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Latent class analysis of a heterogeneous international sample of patients with myalgic encephalomyelitis/chronic fatigue syndrome

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Abstract

Background: Individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) routinely display differences in symptomatology, as well as illness course, onset, duration, and functional disability. Given such diversity, previous work has attempted to identify symptom-based ME/CFS subtypes. However, results have been inconsistent.

Purpose: This study sought to elucidate potential subtypes of ME/CFS as well as explore the impact of subtype membership on health functioning.

Methods: Twelve non-core (i.e., less frequently endorsed) symptoms were included in a latent class analysis of 1,210 adults with ME/CFS. Demographic and illness-related predictors of class membership were evaluated with a multinomial logistic regression. ANOVAs were then performed to determine if there were significant differences across class on the eight subscales of the Short-Form Health Survey (SF-36).

Results: A six-class solution was selected, which consisted of one class that was likely to endorse all non-core symptoms, one class that was unlikely to endorse any non-core symptoms, and four classes that were likely to endorse either one or two non-core symptom domains (i.e., circulatory/neuroendocrine impairment, orthostatic intolerance, and gastro-intestinal distress). Significant functioning differences by class were present for all SF-36 subscales.

Conclusions: These results are suggestive of subtypes of ME/CFS and, if replicated, may assist physicians in providing tailored treatment to patients and allow researchers to form more homogeneous samples.

Keywords

myalgic encephalomyelitis; chronic fatigue syndrome; subtypes; latent class analysis; health functioning

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating illness characterized by post-exertional malaise (PEM), sleep dysfunction, and cognitive impairment [1,2]; however, individuals with this illness present with significant symptom heterogeneity. Individuals with ME/CFS have shown variation in symptomatology, etiology, psychiatric comorbidity, functional disability, illness duration, and physiological abnormalities [3]. Such diversity can interfere with the replication of findings across studies, as well as identifying a potential biomarker for the illness.

Approximately 20 different case definitions have been developed for ME/CFS [4], each requiring a different number, type, frequency, severity, and duration of various symptoms. With little consensus on which criteria are used in research, coupled with variation on the medical and psychiatric conditions that might preclude a diagnosis of ME/CFS, individuals diagnosed with ME/CFS at different research settings could differ substantially from one another [5]. The diagnostic process also varies by clinician; many report uncertainty about how to apply ME/CFS case definitions [6], and there is variability in how physicians apply each case definition [5]. Lack of diagnostic clarity has led to debates about whether ME/CFS represents several illnesses with some symptom overlap, or whether ME/CFS subtypes exist [3,7,8].

Given the possibility that ME/CFS has various subtypes, researchers have employed cluster analysis in an attempt to identify distinct groups of patients. Using this method, ME/CFS subtypes have been identified based on single-nucleotide polymorphisms [9], gene expression [7], sleep phenotypes [10], daily fatigue trajectories [11], and variables associated with Energy Envelope Theory [12]. Such work has provided preliminary evidence that individuals with ME/CFS can be meaningfully grouped using a variety of variables. It should be noted, however, that ‘bottom-up’ statistical approaches such as cluster analysis do not allow for the development and assessment of alternative models, nor can they be flexibly applied (e.g., with the inclusion of covariates to predict individuals’ group membership). These limitations have led researchers to investigate symptom-based ME/CFS subtypes using probabilistic, ‘top-down’ approaches.

In a study conducted by Hickie et al. [13], latent class analysis (LCA) was applied to a patient sample from New South Wales who met the Australian clinical criteria of ME/CFS [14]. The patients completed a 40-item self-report questionnaire designed by Lloyd et al. [14] that included both ‘typical’ and ‘atypical’ symptoms of the illness, as well as a battery of measures that identified functional impairment, illness course and behavior, and psychiatric morbidity. A two-class solution was selected due to its stronger fit statistics. The larger class was characterized by less frequent and severe symptoms (both ‘typical’ and ‘atypical’), a higher proportion of males, shorter illness duration, less disability, less severe illness course, and lower current psychiatric morbidity. The smaller class, by contrast, reported nearly all symptoms at a higher frequency and severity. A subsequent international, eight-center study largely replicated these results using latent profile analysis [15]. These results suggest that individuals with ME/CFS vary by amount of symptoms, but not type of symptoms.

In an attempt to evaluate the symptomology of two heterogeneous illnesses, Sullivan et al. [16] considered American patients who met criteria for ME/CFS [1] and/or fibromyalgia (FM) and included 32 non-cardinal symptoms common to the illnesses in an LCA. The authors chose to interpret a four-class solution, which was characterized by quantitative gradations of severity. The high-endorsement group had significantly more women, a higher proportion of bed-ridden individuals with constant fatigue, and a higher endorsement of lifetime panic disorder and major depression. While such a graded model is informative, because this sample included patients with ME/CFS and FM, it does little to further our understanding of patients with only ME/CFS who grapple with specific types of ancillary symptoms.

In contrast to the aforementioned studies, qualitative differences in class were identified by Sullivan et al. [17] in an analysis of individuals aged 42–64 years from the Swedish Twin Registry who had experienced fatigue in the past six months. Eleven items were entered into an LCA (gender, impairment due to fatigue, fatigue duration of greater than or equal to six months, and the eight Fukuda et al. [1] criteria symptoms). A five-class solution was selected, which the authors termed ‘CFS-like,’ ‘Residual,’ ‘Rheumatic,’ ‘Depressive,’ and ‘Acute Physical Syndrome.’ It should be noted, however, that the intent of this study was to elucidate the heterogeneity of chronic fatigue, as opposed to ME/CFS; additionally, the study included both core and ancillary symptoms of ME/CFS. Both of these methodological decisions might make it difficult to extract subtypes specific to ME/CFS.

Collin and colleagues [18] addressed several limitations of past work in their assessment of two large clinical cohorts from the UK and the Netherlands. In an initial analysis of the UK cohort, nine symptoms derived from the NICE guidelines [19] were entered into an LCA (joint pain, muscle pain, headaches, painful lymph nodes, sore throat, general malaise/flu-like symptoms, dizziness, nausea, and palpitations). The authors deemed a six-class solution optimal, termed: full polysymptomatic, pain-only (muscle/joint), sore throat/painful lymph node, oligosymptomatic, non-dizzy polysymptomatic, and non-throat/lymph polysymptomatic. In an attempt to replicate these findings in the Dutch cohort (diagnosed according to the Fukuda et al. [1] criteria), five symptoms common to the two diagnostic criteria were entered into an LCA (sore throat, painful lymph nodes, headaches, joint pain, and muscle pain). Three of the original phenotypes were replicated: full polysymptomatic, pain-only, and oligosymptomatic. Though such a result indicates that subtypes can exist beyond the high/low symptomology groups frequently identified in prior work, further analysis is needed using ancillary symptoms from other ME/CFS case definitions.

Previous analyses, while not directly comparable due to differing illness criteria, patient pools, and symptoms analyzed, provide preliminary evidence for the existence of distinct groups of patients that vary either quantitatively or qualitatively. However, prior studies had several important limitations that may have precluded their ability to empirically extract symptom-specific subtypes of ME/CFS, such as broad inclusion criteria (e.g., chronic fatigue), mixed samples (e.g., samples that included both ME/CFS and FM), large parameter-to-case ratios, inclusion of psychiatric or unexplained somatic symptoms, and the use of non-validated questionnaires.

The present study focused on identifying subtypes within a large international sample of individuals with ME/CFS. It is hypothesized that results will be more differentiated than prior studies for the following reasons: 1) our sample is comprised of only individuals with a diagnosis of ME/CFS, 2) symptoms are derived from a validated measure of ME/CFS symptomatology, ensuring that the same illness construct is being reliably assessed across all patients, 3) only physical symptoms associated with ME/CFS are included (i.e., psychiatric and ‘non-specific somatic symptoms’ are excluded), 4) only empirically-derived, non-core symptoms are included in the analysis, and 5) there is a higher ratio of participants to number of symptoms, enhancing our ability to delineate additional classes.

Method

Participants

International convenience samples of ME/CFS patients were assembled. Methods of case ascertainment are described below (more detailed information can be found in Jason et al. [20]). See Table 1 for demographic characteristics of the combined sample. Demographic characteristics of the individual samples can be found in Jason et al. [20]. Of the initial sample ($N = 1,269$), 55 participants were removed due to exclusionary medical or psychiatric conditions, lifelong fatigue, or not having a diagnosis of ME/CFS. Additionally, four participants were removed from subsequent analyses due to insufficient data, resulting in a sample of 1,210 participants.

DePaul sample patients and controls.—A convenience sample of adults self-identifying as having ME/CFS was obtained. Eligible participants were at least 18 years old, capable of reading and writing English, and had a current, self-reported diagnosis of ME/CFS. Participants were able to complete the study measures electronically, on paper, or verbally via telephone.

SolveCFS BioBank sample patients and controls.—Participants from this sample were recruited by the Solve ME/CFS Initiative. Data was housed in the SolveCFS BioBank, which provides clinical information and blood samples of individuals who were diagnosed by a licensed physician specializing in ME/CFS. Participants were considered eligible for the present study if they were at least 18 years old and had completed a written informed consent process. Participants completed the study measures either electronically or by hard copy.

Newcastle sample.—Participants from this sample had been referred for a medical assessment at the Newcastle upon Tyne Royal Victoria Infirmary due to a suspected diagnosis of ME/CFS. Upon completion of a comprehensive medical history and examination by an experienced physician, eligible individuals completed a written informed consent process and study measures by hard copy.

Norway sample 1.—Individuals who were at least 18 years old and had received a diagnosis of ME/CFS from a physician or medical specialist were invited to participate in a randomized controlled trial of a ME/CFS self-management program. Participants were recruited from four mid-sized towns in southern Norway, two suburbs of Oslo, and some

surrounding communities. Recruitment sources included healthcare professionals, ME/CFS patient organizations, and the waiting list for a patient education program. All participants completed a written, informed consent process.

Norway sample 2.—Participants from this sample were recruited from an inpatient medical ward for severely ill patients and an outpatient clinic at a multidisciplinary ME/CFS Center. Individuals with a suspected diagnosis of ME/CFS were referred for evaluation, and those who participated completed a written, informed consent process. Individuals were required to be between 18 and 65 years old and capable of reading and writing Norwegian in order to be eligible for inclusion. Participants completed study measures and took part in a comprehensive medical history interview and medical examination, conducted by experienced consultant physicians and a psychologist.

Measures

All participants completed the DePaul Symptom Questionnaire (DSQ) [21], a 54-item self-report measure of ME/CFS symptomatology, demographics, and medical, occupational, and social history. Participants are asked to rate each symptom's frequency over the past six months on a 5-point Likert-type scale, with 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 the time. Additionally, participants rate each symptom's severity over the past six months on a 5-point Likert-type scale, with 0=symptom not present, 1=mild, 2=moderate, 3=severe, and 4=very severe. The DSQ has demonstrated adequate test-retest reliability among both patient and control groups [22], as well as good construct, convergent, and discriminant validity [23]. Additionally, all subscales within the DSQ have displayed excellent internal reliability and, unlike other measures of fatigue, do not exhibit ceiling effects [24]. The DSQ is publically available in the shared library of the Research Electronic Data Capture (REDCap) [25], hosted at DePaul University: <https://redcap.is.depaul.edu/surveys/?s=tRxytSPVVw>

Participants also completed the RAND 36-Item Short-Form Health Survey (SF-36) [26], a self-report measure of eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems (Role Physical), role limitations due to personal or emotional problems (Role Emotional), emotional well-being (Mental Health), social functioning, energy/fatigue (Vitality), and general health perceptions (General Health). Responses are recoded to be on a 100-point scale (with higher scores indicating better health), and particular items are averaged together in order to create eight subscale scores. The SF-36 has demonstrated adequate psychometric properties across diverse patient groups [27] and has shown utility in assessing the functional status of individuals with fatiguing illnesses, including ME/CFS [28].

Statistics

Item selection.—Given that between 90% and 100% of ME/CFS patients endorse 'core' symptoms, such as prolonged fatigue, PEM, neurocognitive problems, and unrefreshing sleep [29], such symptoms would theoretically constitute the ME/CFS 'supertype' (i.e., an entity that contains attributes that are common to all subtypes). Inclusion of core symptoms in an LCA would increase the ratio of parameters to participants (limiting the statistical

power of the analysis) without adding substantive information to the subtypes identified [18]. Therefore, the current study focused on ‘non-core’ symptoms that are less frequently endorsed among patients with ME/CFS. Previous empirical work was utilized in order to select which non-core symptoms would be included in subsequent analyses.

In a factor analysis of patient responses to the DSQ [20], four factors were the maximum number that could be stably extracted due to sample size, three of which contained core symptoms (termed ‘Cognitive Dysfunction,’ ‘PEM,’ and ‘Sleep Dysfunction’) and one of which contained non-core symptoms (termed ‘Autonomic, Neuroendocrine, and Immune Dysfunction’). However, a parallel analysis indicated the existence of additional factors, so an exploratory factor analysis (EFA) was conducted on the large number of items that loaded onto the heterogeneous Autonomic, Neuroendocrine, and Immune Dysfunction factor. This EFA resulted in a three-factor solution: ‘Circulatory/Neuroendocrine Impairment,’ ‘Orthostatic Intolerance (OI),’ and ‘Gastro-intestinal Distress.’ The 12 items that loaded adequately onto these factors were used in the LCA in the present study: chills/shivers, cold limbs, feeling hot/cold for no reason, low temperature, unsteady on feet, dizziness/fainting, shortness of breath, irregular heartbeats, chest pain, stomach pain, irritable bowel problems, and bloating. These items were selected for inclusion in the current study, as their factor loadings were indicative of good construct validity and they were endorsed by an adequate number of individuals in our sample (between 18.0% and 53.0%), suggesting that they had the potential to constitute clinically-relevant illness subtypes.

LCA.—Mplus version 7.3 was used to conduct an LCA, a probabilistic method for identifying unobserved class membership using observed categorical and/or continuous variables (see Hagenaars and McCutcheon [30] for additional information on LCA). Prior to analysis, the 12 aforementioned symptoms were transformed to be dichotomous. Participants who reported on the DSQ that they experienced a symptom at least half the time and of at least moderate severity in the past six months were classed as having that symptom (i.e., if frequency and severity were greater than or equal to 2). Previous work has demonstrated that a frequency/severity threshold of 2/2 is effective in reducing the likelihood of misclassification [29].

In order to examine the appropriate number of latent classes, 1- through 8-class solutions were extracted. Parameter estimates and model fit statistics were determined in an iterative manner using robust maximum likelihood (MLR) estimation. To avoid the issue of local likelihood maxima, 500 random sets of start values were used in the first step of the optimization and the 50 sets with the largest log likelihood values were selected for the second step of the optimization process. For each model, participants were assigned to the class for which they had the greatest probability.

Seven fit statistics were evaluated to identify the appropriate number of classes: Akaike’s information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC (SABIC), normalized entropy, the Vong-Lo-Mendell-Rubin likelihood ratio test (VLMR), the adjusted Lo-Mendell-Rubin likelihood ratio test (LMR), and mean class assignment probabilities. A model with the smallest information criteria values, an entropy value equal to or larger than 0.80, and mean class assignment probabilities equal to or larger than 0.80

would be considered best-fitting. Additionally, the selected model ought to be parsimonious and interpretable.

Class predictors and characteristics.—In order to examine predictors of class membership, an exploratory multinomial logistic regression was performed using eight relevant demographic and illness-related variables, including: gender (male, female), race (White, non-White), Hispanic or Latinx origin (yes, no), education (high school or less, partial or full college, graduate school), work status (on disability, student/homemaker, retired, unemployed, working part- or full-time), how long ago fatigue began (6–12 months, 1–2 years, longer than 2 years, since childhood or adolescence), and mode of onset (both stress and infectious, only stress, only infectious, neither stress nor infectious). To examine the direct effect of recruitment differences on class membership, a Pearson's chi-squared test was performed. Finally, a series of ANOVAs were performed using the eight subscales of the SF-36 to assess if there were significant differences across class in terms of physical and mental/social functioning.

Results

Figure 1 plots the AIC, BIC, and SABIC for each class solution. All three criteria displayed a steep decline from one to two classes. From classes three to eight, the AIC and SABIC decreased at a fairly constant rate, while the BIC reached a minimum at six classes. Table 2 displays additional fit statistics for each model. Only the two class model met the recommended lower bound for entropy (e.g., 0.80 [31]), a measure of class separation, while the remaining models had entropy values between 0.72 and 0.76. Finally, the models were compared on the basis of significance tests derived from two likelihood ratio tests. Only the two, four, five, and six class models had p -values less than 0.05, indicating that the two-class model better explains the data than one-class model, the four-class better than the three-class, and so on.

We chose to interpret a six-class solution, as it minimized the BIC, was favorable to models with fewer classes, and resulted in interpretable classes (i.e., classes with content validity). Though this model's entropy value was 0.04 away from the recommended lower bound, an inspection of the average latent class probability for the most likely latent class membership by latent class revealed that four classes had values 0.80 or higher on the main diagonal. This indicated that, overall, participants were classified with high certainty into their most likely latent class [32]. Therefore, the classification quality for each of the six classes was considered adequate.

The symptom profiles and class proportions for the six-class solution are displayed in Table 3. Class 1 (13.6%) was characterized by a high probability (i.e., above 0.50) of endorsing all twelve symptoms. Class 2 (18.1%) was likely to only endorse symptoms related to gastro-intestinal distress (irritable bowel problems, bloating, and stomach pain). Class 3 (11.7%) was likely to endorse symptoms related to gastro-intestinal distress and circulatory impairment. Class 4 (11.7%) was likely to endorse only circulatory impairment symptoms (chills/shivers, feeling hot/cold for no reason, and cold limbs). The smallest class, Class 5 (10.3%), was likely to endorse circulatory impairment and OI symptoms (feeling hot/cold

for no reason, feeling unsteady on feet, dizziness/fainting, shortness of breath, and irregular heartbeats). The largest class, Class 6 (34.6%), was unlikely to endorse any of the twelve symptoms.

In order to further understand each class, an exploratory multinomial logistic regression was conducted to identify demographic or illness-related predictors of class membership. A test of the full model (i.e., one which included the eight independent variables) against a constant-only model (i.e., one which included no independent variables) was statistically significant, indicating that the full model predicted class membership better than the intercept-only model alone ($X^2 = 268.19$, $df = 95$, $p < .001$). Likelihood ratio tests determined that gender, race, Latinx or Hispanic origin, and mode of onset were not significant predictors of class membership. However, education ($p < .001$), work status ($p < .001$), illness course ($p < .001$), and how long ago fatigue began ($p < .001$) were significant predictors of class membership. It should also be noted that a Pearson's chi-squared test indicated that there were significant differences in class assignment by study sample ($X^2(20, N = 1210) = 152.64$, $p < .001$). The BioBank sample placed more individuals into Class 6 and the Norway 1 sample placed less individuals into Class 6 than would be expected, implying that the Norway 1 recruitment methods resulted in a generally more symptomatic group of ME/CFS patients (and vice versa for BioBank).

Regression results indicated that, relative to Class 6, Classes 1, 3, and 5 were more likely to have a high school diploma or less ($p < .001$, $p = .04$, and $p = .01$, respectively), while Class 3 was less likely to have a college degree or some college education ($p = .03$). Classes 1–5 were more likely to be on disability than Class 6 ($p < .01$, $p < .01$, $p = .02$, $p = .04$, and $p < .01$, respectively) and Class 3 was less likely to be retired ($p = .04$). Classes 1 and 5 were more likely to endorse a 'constantly getting worse' illness course ($p = .01$ and $p = .04$, respectively) and Class 1 was less likely to endorse a 'relapsing and remitting' course ($p = .01$). Finally, compared to Class 6, Classes 1 and 4 were more likely to have a fatigue that began 1–2 years ago ($p = .05$ and $p = .01$, respectively), while Classes 1 and 5 were less likely to have a fatigue that began longer than 2 years ago ($p < .01$ and $p = .02$, respectively). Further inspection of this variable revealed that, across all classes, few individuals stated that their fatigue began 6–12 months ago or 1–2 years ago. Of note were Classes 1 and 5, which had the highest proportion of individuals who had experienced fatigue since childhood or adolescence (24.2% and 18.7%, respectively).

In order to explore the functional implications of belonging to each class, two multivariate analyses of variance (MANOVAs) were performed using subscales of the SF-36, one of which included physical subscales (i.e., Physical Functioning, Role Physical, Bodily Pain, and General Health) and one of which included mental/social subscales (i.e., Vitality, Social Functioning, Role Emotional, and Mental Health). Both analyses returned a significant Box's M test ($p < .001$), indicating that they violated the MANOVA assumption of homogeneity of covariance matrices. We proceeded to conduct individual analyses of variance (ANOVAs) (or adjusted F -tests, in cases of unequal variances) for each SF-36 subscale (see Table 4).

Significant functioning differences by class were present for all subscales: Physical Functioning ($F(5, 886.77) = 33.43, p < .001$), Role Physical ($F(5, 918.15) = 4.21, p = .001$), Bodily Pain ($F(5, 886.71) = 47.29, p < .001$), General Health ($F(5, 1140) = 11.94, p < .001$), Social Functioning ($F(5, 869.34) = 12.12, p < .001$), Vitality ($F(5, 1142) = 4.04, p = .001$), Mental Health ($F(5, 827.18) = 6.17, p < .001$), and Role Emotional ($F(5, 867.59) = 2.56, p = .03$). Sidak and Games-Howell post hoc tests revealed significant differences between classes across all SF-36 subscales, with the exception of Vitality (see Table 4). Overall, Class 6 (the least symptomatic class) and Class 4 (characterized by circulatory symptoms) demonstrated the highest levels of physical and emotional functioning (see Figure 2). Conversely, Class 1 (the most symptomatic class) exhibited the most physical and emotional impairment, although Class 5 (characterized by both OI and circulatory symptoms) also demonstrated low Physical Functioning and Vitality scores.

Discussion

In this study, we used LCA with the intent to identify subtypes of ME/CFS. The resulting six-class solution included one class that was likely to endorse all symptoms, one class that endorsed none of the symptoms, one class with primarily gastro-intestinal symptoms, one class with primarily circulatory symptoms, one class with gastro-intestinal and circulatory symptoms, and one class with circulatory symptoms and OI. Previous studies have extracted classes with high and low symptomatology [13,15], but, to our knowledge, this study is one of the first to use LCA to extract symptom-specific subtypes from a sample of only ME/CFS patients.

Our results lend credence to the proposed multi-systemic nature of ME/CFS [2]. The existence of subtypes provides evidence against a uniform presentation of ME/CFS and disputes the validity of diagnostic criteria that require multiple non-core symptoms. The subtypes presented here, if replicated, may allow researchers to obtain more homogenous samples, enhancing their ability to identify biological markers and replicate study results. Additionally, awareness of ME/CFS subtypes could improve clinicians' ability to develop individualized plans of care. For instance, a patient in Class 5 could benefit from home orthostatic training [33] and medicinal methods of modulating temperature in addition to traditional pacing techniques [34].

While all individuals in our sample had a diagnosis of ME/CFS and were experiencing core symptoms of the illness (e.g., PEM), class membership had implications for various domains of health. Individuals who were unlikely to experience any non-core symptoms (Class 6) as well as those grappling with just circulatory symptoms (Class 4) tended to exhibit the best physical and mental/social functioning. In contrast, those with gastrointestinal symptoms or OI demonstrated greater functional impairment. Such results fall in line with previous literature, which has documented the impairment in work and health-related quality of life experienced by those with IBS [35] and POTS [36].

Furthermore, class membership was associated with various demographic characteristics. Classes that were likely to endorse a large number of the non-core symptoms (Classes 1, 3, and 5) were more likely to have lower levels of educational attainment than the least

symptomatic class (Class 6). Previous work has demonstrated how chronic illnesses limit children's ability to attend school [37] and lead to children being underserved in the educational system [38]. These factors lower their odds of graduating from college [39]. It is a possibility that ME/CFS patients who developed their illness during childhood, or those with more symptoms, experienced greater educational disruption and had increased barriers to academic achievement than those with fewer symptoms.

Class assignment also appeared to have important implications for work status and illness course. As expected, all of the classes characterized by non-core symptom endorsement were more likely to be on disability than Class 6. Other studies of chronic illness have demonstrated that patients with higher levels of functional disability are more likely to be approved for disability benefits [40]. Given the higher degree of physical and mental/social impairment exhibited by individuals with non-core symptoms in the current study, it would be conceivable that they are more likely to apply for and/or obtain government assistance. However, one must also consider the prejudice and difficulties individuals with ME/CFS face when applying for disability [41]. A claimant with ME/CFS may appear to present discrepant information if their self-report form describes their symptoms on 'bad days,' but the examining medical practitioner visits on a 'good day.' Given the greater likelihood of Class 6 to endorse a "relapsing and remitting" illness course (i.e., having 'good' periods with no symptoms alternating with symptomatically 'bad' periods), it would not be unusual for this group to have lower levels of disability benefits than classes with more consistent illness trajectories (such as Classes 1 and 5).

Though this study had a large sample size that facilitated its use of LCA, it also had several limitations. First, the use of convenience sampling reduces generalizability. Though the current sample was predominantly comprised of Caucasian women, community-based sampling procedures result in demographic profiles closer to those of the general population [42]. Secondly, class separation was less than ideal, as evidenced by an entropy value 0.04 lower than the recommended level; however, the selected model demonstrated generally strong fit statistics, balancing LCA's goals of interpretability and class homogeneity with class separation. Thirdly, the ideal number of latent classes is not empirically identified in LCA, so this value must be derived indirectly (i.e., through the comparison of fit statistics across models and an evaluation of the interpretability of each model). Due to the subjectivity involved in this process, different groups of researchers could determine different models to be 'best fitting,' even after presented with the same results. However, this limitation is present in all latent variable models. Fourthly, the value of any statistical model is in its replicability. Only after additional studies have replicated the results presented here with different samples of ME/CFS patients will the six-class model be considered valid.

Beyond the aforementioned considerations, our study has several strengths. Unlike previous work that determined which ME/CFS symptoms were 'atypical' in an *a priori* manner [13], the symptoms in our analysis were derived empirically from a validated measure of ME/CFS symptomology. The number of symptoms entered into our analysis was also smaller than in prior studies (in line with the method used by Collin et al. [18]), enhancing our ability to unearth clinically relevant symptom-based subtypes. Additionally, our sample was substantial, international, and included participants that were recruited by diverse means.

Finally, the identification of classes that differ by *type* of symptoms rather than just *quantity* of symptoms is a relatively novel result among analyses of samples of ME/CFS patients. These results, if replicated, may assist physicians in providing tailored treatment to patients, allow researchers to form more homogeneous samples, and aid in the development of empirically derived diagnostic criteria for ME/CFS.

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Figure 1.

Likelihood Criteria by the Number of Latent Classes

Notes. AIC = Akaike's information criterion. BIC = Bayesian information criterion.

SAABIC = sample-size adjusted BIC.

Figure 2.
Graphical Representation of Average SF-36 Subscale Scores by Class

Table 1

Demographic Characteristics of the Combined Sample (n = 1,210)

	<i>M</i>	<i>(SD)</i>
Age	49.8	(13.8)
Other demographic information	%	(<i>n</i>)
Gender		
Female	82.4	(976)
Male	17.6	(208)
Race		
White	97.9	(1,160)
Non-White	2.1	(25)
Latinx		
No	98.2	(1,158)
Yes	1.8	(21)
Education		
High school diploma or less	17.9	(211)
College degree or partial college	65.5	(773)
Graduate degree	16.6	(196)
Work status		
On disability	55.0	(651)
Working (full- or part-time)	18.8	(222)
Retired	11.2	(133)
Unemployed	10.1	(120)
Student or homemaker	4.8	(57)
Marital status		
Married or living with partner	55.2	(655)
Never married	26.8	(318)
Divorced	14.2	(169)
Widowed	2.0	(24)
Separated	1.7	(20)

Table 2

Goodness-of-fit Statistics for LCA Model Selection

Classes	Log likelihood	H0 value	Replications out of 50	AIC	BIC	SABIC	Entropy	VLMR test <i>p</i> -value	LMR test <i>p</i> -value
1	-9,213		50	18,450	18,512	18,474			
2	-8,192		50	16,433	16,561	16,481	0.80	0.00	0.00
3	-8,044		27	16,164	16,358	16,237	0.73	0.17	0.17
4	-7,904		48	15,910	16,170	16,008	0.74	0.00	0.00
5	-7,817		26	15,762	16,089	15,885	0.76	0.05	0.05
6	-7,765		35	15,683	16,076	15,831	0.76	0.01	0.01
7	-7,730		26	15,640	16,099	15,813	0.76	0.11	0.11
8	-7,699		30	15,605	16,130	15,803	0.72	0.39	0.39

Notes. Replications out of 50 = the number of times the best log likelihood value was replicated by 50 starting value sets in the second step of the optimization process. AIC = Akaike's information criterion. BIC = Bayesian information criterion. SABIC = sample-size adjusted BIC. VLMR test = Yong-Lo-Mendell-Rubin likelihood ratio test. LMR test = adjusted Lo-Mendell-Rubin likelihood ratio test. Smallest information criteria, the largest entropy value, and *p*-values 0.05 are bolded.

Table 3

Symptom Profiles and Class Proportions for Six-Class Solution

	Class 1 (n = 165, 13.6%)	Class 2 (n = 219, 18.1%)	Class 3 (n = 142, 11.7%)	Class 4 (n = 141, 11.7%)	Class 5 (n = 124, 10.3%)	Class 6 (n = 418, 34.6%)
Irritable bowel problems	0.94	0.87	0.87	0.23	0.29	0.17
Bloating	0.91	0.85	0.89	0.18	0.33	0.16
Stomach pain	0.92	0.73	0.83	0.11	0.18	0.06
Chills/shivers	0.83	0.04	0.92	0.58	0.42	0.01
Low temperature	0.53	0.10	0.51	0.42	0.24	0.03
Feeling hot/cold for no reason	0.95	0.49	0.92	0.78	0.71	0.17
Cold limbs	0.87	0.40	0.89	0.84	0.60	0.24
Unsteady on feet	0.86	0.42	0.36	0.20	0.93	0.14
Dizziness/fainting	0.87	0.27	0.31	0.23	0.90	0.11
Shortness of breath	0.85	0.36	0.29	0.21	0.63	0.18
Irregular heartbeat	0.74	0.24	0.20	0.16	0.53	0.06
Chest pain	0.65	0.18	0.07	0.12	0.29	0.05

Notes. Conditional probability values greater than chance (i.e., above 0.50) are bolded. The first three symptoms correspond to the Gastro-Intestinal Distress domain, the next four symptoms to the Circulatory/Neuroendocrine domain, and the last five symptoms to the Orthostatic Intolerance domain.

Table 4

Average SF-36 Subscale Scores by Class

	Class 1		Class 2		Class 3		Class 4		Class 5		Class 6		Sig.
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	
Physical functioning	21.5	(17.2) ²³⁴⁶	33.8	(21.9) ¹⁴⁵⁶	34.1	(20.8) ¹⁴⁵⁶	44.3	(24.2) ¹²³⁵	25.8	(21.3) ²³⁴⁶	43.9	(24.6) ¹²³⁵	***
Role physical	2.6	(9.6) ⁶	3.8	(12.9) ⁶	4.1	(13.4)	6.6	(16.0)	5.4	(15.7)	7.9	(21.7) ¹²	**
Bodily pain	24.6	(17.9) ²³⁴⁵⁶	36.0	(19.6) ¹⁴⁶	31.8	(20.7) ¹⁴⁶	43.9	(21.8) ¹²³⁵⁶	33.7	(22.9) ¹⁴⁶	51.1	(25.0) ¹²³⁴⁵	***
General health	21.4	(15.6) ⁴⁶	26.1	(15.8) ⁶	24.1	(13.5) ⁶	30.4	(17.3) ¹	24.4	(15.1) ⁶	31.0	(16.8) ¹²³⁵	***
Social functioning	17.6	(17.7) ²³⁴⁶	27.3	(22.7) ¹	25.4	(20.8) ¹⁶	32.2	(25.0) ¹⁵	22.4	(22.1) ⁴⁶	32.5	(25.1) ¹³⁵	***
Mental health	61.5	(22.0) ³⁴⁶	67.2	(19.3)	68.7	(19.0) ¹	71.5	(15.5) ¹	66.9	(20.2)	70.2	(17.1) ¹	***
Role emotional	57.0	(44.4) ⁴⁶	65.4	(44.1)	65.2	(43.8)	73.1	(40.3) ¹	65.8	(43.9)	69.4	(41.2) ¹	*
Vitality	12.2	(13.9)	14.0	(14.9)	15.8	(15.0)	17.5	(16.5)	11.9	(13.3)	16.9	(15.9)	***

* Notes: = *p* .05** = *p* .01*** = *p* .001¹ = significantly different from Class 1² = significantly different from Class 2³ = significantly different from Class 3⁴ = significantly different from Class 4⁵ = significantly different from Class 5⁶ = significantly different from Class 6