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Chronic Fatigue Syndrome (CFS) symptom-based phenotypes in two clinical cohorts of adult patients in the UK and The Netherlands

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Running head: Adult chronic fatigue syndrome phenotypes

ABSTRACT

Objective: Studies have provided evidence of heterogeneity within chronic fatigue syndrome (CFS), but few have used data from large cohorts of CFS patients or replication samples.

Methods: 29 UK secondary-care CFS services recorded the presence/absence of 12 CFS-related symptoms; 8 of these symptoms were recorded by a Dutch tertiary service. Latent Class Analysis (LCA) was used to assign symptom profiles (phenotypes). Regression models were fitted with phenotype as outcome (in relation to age, sex, BMI, duration of illness) and exposure (in relation to comorbidities and patient-reported measures).

Results: Data were available for 7,041 UK and 1,392 Dutch patients. Almost all patients in both cohorts presented with post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep, and these 3 symptoms were excluded from LCA. In UK patients, six phenotypes emerged: 'full' polysymptomatic (median 8, IQR 7-9 symptoms) 32.8%; 'pain-only' (muscle/joint) 20.3%; 'sore throat/painful lymph node' 4.5%; 'oligosymptomatic' (median 1, IQR 0-2 symptoms) 4.7%. Two 'partial' polysymptomatic phenotypes were similar to the 'full' phenotype, bar absence of dizziness/nausea/palpitations (21.4%) or sore throat/painful lymph nodes (16.3%). Women and patients with longer duration of illness were more likely to be polysymptomatic. Polysymptomatic patients had more severe illness and more comorbidities. LCA restricted to 5 symptoms recorded in both cohorts indicated 3 classes (polysymptomatic, oligosymptomatic, pain-only), which were replicated in Dutch data.

Conclusions: Adults with CFS may have one of 6 symptom-based phenotypes associated with sex, duration and severity of illness, and comorbidity. Future research needs to determine whether phenotypes predict treatment outcomes, and require different treatments.

Keywords: chronic fatigue syndrome; latent class analysis; phenotypes; symptom profiles

INTRODUCTION

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or, more recently, systemic exertion intolerance disease (SEID) (Institute of Medicine, 2015), is defined as persistent or recurrent debilitating fatigue that is not lifelong, or the result of ongoing exertion, or alleviated by rest, or explained by other conditions, and which results in a substantial reduction in activity (NICE, 2007). CFS imposes a huge burden on patients, carers and families (Horton *et al.*, 2010, Nacul *et al.*, 2011, Sabes-Figuera *et al.*, 2010). In the UK, adults who attend NHS specialist CFS services have been ill for a median duration of 3 years, and half of those who were employed at the onset of their illness have ceased working (Collin *et al.*, 2011). A meta-analysis of prevalence studies based on clinically-confirmed cases in several countries indicates a prevalence of 0.76% (95% CI 0.23% to 1.29%) (Johnston *et al.*, 2013).

CFS is an illness of unknown aetiology and pathogenesis, and of varied symptomatology (Prins *et al.*, 2006). Heterogeneity in the symptom profile of CFS can be confusing for clinicians, fuelling debate over diagnostic criteria, and posing an obstacle to biomedical research that aims to find biomarkers of CFS (Jason *et al.*, 2005). Several studies have investigated heterogeneity (phenotypes) in adult (Hickie *et al.*, 2009, Hickie *et al.*, 1995, Janal *et al.*, 2006, Sullivan *et al.*, 2005, Sullivan *et al.*, 2002, Vollmer-Conna *et al.*, 2006, Wilson *et al.*, 2001) and paediatric (May *et al.*, 2010) CFS patients. Despite between-study variation in the factors analysed and the methods used, these studies have demonstrated some consistency in classifying CFS phenotypes, including: a 'polysymptomatic' phenotype; a 'sore throat/painful lymph node' phenotype; phenotypes classified according to the presence/absence of musculoskeletal pain; and a dose-response effect in the number of symptoms and the overall severity of CFS. However, only one of the above studies conducted a replication analysis (Aslakson *et al.*, 2009).

The relationship between CFS phenotypes and treatment outcomes remains relatively unexplored. Three studies have shown that CFS patients who present with pain symptoms have less favourable outcomes (Cella *et al.*, 2011, Crawley *et al.*, 2013, Knoop *et al.*, 2007b). If symptom-based CFS phenotypes predict treatment outcomes, then simple decision-making algorithms based on symptom profiles could be used by clinicians and therapists to deliver individualised treatments.

In our study, we aimed to delineate symptom-based CFS phenotypes using data from a large clinical cohort of CFS patients from the UK, and to replicate our results in a clinical cohort of Dutch CFS patients. We aimed to investigate how these phenotypes were related to age, sex, and duration of illness, common CFS comorbidities (migraine, irritable bowel syndrome, anxiety and depression), and patient-reported measures of illness severity and quality-of-life.

METHODS

UK CFS patient cohort

Study population

Patient data were extracted from the CFS National Outcomes Database (NOD). The NOD is a centralized repository of pseudonymised clinical assessment and patient-reported outcome data which are routinely collected by NHS specialist CFS services across England. The NOD has been hosted by the University of Bristol since 2006, primarily for the purpose of evaluating NHS adult and paediatric CFS services. For this study, we used data from patients assessed and treated by 29 NHS services during the period 01/06/2010 to 31/05/2013.

Symptoms, comorbidities and patient-reported measures

Clinical teams either sent photocopies of clinical assessment forms and patient questionnaires to the NOD team in Bristol for data entry or they entered data into their own local database which were transferred electronically to the NOD team at regular intervals. A CFS diagnosis was made

(or confirmed) at an initial clinical assessment appointment in accordance with NICE guidelines (NICE, 2007). The latter include a set of 12 persistent/recurrent symptoms, namely: sleep disturbance/unrefreshing sleep; joint pain; muscle pain; headaches; painful lymph nodes; sore throat; cognitive dysfunction; post-exertional malaise; general malaise/flu-like symptoms; dizziness; nausea; palpitations. Clinicians recorded the presence/absence of each symptom, with the guidance that the symptom should have persisted/recurred during 4 or more consecutive months, did not predate the fatigue and was not caused by some other medical condition. The recording of symptomatology in NHS specialist CFS services is part of the overall triage and assessment process, with multidisciplinary input from clinicians and therapists who have extensive experience in the diagnosis and treatment of CFS. Clinicians also record the presence/absence of 6 common comorbidities (migraine, Irritable Bowel Syndrome, Fibromyalgia, Chronic Regional Pain Disorder, depression, and anxiety), the patient's height and weight, and the duration of illness (months since onset of chronic fatigue). At assessment patients complete standard questionnaires which provide quantitative measures of fatigue (Chalder Fatigue Scale (Chalder *et al.*, 1993)), physical function (RAND SF-36 (Ware and Sherbourne, 1992)), mood (Hospital Anxiety & Depression Scale (HADS) (Snaith, 2003)), pain (visual analogue pain rating scale), self-efficacy (Stanford Self-Efficacy for Managing Chronic Disease 6-Item Scale (Lorig *et al.*, 2001)), sleepiness (Epworth Sleepiness Scale (Johns, 1991)), and quality-of-life (EQ-5D (EuroQol, 1990)). Psychiatric comorbidity that could explain the presence of fatigue was ruled out by clinical interview at the specialist service with experienced clinicians, using the HADS questionnaire.

Dutch CFS patient cohort (replication sample)

Study population

The Dutch cohort comprised adults diagnosed with CFS at a tertiary specialist care centre during the period 2007-2012 in accordance with Centers for Disease Control and Prevention (CDC)

criteria (Fukuda *et al.*, 1994, Reeves *et al.*, 2003) and Dutch guidelines (CBO, 2013, Prins *et al.*, 2003). A Checklist Individual Strength (CIS20-R) fatigue severity subscale score ≥ 35 (Vercoulen *et al.*, 1994) and a Sickness Impact Profile (SIP) score ≥ 700 were used as operational criteria for fatigue that was severe enough to cause substantial functional impairment (Knoop *et al.*, 2007a). Consultants of the outpatient clinic of the Department of Internal Medicine assessed the medical status of all patients and decided whether patients had been sufficiently evaluated to rule out a medical explanation for the fatigue. If patients had not been sufficiently examined, they were seen for full physical examination, case history evaluation and laboratory tests. Psychiatric comorbidity that could explain the presence of fatigue was ruled out by clinical interview at the specialist service with experienced clinical psychologists using Beck Depression Inventory for Primary Care (BDI-PC) (Beck *et al.*, 1997, Brown *et al.*, 2012) and SCL-90 (Arrindell *et al.*, 2004) questionnaires.

Symptoms, comorbidities and patient-reported measures

CDC diagnostic criteria include a set of 8 persistent/recurrent symptoms occurring during 6 or more consecutive months: unrefreshing sleep; pain in several joints; muscle pain; headache; tender lymph nodes; sore throat; impaired memory; impaired concentration; and feeling ill after exertion. Patients were asked “Which of the following complaints did you experience during the last 6 months?” and, if affirmative, whether the symptom had been experienced for “less than” or “longer than” 6 months. We coded responses of “Not at all” and “Sometimes (each month)” as ‘symptom absent’ and responses of “Sometimes (each week)” and “Daily” as ‘symptom present’. The latter also required the symptom to have been experienced for “longer than” 6 months. ‘Post-exertional malaise’ was in response to a question asking whether symptoms were worse after physical effort; ‘Cognitive dysfunction’ was based on an affirmative response to one or both of two separate questions about forgetfulness and concentration; ‘Sleep disturbance’ was in response to a question asking whether the patient woke up unrefreshed. Responses were recorded by self-

completed questionnaire. At assessment patients complete standard questionnaires which provide quantitative measures of: fatigue (Chalder Fatigue Scale (Chalder *et al.*, 1993) and CIS20-R (Vercoulen *et al.*, 1994)); physical functioning (RAND SF-36 (Ware and Sherbourne, 1992)); mood (BDI-PC); and a 7-item self-efficacy scale (Prins *et al.*, 2001).

Ethical approvals

The North Somerset & South Bristol Research Ethics Committee determined that collection and analysis of these CFS patient data did not require ethical review by an NHS Research Ethics Committee or approval by NHS Research and Development offices (REC ref. 07/Q2006/48). The medical-ethical committee of the Radboud University Nijmegen Medical Centre ruled that the collection and analysis of Dutch CFS patient data did not require ethical review. Dutch CFS patient data were collected as part of routine clinical practice.

Statistical methods

CFS phenotypes (primary and replication analyses)

Our latent class analysis (LCA) was based on symptoms recorded in UK and Dutch patient data. We planned to conduct our primary analysis using 12 symptoms recorded in UK patients, and our replication analysis using the restricted set of 8 symptoms recorded in both UK and Dutch patient data. All analyses were carried out using Mplus version 7.11 (Muthén and Muthén, 2013). LCA identifies subtypes of related cases (latent classes, or ‘phenotypes’) from multivariate categorical data – in this case, responses to questions about presence/absence of each symptom (Rabe-Hesketh and Skrondal, 2008). LCA aims to determine the minimum number of latent classes that describe the observed patterns of responses in the data. In LCA, each individual is ‘assigned’ (probabilistically) to one of a pre-defined number of discrete latent classes on the basis of their responses to the symptom questions. The optimum class solution, i.e. the optimum number of classes, is selected by inspection and comparison of various model fit statistics (Nylund *et al.*,

2007), including: 1) Bayesian Information Criterion (BIC); 2) bivariate model fit - a test of the conditional independence assumption (within each class, there should be no association of one symptom with another, because all associations between symptoms are accounted for by class membership); 3) entropy - a measure of how well individuals have been classified (based on class membership probabilities) - a value of '1' indicates perfect separation of the classes; 4) Lo-Mendell-Rubin adjusted likelihood ratio test for c compared with c-1 classes; and 5) bootstrapped likelihood ratio test (BLRT) for c compared with c-1 classes. Selection of the optimum latent class solution, particular when the statistical selection criteria are inconclusive, may also be informed by subjective input, including: clinical/biological plausibility, prior knowledge of likely heterogeneity within CFS, and the clinical and epidemiological utility of any solution.

Factors associated with CFS phenotypes

The associations of risk factors with CFS phenotype were estimated using a series of multinomial logistic regression models. Parameter estimates were obtained using an implementation in Mplus of the 3-step method proposed by Jeroen Vermunt (Asparouhov and Muthen, 2013, Vermunt, 2010). Models were derived initially using the normative latent class as the baseline category for the outcome. The models were then re-parameterized to investigate possible differences between the classes, using each class in turn as reference class. This method has been shown to produce less biased estimates than traditional 3-step methods, such as probability weighting and modal class assignment, whilst avoiding the problem of covariates impacting on the measurement model itself (Vermunt, 2010).

Associations of CFS phenotypes with comorbidities and patient-reported measures

The associations of CFS phenotypes with comorbidities as binary outcomes (migraine, IBS, anxiety, depression and 'other') were estimated as odds ratios using a 3-step approach in Mplus as described above. Estimates were adjusted for the potential confounding effects of age, sex and

duration of illness. Mean values of patient-reported measures (fatigue, physical function, depression, anxiety, pain, sleepiness, self-efficacy, and quality-of-life) across the latent classes were estimated using the same 3-step approach. Evidence for overall variation of each patient-reported measure across latent classes was obtained using a Wald test, assuming homogeneous variance.

CFS phenotypes (sensitivity analyses)

We decided *a priori* not to include in our LCA factors which we considered to be: a) patient characteristics potentially associated with class assignment (age, sex, duration of illness, BMI); b) secondary to, or co-occurring with, CFS, i.e. comorbidities; c) markers of severity of CFS, i.e. patient-reported continuous measures of fatigue, physical function, self-efficacy, etc. However, we did perform sensitivity analyses in which we added some of these factors to our symptom-based LCA, specifically: sleep apnoea/hypnoea (for which we used, by proxy, an Epworth Sleepiness Scale score ≥ 11); obesity (BMI $\geq 30\text{kg/m}^2$); comorbid anxiety (from medical history or HADS anxiety score ≥ 11); and comorbid depression (from medical history or HADS depression score ≥ 11). The aim of these sensitivity analyses were to investigate whether these additional factors contributed to further delineation of CFS phenotypes and/or were consistent with findings from studies which had used factors other than symptoms.

RESULTS

UK and Dutch patient characteristics

Data were available for 7,041 UK and 1,392 Dutch patients. Demographic characteristics of the UK and Dutch patients were broadly similar (**Table S1**), although the Dutch cohort was slightly younger (mean age 37.2 (95% CI 36.6 to 37.9) years, compared to 40.5 (40.2 to 40.7) years, $P<0.001$) and had a slightly higher proportion of men (25.6% compared to 22.1%, $P=0.004$). Dutch patients had lower Chalder fatigue (median 25 compared to 28) and higher SF36 physical function (median 55 compared to 40, where high score = less disabled) scores ($P<0.001$ for both).

CFS symptoms in UK and Dutch (NL) patients

Symptoms of post-exertional malaise (UK 96.5%, NL 87.5%), cognitive dysfunction (UK 94.1%, NL 92.1%), and sleep disturbance (UK 95.3%, NL 96.8%) occurred in almost all patients in both cohorts (**Table 1**). These 3 symptoms were excluded from the primary and replication analyses, because they did not contribute to differentiation of latent classes. Hence, the primary analysis in UK patient data was based on 9 symptoms, and the replication analysis in UK and Dutch data on 5 symptoms. A lower proportion of male and female Dutch patients presented with each symptom than their same-sex UK counterparts (all $P\leq 0.006$), with the exception of cognitive dysfunction and sleep disturbance among men, and sleep disturbance among women, which occurred equally in both cohorts.

CFS phenotypes in UK patients (primary analysis)

An optimal 6-class solution was identified from the 9 symptoms remaining after exclusion of post-exertional malaise, cognitive dysfunction, and sleep disturbance (**Figure 1, Table S2**): 32.8% of patients presented with a ‘full’ polysymptomatic phenotype (median 8, IQR 7-9 symptoms); 20.3% with a muscle/joint ‘pain-only’ phenotype (median 3, IQR 2-4 symptoms); 4.5% with a ‘sore throat/painful lymph node’ polysymptomatic phenotype (median 4, IQR 3-5 symptoms); and

4.7% with an ‘oligosymptomatic’ phenotype (median 1, IQR 0-2 symptoms). The other 2 ‘partial’ polysymptomatic phenotypes were similar to the ‘full’ phenotype, differentiated largely by absence of dizziness/nausea/palpitations (‘Non-dizzy polysymptomatic’; 21.4%; median 6, IQR 5-6 symptoms) or absence of painful lymph nodes/sore throat (‘Non-throat/lymph polysymptomatic’; 16.3%; median 5, IQR 5-6 symptoms).

Associations of age, sex, BMI, and duration of illness with CFS phenotypes (UK patients)

Patients presenting with a polysymptomatic phenotype were more likely to be female and to have been ill for longer, compared with patients presenting with the oligosymptomatic phenotype (**Table 2**). These associations were most evident for the ‘full’ polysymptomatic phenotype: the odds of presenting with this phenotype were almost 4 times higher among women *versus* men (odds ratio (OR) 3.75 (95% CI 2.78 to 5.06)); and more than 2 times higher among patients who had been ill for ≥ 10 *versus* 1-2 years (OR 2.36 (1.39 to 4.00)). There were no clear patterns in the association of age with phenotype, although the oldest (60+ years) *versus* youngest (18-29 years) patients had lower odds of presenting with the ‘full’ polysymptomatic phenotype and with 2 of the 3 ‘partial’ polysymptomatic phenotypes. Obese patients (BMI ≥ 30 kg/m²) were almost 3 times more likely to present with a pain-only (OR 2.75 (1.33, 5.74)) than with an oligosymptomatic phenotype, and also had higher odds of presenting with ‘full’ and ‘non-dizzy’ polysymptomatic phenotypes.

Associations of CFS phenotypes with comorbidities (UK patients)

Patients presenting with a polysymptomatic phenotype were more likely to have a comorbid diagnosis of Irritable Bowel Syndrome (IBS), compared to patients presenting with the oligosymptomatic phenotype (**Table 3**). The ‘full’ polysymptomatic phenotype had the highest risk of comorbid IBS (OR 4.81 (3.12 to 7.40)) followed by patients presenting with a ‘non-throat/lymph’ phenotype, i.e. all symptoms except painful lymph nodes and sore throat (OR 3.47

(2.20 to 5.49)). This pattern was also evident for migraine and ‘other’ (not specified) comorbidities. Comorbid anxiety and depression were associated only with the ‘full’ polysymptomatic phenotype: OR 1.54 (1.11 to 2.15) and OR 1.56 (1.11 to 2.20), respectively. Fibromyalgia as a comorbidity was reported for 39% of patients classified with the ‘pain-only’ phenotype, and 31% of those with the full polysymptomatic phenotype; too few patients (<3%) with the oligosymptomatic phenotype had comorbid fibromyalgia to allow estimation of odds ratios with this as the reference group.

Associations of CFS phenotypes with patient-reported measures (UK patients)

There was strong evidence of variation in each of the patient-reported measures across the 6 classes (**Table 4**). Patients who presented with the ‘full’ polysymptomatic phenotype had greater severity of illness (lower physical function score), higher levels of pain, anxiety, and depression, and worse quality-of-life (lower EQ-5D and self-efficacy scores) than ‘oligosymptomatic’ patients. Although ‘oligosymptomatic’ patients had less physical disability (high SF-36 scores), their mean level of fatigue was similar to polysymptomatic patients. Patients presenting with the ‘sore throat/painful lymph node’ phenotype (Class 4) reported remarkably low fatigue scores, and their physical function scores were higher than those reported by oligosymptomatics, i.e. they were less physically disabled.

Sensitivity analyses (UK patients)

Sensitivity analyses showed that two factors included in several other studies namely, sleep apnoea/hypnoea (Epworth Sleepiness Scale score ≥ 11) and obesity (BMI $\geq 30\text{kg/m}^2$), did not contribute to further differentiation of the phenotypes, but merely confirmed the associations found in our primary analyses between polysymptomatic and pain-only phenotypes and higher odds of obesity and levels of daytime sleepiness, i.e. LCA based on 9 symptoms plus sleep apnoea/hypnoea and obesity yielded a 6-class solution in which the probabilities of sleep

apnoea/hypnoea and obesity increased in order from the lowest (oligosymptomatic) to highest (full polysymptomatic) (**Table S4, Figure S1**).

When we added presence/absence of other comorbidities to our LCA, the pattern that emerged was for each of the six previously-defined symptom-based phenotypes to be further subdivided according to the presence/absence of each comorbidity. This led to a multiplicity of classes, with model fit statistics tending towards a 12-class solution (**Table S3**). The 6-class solution had symptom profiles matching those found in our main (symptom-only) analysis, with probabilities for each comorbidity being similar to those obtained in our analysis of associations of CFS phenotypes with comorbidities, i.e. by treating comorbidities as binary outcomes (**Table S4, Figure S1**).

CFS phenotypes among UK and Dutch patients (replication analysis)

LCA based on the restricted set of 5 symptoms which had been recorded in both Dutch and UK patients, i.e. excluding post-exertional malaise, cognitive dysfunction and sleep disturbance, indicated 3- and 4-class solutions in the UK data, both of which were replicated in the Dutch data (**Table S5**). The classes in the 3-class solutions were aligned with the ‘full’ polysymptomatic, ‘pain only’ and ‘oligosymptomatic’ phenotypes that we had identified within the 6-class solution based on 9 symptoms in the UK patient data (**Figure 2**). The 4-class solutions for both cohorts were similar in that they delineated a ‘sore throat/painful lymph node/headache’ phenotype, as seen in the UK patient data 6-class 9-symptom solution (**Figure 3**).

The proportions of patients assigned to each of the classes differed between the UK *vs* Dutch (NL) cohorts, e.g.: ‘full’ polysymptomatic 53.2% UK *vs* 25.4% NL; ‘pain-only’ 37.6% UK *vs* 51.9% NL; ‘oligosymptomatic’ 9.2% UK *vs* 22.6% NL (**Figure 2**). The almost 3-fold higher odds of women in the UK cohort having the ‘full’ polysymptomatic *vs* oligosymptomatic phenotype (OR

2.76 (2.23 to 3.42)), and the 50% lower odds of being in the oldest (60+ years) compared with the youngest (18-29 years) age groups (OR 0.50 (0.33 to 0.75)), were not evident in the Dutch cohort (**Table 5**). In both cohorts, each of the four patient-reported measures (fatigue, physical function, depression, and self-efficacy) in ‘full’ polysymptomatic patients were indicative of more severe illness and worse quality-of-life than was reported by oligosymptomatic patients (**Table 5**).

DISCUSSION

In the largest study of CFS patients to date, we found 6 phenotypes based on 9 common symptoms in CFS patients attending UK specialist services, and we replicated 3 phenotypes (based on 5 of these symptoms) in CFS patients attending a Dutch specialist service. It is clear from both patient cohorts that post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms, although this may reflect the diagnostic processes in each country. We found that symptom-based CFS phenotypes were strongly associated with patient-reported measures of illness severity and with comorbidities, suggesting that different approaches to treatment of CFS might be warranted.

The main strengths of our study lie in the large sample size of our UK patient cohort, in our replication of CFS phenotypes and their associations with patient-reported measures in a different health care setting, and that all patients were diagnosed at specialist CFS services in either secondary (UK) or tertiary (NL) specialist CFS facilities. Of the dozen or so CFS phenotype studies published since 1995 (Jason *et al.*, 2005), only one had a sample size approaching ours: a multi-country study by Hickie *et al* which was based on a sample of 37724 people, of whom 1958 were formally diagnosed with CFS (Hickie *et al.*, 2009). A twin registry-based study in Sweden was based on a sample of 5,330 (Sullivan *et al.*, 2005), but only 732 (2.4%) were classified as having a CFS-like illness (Evengard *et al.*, 2005). Only one previous study has conducted a replication analysis, using a relatively small sample (Aslakson *et al.*, 2009).

Another strength of our study is that, unlike previous studies (with the exception of Janal *et al.* (2006)), our analysis was based on the presence/absence of a core set of 12 commonly-reported CFS symptoms. Previous CFS phenotype studies have been based on longer lists of, for example, 38 (Hickie *et al.*, 1995), 55 (Wilson *et al.*, 2001), and 32 (Sullivan *et al.*, 2002) typical and atypical symptoms. We adopted our approach because symptom-based phenotypes could, in principle, be identified as part of routine clinical practice in UK and Dutch specialist CFS services, where these symptoms are already routinely recorded when patients are assessed. Whether such phenotypes are clinically important in practice remains to be determined, by investigating how they relate to treatment response. Precedent for the importance of improved subtyping in advancing our understanding of pathophysiology and personalised treatments include the differentiation of depressive disorders into unipolar and bipolar affective conditions (with different treatments indicated for each, i.e. antidepressants contra-indicated for bipolar depression), and juvenile idiopathic arthritis (JIA) being subdivided into oligo- and polyarthritis phenotypes. In JIA, phenotypic analyses revealed subtypes which were more homogeneous than those defined by expert consensus, and which had very distinct disease trajectories (Eng *et al.*, 2014). In depressive disorders, latent class analysis indicated subtypes (differentiated by symptoms such as insomnia and appetite) which predicted remission after citalopram treatment (Ulbricht *et al.*, 2015).

Differences in patient characteristics and CFS phenotypes between the two cohorts could be attributable to differences in UK and Dutch referral pathways, clinical settings and diagnostic criteria. Dutch patients were diagnosed in accordance with CDC criteria (Fukuda *et al.*, 1994, Reeves *et al.*, 2003), which require fatigue of ≥ 6 months' duration plus the presence of at least 4 symptoms (including feeling ill after exertion, impaired memory or concentration, and unrefreshing sleep), compared to fatigue of ≥ 4 months' duration and no specific symptom requirements in UK NICE guidelines (NICE, 2007). Dutch patients also had to exceed thresholds

for fatigue (CIS20-R) and disability (SIP) (Knoop *et al.*, 2007a). However, the substantial differences in the proportions of Dutch *versus* UK patients presenting with each CFS phenotype in our replication analyses are perhaps more likely to be a consequence of other differences in the assessment pathway, in particular, more rigorous psychological assessment to exclude somatic or psychiatric disorders.

If Dutch patients with comorbidities were more likely to be excluded, this may explain the lower proportion of Dutch *versus* UK CFS patients with the ‘full’ polysymptomatic phenotype, given that patients with this symptom profile were more likely to have comorbidities. UK patient data for our study were obtained from NHS specialist CFS services, in which an average of 80% of referred patients were diagnosed with CFS (Collin *et al.*, 2012). Case note review has shown that 40-50% of referrals to such services could have alternative diagnoses, mainly of psychological or sleep disorders, or other chronic conditions (Devasahayam *et al.*, 2012, Newton *et al.*, 2010). Conversely, the lower proportion of UK patients with a ‘pain-only’ phenotype may indicate higher rates of fibromyalgia diagnoses and onward referral to specialist pain clinics. UK data showed a positive association between longer duration of illness and presentation with polysymptomatic phenotypes. If this association is a consequence of ‘accrual’ of symptoms over time (rather than an aetiological difference in oligo- versus polysymptomatic phenotypes), and if referral to UK specialist services is slower than in the Netherlands, then we would expect a higher proportion of UK patients to present with polysymptomatic phenotypes. We did not have data on duration of illness in Dutch patients with which to test the latter hypothesis.

Dutch patients had lower levels of fatigue and higher levels of physical function than UK patients, and sex was not associated with phenotype. However, the same trends in patient-reported outcomes (fatigue, physical function, depression and self-efficacy) across the CFS phenotypes were seen in both UK and Dutch data. We do not know the extent to which our findings are

generalizable to ‘undetected’ CFS cases in the wider population, because both of our cohorts comprised patients who had access to specialist CFS services. Our analysis was based on presence/absence of symptoms, without consideration of symptom frequency or severity. Analysing symptoms by their frequency or severity might have yielded different results.

Our findings in the context of other studies

Our CFS phenotypes broadly replicate the results of earlier studies which have attempted to delineate symptom profiles among CFS patients or people with a CFS-like illness. Most notably, several studies found a polysymptomatic phenotype which affected a proportion of patients similar to that observed in our study. Compared with the 33% of patients assigned to this phenotype in our 6-class solution, the proportions of polysymptomatic (labelled by some authors as ‘somatoform’) patients in these other studies were 27% of 565 Australian patients (Hickie *et al.*, 1995), 32% of 744 patients from the UK, USA and Australia (Wilson *et al.*, 2001), and 28% of 157 patients from the USA (Janal *et al.*, 2006). One study assigned a high proportion (53%) of its 646 participants to two polysymptomatic classes, but the cohort comprised CFS and fibromyalgia patients (Sullivan *et al.*, 2002). Conversely, a lower proportion (14%) of polysymptomatics was found in a Swedish cohort of 5330 twins, but only 48% of this cohort had fatigue of ≥ 6 months’ duration (Sullivan *et al.*, 2005). Given that twins who had fatigue of ≥ 6 months’ duration plus ≥ 4 of the 8 CDC symptoms had very high probabilities of being in this polysymptomatic class, the true proportion would be closer to 28%, similar to the proportion observed in our study. The Swedish twins study reported a 5-classes, 4 of which had symptom profiles similar to those in our UK data, namely: polysymptomatic, oligosymptomatic, muscle/joint pain-only, and sore throat/tender lymph nodes. In our sensitivity analyses, we found that obesity and sleep apnoea/hypnoea did not contribute to delineation of CFS phenotypes, which is inconsistent with several earlier studies (Aslakson *et al.*, 2009, Aslakson *et al.*, 2006, Vollmer-Conna *et al.*, 2006). These studies differed considerably from ours in methodology (LCA based on a similar set of 12 symptoms, but with the addition of

26 other biological and clinical measurements, many as continuous variables) and study population (population-based samples from Georgia and Kansas, USA, comprising CFS, chronically-fatigued and healthy participants). That sleep apnoea/hypnoea did not differentiate latent classes in our analysis may be because the Epworth Sleepiness Scale does not have high sensitivity and specificity for this disorder (Pataka *et al.*, 2014, Ulasli *et al.*, 2014), or because patients with this disorder were excluded by clinicians at assessment.

Four of the five studies reported, as we did, that the polysymptomatic phenotype was more likely to occur in women, and was associated with a more severe illness of longer duration and with comorbid mood disorders (Hickie *et al.*, 1995, Sullivan *et al.*, 2005, Sullivan *et al.*, 2002, Wilson *et al.*, 2001). Other consistencies between the results from our study and other CFS latent class and/or factor analysis studies include evidence for musculoskeletal pain and sore throat/painful glands as key phenotypic delineators (Hickie *et al.*, 2009, Janal *et al.*, 2006, Sullivan *et al.*, 2005).

Implications for practice and future research

The two main implications of our study are: a) post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms; and b) having made a diagnosis, patient profiling (subtyping) based on a set of common symptoms could form the basis for individualized treatment approaches. In support of the latter notion, we found substantial variation in patient-reported measures across our phenotypes. For example, CFS patients presenting with a sore throat/painful lymph node phenotype had a mean Chalder Fatigue score within 1 standard deviation (SD) of the mean score for adult attendees at UK general practice (14.2 ± 4.6) (Cella and Chalder, 2010), and an SF-36 physical function score within 1 SD of the mean score for the UK working age population (84 ± 24) (Bowling *et al.*, 1999). These patients appear to be different from those presenting with a polysymptomatic phenotype. Three studies have shown that CFS patients who present with pain symptoms have less favourable treatment outcomes (Cella *et al.*,

2011, Crawley *et al.*, 2013, Knoop *et al.*, 2007b). We found considerable overlap between CFS and fibromyalgia in our ‘full’ polysymptomatic and ‘pain-only’ phenotypes, reflecting the phenotypic similarity of these diseases (Sullivan *et al.*, 2002). CFS patients with pain symptoms may respond to tailored interventions. For example, our ‘pain-only’ CFS phenotype was associated with obesity, raising the possibility that weight loss could ameliorate pain symptoms, as has been shown for fibromyalgia (Ursini *et al.*, 2011).

The three ‘cardinal’ symptoms may simply reflect the diagnostic criteria used in the UK and the Netherlands. For example, UK NICE guidelines specify that healthcare professionals should consider the possibility of CFS/ME if a person has fatigue with several features, including fatigue “characterised by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days)” (NICE, 2007).

Our next step will be to investigate associations between our CFS phenotypes and 12-month treatment outcomes in a follow-on study, which will also serve to replicate our phenotypes using a second large CFS patient sample from the same NHS services. Some of the specific factors used in our study and earlier studies, e.g. pain, may warrant more detailed phenotypic analysis, as has been done for sleep abnormalities (Gotts *et al.*, 2013). Associations of symptom-based phenotypes with ‘other’ comorbidities, such as postural orthostatic tachycardia syndrome (Lewis *et al.*, 2013), also need to be explored. Longitudinal models based on repeated measures of symptoms and other biological and clinical measurements could be used to investigate why a triggering event, such as an acute infection, leads to CFS in a small minority of people, to further investigate whether more symptoms at onset predict a chronic course or whether a chronic course leads to the development of more symptoms (Friedberg *et al.*, 2000, Nisenbaum *et al.*, 2000, Nisenbaum *et al.*, 2004), and to investigate why some patients do not respond to treatment.

CONCLUSION

We have identified CFS phenotypes that are consistent with earlier studies, are replicated in two large patient cohorts, and have potential diagnostic and prognostic utility because they are based on routinely-recorded CFS-related symptoms. We have shown that, among the 8-12 symptoms listed in the diagnostic criteria for patients in our two study cohorts, post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep could be regarded as cardinal symptoms. We further characterised our symptom-based CFS phenotypes in terms of their associations with patient characteristics, comorbidities, and patient-reported measures, thereby providing qualitative evidence on which to base testable hypotheses around the clinical management of CFS.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org and have no competing interests to report.

Table 1: Presence of symptoms among UK and Dutch adult CFS patients at time of clinical assessment

Symptom	UK adult CFS patients			Dutch adult CFS patients		
	Female	Male	Overall	Female	Male	Overall
	n=5,488	n=1,553	n=7,041	n=1,036	n=356	n=1,392
Post-exertional malaise	5,309 (96.7%)	1,485 (95.6%)	6,794 (96.5%)	916 (88.4%)	302 (84.8%)	1,218 (87.5%)
Cognitive dysfunction	5,194 (94.6%)	1,430 (92.1%)	6,624 (94.1%)	958 (92.5%)	324 (91.0%)	1,282 (92.1%)
Sleep disturbance/unrefreshing sleep	5,258 (95.8%)	1,454 (93.6%)	6,712 (95.3%)	1,007 (97.2%)	341 (95.8%)	1,348 (96.8%)
Muscle pain	4,866 (88.7%)	1,269 (81.7%)	6,135 (87.1%)	700 (67.6%)	248 (69.7%)	948 (68.1%)
Joint pain	4,237 (77.2%)	1,049 (67.6%)	5,286 (75.1%)	607 (58.6%)	201 (56.5%)	808 (58.1%)
Headaches	4,052 (73.8%)	1,020 (65.7%)	5,072 (72.0%)	574 (55.4%)	186 (52.3%)	760 (54.6%)
Painful lymph nodes	2,703 (49.3%)	585 (37.7%)	3,288 (46.7%)	247 (23.8%)	62 (17.4%)	309 (22.2%)
Sore throat	3,129 (57.0%)	696 (44.8%)	3,825 (54.3%)	195 (18.8%)	56 (15.7%)	251 (18.0%)
General malaise or ‘flu-like’ symptoms	4,042 (73.7%)	1,091 (70.3%)	5,133 (72.9%)	Not recorded	Not recorded	Not recorded
Dizziness	3,279 (59.8%)	815 (52.5%)	4,094 (58.2%)	Not recorded	Not recorded	Not recorded
Nausea	2,650 (48.3%)	549 (35.4%)	3,199 (45.4%)	Not recorded	Not recorded	Not recorded
Palpitations	2,038 (37.1%)	470 (30.3%)	2,508 (35.6%)	Not recorded	Not recorded	Not recorded

Table 2: Factors associated with CFS phenotype (reference class = class 1 ‘oligosymptomatic’)^a

		Class 2	Class 3	Class 4	Class 5	Class 6
		Non-throat/lymph polysymptomatic	Pain-only (muscle/joint)	Throat/lymph polysymptomatic	Non-dizzy polysymptomatic	Full polysymptomatic
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Sex ^b		1.82 (1.32, 2.53)	1.62 (1.18, 2.22)	1.44 (0.95, 2.18)	2.14 (1.56, 2.93)	3.75 (2.78, 5.06)
Age group (years) ^c	30-39	1.11 (0.69, 1.79)	1.18 (0.73, 1.91)	1.40 (0.80, 2.45)	1.19 (0.75, 1.89)	1.12 (0.73, 1.72)
	40-49	0.94 (0.60, 1.46)	1.30 (0.83, 2.02)	0.65 (0.36, 1.14)	1.02 (0.67, 1.56)	0.90 (0.61, 1.34)
	50-59	0.87 (0.54, 1.41)	1.39 (0.87, 2.23)	0.47 (0.24, 0.92)	1.04 (0.66, 1.64)	0.69 (0.45, 1.07)
	60+	0.71 (0.42, 1.22)	0.72 (0.42, 1.25)	0.17 (0.06, 0.50)	0.43 (0.24, 0.74)	0.29 (0.17, 0.48)
Duration of illness (years) ^d	1-2	1.01 (0.62, 1.65)	1.08 (0.67, 1.74)	0.75 (0.41, 1.39)	1.17 (0.74, 1.85)	1.47 (0.95, 2.28)
	3-4	1.60 (0.93, 2.76)	1.44 (0.84, 2.48)	1.20 (0.62, 2.32)	1.27 (0.74, 2.16)	2.09 (1.27, 3.44)
	5-10	1.02 (0.62, 1.67)	1.18 (0.73, 1.89)	0.66 (0.36, 1.24)	1.07 (0.67, 1.70)	1.70 (1.10, 2.61)
	10+	1.79 (1.01, 3.18)	1.76 (1.00, 3.10)	0.79 (0.37, 1.70)	1.62 (0.93, 2.81)	2.36 (1.39, 4.00)
BMI (kg/m ²) ^e	20-24.9	0.75 (0.42, 1.35)	1.39 (0.74, 2.61)	0.77 (0.37, 1.60)	1.09 (0.60, 1.98)	0.88 (0.52, 1.50)
	25-29.9	0.78 (0.43, 1.44)	1.65 (0.86, 3.17)	0.74 (0.34, 1.61)	1.24 (0.66, 2.31)	0.97 (0.56, 1.70)
	30+	1.35 (0.67, 2.71)	2.76 (1.33, 5.74)	0.80 (0.32, 2.02)	2.25 (1.11, 4.55)	2.02 (1.06, 3.84)

^a Class 1 (reference) = oligosymptomatic; Class 2 = all symptoms except painful lymph nodes and sore throat; Class 3 = pain only (muscle and joint); Class 4 = sore throat, painful lymph nodes, headache and flu-like symptoms; Class 5 = all symptoms except dizziness, nausea and palpitations; Class 6 = full polysymptomatic

^b Reference category = male; ^c Reference category = age 18-29 years; ^d Reference category = up to 1 year; ^e Reference category <20 kg/m²

Table 3: Associations of CFS phenotypes with comorbidities^a

	Odds Ratio (95% CI)	Adjusted OR (95% CI) ^b
Migraine		
Class 1 ‘Oligosymptomatic’	1.00 (ref)	1.00 (ref)
Class 2 ‘Non-throat/lymph polysymptomatic’	2.49 (1.57, 3.94)	2.26 (1.39, 3.66)
Class 3 ‘Pain-only’	1.07 (0.66, 1.74)	0.94 (0.57, 1.56)
Class 4 ‘Throat/lymph polysymptomatic’	1.25 (0.68, 2.30)	1.18 (0.62, 2.22)
Class 5 ‘Non-dizzy polysymptomatic’	1.09 (0.68, 1.76)	1.02 (0.62, 1.69)
Class 6 ‘Full polysymptomatic’	3.70 (2.41, 5.66)	3.08 (1.97, 4.83)
Irritable Bowel Syndrome		
Class 1 ‘Oligosymptomatic’	1.00 (ref)	1.00 (ref)
Class 2 ‘Non-throat/lymph polysymptomatic’	3.33 (2.18, 5.08)	3.47 (2.20, 5.49)
Class 3 ‘Pain-only’	1.10 (0.70, 1.72)	1.06 (0.65, 1.72)
Class 4 ‘Throat/lymph polysymptomatic’	1.79 (1.05, 3.05)	1.79 (1.00, 3.21)
Class 5 ‘Non-dizzy polysymptomatic’	1.96 (1.29, 2.99)	1.82 (1.15, 2.89)
Class 6 ‘Full polysymptomatic’	5.53 (3.72, 8.21)	4.81 (3.12, 7.40)
Depression		
Class 1 ‘Oligosymptomatic’	1.00 (ref)	1.00 (ref)
Class 2 ‘Non-throat/lymph polysymptomatic’	1.37 (0.97, 1.94)	1.29 (0.88, 1.89)
Class 3 ‘Pain-only’	1.21 (0.85, 1.70)	1.14 (0.79, 1.66)
Class 4 ‘Throat/lymph polysymptomatic’	0.69 (0.43, 1.12)	0.61 (0.36, 1.05)
Class 5 ‘Non-dizzy polysymptomatic’	0.95 (0.68, 1.34)	0.90 (0.62, 1.30)
Class 6 ‘Full polysymptomatic’	1.64 (1.20, 2.25)	1.56 (1.11, 2.20)
Anxiety		
Class 1 ‘Oligosymptomatic’	1.00 (ref)	1.00 (ref)
Class 2 ‘Non-throat/lymph polysymptomatic’	1.23 (0.88, 1.72)	1.27 (0.88, 1.83)
Class 3 ‘Pain-only’	1.00 (0.72, 1.40)	1.02 (0.71, 1.47)
Class 4 ‘Throat/lymph polysymptomatic’	0.74 (0.47, 1.16)	0.75 (0.45, 1.23)
Class 5 ‘Non-dizzy polysymptomatic’	0.87 (0.62, 1.20)	0.87 (0.60, 1.25)
Class 6 ‘Full polysymptomatic’	1.55 (1.15, 2.10)	1.54 (1.11, 2.15)
Other comorbidity		
Class 1 ‘Oligosymptomatic’	1.00 (ref)	1.00 (ref)
Class 2 ‘Non-throat/lymph polysymptomatic’	2.56 (1.45, 4.51)	2.08 (1.16, 3.74)
Class 3 ‘Pain-only’	1.62 (0.91, 2.90)	1.34 (0.74, 2.43)
Class 4 ‘Throat/lymph polysymptomatic’	1.70 (0.84, 3.45)	1.45 (0.68, 3.07)
Class 5 ‘Non-dizzy polysymptomatic’	1.65 (0.94, 2.91)	1.60 (0.90, 2.86)
Class 6 ‘Full polysymptomatic’	2.38 (1.39, 4.07)	2.34 (1.35, 4.04)

^a Class 1 = oligosymptomatic; Class 2 = all symptoms except painful lymph nodes and sore throat; Class 3 = pain only (muscle and joint); Class 4 = sore throat, painful lymph nodes, headache and flu-like symptoms; Class 5 = all symptoms except dizziness, nausea and palpitations; Class 6 = full polysymptomatic

^b Odds Ratios (OR) adjusted for age, sex and duration of illness

Table 4: Patient-reported measures (mean (95% CI)) in CFS phenotypes^a

	Chalder Fatigue (range 0 to 33)	SF36 Physical Function (range 0 to 100)	HADS Depression (range 0 to 21)	HADS Anxiety (range 0 to 21)	Visual Analogue Pain Rating (range 0 to 100)	Epworth Sleepiness (range 0 to 24)	Self-efficacy (range 1 to 10)	EQ-5D (range -1 to +1)
Class 1 'Oligosymptomatic'	26.1 (25.5, 26.7)	56.4 (53.6, 59.2)	8.39 (7.95, 8.82)	8.20 (7.71, 8.69)	15.0 (13.2, 16.9)	9.01 (8.42, 9.60)	5.29 (5.08, 5.49)	0.634 (0.612, 0.656)
Class 2 'Non-throat/lymph polysymptomatic'	28.0 (27.8, 28.3)	40.3 (38.6, 42.1)	10.3 (9.96, 10.6)	10.7 (10.4, 11.1)	53.4 (51.0, 55.8)	10.7 (10.3, 11.1)	4.05 (3.92, 4.19)	0.426 (0.400, 0.452)
Class 3 'Pain-only'	27.0 (26.6, 27.3)	42.5 (40.9, 44.0)	9.65 (9.39, 9.91)	9.64 (9.36, 9.91)	56.0 (54.3, 57.8)	11.1 (10.7, 11.4)	4.43 (4.30, 4.55)	0.438 (0.418, 0.459)
Class 4 'Throat/lymph polysymptomatic'	17.6 (16.4, 18.8)	63.2 (60.8, 65.5)	8.31 (7.90, 8.72)	9.02 (8.51, 9.53)	16.8 (15.0, 18.6)	9.14 (8.56, 9.72)	5.36 (5.12, 5.60)	0.618 (0.596, 0.641)
Class 5 'Non-dizzy polysymptomatic'	27.3 (27.0, 27.6)	47.1 (45.5, 48.7)	9.43 (9.17, 9.68)	9.51 (9.21, 9.82)	49.7 (47.7, 51.7)	10.5 (10.1, 10.8)	4.64 (4.51, 4.78)	0.514 (0.495, 0.533)
Class 6 'Full polysymptomatic'	28.8 (28.6, 29.0)	34.6 (33.5, 35.6)	11.1 (10.9, 11.3)	11.9 (11.7, 12.1)	60.9 (59.6, 62.1)	12.2 (11.9, 12.5)	3.70 (3.62, 3.79)	0.324 (0.307, 0.341)

^a Class 1 = oligosymptomatic; Class 2 = all symptoms except painful lymph nodes and sore throat; Class 3 = pain only (muscle and joint); Class 4 = sore throat, painful lymph nodes, headache and flu-like symptoms; Class 5 = all symptoms except dizziness, nausea and palpitations; Class 6 = full polysymptomatic. Wald-type omnibus test of variation across the 6 classes yielded $P < 0.001$ for all of the patient-reported measures.

Table 5: Characteristics of UK and Dutch adult CFS patients according to phenotype

		UK adult CFS patients ^a			Dutch adult CFS patients ^a		
		Class 1 (9.2%) oligosymptomatic (Reference)	Class 2 (37.6%) pain only Odds ratio (95% CI)	Class 3 (53.2%) full polysymptomatic Odds ratio (95% CI)	Class 1 (22.6%) oligosymptomatic (Reference)	Class 2 (51.9%) pain only Odds ratio (95% CI)	Class 3 (25.4%) full polysymptomatic Odds ratio (95% CI)
Sex ^b		-	1.47 (1.18, 1.83)	2.76 (2.23, 3.42)	-	0.89 (0.61, 1.29)	1.14 (0.76, 1.72)
Age group (years) ^c	30-39	-	1.08 (0.80, 1.46)	0.93 (0.71, 1.22)	-	1.43 (0.95, 2.15)	1.32 (0.86, 2.03)
	40-49	-	1.59 (1.18, 2.14)	1.13 (0.86, 1.48)	-	2.79 (1.73, 4.51)	2.15 (1.30, 3.55)
	50-59	-	1.89 (1.35, 2.65)	1.06 (0.78, 1.45)	-	4.40 (2.30, 8.44)	3.03 (1.54, 5.95)
	60+	-	1.48 (0.99, 2.23)	0.50 (0.33, 0.75)	-	2.03 (0.76, 5.45)	0.83 (0.24, 2.87)
		Mean (95% CI) ^d	Mean (95% CI) ^d	Mean (95% CI) ^d	Mean (95% CI) ^d	Mean (95% CI) ^d	Mean (95% CI) ^d
Fatigue (Chalder, range 0-33)		24.6 (24.0, 25.1)	27.0 (26.8, 27.2)	27.8 (27.6, 28.0)	23.0 (22.2, 23.7)	24.5 (24.0, 24.9)	25.8 (25.2, 26.3)
Physical function (SF36, range 0-100)		60.4 (58.6, 62.2)	41.5 (40.5, 42.5)	39.5 (38.7, 40.3)	68.8 (66.8, 70.9)	56.9 (55.5, 58.2)	48.0 (46.1, 49.8)
Depression ^e		8.30 (8.01, 8.59)	9.88 (9.71, 10.1)	10.5 (10.4, 10.7)	2.68 (2.44, 2.91)	3.15 (2.97, 3.33)	3.53 (3.28, 3.79)
Self-efficacy ^f		5.32 (5.18, 5.47)	4.29 (4.22, 4.37)	4.04 (3.98, 4.11)	17.7 (17.4, 18.0)	16.9 (16.7, 17.1)	16.7 (16.4, 17.0)

^a Class 1 = ‘oligosymptomatic’; Class 2 = ‘pain only’ (muscle, joint, headache); Class 3 = ‘full’ polysymptomatic

^b Reference category = male

^c Reference category = age 18-29 years

^d Wald-type omnibus test of variation across the 3 classes yielded P<0.001 for all of the patient-reported measures

^e UK patients, HADS, range 0-21; Dutch patients, 7-item BDI-PC, range 0-21

^f UK patients, Stanford Self-Efficacy for Managing Chronic Disease 6-Item Scale, range 1-10; Dutch patients, 7-item Self-Efficacy scale, range 7-28

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