.

Energy Quotient

Energy quotients were calculated from information provided on the DSQ and used to assess how much energy participants were expending in comparison to how much they had available. The Energy Envelope theory suggests that patients who monitor their activity and are mindful not to overexert themselves will experience better health outcomes and fewer symptoms such as Post-Exertional Malaise (PEM) [26]. Using a Likert scale ranging from one (no energy) to 100 (pre-illness energy level), participants were asked to rate their available and expended energy yesterday and last week. To calculate energy quotients for both yesterday and last week, expended energy levels were divided by available energy levels and then multiplied by 100. Scores over 100 indicate overextension and scores under 100 indicate under extension. Due to multiple outliers, a winsorizing technique was used to minimize their effect. Energy scores within the top 5th percentile were replaced with the value corresponding to the 95th percentile.

Statistical Analysis

A series of one-way ANOVAs were used to compare mean differences between illness subtypes for the following categories: SF-36 subscales, DSQ symptom items, illness duration, age, and energy quotients. Missing data were handled using pair wise deletion and all analyses were performed using SPSS software (version 21). The Games-Howell post-hoc test was used to examine significant differences between groups.

Results

Illness Course Groups

Most the sample (59.7%), described the course of their illness as Fluctuating, with symptoms periodically alternating between getting better and getting worse but never disappearing completely. Constantly Getting Worse comprised the second largest group, representing 15.9% of the sample. Similarly, 14.1% of the sample described their illness as Persisting, which was characterized by having no changes in symptomatology. The Relapsing and Remitting group represented 8.5% of the total sample, and was defined by having “good” periods with no symptoms alternating with symptomatically “bad” periods. The remaining 1.9% of the sample described their illness as Constantly Getting Better.

Demographics

Table 1 shows the demographic information for each illness course subtype. A series of chi-square tests were performed and no significant relationship was found between illness course groups and gender, race, ethnicity, marital status, education, or work status. In addition, a series of one-way ANOVAs determined the groups did not differ significantly in age at time of self-report, age at diagnosis, or illness duration.

DSQ Domain Differences

Table 2 shows the means and standard deviations for DSQ domain composites for each illness course group, along with the total sample. There were significant differences in symptom scores between groups for the following domains: the Immune Domain ($F(4, 535) = 5.3, p = .000$), the Pain Domain ($F(4, 535) = 6.8, p = .000$), the Post-Exertional Malaise Domain, $F(4, 535) = 18.7, p = .00$, the Sleep Domain ($F(4, 535) = 5.1, p = .002$), the Gastrointestinal Domain ($F(4, 535) = 4.6, p = .001$) and the Orthostatic Intolerance Domain ($F(4, 535) = 4.6, p = .001$). The Constantly Getting Worse group generally reported higher levels of symptom severity and frequency when compared to the other groups, while the Constantly Improving group reported lower levels of symptom severity and frequency compared to the other groups. The remaining three groups had intermediate scores on these domains.

SF-36 Subscale Scores

Table 3 shows the means and standard deviations for each SF-36 subscale across each illness course subtype, as well as for the entire sample. There were significant differences in functioning scores between groups for the following subscales: Role Physical ($F(4, 519) = 18.7, p = .000$), Bodily Pain ($F(4, 519) = 9.01, p = .000$), Physical Functioning ($F(4, 520) = 10.01, p = .000$), Vitality ($F(4, 520) = 11.4, p = .000$), General Health ($F(4, 515) = 4.5, p = .001$), and Mental Health ($F(4, 519) = 2.7, p = .03$). The Constantly Getting Worse group reported significantly worse functioning on all subscales except the General Health and the Role Emotional subscales.

Energy Envelope

Table 4 displays the means and standard deviations on reported levels of fatigue and energy for the five subtypes, as well as for the entire sample. There were significant differences between groups in Past Week Fatigue scores ($F(4, 506) = 11.60, p = .00$) and Past Week Available Energy scores ($F(4, 509) = 14.55, p = .00$). The Constantly Getting Worse group and the Persisting group reported significantly more fatigue than the remaining three groups. There was also a significant difference for Past Week Energy Quotients between illness subtypes ($F(4, 497) = 6.01, p = .00$). Scores describing participants' fatigue and energy levels for yesterday are also shown in Table 4.

Discussion

The present study explored factors associated with differing self-reported illness course experiences: Constantly Getting Worse, Constantly Improving, Persisting, Relapsing and Remitting, and Fluctuating. The findings suggest that this method of grouping patients is a promising way to examine subtypes of CFS with distinct patterns of symptomology and levels of functioning. The majority of participants in our sample (59.7%) defined the course of their illness as Fluctuating, which was described as “symptoms periodically get better and get worse, but never disappear completely.” In general, this group reported the third most severe scores related to their levels of symptomology, functioning, available energy, and fatigue. Overall, these results suggest that the majority of participants experienced a moderate level of illness severity when compared to other subtypes.

The Constantly Getting Worse group, representing 15.9% of the sample, demonstrated the most severe and frequent symptoms on every DSQ domain, as well as the lowest levels of functioning on the majority of SF-36 subscales. Additionally, the Constantly Getting Worse group reported overextending their personal energy envelopes to significantly higher degree compared to the average patient. In short, the illness experiences of those within this subtype seem distinctly more severe compared to the majority of patients experiencing ME or CFS.

Participants that identified with the Persisting illness course subtype comprised 14.1% of the total sample. This illness course was described to them as having no changes in symptomatology. Overall, this group did not display a consistent pattern with regards to severity of symptoms and levels of functioning. On some DSQ domains, such as the Gastrointestinal, Orthostatic Intolerance, and Neuroendocrine/Circulatory, this group reported low severity and frequency of symptoms. However, on other DSQ domains and SF-36 subscales, this group ranked behind the Constantly Getting Worse group in terms of the highest levels of symptom frequency and severity and the lowest levels of functioning. Therefore, the results indicated that this group showed a moderate to high level of severity. In fact, the only significant difference between the Persisting group and the majority group (Fluctuating) was on the Vitality subscale of the SF-36, on which the Persisting group reported lower functioning. In addition, the Persisting subtype reported significantly higher levels of fatigue, as well as less available energy when compared to the Fluctuating group. However, due to the relatively few differences that occurred between these groups, future investigation is needed to further explore the distinctive illness experience of this subtype.

Participants among the Relapsing and Remitting group represented 8.5% of the total sample. This illness course was described as involving “good” periods with no symptoms, alternating with symptomatically “bad” periods. Overall, this group reported moderate levels of symptomology and functioning when compared to other groups. However, our findings do not indicate substantial differences in experiences between those in the Relapsing and Remitting group and the Fluctuating group. The only scores which significantly differed were the Mental Health subscale scores of the SF-36, on which the Relapsing and Remitting group reported higher functioning. Because of this, it is difficult to specify a distinct symptomatic profile for this group, and future research may consider combining these two subtypes. Indeed, when we repeated all analyses with the Fluctuating and Relapsing and Remitting groups combined, we found that collapsing these subtypes did not result in noticeable changes in the overall findings. Because the approach taken here was exploratory in nature, we decided that keeping these subtypes separate for now could prove to be important for future analyses. However, further examination is needed to better understand the differences between symptomology and functioning for these illness courses.

Finally, the Constantly Improving group, comprising 1.9% of the total sample, consistently displayed a pattern of lower frequency and severity for symptoms on the DSQ and better overall functioning as demonstrated on the SF-36 subscales. Additionally, on average this group tended to expend more energy than they had available. This supports past research which suggests that some patients may be more able to overextend themselves with little consequence to their symptomology and functioning [27]. However, as only a small proportion ($n = 10$) of the present sample endorsed Constantly Improving as their illness trajectory, the conclusions that can be drawn about their illness experiences are limited. Nonetheless, the fact that there are so few participants within this subtype supports findings that suggest recovery from these debilitating illnesses is rare [28].

While the subtypes presented in this study provide promise in classifying more homogenous groups of patients, the approach taken had several limitations. First, it is difficult to assess participants’ illness experiences over time when using measures completed at a single time point. Items on the DSQ ask participants to rate the frequency and severity of their symptomatology over the past 6 months. Likewise, items on the SF-36 ask participants to rate their levels of functioning on a “typical day” over the past four weeks. The format of these items proves especially problematic for assessing the experiences of those within the Fluctuating and Relapsing and Remitting groups. As the nature of these groups’ illness course involves a variation in symptoms over time, when asking them to average their functioning and symptomology over time, we fail to capture a complete appreciation for the patterns of their illness.

Another limitation of the current study is that the majority of participants identified as Caucasian. This differs from the demographic distribution found in past community-based samples, which have documented higher levels of CFS diagnosis in ethnic minorities and those with lower socioeconomic status [29]. It would be important to consider whether patients from minority backgrounds differ in their illness course experiences, as studies have shown differences in patterns of symptom severity and functional status between different sociocultural samples [30]. However, the use of multiple geographically distinct collection

sites was an advantage in that it lends support for the possibility of generalizing these results over multiple recruitment settings and geographic locations. Future studies should include greater ethnic and sociocultural diversity as well as consider utilizing a longitudinal design to more accurately measure each participant's illness course. Measuring how symptoms and levels of functioning change over time would help distinguish clear patterns between subtypes and allow for further verification of the distinctiveness of these illness courses.

Conclusions

These preliminary findings demonstrate that illness course subtypes can account for significant differences in the experiences of patients with CFS and ME. The severity and frequency of symptoms, levels of functioning, and utilization of energy were shown to differ significantly between illness course subtypes. Continuing to explore and develop the illness course classification approach is an important step in furthering treatment and research for this debilitating illness. Not only will this lead to a more nuanced understanding of treatment efficacy and prognosis, but it will allow researchers to consistently categorize patients by illness subtype increasing the specificity of their research. This would likely ultimately lead to more consistent findings within the field.

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Table 1

demographic information for patients in each illness subtype (N=541)

	Constantly improving (N=10)		Relapsing & Remitting (N=46)		Fluctuating (N=323)		Persisting (N=76)		Constantly getting worse (N=86)	
	M (SD)	% (N)	M (SD)	% (N)	M (SD)	% (N)	M (SD)	% (N)	M (SD)	% (N)
Age	42.55 (18.02)		46.11 (13.87)		45.29 (12.84)		47.58 (13.78)		48.85 (12.67)	
Age of Diagnosis	36.30 (15.01)		35.51 (12.49)		37.93 (11.66)		38.84 (10.94)		39.84 (11.70)	
Duration of Illness	13.10 (10.02)		8.03 (6.78)		8.64 (7.27)		10.05 (8.47)		9.70 (7.74)	
		% (N)		% (N)		% (N)		% (N)		% (N)
Gender										
Male	20.00 (2)		8.76 (4)		14.33 (46)		22.37 (17)		17.44 (15)	
Female	80.00 (8)		91.30 (42)		85.67 (275)		77.63 (59)		82.56 (71)	
Race										
White										
Asian or Pacific islander	100.00 (10)		100.00 (45)		97.52 (314)		100.00 (75)		97.67 (84)	
Other	0.00 (0)		0.00 (0)		0.62 (2)		0.00 (0)		0.00 (0)	
	0.00 (0)		0.00 (0)		1.86 (6)		0.00 (0)		2.32 (2)	
Ethnicity										
Non-Hispanic	100.00 (10)		100.00 (45)		98.41 (310)		100.00 (73)		98.80 (83)	
Hispanic	0.00 (0)		0.00 (0)		1.59 (5)		0.00 (0)		1.20 (1)	
Marital Status										
Married	22.22 (2)		59.09 (26)		58.31 (186)		54.05 (40)		50.00 (43)	
Separated	0.00 (0)		2.27 (1)		1.25 (4)		1.35 (1)		2.32 (2)	
Widowed	0.00 (0)		0.00 (0)		0.94 (3)		0.00 (0)		0.00 (0)	
Divorced	22.22 (2)		9.09 (4)		12.54 (40)		13.51 (10)		15.11 (13)	
Never Married	55.56 (5)		29.55 (13)		26.96 (86)		31.08 (23)		32.56 (28)	
Education										

	Constantly improving (N=10)	Relapsing & Remitting (N=46)	Fluctuating (N=323)	Persisting (N=76)	Constantly getting worse (N=86)
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
High School	40.00 (4)	39.13 (18)	27.67 (88)	31.51 (23)	34.94 (29)
Partial college	20.00 (2)	13.04 (6)	12.26 (39)	10.96 (8)	7.23 (6)
College degree	20.00 (2)	26.09 (12)	35.53 (113)	28.77 (21)	37.35 (31)
Graduate degree	20.00 (2)	21.74 (10)	24.53 (78)	28.77 (21)	20.48 (17)
Work Status					
On Disability	40.00 (4)	47.83 (22)	62.42 (201)	69.33 (52)	67.44 (58)
Retired	10.00 (1)	6.52 (3)	7.76 (25)	13.33 (10)	8.17 (7)
Working	20.00 (2)	30.43 (14)	17.39 (56)	12.00 (9)	13.95 (12)
Not working	30.00 (3)	15.22 (7)	12.42 (40)	5.33 (4)	10.47 (9)

Similar letters denote significant differences

* p < .05

** p < .01

Table 2

ANOVA results for mean differences on DSQ domains between illness subtypes

	Constantly Improving	Relapsing & remitting	fluctuating	Persisting	Constantly getting worse	Total sample
Post-Exertional Malaise	34.58 _{abc}	61.10 _{de}	68.82 _{af}	74.72 _{bd}	79.55 _{cef}	70.05 **
Minimum exercise makes tired	42.50 _{ab}	67.77 _c	74.90 _d	80.50 _a	85.73 _{bcd}	76.21 **
Drained/sick after mild activity	35.00 _{ab}	62.77 _{cd}	70.52 _{ef}	78.78 _{ace}	83.38 _{bdf}	72.40 **
Soreness after mild activity	27.50 _{abcd}	67.93 _{ae}	70.80 _{bf}	77.30 _c	81.47 _{def}	72.35 **
Dead/heavy feeling after exercise	35.00 _{ab}	59.88 _{cd}	71.15 _e	76.73 _{ac}	83.17 _{bde}	72.13 **
Mentally tired after slightest effort	31.25 _{abc}	56.52 _d	62.30 _{ae}	69.57 _b	72.91 _{cde}	63.92 **
Muscle weakness	36.25 _a	52.17 _b	62.46	64.53	71.17 _{ab}	62.76 **
Sleep	45.50	57.41 _a	59.66 _b	62.15	68.00 _{ab}	60.87 **
Unrefreshing sleep	58.75 _a	73.33 _b	81.38	84.70	86.76 _{ab}	81.61 **
Problems staying a sleep	46.25	59.37	59.09	60.16	67.48	60.34
Problems falling a sleep	53.75	52.98	57.76	58.71	66.32	58.78
Need to nap daily	26.25 _{abc}	46.94 _d	55.39 _{ae}	60.03 _b	67.24 _{cde}	56.64 **
Waking up early	42.50	50.85	43.63	46.60	51.93	45.94
Neurocognitive	47.85	59.37	60.69 _a	65.35	68.66 _a	62.25 **
Difficulty paying attention	48.75	69.70	71.79 _a	78.94	81.54 _a	73.73 **
Problems remembering	53.75	65.21	66.73	72.58	74.32	68.35 *
Can only focus on one thing at a time	48.75	61.41	62.07 _a	68.75	74.60 _a	64.66 **
Difficulty expressing thoughts	56.25	62.22	60.68	67.51	68.01	62.85
Absent-mindedness	52.50	56.66	59.86	61.75	66.90	60.84
Slowness of thought	41.25	54.89	57.39	57.56	60.84	57.44
Difficulty understanding	33.75	45.38	46.09	50.00	54.46	47.67 *
Innate	14.47 _{abcd}	32.31 _a	37.90 _b	37.59 _c	42.17 _d	37.63 **
Flu-like symptoms	21.25 _{abcd}	48.36 _a	54.90 _b	55.75 _c	60.88 _d	54.79 **
Sore throat	9.72 _{abcd}	33.33 _a	38.97 _b	38.00 _d	42.57 _d	38.44 **
Tender lymph nodes	16.25 _a	31.39	36.55	40.41 _a	40.44	36.91 *

	Constantly Improving	Relapsing & remitting	fluctuating	Persisting	Constantly getting worse	Total sample
Fever	10.00	16.19	20.55	12.86	24.09	19.75
Neuroendocrine/circulatory	38.43	42.54	47.91	42.34	49.04	46.76
Cold limbs	47.50	49.72	56.90	55.66	55.88	55.79
Feeling hot/cold for no reason	52.50	53.53	56.25	51.43	57.13	55.42
Chills/shivers	38.75	41.57	45.47	35.44	47.50	43.92
Low temperature	15.00	29.34	33.00	26.50	35.86	31.89
Pain	32.50_{abc}	49.72_d	61.99_a	63.48_b	69.26_{cd}	61.76
Muscle pain	32.50 _{abc}	52.77 _{de}	64.94 _a	68.91 _{bd}	73.52 _{ce}	65.24
Joint pain	32.50 _a	47.82 _b	58.67	58.50	65.00 _{ab}	58.23
Gastrointestinal	23.33_a	45.08	47.90	40.23_b	52.89_{ab}	46.91
Irritable bowel problems	25.00	50.00	50.85	40.78 _a	59.37 _a	50.21
Bloating	21.25	46.19	49.02	42.26	52.25	47.81
Stomach pain	23.75	38.85	43.88	37.58	46.91	42.67
Orthostatic intolerance	18.00_a	35.08	37.29	34.31	42.41_a	37.14
Unsteady on feet	20.00	41.84	42.89	43.83	43.52	42.61
Dizziness/fainting	20.00	37.77	42.00	42.43	45.29	41.81
Shortness of breath	17.50 _a	37.50	39.90	34.86 _b	48.67 _{ab}	39.97
Irregular heart beats	17.50 _a	30.27	34.00	26.66 _b	41.86 _{ab}	33.57
Chest pain	15.00	27.17	27.17	23.32	32.79	27.29

Similar letters denote significant differences

* p < .05

** p < .01

ANOVA results for mean (SD) differences on SF-36 subscales between illness subtypes

Table 3

	Constantly Improving	Relapsing & Remitting	Fluctuating	Persisting	Constantly Getting Worse	Total Sample
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Role Physical	52.50 (29.93) ^{abcd}	5.36 (17.92) ^a	6.53 (18.88) ^b	3.89 (11.73) ^c	4.22 (11.59) ^d	6.57 (18.36) ^{**}
Vitality	40.00 (27.39)	24.38 (15.16) ^{ab}	19.19 (15.61) ^{cd}	12.65 (15.08) ^{ac}	13.25 (14.49) ^{bd}	18.12 (16.21) ^{**}
Social Functioning	53.75 (40.41)	36.34 (26.70) ^{ab}	28.30 (22.49) ^c	22.20 (23.24) ^a	14.43 (18.15) ^{bc}	26.35 (23.76) ^{**}
General Health	43.80 (19.84)	33.05 (14.23) ^a	28.30 (16.65)	25.16 (15.00) ^a	25.05 (18.29)	28.03 (16.80) ^{**}
Physical Functioning	58.83 (36.70)	44.81 (22.94) ^{ab}	38.01 (22.31) ^c	31.64 (20.63) ^a	25.89 (20.98) ^{bc}	36.10 (23.01) ^{**}
Bodily Pain	70.40 (21.77)	48.56 (23.58) ^d	39.39 (22.02) ^{de}	37.72 (25.96) ^b	30.96 (24.66) ^{cde}	39.14 (23.89) ^{**}
Mental Health	77.60 (15.57) ^{abc}	77.67 (13.78) ^{ab}	69.24 (18.06) ^a	69.66 (20.65)	68.56 (18.05) ^b	70.04 (18.23) [*]
Role Emotional	93.33 (21.08)	79.07 (37.81)	72.69 (40.75)	76.58 (39.68)	80.32 (37.19)	75.38 (39.40)

Similar letters denote significant differences

* p < .5

**

p < .01

Table 4
ANOVA results for mean (SD) differences in fatigue and energy between illness subtypes

	Constantly Improving	Relapsing & Remitting	Fluctuating	Persisting	Constantly Getting Worse	Total Sample
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Past week						
Fatigue	45.60 (25.23) _{ab}	61.70 (21.78) _{cd}	67.55 (20.19) _{ef}	77.39 (17.86) _{ace}	77.05 (19.97) _{bdf}	69.55 (20.91) _{**}
Energy quotient	121.76 (55.03)	119.73 (49.34)	109.03 (42.46) _a	122.39 (54.35)	139.19 (70.75) _a	116.79 (51.41) _{**}
Available energy	45.00 (19.72) _{ab}	35.27 (15.77) _{cd}	31.19 (16.16) _{ef}	23.81 (13.41) _{ace}	20.27 (14.17) _{bdf}	29.00 (16.33) _{**}
Expended energy	55.00 (20.68) _{ab}	41.71 (20.15) _{cd}	33.69 (19.86)	28.85 (16.67) _{ac}	29.67 (21.15) _{bd}	33.50 (20.15) _{**}
Yesterday						
Fatigue	46.10 (27.49) _a	55.20 (25.92) _{bc}	66.38 (22.20) _d	76.15 (17.95) _{acd}	73.39 (24.56) _b	67.51 (23.28) _{**}
Energy quotient	120.00 (53.17)	113.52 (51.99)	100.07 (38.55) _a	113.45 (50.68) _b	139.73 (61.82) _{ab}	109.49 (47.92) _{**}
Available energy	46.50 (19.44) _{ab}	32.44 (16.87) _{cd}	27.86 (16.40) _e	23.63 (14.48) _{ac}	18.05 (12.53) _{bde}	26.51 (16.40) _{**}
Expended energy	60.50 (25.65) _{abc}	37.16 (24.50)	28.19 (18.95) _a	27.13 (19.10) _b	27.00 (24.78) _c	29.24 (21.17) _{**}

Similar letters denote significant differences

* p < .05

** P < .01